A RANDOMISED CONTROL TRIAL TO KNOW THE SAFETY AND EFFICACY OF ORAL MIFEPRISTONE IN PREINDUCTION OF LABOUR IN POST DATED PREGNANCY"

BY

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Dissertation submitted to

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

MASTER OF SURGERY

IN

OBSTETRICS AND GYNAECOLOGY

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ACKNOWLEDGEMENT

With Privilege and respect, I express my profound gratitude and indebtedness to my Guide and esteemed teacher **Dr.S.R.BIDRI**, Professor and Unit Chief Department of Obstetrics and gynaecology. **Shri B.M. Patil Medical College, Vijayapura,** for his constant inspiration, valuable suggestion, extensive encouragement and support, great care and attention to details which he rendered in pursuit of my post graduate studies and in preparing this dissertation.

My heartfelt gratitude to **Dr. S. R. Mudanur,** Professor, HOD of Obstetrics and Gynaecology, Shri B.M..Patil Medical College, Vijayapura, for the valuable guidance and encouragement during my postgraduate training and in the preparation of this dissertation. I express my sincere thanks to my dear teacher, **Dr(Prof) V.R. Gobbur, Dr (prof) P.B.JAJU, , Dr.(Prof) Neelamma patil, Dr. Girija Hanjagi, Dr. Rajasri Y, Dr. Shobha G, Dr. Aruna Biradar Dr. Sangamesh Mathpathi, Dr. Preeti Patil., Dr. Shreedevi Kori , Dr. Shruti R. B., Dr Basavraj, Dr.Shivakumar Pujeri for their kind co-operation and guidance. I am thankful for Dr. Rajesh Honnutagi,** Medical Superintendent, Shri. B.M. Patil Medical College Hospital and Research Centre and **Dr. Arvind Patil**, Principal, B.L.D.E.U's Shri. B.M. Patil Medical College Hospital and Research Centre, Vijayapura, for permitting me to conduct & utilize resources in completion of my work.

I am also thankful to my fellow post graduates and all my friends for their Suggestions and support. I am deeply indebted to my patients who willingly consented themselves to be part of this study. I would like to take this opportunity to express my heartfelt gratitude towards my parents(**MY ROLE MODELS**) who have

been source of inspiration, motivation and strength, **Shri Thota.N. Hussainaia, Mrs Parvathi Devi**, brother **Mr.T.Sai Jayanth Royal** and my co brothers and sisters.

All interns who have helped me my thanks to all the non –teaching staff of my department ,nursing staff and all the Hospital staff for their co-operation in my study. A word of gratitude to **Mrs.Vijaya Sorganvi, Shri. B.M. Patil Medical College, Vijayapura,** for her patient guidance. And before my dissertation, I bow to the almighty for being with me throughout the journey.

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ABSTRACT

Background and Objectives:

The aim of present study is to evaluate the safety and efficacy of oral mifepristone and dinoprostone gel for pre induction cervical ripening versus dinoprostone alone in postdated pregnancy.

Methods :

- The following study included 130 pregnant women as samples with diagnosis of post dated pregnancy and due for induction of labor. Detailed history of all the patients taken according to the proforma and complete examination and all necessary investigations done. Informed written consent has taken from the participants.
- The sample size for the study is 130. Women will be randomized into two groups according to computer generated randomized table. The number of participants in study group will be 65 and control group will be 65.
- Women randomized to study group will receive one tablet Mifepristone 200 mg per oral at the moment of enrollment, later on patient will be reviewed for Bishops score after 24 hours. The participants in control group will not receive anything.
- After 24 hours, both groups will receive dinoprostone gel 0.5 mg every 6th hourly until Bishops score is > 8 or maximum for 3 doses.
- Before each dose of dinoprostone gel fetal wellbeing will be evaluated by clinical examination and Cardiotocography .
- If with 3 doses of dinoprostone gel the Bishops score not improved then the induction will be categorized as failed induction.

- When the women entered in active labor, augmentation of labor will be done by using Oxytocin drip, but not earlier than 6 hours from last dose of PGE2 gel application.

RESULTS :

The age range varied from < 20 years to > 30 years. Most common age group in mifepristone along with cerviprime group is < 20 years constituted 24 (36 %) patients and in cerviprime group is 20-24 years ,constituted 37 with (56 %) . The mean age of mifepristone and cerviprime group and dinoprostone gel alone group is 22.82 and 23.66 years respectively. In the present study we observed the number of multiparous women were higher than primiparous women. Multiparous and primiparous women are 52.3% and 47.7% respectively in mifepristone and cerviprime group; and in dinoprostone gel alone group respectively. The commonest side effects observed in control group as constituted 5 % patients each. While analyzing for side effects we found a highly significant difference in two groups. The time taken from induction to active phase is higher in study group with mean 17.21 ,than in control group with mean 10.53. Time taken from induction to delivery was higher in study group with mean 22.10, and in control group with mean 15.063. Total number of vaginal deliveries in study group was lesser than in control group with mean values 62.5 % and 67.7 % respectively.

Conclusion :

This study reveals that oral mifepristone along with cerviprime is very safe and an effective drug for pre induction cervical ripening. It has an advantage of, better patient compliance and acceptance, reduced oxytocin requirement, ease of

administration .The drug has less side effects on uterine contraction and no major maternal complications. This drug has safe neonatal outcome.

This drug is more effective in multigravida when compared to primigravida. Hence mifepristone offers advantages over PGE2 gel which is currently used for preinduction cervical ripening.

Key words : Mifepristone, cerviprime, induction, cervical ripening

LIST OF ABBREVATIONS USED

ACOG	– American college of obstetrics and gynaecology
RCOG	– Royal college of obstetrics and gynaecology
PG	– Prostaglandins
PGE 1	– Prostaglandin E1
PGE 2	– Prostaglandin E2
PGF 2 œ	– Prostaglandin F2 alpha
ARM	– Artificial Rupture of membranes
PPH	– Post partum hemorrhage
MAS	– Meconium Aspiration syndrome
NICU	– Neonatal intensive care unit
NN	– Neonatal mortality
PR	– progesterone receptor
GAG	– Glycosaminoglycans
GHTN	– Gestational hypertension

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INTRODUCTION

Human parturition has been named as labor in recognition of the hard work that the parturient as well as the uterine myometrium have to perform in order to deliver the fetus. Labor has been defined as series of events that take place in the genital organs in an effort to expel the products of conception like fetus, placenta and membranes out of the womb through the vagina into the outer world [1].

WHO defined normal labor as a "spontaneous in onset, low risk at the start of the labor and remaining so throughout labor and delivery" in 1997. The infant is born spontaneously in the vertex presentation between 37 to 42 completed weeks of period of gestation, mother and infant are in good condition after delivery with no morbidity.

According to Turnbull (1976) - **"The spontaneous onset of labor is a robust and effective mechanism…. And should be given to operate on its own. We should only induce labour when we are sure that we can do better"** [2] **.**

Labor is an inevitable consequence of pregnancy. The timing of onset of labor may vary widely. There are two events which can prevent the onset of labor once pregnancy has become well established, surgical removal of the fetus and the death of the undelivered mother [3].

Induction of labor is an obstetric procedure, it is designed to pre attempt the natural process of labor by initiating its onset artificially, before labor occurs spontaneously [4]. When continuation of pregnancy presents a threat to the life or well being of the mother or unborn child. The infant should be delivered in a good condition, in an acceptable time frame and with minimal maternal discomfort or side effects. The aim of successful induction is to achieve vaginal delivery [5].

The ideal method of induction of labour would mimic exactly the spontaneous onset of labour . Not surprisingly no method of induction currently available does this [5].

Induction is indicated when the benefits to either the mother or the fetus outweigh those of continuing the pregnancy. The American college of Obstetricians and Gynecologists (1999a) does not support elective induction, except for logistical reasons such as risk of rapid labour, the women lives a long distance from the hospital or for psychosocial indications [6].

Induction of labor has two important components, cervical ripening and stimulation of uterine contractions to achieve dilation of cervix and delivery of the fetus [7]. It is well recognized that the success of induction of labour, which ultimately aims at achieving vaginal delivery, depends to a great extent on the favorability of the cervix or its readiness to go into labour. Agents used for cervical ripening may lead in the establishment of contractions to women with unfavorable cervix [8]. Pharmacological methods like Prostaglandins (PGE1 + PGE2) , relaxin and mechanical methods like Hygroscopic cervical dilators, membrane stripping, trans cervical catheter, etc are available for pre induction cervical ripening.

Mifepristone is a 19 nor – Steroid with a greater affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level [8]. As a fall in the level of progesterone considered one of the important events in the onset of spontaneous labour, it therefore seems likely that this drug may be useful on induction.

The present day obstetrics, calls for induction for a myriad of obstetrical, medical and fetal indications, that include valid indications which include emergency situations like premature rupture of membranes with chorio amnionitis, severe preeclampsia etc., to

several relative indications which may amount to or approximate an elective induction such as a residence at an appreciable distance from an obstetric facility or history of rapid labor in the previous pregnancy [3].

Compromise to maternal longevity, accounts for the majority of indications for induction of labour, while the wide diversity of fetal indications are most often not compromising to their survival or morbidity. Favourability of the cervix is a need for labour induction. Research in this direction has helped in the development of various methods to 'ripen' the cervix prior to uterine contractions[9].

The discovery of prostaglandins, and lately the antiprogesterones, have made labour induction at the disposal of the obstetrician, enabling the delivery of the patient as and when required, thus allowing a carefully planned active management, and in bringing down the trauma of a prolonged or protracted and painful labour for the patient, to give her a healthy baby without compromising her health [10].

A number of studies have looked at the efficacy of mifepristone on cervical ripening. There is a reduction in the induction delivery interval when induction is performed after mifepristone and a trend to a reduction in the rate of ceasarean section (Wing et al 2000) [11].

AIMS AND OBJECTIVES

Objective of the study:

1) To compare the efficacy and safety of oral Mifepristone, and endocervical PGE2 gel for pre induction cervical ripening in term pregnancies and prolonged pregnancies.
2) To evaluate the effect of these drugs on parturition and neonatal outcome.
3) To critically evaluate the effect of these drugs on primigravida and multigravida.
4) To study improvement in bishop score.
5) Necessity for augmentation of labour.
6) To study induction delivery interval.
7) Maternal and fetal outcome.

NEED FOR THE STUDY

- Labor induction in post dated pregnancy is required in 10 to 20 percent of women .Medications that ripen cervix in a short period of time play an important role in modern obstetrics.
- The aim of successful induction is to achieve vaginal delivery when continuation of pregnancy is threat to life of mother and her unborn child.
- Methods commonly available for pre induction cervical ripening are Mifepristone etc…
- Methods commonly available for the purpose of induction are artificial rupture of membranes, Oxytocin, Dinoprostone, Misoprostol etc..
- Dinoprostone gel (PGE2) requires an intracervical application, needs refrigeration and is expensive .Mifepristone does not requires cold chain for storage and cost effective.

REVIEW OF LITERATURE

Induction of labor is common in obstetric practice. According to the most current studies, the rate of induction varies from 9.5 to 33.7 percent of all pregnancies annually [9]. In the absence of a ripe or favorable cervix, a successful vaginal birth is less likely.

Induction of labour is one of the most commonly performed interventions in modern obstetrics with up to 20% of pregnant women having labour induced in some countries [11].

Induction rates have been influenced by several reports worldwide, which claimed that an active induction policy, led to substantial reduction in perinatal and maternal morbidity and mortality.

Induction can be defined as an intervention intended to artificially initiate uterine contractions resulting in the progressive effacement and dilatation of the cervix which will result in the birth of the baby by vaginal route.

The amount of uterine pressure to dilate a ripe cervix is thought to be approximately 1600 mm Hg, while the pressure to dilate an unripe cervix is estimated to be greater than 5 times that, or 10,000 mm Hg. Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected[10].

INDUCTION :

Induction implies initation of uterine contractions after the period of viability by any method of medical, surgical or combined for the purpose of vaginal delivery [3].

The incidence of induction of labour varies widely in different parts of the world. It is 10-15% in developing countries and 10-25% in the developed world [11]. At Parkland Hospital, approximately 30% of labour were induced or augmented using oxytocin.

Augmentation :

Augmentation of labor is the process of stimulation of uterine contractions both in frequency and intensity, that are already present but found to be inadequate [3].

CERVICAL RIPENING

Cervical ripening is a process by which the cervix becomes soft ,compliant and partially dilated .It is due to a combination of biochemical ,endocrine ,mechanical events [12].

The aim of induction of labor is to achieve vaginal delivery in advance of the normal, natural timing of parturition. Thus, the obstetrician is attempting to induce Prematurely the two interlink components of labour, cervical ripening and uterine contractility. Cervical ripening, whether physiological or pharmacological, is the Conversion of rigid cervical sphincter associated with maintenance of pregnancy to a Compliant and readily dilating structure. The objective of the pharmacological induction of a physiological process is an attempt to mimic the natural process as Closely as possible [14] .

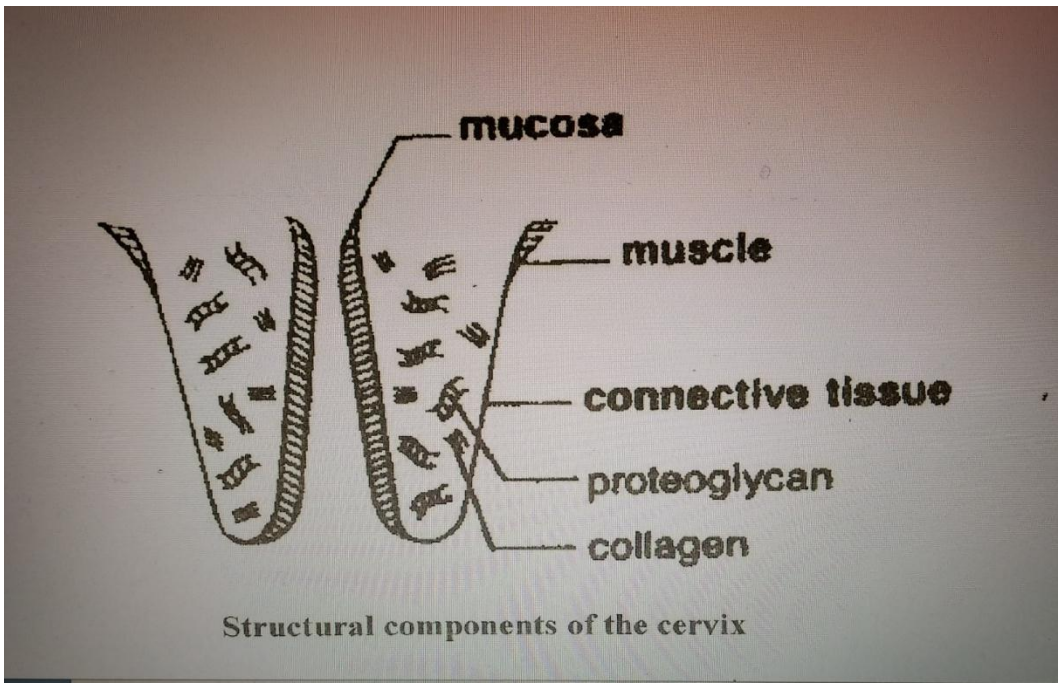


FIG : 1 Structural components of cervix

Physiology of cervical ripening :

Changes in cervical connective tissue :

Cervix is composed of collagen, smooth muscles and connective tissue 'ground substance' containing glycosaminoglycans .Cervix is predominantly composed of type 1 (66 %) and type 3 (33 %) collagen .These predominantly found collagen fibrils ,which are bound together into dense bundles conferring on cervix , the rigidity which characterizes its non-pregnant and early pregnant state. The collagen bundles are embedded in a ground substance, comprising large molecular weight proteoglycan complexes containing variety of glycosaminoglycans (GAG). The most abundant GAG in the cervix are chondriotin sulphate and dermatin sulphate, which are highly negatively charged and hydrophobic. Hyaluronic acid binds which is hydrophilic and least strongly binds with the GAG molecules and will act to destabilize the collagen fibrils ,while GAG containing iduronic acid as opposed to glucuronic acid such as dermatan sulphate binds strongly and promotes tissue stability (obrink, 1973)[63]. Changes in the proteoglycan, GAG composition can therefore alter the collagen binding and facilitate collagen breakdown.

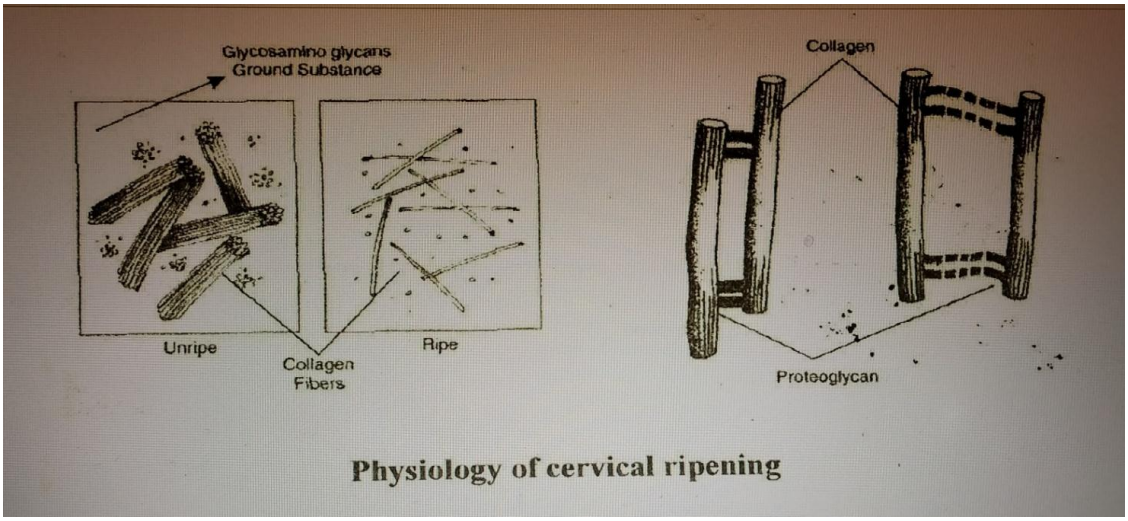


FIG : 2 , Physiology Of Cervical Ripening (1 a)

In non – pregnant state ,the cervix consist of 80 % of water and in late pregnancy it increases to 86 % .The collagen fibrils and GAG is produced by fibroblasts, constitutes the major cellular component of the cervical connective tissue .A small amount of elastin is present in cervix, which is having an important role in cervical physiology. There is reduction in elastin during pregnancy. Absent or reduced elastin fibers results in incompetent cervix.

The changes associated with cervical ripening include a reduced collagen concentration with in the tissue, an increase in water content and a change in GAG content [60].Fibroblast activation occurs and local prostaglandin production increases. An inflammatory infiltrate also occurs at term in parallel with this ripening process, stroma becomes edematous and highly vascularised. The above changes in the cervical connective tissue are widely accepted.

The cervical connective tissue at term show widely scattered and dissociated collagen fibrils with an increase in ground substance when compared to early pregnant and non-pregnant state (Danforth et all 1960) [61].

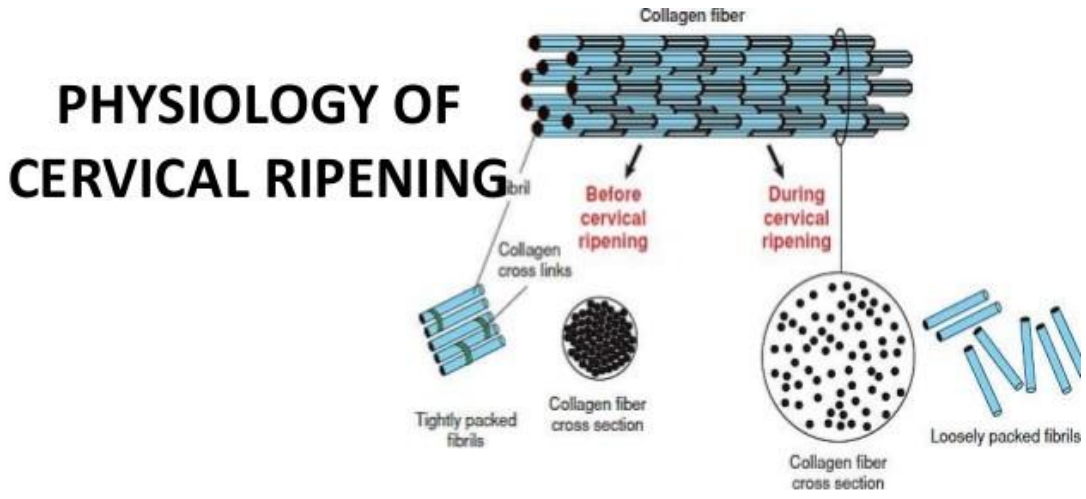


Fig : 3 Physiology Of Cervical Ripening (1 b)

A variety of mechanism have been postulated to explain the reduction in collagen concentration, including increased collagenolysis .Collagen is amenable to breakdown by only two enzymes :

1) Collagenase produced by fibroblasts and leucocytes and
2) Elastase produced by microphages, polymoorphs and eosinophils.

The collagen fragments by these enzymes can be further broken down by non- specific proteases. The changes of cervical ripening do not appear simply due to collagen breakdown but also due to change in GAG and water content s. During labor, the total GAG concentration in the cervix does not change significantly ,but there is relative increase in hyaluronic acid and decrease in chondriotin sulphate (Von Maillot et al 1979) [62],compared to non – pregnant cervix .

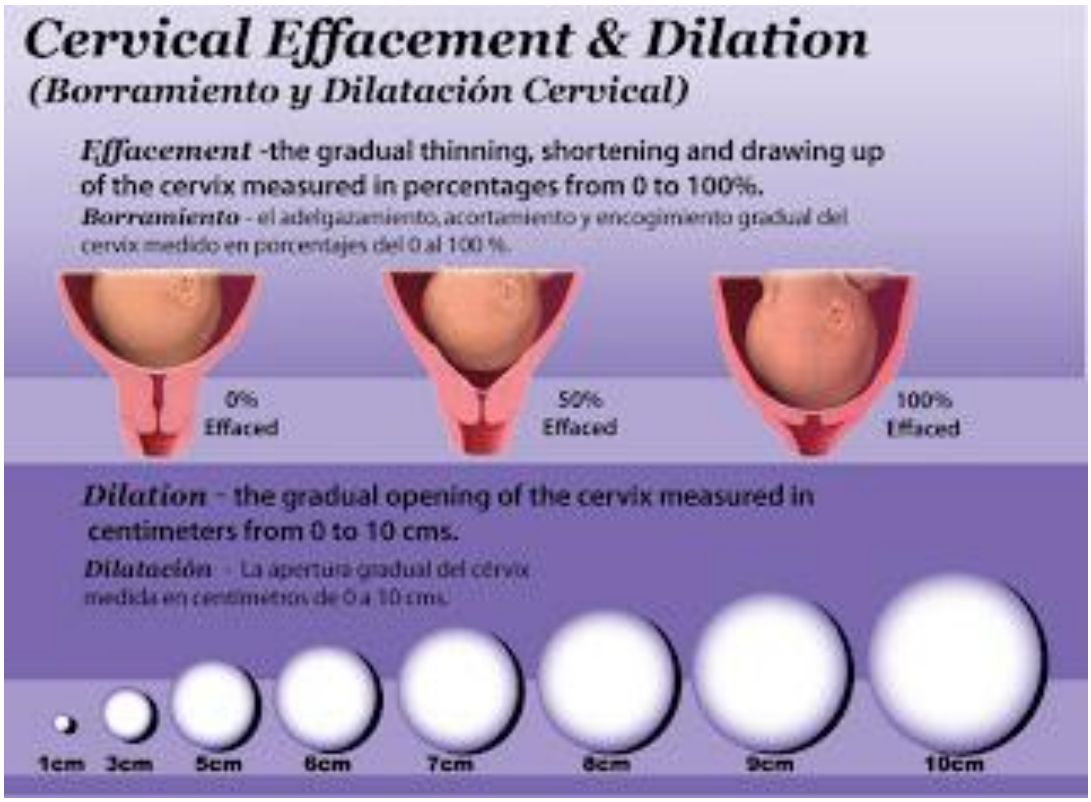


FIG : 4 Cervical Dilatation and Effacement

Control of cervical ripening :

It is assuming that cervical ripening is an active process rather than a passive process due to increased uterine activity . In normal study cervical ripening occurs even when the cervix is physiologically isolated from the uterus and ripening can occur in the absence of uterine activity .

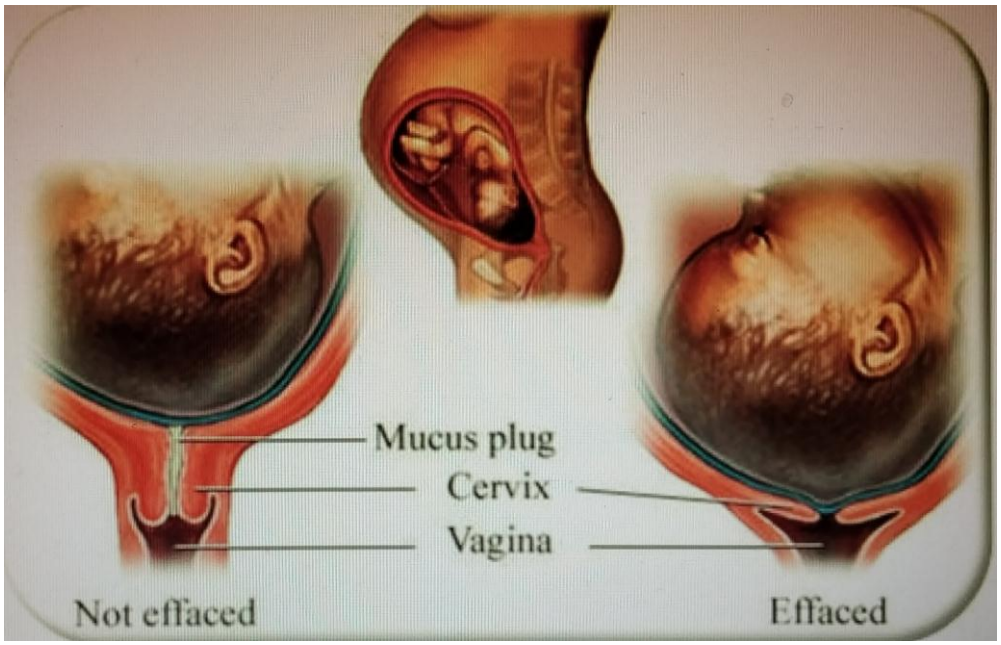


FIG : 5 Cervical Effacement

Prostaglandins :

Prostaglandins play an important role in the control of cervical ripening .The main prostaglandins produced by cervix are PGE 2, PGI2 and to a lesser extent PG F2 .There production increases at term ,suggesting that they have physiological role in ripening and a further sharp increase accompanies parturition.In addition ,amniotic fluid concentration of PGE 2 and PGF 2 have been shown to co- relate directly with cervical ripening in women at term who were not in labor (Calder 1980)[15] .

Natural and synthetic PG s can ripen the cervix at any stage in pregnancy. There are two possible pathways in which PG s can bring about ripening.

1) Prostaglandins can induce collagen breakdown and
2) Prostaglandins can alter the collagen binding and tissue hydration by altering the GAG, proteoglycan composition.

Another possible mechanism is that PGE2 may induce proteolytic breakdown of proteoglycan complexes which would also cause increase in free hyaluronic acid content.

Oestriol :

Oestriol can stimulate PG production where there has been previous exposure to progesterone and has been used to bring about cervical ripening in the clinical situation. This effect may be due to, at least in part ,to induction of PG synthesis .In addition, estradiol has been linked to an increase in collagenase activity (Mochizuki & Tojo) [64].

Progesterone :

Progesterone appears to have an inhibitory effect on cervical ripening and parturition in animals where , a fall in progesterone at term results in ripening and initiation of labor .Progesterone is a potent anti –inflammatory agent .This is supported by the ripening effect of an –progestin on cervix prior to termination of pregnancy .

HISTORY OF INDUCTION OF LABOR :

History of labour induction, antedates back over the past three to four centuries, which has been accomplished by an innumerable number of mechanical and pharmacological methods.

The human race for centuries found reasons to interfere with pregnancy by trying to hasten its conclusion. Often this consisted of attempts to procure the abortion

of unwanted pregnancies, but other more positive motives arose from the desire to relieve the mother of a life threatening pregnancy or to achieve mechanically more favorable vaginal delivery of a smaller premature baby through a constricted birth canal. Through time, as a better perception of fetal and maternal risks developed alongside more efficient methods of labour induction, the indications shifted more commonly to serve the interest of the fetus perceived to be in jeopardy.

Methods of Ripening of cervix prior to induction of labour :

Methods that have been historically applied to induction of labor can be classified in to three categories :

1) Mechanical methods
2) Pharmacological methods
3) Surgical methods.

Mechanical methods :

1. **Amniotomy or artificial rupture of memberanes or the ENGLISH METHOD** was the first really effective method of induction of labour, practiced by Thomas Denman in 1756. Scheel's method [50].

   Amniotomy is the deliberate artificial rupture of the membranes ,use for induction of labor .The procedure is only possible if the membranes are physically accessible .Although there is limited evidence for amniotomy when the cervix is unfavourable, the practice is not recommended because of the invasiveness of the procedure and the potential risks of infection when amniotomy is performed at the start of labor .In the case of an unfavourable cervix ,although amniotomy appears to be effective it is associated with more frequent need for oxytocin augmentation when compared with vaginal PGE

2. Amniotomy alone should not be used as a primary method of induction of labor unless there are specific clinical reasons for not using vaginal PGE 2 ,in particular the risk of uterine hyperstimulation.

2. **Electricity for labour induction** (Herder 1802, Schreiver 1843, Renford 1842, Henning 1856, Theobald 1973)

The electrical induction of labor with the transistor pulse generator and pulse current measuring device . Afferent stimuli from the uterus to the hypothalamus not only cause reflex liberation of oxytocin (Ferguson, 1941) , but may also sensitise placental hormone release [52] .

3. **Stripping or sweeping of membranes by using the forefinger** (Hamilton 1810) [63,64,65] .

Stripping /sweeping of the membranes was used as a method for inducing labour at least as early as 1810 .Increased local production of prostaglandins following vaginal examination for membrane sweeping provides an explanation for the effect of this procedure on pregnancy duration .Vaginal examination allows an assessment of the cervix which helps in clinical decision making which is carried out in late pregnancy , when consideration is being given to induction ,it offers the opportunity to undertake membrane sweeping .If the women are on the threshold of spontaneous labor , a membrane sweep may be all that is required to initiate it ,thus reducing the need for formal induction of labor . The procedure entails passage of the examining finer through the cervix so that it can be rotated against the wall of the uterus beyond the internal cervical os ,there by stripping the chorion away from the deciduas (the deciduas is the richest source of PGE 2 within the uterus) .Clearly if the cervix will not admit a finger it may not be possible to

strip the membranes but in such cases massaging around the cervix in the vaginal fornices may achieve a similar effect [54].

Compared with no sweeping, sweeping reduces the need for formal induction of labor .Additional membrane sweeping may be beneficial .Membrane sweeping is an important and integral part of preventing prolonged pregnancy, and should be scheduled to be discussed with the woman at her routine antenatal visit ,prior to formal induction of labor .woman should be offered a vaginal examination for membrane sweeping[62] .

At the 40 and 41 weeks antenatal visits, multiparous woman should be offered a vaginal examination for membrane sweeping .

At the 41 weeks antenatal visit , parous woman should be offered a vaginal examination for membrane sweeping. When a vaginal examination is carried out to assess the cervix , the opportunity should be taken to offer the woman a membrane sweep .Additional membrane sweeping may be offered if labor does not start spontaneously .

4. **Massage of the uterus** (Uslamer and d'Outrepont 1820)
5. **Breast Stimulation :** (Friedrich 1939 [20])

It is known that breast stimulation results in the production of endogenous oxytocin in pregnant and non –pregnant woman ,causing uterine contractions .There is evidence that breast stimulation may be effective as a method of induction .However , interpretation of the results was problematic owing to the poor quality of the studies reviewed and the heterogenous populations ,including high- risk woman from developing countries .There is inconsistency in the timing ,methods and frequency of breast stimulation described in these studies ,making guidance on this method difficult .

6. **Sponge tents in the cervix** (Brunninghousen 1820)
7. **Instrumental dilatation of the cervix** has been an age-old method.
8. **Vaginal tampoons** (Scholler 1842).
9. **Cervical tampoons** (Kehrer 1888).
10. **Extra amniotic injection of fluid** or the **COHEN'S METHOD** (1846) or Glycerin (Pelzer 1891) and Artes' Paste.
11. **Sexual intercourse :**

    The role of sexual intercourse in stimulating labor is not well understood .It has been suggested that human semen is a biological source of high prostaglandins concentration and the action of sexual intercourse may stimulate uterine contractions .There may be an endogenous release of oxytocin as a result of orgasm ,in the absence of sufficient evidence to prove either effectiveness or harm ,sexual intercourse as a method of induction of labor is not recommended .This method should not be used as a method of induction of labor .
12. **Introduction of a catheter** or the **KRAUS' METHOD** (Moir 1855)

    After introduction of hydrostatic bag placement in the cervix ,a century later ,modern obstetrician followed the same principle for Foleys catheter introduction and induction of labor .
13. **Hot vaginal douche** (Kinisch 1856)
14. **Hot carbolic douche** (Scanzoni 1856)
15. **Rubber bags in the cervix** (Barnes 1861):

    Hydrostatic bag placed through the cervix and filled with water for induction of labour.

    Similar approach was later taken by Camille champetier de Ribes (1848 -1935) in Paris and by James Vorhees (1869 -1929) in New York .

16. Matreurynter (Tarnier 1862), small rubber balloons made of pig's bladder.

17. Hygroscopic cervical dilators (Kramner 1995, Gilson 1996)

18. Laminaria tent (Wilson 1865)

19. Accupuncture :

Acupuncture involves the insertion of very fine needles into specific points of the body .It has been hypothesized that neuronal stimulation by acupuncture may increase uterine contractility .It is also gaining acceptance as a method to alleviate labour pains and ripen cervix .In the absence of sufficient evidence that proves either, effectiveness or harm ,acupuncture as a method of induction of labour is not recommended [64] .

20. Balloon catheter for cervical dilatation (Baners and Woodman 1863)

21. Paracentesis of amniotic fluid usually with injection of irritant Solutions

22. Extra amniotic saline infusion – EASI (Schreyer 1989) .

23. Castor oil ,hot baths and enemas :

Castor oil has been widely used as a traditional method of initiating labour in midwifery practice .However ,the mechanism is poorly understood .There is limited and conflicting evidence relating to the effects of castor oil for cervical priming and induction of labour .Castor oil is unpleasant to ingest and causes nausea .There is no available evidence relating to hot baths or enemas as inducing agents .Castor oil ,hot baths and enemas as methods of induction should not be offered .

24. Herbal supplements :

The use of herbal supplements to promote health has become popular**.** It is believed by some that drinking herbal beverages teas while pregnant nourishes and tones the uterus, supporting optimal health in pregnancy .There

is no evidence available to determine the effects of herbal supplements as an induction agent. Herbal supplements as a method of induction of labour should not be offered**.**

PHARMACOLOGICAL METHODS :

Oxytocin :

Oxytocin was the first polypeptide hormone synthesized, which was an important milestone in labour induction. Its discovery won a Nobel prize for Du Vigneaud in 1953 and the efforts of Turnbull and Anderson (1968) led to its acceptance in routine obstetric practice [49.] "Physiological drip" (or) dilute intravenous infusion was introduced by Geoffrey Theobald pharmacologically sound approach of oxytocin titration was introduced by Alec Turnbull and Anne-Anderson (1960).

However, it was noted that this method of induction resulted in more postpartum hemorrhage than induction with prostaglandins (Howarts and Botha 2001)[23]. When compared to induction with prostaglandins, evidence suggests that oxytocin induction is associated with a lower chance of delivery within 24 hours; there was no difference in the rate of cesarean section. However, subgroup analysis reveals more information showing that:

In primigravida women, there is a reduction in the number of women satisfied with the method of induction when oxytocin is used.

- In women with an unfavorable cervix, that oxytocin induction is associated with a higher rate of cesarean section
- In women with a favorable cervix, induction with oxytocin is associated with greater satisfaction.

Prostaglandins :

The discovery of Prostaglandins in the 1930's from human semen and its elucidation in the biological role in the parturition process, has revolutionized the process of labour induction and has been the greatest armamentorium in the induction of labour for the present day obstetrician.

Prostaglandins are autocoids detected in almost all tissues and body fluids including lungs, heart, stomach, adrenals, liver, spleen, kidney, central nervous system, uterus, vesical gland and seminal fluid. Named by Von Euler of Sweden in 1935, who extracted it from the seminal vesicle. Sune Bergstrom of Sweden received a Nobel Prize for its synthesis in 1932.

Most protocols recommend the use of intra cervical prostaglandin in women with an un favourable cervix and intact membranes; however, there are benefits in giving prostaglandin to all women undergoing induction regardless of cervical score. Meta-analysis by the Clinical Effectiveness Support Group at the Royal College of Obstetricians and Gynecologists showed improved rates of successful vaginal delivery, lower rates of cesarean section and higher levels of maternal satisfaction in women induced with prostaglandin compared to oxytocin However, amniotomy and oxytocin infusion are effective in women with a favourable cervix and in areas where resources are limited, the cheapness of this method may outweigh the consideration of maternal satisfaction. Vaginal PGE2 tablets appear to be as effective as gel formulations and their use may offer financial savings. In 1992 FDA approved PGE2 (0.5mg intracervically) for cervical ripening and labour induction [48].

Misoprostol is a synthetic analogue of prostaglandin E 1and is less expensive, more stable and easier to store than PGE 2.These factors have led to the suggestion that misoprostol will allow the use of prostaglandin for induction in areas of the world

that have been unable to afford this luxury (EI Refacy and Jauniaux 1997) [26].The American college of Obstetricians and Gynaecologist has issued that misoprostol is a safe and effective drug for the induction of labor when appropriately used (ACOG 1999,2000) [2] .In the UK the Royal college of obstetricians has reminded more cautious, agreeing that misoprostol is a cheap and effective agent for inducing labor but due to safety concerns ,feel that further clinical trials are required prior to recommending it's use in general obstetric practice (RCOG 2001 a) .

RU -486 (or) mifepristone:-

The Compound was discovered by Researchers at Roussel uclaf of France in 1980 while they were studying glucocorticoid receptor antagonists. Etenne – Emile Baulieu recognized its anti progesterone activities and saw its potential for the induction of medical abortion the drug was first licensed in France in 1988, for use in Combination with a Prostaglandian, under the name of mifegyne.

FIG : 6 Mifepristone

A number of studies have looked at the efficacy of Mifepristone on cervical ripening .There is a reduction in the induction delivery interval when induction is performed after Mifepristone and a trend to a reduction in the rate of caesarean (Wing et al 2000).

In order to be successful, induction of labor must fulfill three criteria,

1st – It should result in labor namely adequate uterine contractions and progressive dilatation of the cervix .

2nd- This labor should result in vaginal delivery ,as there is a little purpose in bringing, about labor as a mere preparation for caesarean section.

3rd – In viable pregnancies these aims must be achieved with minimal risk to both mother and fetus.

The human cervix is an organ of diverse properties. Ripening of the cervix takes place during pre labor phase, resulting in increased softening, effacement and early dilatation.

Pharmacologically and physiologically prostaglandins have two direct actions associated with labor ripening of the cervix and a direct oxytocin effect .Labor was one of the first indications for the use of prostaglandins in obstetrics.

The method of administration that has been explored thoroughly via endocervical dinoprostone or prostaglandin E 2. Though this is widely used it is expensive and required refrigeration for storage with warming before use. It was only a matter of time before a comparably cheap, safe and effective vaginally administered prostaglandin with limited side effects.

The American college of Obstetricians and Gynecologists (1999a) does not support elective induction, except for logistical reasons such as risk of rapid 2 labours, the women lives a long distance from the hospital or for psychosocial indications [32].

Induction of labour has two important components, cervical ripening and stimulation of uterine contractions to achieve dilatation of cervix and delivery of the

fetus. It is well recognized that the success of induction of labour, which ultimately aims at achieving vaginal delivery depends to a great extent on the favorability of the cervix or its readiness to go into labour. Agents used for cervical ripening may lead in the establishment of contractions to women with unfavorable cervix [30].

The most important decision to be made when considering induction of labour is whether or not the induction is justified. How it is to be achieved, is a secondary decision. Whatever method is chosen to implement a justified decision to induce labour, uterine contractility and maternal and fetal wellbeing should be monitored closely [28].

In the present world, there is a spectrum of valid indications for induction of labour. The concept of elective induction for the convenience of the obstetrician and the patient, is not recommended by the ACOG at present, but this practice is recommended or indicated when the benefits for the mother and fetus outweigh those of continuing the pregnancy and to achieve vaginal delivery, thus avoiding an unnecessary caesarean section.

The present day obstetrics, calls for induction for a myriad of obstetrical, medical and fetal indications, that include valid indications which include emergency situations like premature rupture of membranes with chorioamnionitis, severe preeclampsia etc., to several relative indications which may amount to or approximate an elective induction such as a residence at an appreciable distance from an obstetric facility or history of rapid labour in the previous pregnancy[28].

Compromise to maternal longevity, accounts for the majority of indications for induction of labour, while the wide diversity of fetal indications are most often not compromising to their survival or morbidity.

Favorability of the cervix is a need for labour induction. Research in this direction has helped in the development of various methods to 'ripen' the cervix prior to uterine contractions[26]. The discovery of prostaglandins, and lately the antiprogesterones, have made labour induction at the disposal of the obstetrician, enabling the delivery of the patient as and when required, thus allowing a carefully planned active management, and in bringing down the obstetrician, enabling the delivery of the patient trauma of a prolonged or protracted and painful labour for the patient, to give her a healthy baby without compromising her health.

A number of studies have looked at the efficacy of mifepristone on cervical ripening. There is a reduction in the induction delivery interval when induction is performed after mifepristone and a trend to a reduction in the rate of ceasarean section (Wing et al 2000). Sir Henry Dale (1815-1968) made the first observation that posterior pituitary caused uterine contractions. Pitocin was first extracted from the posterior pituitary gland in 1906, and Blair– Bell described its application in the pregnant uterus in 1909. In 1910, it was used for augmentation in cases of uterine inertia, but maternal deaths from shock were reported after intramuscular injection of pitocin. Its use for induction was first reported by Theo bald in 1952.

These studies in recent literature over the last two decades, shows the efficacy of mifepristone not only in first and second trimester induced medical abortions, but also its use of late, as a safe, orally effective cervical ripening and labour inducing agent.

Other Therapeutic Agents:

Purified Porcine Ovarian Relaxin (1-4mg)

Relaxin has been used both vaginally and intracervically to induce labour but studies have failed to show any benefit compared to prostaglandin (Kelly 2002b)[26].

Hyaluronidase :

Hyaluronidase given by cervical injection has been postulated to increase cervical softening by increasing tissue water content. The problems associated with its administration and the lack of evidence of any benefit associated with using it, is such that its use cannot be recommended.[27]

ESTRADIOL:

Estradiol in tylose gel is not commonly used as an induction agent but has been used previously in the belief that they may stimulate prostaglandin release. There is no evidence to confirm or refuse their efficacy and their use is therefore of historical interest only.

Indications for Induction of Labour :

The indications for induction of labour are, where the benefits of delivering the fetus at a specified point of time, outweighs the benefits of allowing the pregnancy to continue. There are two main types of induction, namely Indicated Induction and Elective induction.

I. Indications :

1. For high risk pregnancies where there is risk to both the mother and the fetus.

   a. Preclampsia and eclampsia Hypertension

   b. Renal disease complicating pregnancy.

   c. Premature rupture of membranes and chorioamnionitis.

2. Where there is increased likely risk to mother, if termination is not advocated

   a. Intrauterine death

   b. Abruptio placenta

3. Where the fetus is at risk

   a. Post term pregnancies

   b. Chronic placental insufficiency

c. Rh isoimmunisation

d. Maternal diabetes complicating pregnancy

e. Previous unexplained still births

f. Intrauterine growth restriction

g. anomalous baby

II. Contra indications :

1. When vaginal delivery is contraindicated-
    a. Major degrees of cephalo pelvic disproportion
    b. Previous VVF repair
    c. Pelvic tumour
    d. Carcinoma cervix
    e. Active genital herpes infection.
2. Malpresentations.
3. Placental abnormalities like Vasa praevia and Type III and IV placenta praevia.
4. Appreciable macrosomia
5. Severe hydrocephalus
6. Non reassuring fetal heart rate

a. Elective induction :

Logistic factors such as distance from the hospital or a history of rapid labor and delivery may be reasonable indications. But elective induction (without medical or obstetric indications) is generally not recommended.

b. Indicated Induction

Commonly accepted indications

- Pregnancy induced hypertension
- Prelabour rupture of membranes
- Chorioamnionitis
- Severe intrauterine growth restriction
- Isoimmunization
- Maternal medical problem
  - Diabetes mellitus
  - Renal disease
  - Lupus
  - Fetal demise
- Prolonged pregnancy
- Oligohydramnios

Outcome of Induction :

Factors influencing the outcome of induction :

The process of pre labor cervical softening and dilatation is a part of a continuum, which culminates in spontaneous labor.

The success of any method of induction depends largely on

(1) Parity and

(2) The state of cervix at the beginning of induction. In most centers, the modified Bishop score (1964) is used to assess the favorability of the cervix both prior to and following induction. The partogram aids in assessing the progress of labosr.

Some definitions, useful for assessing the success or failure of induction are enlisted below.

Successful Induction:

Successful induction is defined as ("Vaginal delivery of an infant in good condition with minimum maternal discomfort and side effects, within a specified framework of time").

Failed Induction:

Defined by Duff et al (1984), (as the failure to enter the active phase of labour, after twelve hours of regular uterine contractions). Failed Induction, is diagnosed when, a patient who was induced, does not deliver vaginally, in the absence of fetal distress, with acute events like abruption or cord prolapse and failure of progress due to cephalopelvic disproportion or malposition and or if the patient has not entered the active phase of labour despite adequate management for twelve hours (Arulkumaran et al 1985).

RISKS OF INDUCTION OF LABOUR :-

Increase in caesarean Section rate:

The risk of ceasarean section increased nearly threefold in primigravid women (11.8% Vs 27.9%) and doubled in multigravid women (3.4% Vs 8.5%) who were induced compared to those labouring spontaneously (RCOG 200 lb).

Uterine Hyper Contractility:-

Uterine hypertonus is defined as a single uterine contraction that lasted 2 or more minutes.

Tachysystole is defined as at least 12 contractions in 20 minutes. Hyperstimulation is defined as either hypertonus (or) tachysystole associated with abnormal FHR pattern.

Misoprostol was associated with significantly increased risk of tachysystole or hyper stimulation when compared with PGE 2 gel (WING and Coworkers 1995a, 1995b).

Induced labour is associated with on increased risk of postpartum hemorrhage.

Prolonged induction is associated with a small increase in the risk of infectious morbidity with an estimated 10% incidence noted after 40hrs of induction (Bahn et al 1998).

Oxytocin induction has been reported to increase the risk of neonatal Hyperbilirubinemia.

Iatrogenic prematurity occurs inadvertently and a review of the gestational age prior to induction is essential.

The reasons for the rising rates of induction of labor can be complex and multifactorial (Rayburn and Zhang 2002 :

- Improved ability of physicians to determine gestational age accurately with early dating scans ,thus avoiding the possibility of iatrogenic prematurity .
- Widespread availability of cervical ripening agents .
- Improved knowledge of methods and indications for induction ;
- More relaxed attitudes towards marginal/elective indications, both of the physician and the patient
- Litigation constraints.

Counseling the couple prior to induction:

- It is essential to have good communication with the woman and her family prior to induction; wherever possible this should be supported by evidence-based and preferably, written information. While counseling, the following need to be discussed (RCOG 2008):

- The indications for induction; more specifically, the risk associated with continuing the pregnancy
- The time and procedure of induction
- Arrangements for support during labor
- Pain relief measures since induced labor may be more painful.
- The need for close monitoring of the fetal heart rate (including electronic fetal monitoring in labor)
- Alternative options available to the mother if she refused induction
- The risks associated with induction of labor, specifically with the inducing agent used.
- The chances of failure of induction and the options available in case of failure.

Criteria of an ideal inducing agent:

An ideal inducing agent is one which:

- Achieves onset of labor within the shortest possible time.
- Does not result in greater pain and hence does not require greater analgesics as compared to spontaneous labor
- Has a very low incidence of failure to induce labor
- Does not increase the rate of cesarean or operative vaginal deliveries as compared to spontaneous labor.
- Does not increase perinatal morbidity compared to spontaneous labor.
- We are yet to find an ideal inducing agent. Hence, the decision for induction should be well thought out and communicated to the woman concerned.

Methods to assess cervical ripening

- Bishop score
- Lange score

Bishop Score :

Parameters	0	1	2	3
Dilatation of cervix	closed	1-2	3-4	5 +
Effacement of cervix	0-30	40-50	60-70	>80
Consistency of cervix	firm	Medium	soft	-
Position of cervix	Posterior	Medium	Anterior	-
Station	-3	-2	-1,0	+1 ,+2

Total score : 13

Favourable score : 6-13

Un favourable score : 0-5

MIFEPRISTONE (RU 486)

Introduction:

Mifepristone is an antiprogestin. There are two types of antiprogestin

- Type I -RU486, ZK 112993
- Type II – ZK 98299.

Structure:

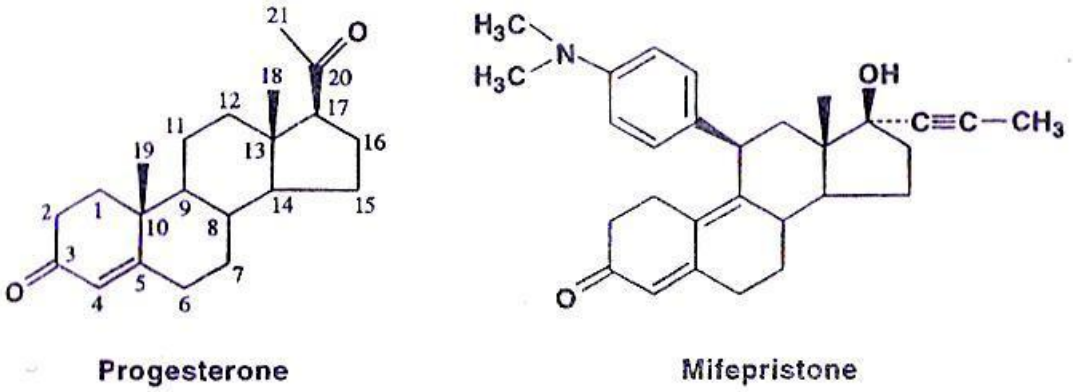


Fig : 7 Mifeprstone chemical structure

Mifepristone is a 19 nor steroid, chemically referred to as 11 beta-(4- dimethyl amino phenyl)-4, 9-dien-3-one. It is an antiprogestrone. It has a molecular formula of C19H35NO26. Its molecular weight is about 429.6. The dimethyl amino phenyl side chain at position 11, which is a hydrophilic 28 moiety, appears to be essential for the antiprogestronic activity. It also has antiglucocorticoid and antiandrogen activity.

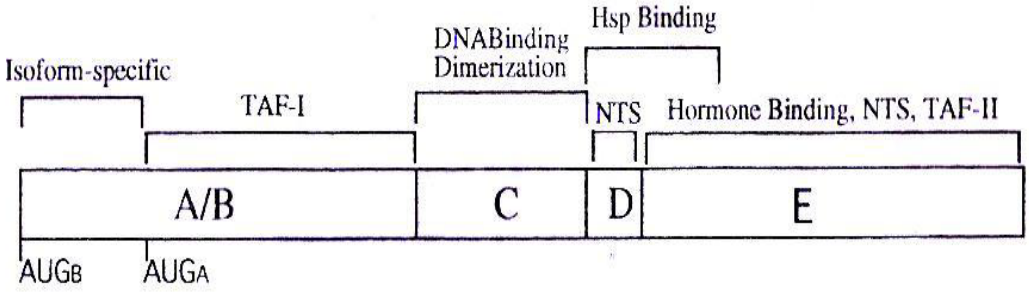


Fig : 8

The structure of the gene encoding both isoforms (PRA and PRB) of the progesterone receptor includes the location of the n-terminal initiation codon for each isoform (AUGB and AUGA). The basic structure of this gene is shared by all members of the steroid, thyroid, vitamin D, retinoic acid and orphan receptor superfamily, with five functional domains: an n-terminal transactivation domain (A/B), a DNA-binding domain (C), a hinge region (D) and a hormone-binding domain (E). Regions important for heat shock protein binding (HSP), nuclear translocation (NTS) and transcriptional activation (TAF-I, -II) are also indicated.[32]

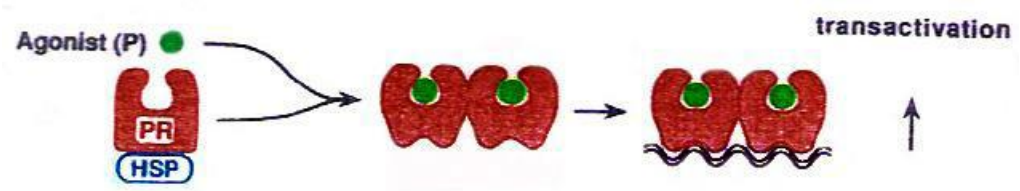
Mifepristone acts as a competitive receptor antagonist at the progesterone receptor in the presence of progesterone and acts as partial agonist in the absence of progesterone. Mifepristone at doses greater or equal to 1mg/kg antagonize the endometrial and myometrial effects of progestrerone. Antiglucocorticoid effect of Mifepristone is manifested at doses greater or equal to 5.5 mg/kg and 29 anti androgneic effect in animals is seen with prolonged administration of very high doses of 10-100 mg/kg

The anti progestin action of mifepristone is mediated by the PR, a ligand activated transcription factor with domains for DNA binding, hormone binding and transactivation. The amino acid glycine at position 722, which is in the hormone-binding domain of the human PR, appears to be critical for mifepristone binding and action. Substitution of glycine with cysteine in the human PR generates a receptor that no longer binds mifepristone.

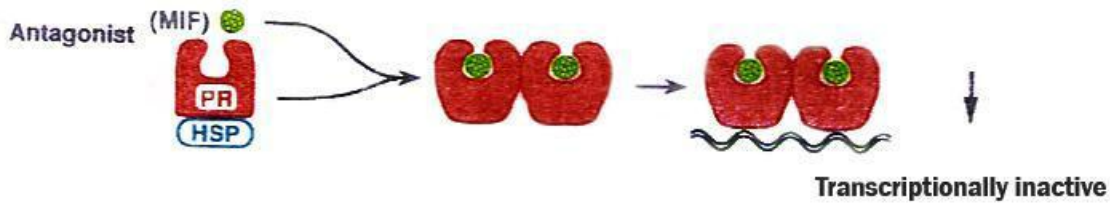
Mechanism of action :

Progesterone and mifepristone produce a confirmational change in the form of the PR that permits it to bind to DNA.[30]

Agonist (Progesterone)



Antagonist (mifepristone)



PR – Progesterone receptor

HSP – Heat Shock Protein

FIG : 9 Mechanism of action of Mifepristone

In the absence of ligand the progesterone receptor is associated with heat shock proteins. Binding of progesterone or mifepristone induces conformational

changes resulting in dissociation of HSP and dimerization of PR. The PR complex binds to specific progesterone response elements in the promoter regions of progesterone responsive genes. Progesterone – PR complex is transcriptionally active resulting in agonistic effects whereas mifepristone – PR complex is not transcriptionally active resulting in antagonistic effects[28].

Under certain circumstances as in the absence of progesterone, mifepristone display progesterone agonistic activity It is related to the existence of two isoforms of PR, PR-A and PR-B. PR-B behaves as a partial agonist in the presence of mifepristone. When PR-A and PR-B are present together the antagonistic effects of PR-A can override the agonistic effects of PR-B. So agonistic or antagonistic action depends on relative expression of PR-A and PR-B in target tissues.

Pharmaco Kinetics :

Mifepristone is administered orally and is readily absorbed.

Metabolism in splanchnic circulation reduces its bioavailability to 40%. Metabolic clearance rate is 0.55l/kg / day. It does not bind to cortisol binding globulin or sex steroid binding globulin[34].

Serum mifepristone levels reached a maximum in one hour after oral administration of single dose ranging from 50 to 800mg. After single dose of 100mg or less the disappearance of mifepristone follows first order kinetics with a half life of 20-25 hours. After higher doses 200-800mg there is an initial redistribution phase of 6-10 hours followed by a plateau in serum levels for 24 hours or more.

The major excretory pathway is fecal with less then 10% being recovered in urine. Metabolism involves two step demethylation and hydroxylation.[32] The expression of inducible nitric oxide synthase in cervical cells of women. This

Ripening is one of the mechanisms by which mifepristone initiates cervical ripening. Labour and reduces need for prostaglandins (Lelaidier et al 1993)18. There is a reduction in the induction delivery interval when induction is performed after mifepristone and a trend to a reduction in the rate of cesarean section (Wing et al 2000)17. Mifepristone or RU 486, an antiprogesterone is a receptor level antagonist, licensed in the U.K in July 1991. Mifepristone is a 19-norsteroid with a great affinity for the progesterone receptor and thus blocks the action of progesterone at a cellular level. As a fall in the level of progesterone is considered one of the important events in the onset of spontaneous labour, it therefore seems likely that this drug may be useful in induction[26]. A number of studies have looked at the efficacy of mifepristone in cervical ripening. When compared to placebo, 200mg oral mifepristone increases the chances of spontaneous onset of labor.

Pregnant uterus:

Mifepristone acts on receptors in decidua resulting in progesterone withdrawal to endometrium, disruption of placental function and uterine bleeding. Mifepristione stimulate release of PGF2α.[33,46,47] The increase in prostaglandin is due to marked reduction in the activity and tissue concentration of prostaglandin dehydrogenase, the key enzyme involved in the control of prostaglandin catabolism by mifepristone[21].

Mifepristone increases the sensitivity of the myometrium to prosta glandin due to increase in number of gap junctions so that synchronization of uterine muscle contractility occurs. This causes enhanced electrical activity resulting in opening of voltage dependent calcium channels, which causes calcium influx and thereby muscle contraction.[53]

Mifepristone causes cervical ripening in women undergoing termination of pregnancy. Mifepristone causes cervical ripening directly or through the blockage of

progesterone receptors[49]. Mifepristone stimulates the release of nitric oxide and the expression of inducible nitric oxide synthase in cervical cells of women. This is one of the mechanism by which mifepristone initiates cervical ripening[52].

Other Uses:-

1. Termination of early pregnancy :

Medical abortion became an option for early abortion in India when in April 2002; the Drugs Controller General approved the use of Mifepristone to terminate early pregnancies. In December 2006, the Drugs Controller General of India granted the permission to manufacture misoprostol and approved its use for gynecological conditions like cervical ripening, prevention of post partum hemorrhage and first trimester abortion with mifepristone[55].

While in India, a combination of mifepristone and misoprostol is recommended for termination of early pregnancy up to 49 days/seven weeks from the last menstrual period (LMP); WHO recommends their use up to 63 days or nine weeks from LMP (WHO, 2003).[14]

Mechanism of action:

Mifepristone is an anti-progestin, which stops the pregnancy from growing, detaches it from the lining of the uterus and softens the cervix.[56,57]

Recommended Drug Protocol :

Day 1	200 mg Mifepristone orally	Anti D if Rh negative
Day 3	400 mcg Misoprostol Orally /vaginally	Analgesics
Day 15	Confirm completion of abortion by USG	Contraceptive

2) Contraceptive :

Mifepristone, a novel estrogen free contraceptive when administered in low doses daily (2 to 10mg), it inhibits ovulation, menstruation and significantly suppresses effects on the endometrium.33 However, due to continuation of variable degree of follicular development, unopposed estrogen can cause hyperplastic or malignant changes in the endometrium. But in 2003, Baird ST et al, in their study reported that mifepristone <10mg per day neither caused endometrial hyperplasia nor the significant effect on the HPA-axis. Mifepristone also maintained bone density, lipids & sense of well being. Mifepristone as a postcoital contraceptive inhibits ovulation, blocks implantation by causing a delay in maturation of endometrium and causes regression of the corpus luteum in the majority of women when given in the middle or late luteal phase.[35,47,53]. In these trials single dose of 600mg of mifepristone given within 72 hours of unprotected intercourse was 100 percent effective as an emergency contraceptive.[37]

3. Uterine myoma

For safe and effective non-surgical treatment of symptomatic fibroids, high-dose progestin therapy and GnRh agonists have been shown to decrease overall uterine volume by 50 percent at the end of 3 months therapy. On a long term basis, mifepristone blocks progesterone dependent growth factors, reduces blood supply due to vascular changes and decreases inhibition of progesterone estrogen receptor gene transcription by the progesterone receptor - A isoform, these are some of the mechanisms causing the antiproliferative activity of mifepristone. Mifepristone can be used in uterine fibroids as an alternative to GnRh anlogues in the preoperative application and if the safety of long term low dose mifepristone is established,

perimenopausal women with large, symptomatic fibroid could avoid hysterectomies by using mifepristone till menopause .[45,36]

4. Endometriosis :

Mifepristone through antioxidant property does not allow endometriosis to proliferate. However, the use of mifepristone for the treatment of endometriosis requires additional studies.[46]

5. Ovarian Cancer:

Mifepristone inhibits ovarian cancer cells growth by inducing G1 cell cycle arrest and blocking the G1-S phase transition without causing cell death. This growth arrest is observed by a decline in cyclin – dependent kinase 2 (cdk2) protein level and activity. In 2003, Xu M et al reported that ovarian cancer cells expressed glucocorticoid receptors. Mifepristone may drive its anticancer action by binding to glucocorticoid receptors with an affinity similar to that for progesterone receptors and as an antioxidant to drive G1 arrest through a p53 independent p21. In 2000, Rocereto TF et al in their small trial conducted with 44 patients suffering from recurrent epithelial ovarian cancer whose tumors had become resistant to standard chemotherapy, mifepristone administration showed desirable effects against some of the tumors. Thus, mifepristone is a single agent potent blocker of ovarian cancer growth, however, the feasibility of using mifepristone to enhance the efficacy of conventional chemotherapy for ovarian cancer requires further investigations.

6. Premenstrual Syndrome:

The sex steroid dependency of this disorder has been well established by the absence of PMS in castrated women and women treated with GnRH agonist analogues. Because the main symptom complex occurs in the luteal phase when serum progesterone is at the highest level, it was proposed that an antiprogestin, such

as RU 486, may be useful in treatment of PMS. 44 Dosing schedules such as low dose daily administration to induce a acyclic pattern may yet prove to be efficacious in the treatment of PMS.

7. Ectopic Pregnancy:

The role of antiprogestin in the medical therapy of ectopic pregnancy remains to be clearly defined. Certainly, the timing, dosing, and efficacy of RU 486 treatment in this scenario await future studies.

8. Abnormal Uterine Bleeding:

It has been suggested by some that antiprogestins may be useful in treatment of dysfunctional uterine bleeding. No clinical experience in this venue has been published. If adenomyosis is the etiology of menorrhagia, it may be expected that treatment with an antiprogestin may be useful.

9. Breast Cancer:

It has been observed that estrogen and progesterone in low doses stimulates breast cancer growth but in high doses both inhibit breast cancer growth. Tamoxifen, the antiestrogen, remains the first line therapy for advanced estrogen-receptor-positive tumor because of its efficacy, safety and convenience. Antiestrogen (Tamoxifen) and antiprogestin produce tumor regression but either agent alone only produces tumor stasis. Tamoxifen down regulates the estrogen receptor but it favors agonist activities and therefore up regulates the progesterone receptor. Mifepristone down regulates both estrogen and the progesterone receptors. The finding suggests that tamoxifen cannot inhibit the progestin-mediated growth-stimulatory effects. Thus, addition of mifepristone to tamoxifen effectively reestablishes tamoxifen growth inhibition. It has been observed that eventually all advanced breast cancer become hormone independent and increasingly resistant to any subsequent therapy as a result there is

limitation in potential utility of antiprogestin and other endocrine therapies for the treatment of advanced disease.

10. Cushing's Syndrome:

Chronic exposure to excessive corticosteroids in Cushing‟s Syndrome leads to the development of multiple metabolic abnormalities such as glucose intolerance, dyslipidemia, hypertension, osteoporosis and weight gain. In 2001 Dwight FM et al reported that extremely ill patient with Cushing‟s syndrome, treated initially unsuccessfully by a combination of conventional surgical, medical and radiotherapeutic approaches responded extremely well up to 25mg/kg/day, long term mifepristone, glucocorticoid receptor antagonist therapy. Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, significant reversal of the patient‟s heart failure, the resolution of the psychotic depression and usual return of HPA axis to normal [28].

11. Meningioma:

Most meningiomas have no estrogen receptors but have substantial concentrations of progesterone receptors. In patients with unresectable meningiomas, objective response and subjective improvement has been noted [32].

Contraindications:-

1. Hemorrhagic disorders (or) concurrent anticoagulant therapy.
2. Inherited Porphyrias
3. Chronic adrenal failure
4. History of allergy to mifepristone
5. Concurrent long term corticosteroid therapy or recent therapy with corticosteroid
6. Chronic medical disorders

7. Age more than 35 years
8. Smokers (> 10 cigaretes /day)

Drug interaction :

On the basis of this drug metabolism by CYP 3a4, Ketoconazole, itraconazole, erythromycin and grape fruit juice may inhibit its metabolism. Rifampicin, Dexamethasone and certain anticonvulsants like Phenytoin, Phenobarbitone and Carbamazepine may induce Mifepristone metabolism .

Mifepristone is contraindicated in the presence of an intrauterine device (IUD), ectopic pregnancy, adrenal failure, hemorrhagic disorders, inherited porphyria and anticoagulant or long term corticosteroid therapy.

Side Effects

Side effects of short term use include abdominal pain, cramping, nausea, vomiting and headache which are dose and treatment duration dependant. Long term administration of Mifepristone is associated with adrenal insufficiency, low serum potassium levels, a slight increase in serum creatinine levels, moderate increase in hepatic enzymes and significant increase in thyrotrophins levels.

PROSTAGLANDINS

Structure

Prostaglandins are biological derivatives of 20 carbon polyunsaturated fatty acids that are released from cell membrane phospholipids. The prostaglandins PGE2 and PGF2 alpha are widely used in obstetric practice.

There are no preformed stores of prostaglandin. They are synthesized locally, in response to appropriate stimulus, at the rates governed by release of arachidonic

acid from cell membrane by the action of lysosomal enzyme phospholipase A2, which is said to be the rate limiting step in prostaglandin biosynthesis.

Free arachidonic acid enters the cyclo-oxygenase pathway and converted to prostaglandin, by the enzyme prostaglandin synthase. In pregnant uterus of human being, free arachidonic acid is converted to prostaglandins in chorion leave and decidua vera, by prostaglandin synthetase specific activity, which is greatest in the amnion.

In the amnion and chorion, PGE2 is formed. In decidua vera, both PGE2 and F2 alpha are formed. The fetal membranes and decidua vera are proved to be the site of synthesis of both arachidonic acid and prostaglandins in amniotic fluid.

The half-life of primary prostaglandins is about five minutes while that of the major metabolite is 8 minutes. The lung is the major site of metabolism of prostaglandins, other sites being the liver and kidney.

Pharmacological actions

Prostaglandins act on almost every other tissue in the body. Some of the best known actions are

a. Stimulation of smooth muscle leading to either relaxation depending upon the receptors involved
b. Changes in the cervical tissue
c. Inhibition of gastric acid secretion and cytoprotection
d. Inhibition and induction of platelet aggregation
e. Increase in vascular permeability
f. Thermoregulation
g. Modification of steroidogenesis in the adrenals and gonads
h. Inhibition of hormone induced lipolysis

i. Release of neurotransmitters in the peripheral nervous system and the potentiation of action of biogenic amines.

However, the most potent action of prostaglandins is their ability to stimulate smooth muscles of the uterus, gut and vasculature. Unlike oxytocin, which is relatively ineffective in early pregnancy prostaglandins, are potent stimulators of uterine myometrium in all stages of pregnancy.

Uses of prostagandins in obstetrics include induction of abortion, termination of molar pregnancy, induction of labour, cervical ripening prior to induction of labour and abortion, acceleration of labour, management of atonic postpartum haemorrhage.

Muscle physiology consists of three important concepts: phasic contraction, tonic tension and relaxation. Phasic contraction is intermittent and may last for a short or a long period of time, whereas tonic tension I fairly constant lasting for prolonged periods. At the myometrial cellular level, prostaglandins have been found to induce both phasic contractions as well as tonic tension with superimposed phasic contractions (Chamley and Parkington 1984). In practical terms, they increase both the resting tone of the uterine myometrium as well as the amplitude and duration of myometrial contractions.

On a molecular level, phasic contractions are due to the influx of sodium ions into the myometrial cell, whereas tonic tension is due the increased availability of intracellular calcium. Both these processes are affected by prostaglandins (Reiner and Marshall 1976).

Prostaglandins also induce the formation of gap junctions between the myometrial cells, which help in the development of coordinated myometrial action, giving the advantages of a functional syncytium.

There is also a differential response according to the type of prostaglandins. PGE2 metabolites peak prior to the onset of established labour, whereas PGF2alpha metabolites peak during labour and correlate directly with the duration of labour. PGE2 has a predominant effect on the cervix, whereas PGF2alpha on the myometrium.

Contraindications :

(a) Hypersensitivity to the compounds

(b) Bronchial asthma

Advantages :

a) It has got powerful oxytocic effects, irrespective of the period of pregnancy.

b) As such it can be used independently especially in induction of abortion with success.

c) It is useful drug not only in induction but also for acceleration of labour.

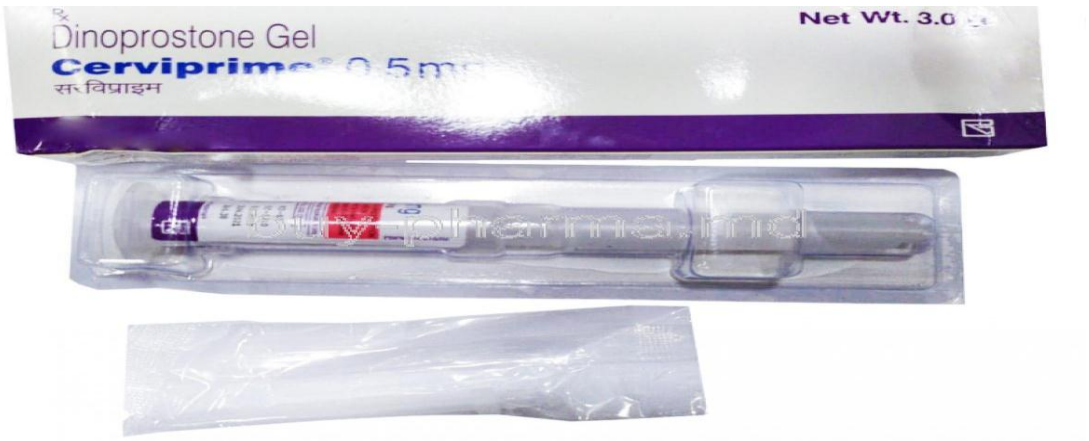


FIG : 10 Dinoprostone gel

Disadvantages :

a) It is costly.

b) Unpleasant side-effects caused by its stimulatory effects on the smooth muscles, which however subside easily due to its rapid metabolism.

c) When used as an abortifacient, extensive cervical laceration may occur.

d) The hyperactivity of the uterus if occurs during induction may continue for a variable period.

SIDE EFFECTS :

(a) Nausea, vomiting and diarrhea are common.

(b) Cramping pain of uterine origin related to the degree of uterine activity.

(c) Unduly forceful uterine contractions.

(d) Anaphylaxis.

Oxytocin :

The word 'oxytocin' means "Quick birth". The structure of oxytocin was determined by Du vigneaud in 1950.

Oxytocin, an octapeptide which is secreted in a pulsatile manner is a neurohormone originating in the hypothalamus and secreted by the posterior lobe of pituitary gland. The half life is 10-12 minutes. The metabolic clearance rate is similar for men, pregnant women and non pregnant women. 20-27 m1/kg/minute. Recent study shows that 40 minutes are required for any particular dose of oxytocin to reach a steady state plasma concentration.

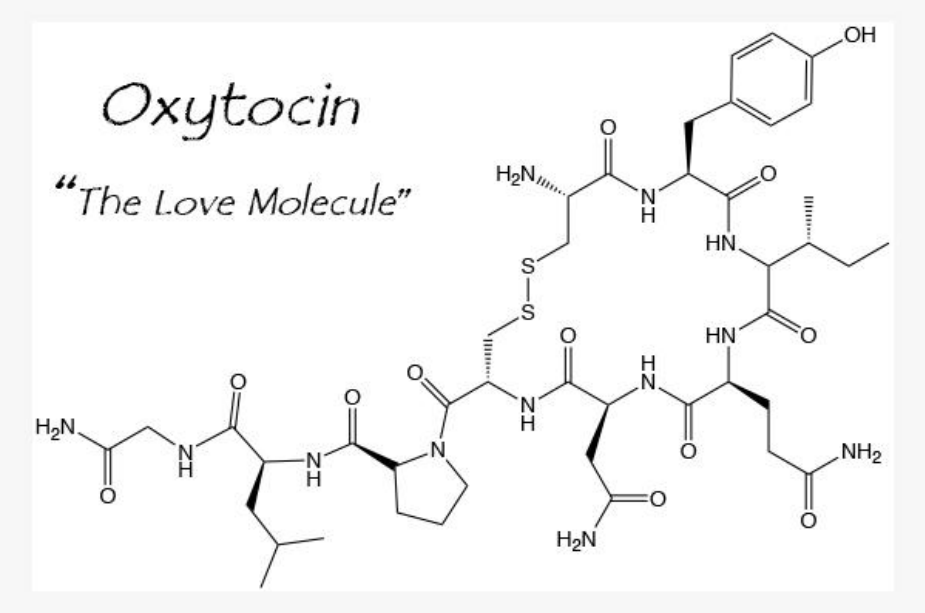


FIG : 11 Oxytocin chemical structure

The sensitivity of uterus to oxytocin increases as pregnancy progresses due to increase in oxytocin receptors in the myometrium and decidua. Oxytocin has direct stimulatory effects on the myometrium and also stimulates decidual prostaglandin production. The direct effect of oxytocin on myometrium is mediated by polyphosphoinositide hydrolysis with production of inositol phosphates that act as a second messenger and lead to the mobilization of interacellular calcium ion. The principles of current clinical usage of intravenous oxytocin, are based on the classic studies of Turnbull and Anderson (1968).

Oxytocin is known to be a very potent uterotonic, causing uterine contractions in a sensitized uterus. The infusion of oxytocin is relatively ineffective in inducing labour in human pregnancies, except for dose near term. Oxytocin is effective, only in those patients in whom preparation of the uterus for active labour is already completed. The plasma concentration of oxytocin in pregnant women is 2-10mcg/ml.

Advantages :

It is cost effective, relatively safe, the dosage can be adjusted and titrated according to the needs in a particular case, when combined with amniotomy induction delivery interval is very short, labour gets established earlier.

Disadvantages :

Patient has to be confined to bed, in large doses it produces water intoxication, there are chances of hyperbilirubinemia, when given in higher doses, rarely it can cause rupture of uterus in multigravida and coronary insufficiency, and the incidence of PPH in induced labour is greater. Hyperstimulation, late deceleration of FHR can occur.

Table.1 : RCOG guidelines for induction of labour (2001)

Time after starting (min)	**Oxytocin dose mu/min)**	**(Volume infused (ml/hour)** Dilution 30 IU Oxytocin in 500 ml normal saline	Dilution 10 IU Oxytocin in 500 ml normal saline
0	1	1	3
30	2	2	6
60	4	4	12
90	8	8	24
120	12	12	36
150	16	16	48
180	20	20	60
210	24	24	72
240	28	28	84
270	32	32	96

MATERIAL AND METHODS

Selection of cases:

A Randomized control study is done to compare the efficacy of oral mifepristone and endocervical PGE2 gel as preinduction cervical ripening agents in term gestation and prolonged pregnancies was done in antenatal women for induction of labour, Pregnant women admitted in the labor ward in Department of Obstetrics and gynecology in BLDE (Deemed to be University) Shri B.M.Patil's Medical College, Hospital and Research Centre, Vijayapura.130 antenatal women were selected for study 65 women received oral mifepristone 200mg, along with dinoprostone and 65 women received endocervical PGE2 gel 0.5mg.

The purpose of the study is to evaluate the safety and efficacy of mifepristone as an orally active inducing agent in women with unfavorable cervix at term (Bishop score < 6).

This Randomized study is done after getting clearance from ethical committee of BLDE (Deemed to be University) Shri B.M. Patil Medical college Hospital and research center. Period of study will be from 1st December 2018- 31stJanuary 2020

- Type of study –A Randomised controlled trial

  Sample size-130**.**

SAMPLING:

On the basis of a study by reference from the article 2017 study conducted by Jitendra D.Mane, Sanjay, Anil kumar singh the anticipated mean ± sd of induction to delivery interval in study group[176.05± 12.87 and 171.75± 12.45 resp. the minimum sample size is 65 per group with 95 % level of significance and 90 % power.

Formula used is

$$N = 2\left[\frac{(Z_{\propto} + z_{\beta}) * S}{d}\right]^2$$

where,

$Z_{\propto}$ = Level of significance =95%

Z_{β}Power of the study =90 %

d =clinically significant difference between two parameters

SD =common standard deviation

STATISTICAL ANALYSIS:

In the present study continuous variables will be presented as mean with standard deviation. Difference in continuous variables will be analyzed with test of significance of difference between two means .The difference in proportion will be tested with Chi-square test, unpaired 't' test and Fishers exact test will be applied for statistical evaluation. The demarcating level of statistical significance will be set at the probability level of 0.05.

INCLUSION CRITERIA

1) Maternal age > 18 years
2) Singleton pregnancy
3) Cephalic presentation
4) Period of gestation more than 40 weeks gestation
5) Reactive NST pattern in live fetus
6) Intact membranes
7) Bishops score <6
8) Past unexplained still birth
9) Pregnancy induced hypertension

EXCLUSION CRITERIA :

1. Women with any contraindication to induction and vaginal delivery;
2. Estimated fetal weight > 4.5 kg or <2000 gm
3. Antepartum hemorrhage (abruption placenta, placenta Previa)
4. Previous caesarean sections
5. Abnormal Doppler studies and NST
6. Severe Oligohydramnios [AFI-< 5]
7. Chorioamnionitis
8. Major Cephalopelvic disproportion
9. Parity > 4
10. Patients requiring immediate delivery
11. Severe pre eclampsia, eclampsia
12. Diabetes mellitus in pregnancy
13. Intrauterine death

On admission, a detailed history, and complete general and obstetric examination is carried out. Vaginal examination is done under strict aseptic precautions and the cervical status, fetal station are assessed. Gestational age calculated by Naegle's rule and a routine obstetric scan for fetal maturity and well-being is done. Once the inclusion criteria are fulfilled and cephalo pelvic disproportion is ruled out, the patient is prepared and transferred to the labour ward. Indication for induction was noted after reaffirming that there is no contraindication for induction.

Informed Consent:

A detailed written informed consent is obtained from the participant and her relatives. The following are addressed in the consent form. Indication for induction of labour, drug to be administered with its dosage and mode of administration, side effect of the drug, risks associated with the administration of these drugs and if complications arise, alternative mode of termination are all discussed.

Treatment Schedule :

Group – I:

65 pregnant women are given tablet mifepristone 200mg orally on day1. They are observed for maternal vitals, uterine activity bleeding or draining pv and fetal heart rate. After the wait period of 24 hours or when the Bishop score is ≥ 6, or when the patient is well in labour whichever is earlier labour is accelerated with oxytocin drip. If the bishop score is 4 or less induced with cerviprime gel.

Group – II :

65 pregnant women pregnant are instilled endocervical PGE2 gel 0.5mg. They are observed for maternal vitals, uterine activity, bleeding or draining pv and fetal heart rate. After the wait period of 6 hours, Bishop score is assessed and repeat cerviprime induction or start of augmentation with oxytocin drip is decided.

Monitoring of the patients :

Maternal vitals, uterine activity and fetal heart rate are monitored clinically. Pervaginal examination is done if there is rupture of membranes or once in 2 hours in active phase of labour. The patient has been monitored for progress of labor ,need for further dosages of cerviprime for induction and augmentation with oxytocin is observed .time duration taken from induction to active stage and induction to delivery

are observed. mode of delivery ,indication for caesarean section are observed. Maternal and neonatal complication are also observed .

Data is analysed and all the values are expressed as mean ± standard deviation or as percentages. Statistical comparison are performed by students paired and unpaired t-test and chi-square test. Statistically significant difference ($P<0.05$).

The efficacy is assessed by the following criteria:

i. Favorability of Bishop score at 24 hrs.
ii. Need for induction with cerviprime gel
iii. The need of oxytocin for augmentation.
iv. Drug administration to delivery interval.
v. The mode of delivery.
vi. Cesarean section rate.
vii. The 5 minute Apgar score, neonatal complications and incidence of neonatal mortality.
viii. Maternal complications.

Success of induction is assessed by the following criteria:

1. Patients who delivered vaginally within 48 hours of the start of induction.
2. Bishop score of ≥ 6 at the end of 24 hours

Failure of induction is assessed by the following criteria:

1. Patients who delivered vaginally after 48 hours of start of induction.
2. Patients who underwent caesarean section.

RESULTS

Table 2 : Distribution of patients according to Age (Years) :

Age (Years)	MIFEPRISTONE AND DINOPROSTONE GEL		DINOPROSTONE GEL ALONE	
	N	Percentage	N	Percentage
< 20	24	36	4	6.2
20 – 24	19	29	37	56
25 – 29	20	30	19	29
30+	2	3	5	7.7
Total	65	100.0	65	100.0

Comments :

Age distribution of the two groups were similar with mean age in study group is 22.82, with standard deviation 3.77. In control group with mean age of 23.66 with standard deviation 3.501 .indicating that both groups were comparable according to age with P value -0.0815.

Graph 1 : Percentage of patients and Age in years .

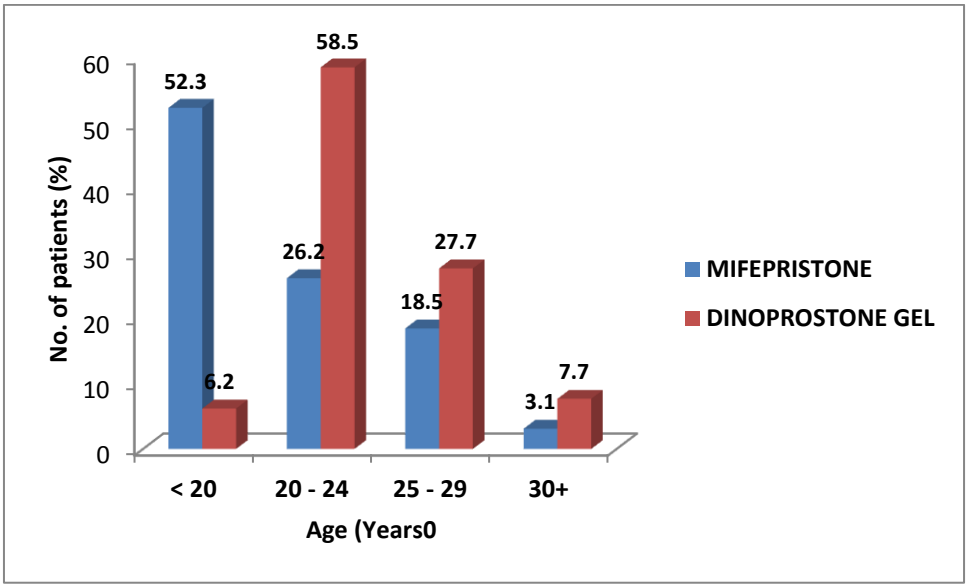


Table 3 : Distribution of patients according to OBSE Score

Indication	MIFEPRISTONE AND DINOPROSTONE GEL		DINOPROSTONE GEL ALONE		Chi square test	P value
	N	Percentage	N	Percentage		
Primi	31	47.7	31	47.7	X^2=0.000	P=1.000
Multi	34	52.3	34	52.3		
Total	65	100.0	65	100.0		
Insignificant						

Comments :

The difference in distribution of the study population according to parity was not statistically significant with P value between the groups 1.000, which is statistically in significant.

Graph 2 : Comparing Obstetrics score

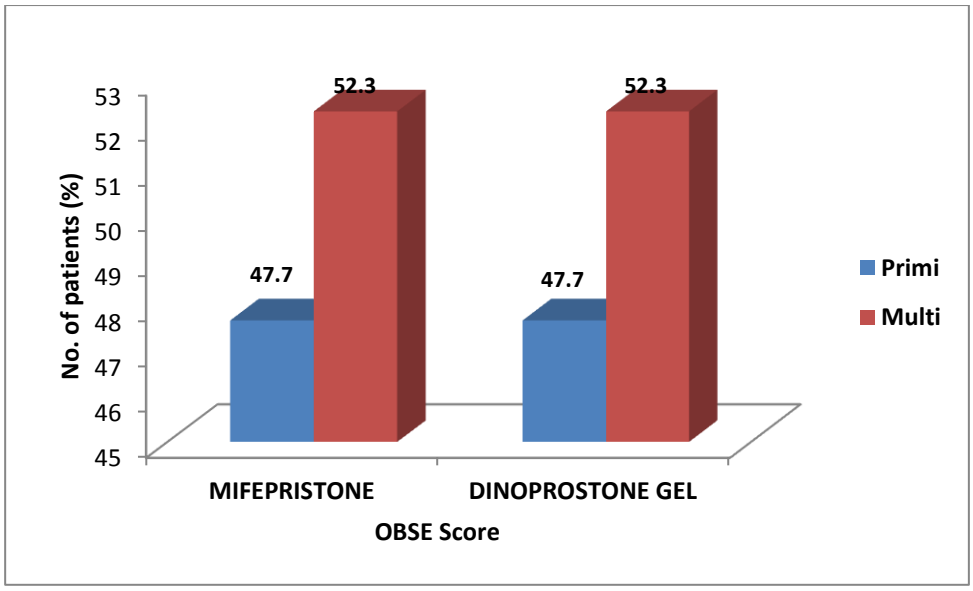


Table: 4 Comparison of Basic variables between two groups

Basic variables	MIFEPRISTONE		DINOPROSTONE GEL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Age	22.82	3.77	23.66	3.501	U=1738.00	P=0.0815
Gestational age	39.66	1.350	39.88	1.241	U=1888.500	P=0.343
Birth weight	2.86	0.342	3.008	0.4016	U=1673.500	P=0.074
In significant						

Graph 3 : comparing basic variables between two groups

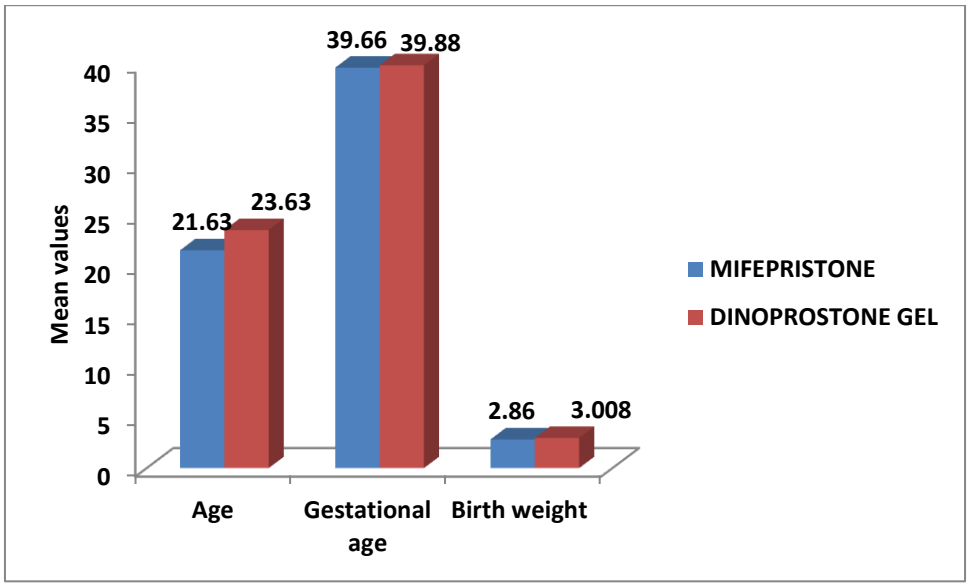


Table: 5 Distribution of patients according to INDICATION FOR INDUCTION

Indication for Induction	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE GEL		Chi square test	P value
	N	Percentage	N	Percentage		
Abnormal Doppler	2	3.1	3	4.6	X^2=1.636	P=0.7142
GHTN	12	18.5	15	23.1		
IUGR	7	10.8	4	6.2		
Prolonged Pregnancy	44	67.7	43	66.2		
Total	65	100.0	65	100.0		
Insignificant						

Comment :

On comparison of patients according to indication for induction in mifepristone along with cerviprime group and cerviprime alone group is prolonged pregnancy is most common with 67.7 % and 66.2 % respectively, gestational hypertension is the second most indication for induction with 18.5 %.

Graph 4 : Percentage according to indication for induction

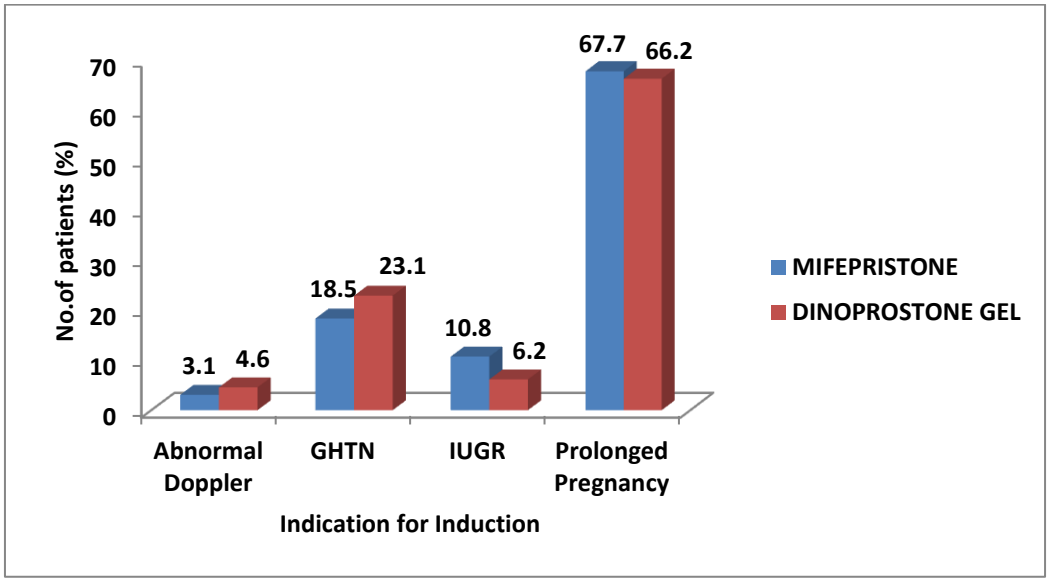


Table: 6 Comparison of Bishops score between two groups

Bishops score	MIFEPRISTONE AND DINOPROSTONE GEL		DINOPROSTONE GEL ALONE		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
At 0th hour	3.62	1.259	2.19	.871	U=713.500	P=0.001*
At 24th hour	7.97	2.845	7.87	2.887	U=1748.500	P=0.950
*:Statistically significant						

Comments :

1) Subjects in the mifepristone and dinoprostone group And from subjects in dinoprostone alone group with respect to baseline Bishops score as the mean difference between the groups is statistically significant with P value -0.001.
2) After 24 hours, Bishops score in mifepristone along with Dinoprostone is higher than in the dinoprostone alone group with statistically significant difference with P value – 0.950 .

Graph 5 : Comparison of Bishops score

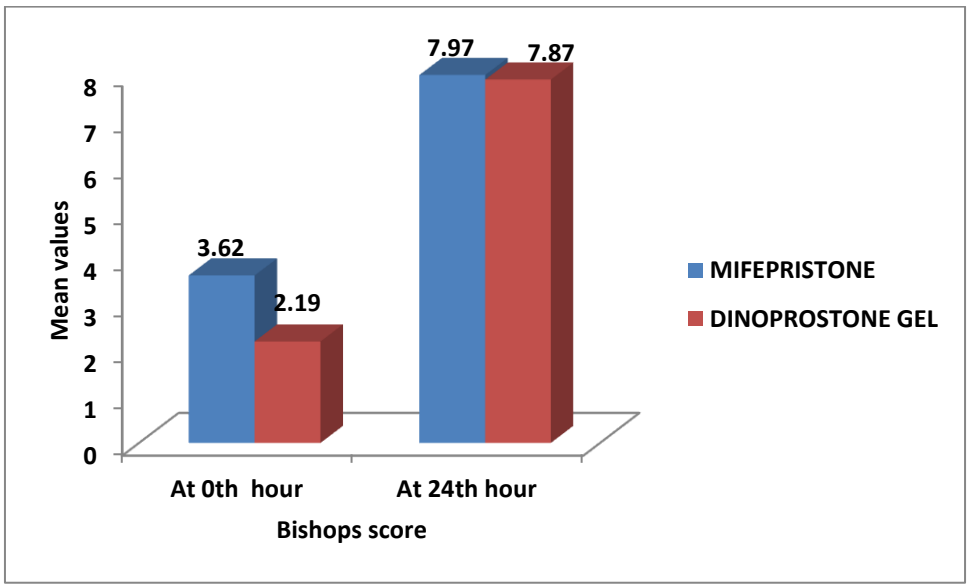


Table: 7 Distribution of patients according to Usage of Gel in between the groups

Indication	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE GEL		Chi square test	P value
	N	Percentage	N	Percentage		
NO	55	84.6	1	1.5	X^2=0.2189	P=0.6399
YES	10	15.4	64	98.5		
Total	65	100.0	65	100		

COMMENTS :

1) In comparison of two groups according to usage of dinoprostone gel in mifepristone along with dinoprostone gel, 84.6 % patients has been progressed without usage of dinoprostone gel in study group.
2) In study group 15.4 % patients has required usageof dinoprostone gel for cervical ripening.

Graph 6 : Comparing usage of Gel in between the two groups :

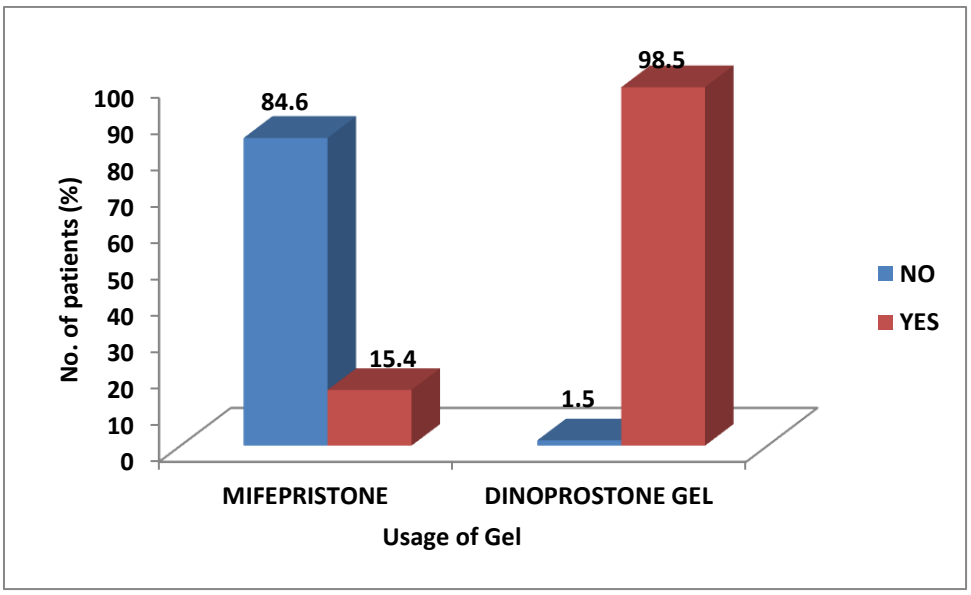


Table: 8 Comparison of Induction between two groups

Induction	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE GEL ALONE		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Induction to active phase	10.53	4.050	17.21	5.968	U=464.500	P=0.001*
Induction to delivery	15.100	5.7089	22.100	5.7089	U=464.500	P=0.001*
***:Highly significant**						

Comments :

1) Subjects in the Mifepristone along with dinoprostone gel group has taken less time for induction to active stage with mean value of 4.050 and 5.968. which is statistically significant.
2) Subjects in the mifepristone along with dinoprostone gel group has taken less time for induction to delivery when compared to dinoprostone gel alone group with mean value of 6.6 ,which is statistically significant.

Graph 7 : Time interval from induction to delivery

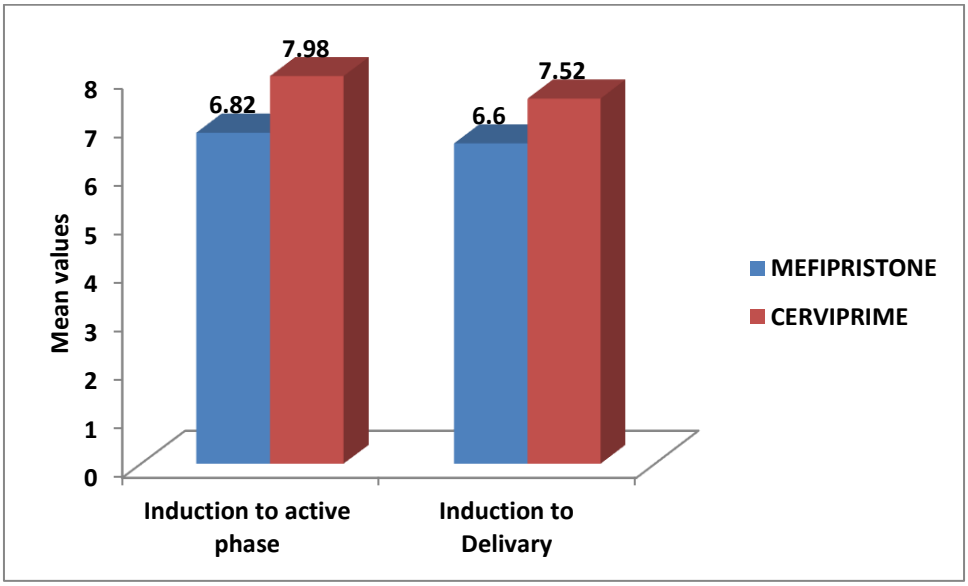


Table: 9 Distribution of patients according to Oxytocin

Oxytocin	MIFEPRISTONE AND DINOPROSTONE GEL		DINOPROSTONE ALONE		Chi square test	P value
	N	Percentage	N	Percentage		
NO	25	38.4	16	24.6	X^2=0.000	P=1.000
YES	40	61.5	49	75.4		
Total	65	100.0	65	100.0		
Insignificant						

Comment :

In comparison of both groups according to usage of oxytocin for augmentation of labor is more percentage in dinoprostone gel alone group with 75.4 %, which is statistically in significant.

Graph 8 : usage of Oxytocin for augmentation

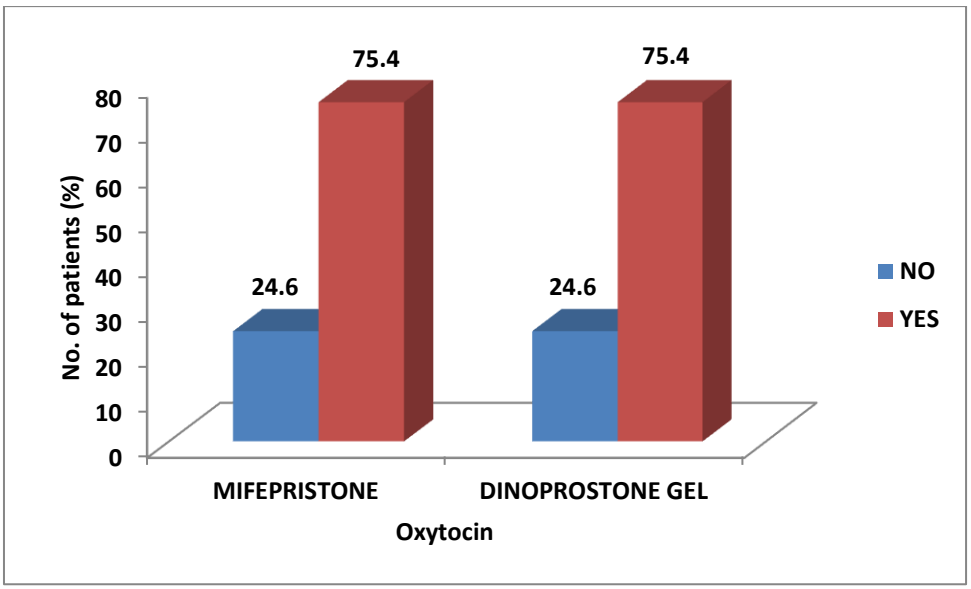


Table : 10 Distribution of patients according to Mode of Delivery

Mode of Delivary	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE ALONE		Chi square test	P value
	N	Percentage	N	Percentage		
FTVD	44	67.7	41	63.0	X^2=0.3059	P=0.5802
LSCS	22	32.3	24	37		
Total	65	100.0	65	100.0		
Insignificant						

Comments :

About 67.7 % of patients delivered vaginally in mifepristone along with dinoprostone gel group when compared to dinoprostone gel alone group.

Table: 11 Comparison of APGAR score between two groups :

APGAR Score	MIFEPRISTONE ALONG WITH DINOPROSTONE		DINOPROSTONE GEL		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
1 min	6.82	0.727	6.60	0.555	U=1762.500	P=0.126
5 mins	7.98	0.820	7.52	1.127	U=1539.000	P=0.005*
***:Highly significant**						

Comments :

In comparison of apgar score in between the two groups at 1 minute and 5 minute is more in study group with mean value of 7.96 .,which is statistically significant.

Graph 9 : Comparison of APGAR score between the two groups

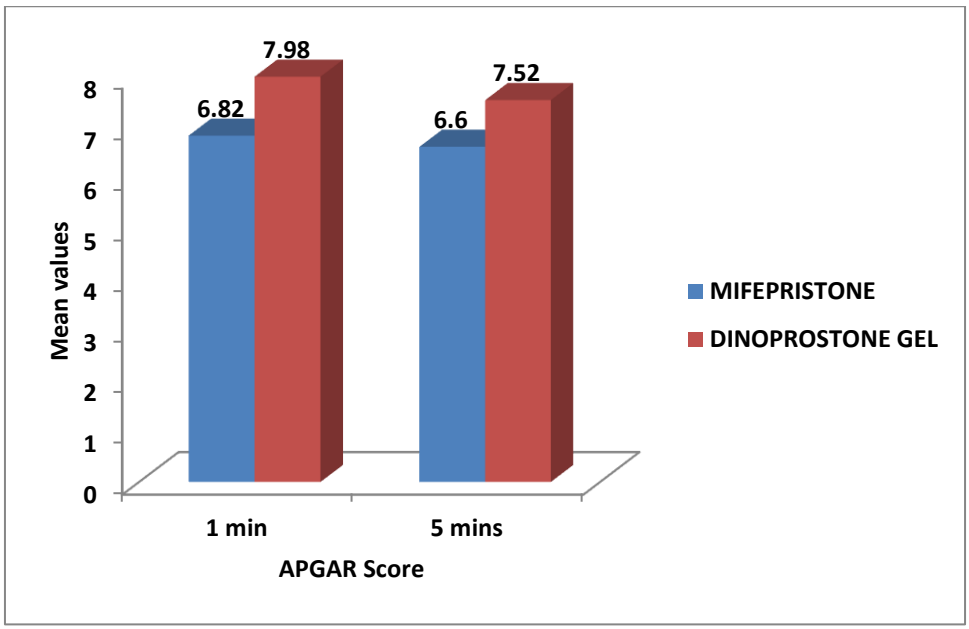


Table: 12 Distribution of patients according to Indication of LSCS

Indication of LSCS	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE ALONE		Chi square test	P value
	N	Percentage	N	Percentage		
FAILED INDUCTION	1	1.5	9	13.8	X^2=16.459	P=0.0212*
FETAL DISTRESS	11	16.9	10	15.4		
MALPRESENTATION-BROW	1	1.5	0	0		
NON REASSURING NST	3	4.6	0	0		
NORMAL	44	67.7	45	69.2		
OLIGOHYDRAMNIOS	1	1.5	0	0		
UTERINE HYPERSTIMULATION SYNDROME	0	0	1	1.5		
POOR BISHOPS SCORE	4	6.2	0	0		
Total	65	100.0	65	100.0		
":Statistically significant						

Comments :

Distribution of patients according to indication for caesarean in mifepristone along with dinoprostone gel group ,most common indication is failed induction which is more in dinoprostone group than in Mifepristone along with dinoprostone group and fetal distress in both the groups with 16.9 % .

Graph 10 : INDICATION FOR LSCS

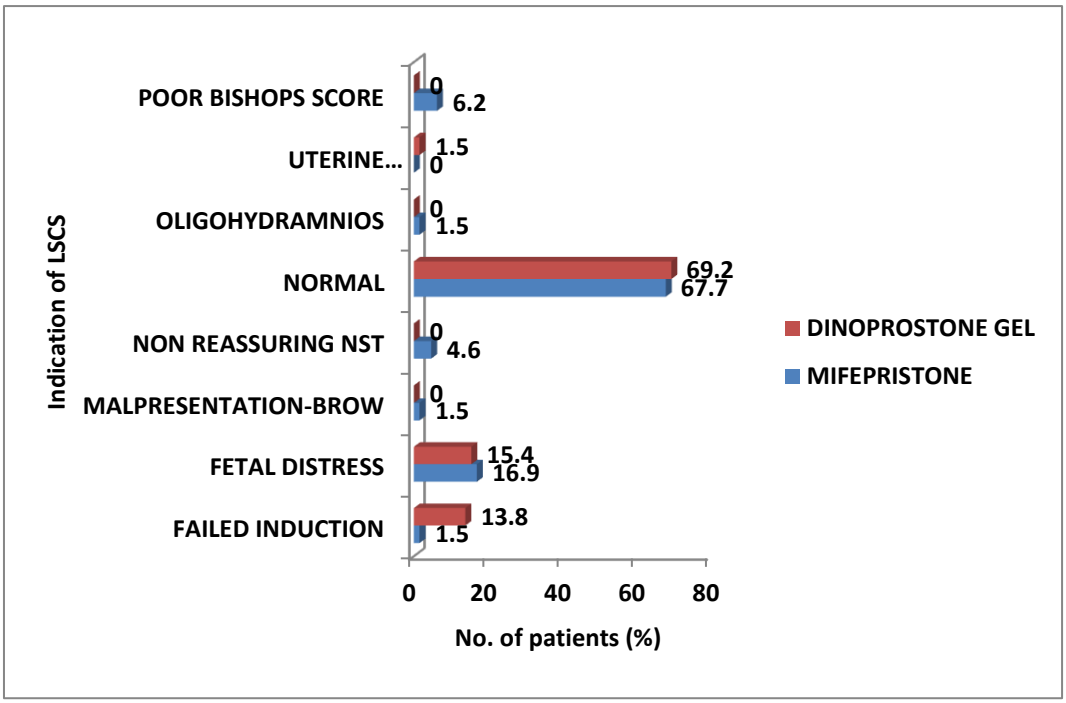


Table : 13 Distribution of patients according to Complications

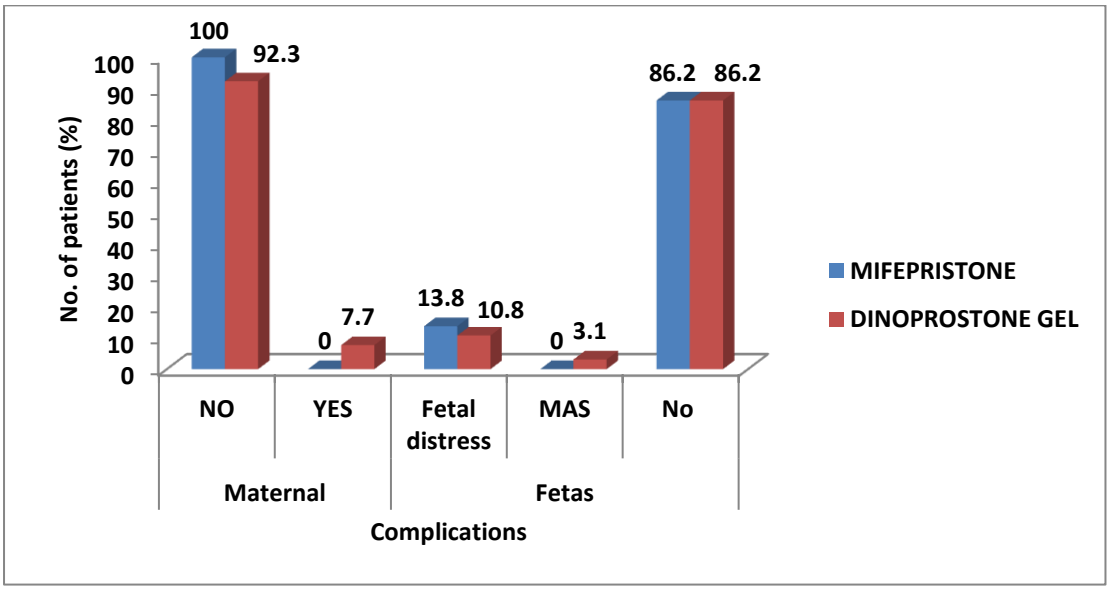
Complications	MIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE GEL		Chi square test	P value
	N	Percentage	N	Percentage		
Meternal						
No	65	100.0	60	92.3	X^2=5.200	P=0.0226 *
Yes	0	00	5	7.7		
Fetal						
Fetal distress	7	10.8	9	13.8	X^2=2.250	P=0.3247
MAS	0	0	2	3.1		
No	56	86.2	56	86.2		
Total	65	100.0	65	100.0		
*: Statistically significant						

Comment :

1) Maternal complication are more in dinoprostone group with 7.7 % like uterine hyperstimulation syndrome than in mifepristone along with dinoprostone gel group.

2) Fetal complication are more in dinoprostone group with 13.8 % than in mifepristone along with dinoprostone group with 10.8 %.

Graph 11 : Maternal and neonatal complications



COMPARISON WITHIN GROUPS

Table : 14 Comparison of Bishops score between 0th hour and 24th hour in Mifepristone along with dinoprostone gel and dinoprostone alone groups

Bishops Score	Descriptive			Wilcoxon signed rank test	P value
	Mean	±SD	Difference in the means (%)		
MIFEPRISTONE ALONG WITH DINOPROSTONE GEL					
0th hour	3.62	1.259	4.35(54.58%)	Z=6.814	P=0.001*
24th hour	7.97	2.845			
DINOPROSTONE GEL					
0th hour	2.18	0.864	5.7(72.33%)	Z=6.463	P=0.001*
24th hour	7.88	2.861			
***:Highly significant**					

Comment :

1) Comparing Bishops score between two groups at 0th hour and 24th hour, showing that more improvement in Bishops score in mifepristone along with dinoprostone group with 7.97 %, than in control group with 7.88 %.

Graph 12 : Comparison of Bishops score at 0th and 24th hour

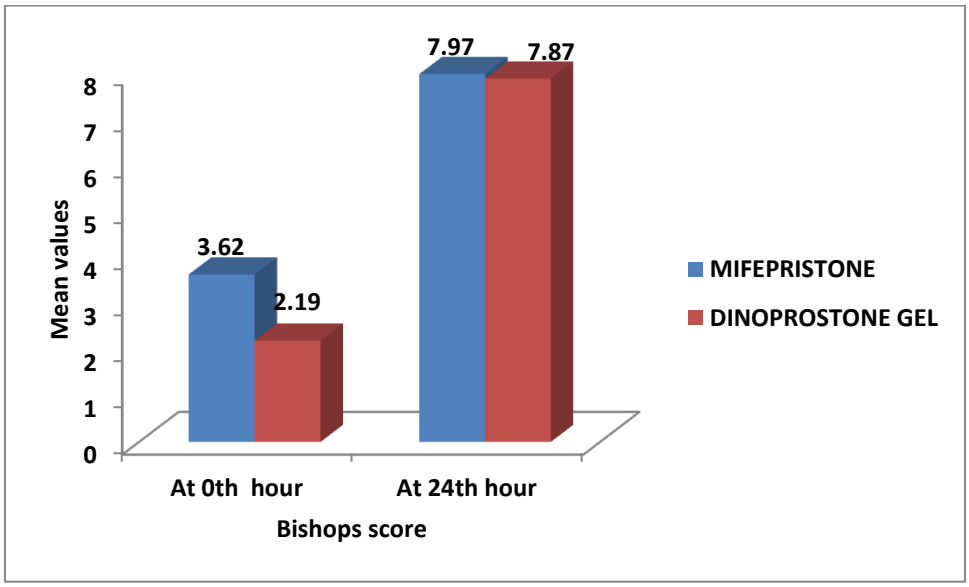


Table: 15 Comparison of Apgar Score between 1st min and 5th min in Mifepristone and Dinoprostone groups

APGAR Score	Descriptive			Wilcoxon signed rank test	P value
	Mean	±SD	Difference in the means (%)		
MIFEPRISTONE AND DIOPROSTONE GEL					
1 minute	6.82	0.727	1.16(14.54%)	Z=7.012	P=0.001*
5 minute	7.98	0.820			
DINOPROSTONE GEL					
1 minute	6.59	0.555	1.04(13.63%)	Z=7.885	P=0.001*
5 minute	7.52	0.612			

Comment :

Comparing Apgar at 1 minute is more in mifepristone along with dinoprostone group than in dinoprostone alone group with mean value of 0.727 and 0.555 respectively.

Graph 13 : Comparison of Apgar Score between 1st min and 5th min in Mifepristone and Dinoprostone group

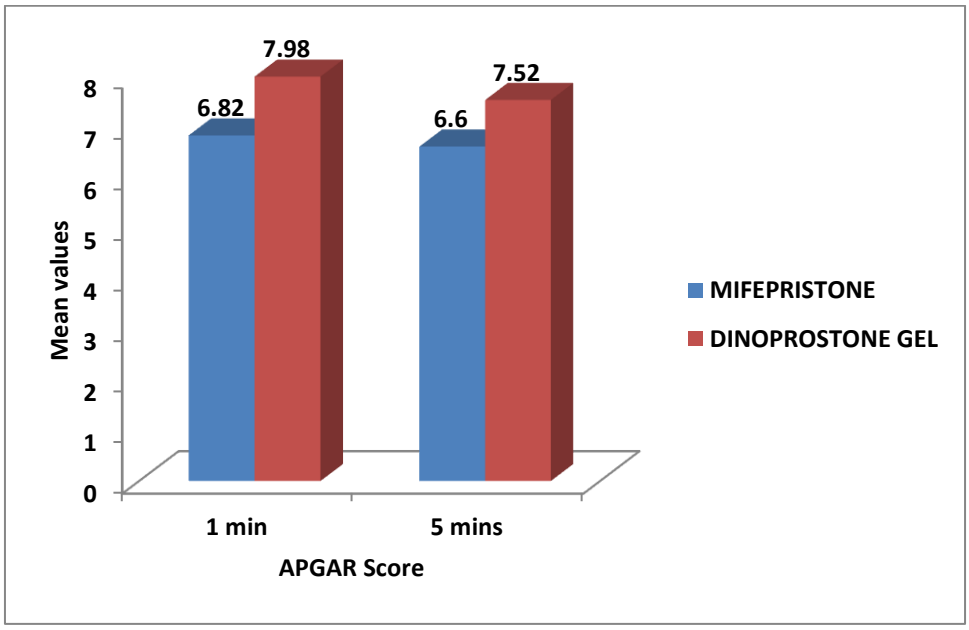


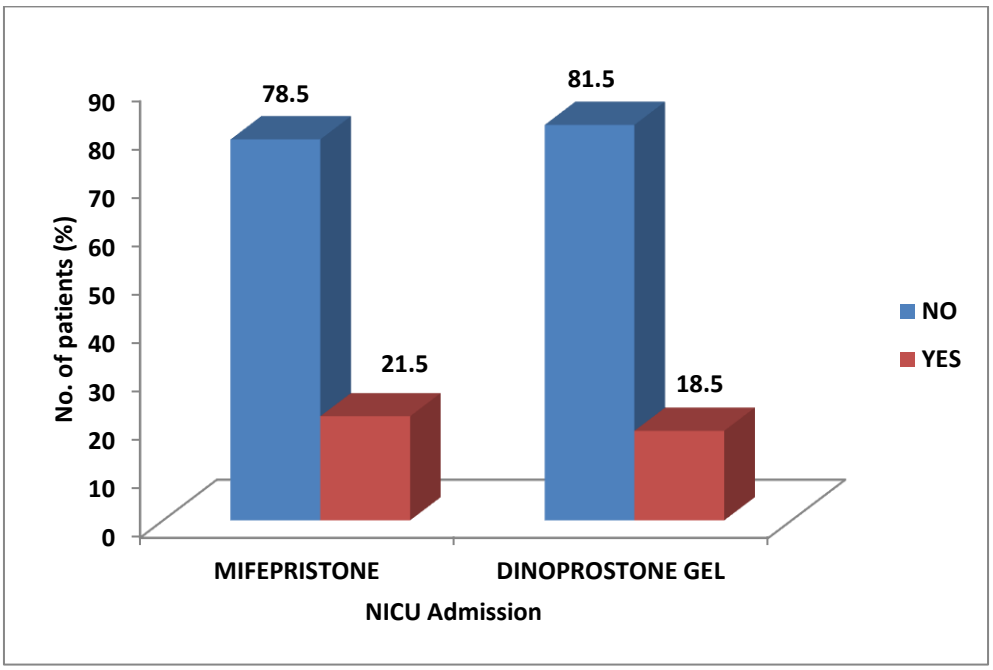
Table: 16 Distribution of patients according to NICU Admission :

NICU Admission	MEIFEPRISTONE ALONG WITH DINOPROSTONE GEL		DINOPROSTONE GEL		Chi square test	P value
	N	Percentage	N	Percentage		
NO	53	81.5	51	78.5	X^2=0.1923	P=0.6610
YES	12	18.5	14	21.5		
Total	65	100.0	65	100.0		
Insignificant						

Comment :

In comparison of need for NICU admissions are less in mifepristone along with dinoprostone group than in dinoprostone group with mean value of 18.5 % , and 21.5 % respectively.

Graph 14 : Comparison of NICU admissions in both the groups



DISCUSSION

The initiation of labor process remains a mystery. It is well known, that progesterone is having an integral part in the maintenance of pregnancy. It is also hypothesized that anti progestin exposure in pregnancy will enhance the process of parturition initiation.

Mifepristone is administered orally which is very convenient and antenatal mothers can be ambulant when compared to cumbersome PGE2 gel administration which has to be instilled endocervically with strict asepsis by technically skilled personnel and needs observation in left lateral position.

Mifepristone is stored at room temperature whereas PGE2 gel storage needs cold chain maintenance the cost of mifepristone is comparable to PGE2 gel. Further need of oxytocin for augmentation is very much reduced with mifepristone when compared to PGE2 gel.

Mifepristone is a steroid compound and progesterone antagonist, which may soften the cervix and cause uterine contractions. There are so many studies showing that, this drug has been effective for elective abortions and medical termination of pregnancy during the first trimester. This lead others to study the effect of mifepristone in term pregnancies as a pre inducing agent.

Results of these studies have demonstrated that mifepristone may ripen the cervix and induce labor ,while not increasing the risk to the fetus.

In this study, total participants comprised of 130 patients with equal number of patients in the study and control group. There is no statistically significant differences between the treatment groups in comparison of age and gestational age of patients. 62 (47.7 %%) patients are primigravida, 68 (52.3 %) are multigravida, with no significant difference across the groups.

The mean bishop score at inclusion is 3.62 in the study group and 3.10 in the control group with significant differences between the groups. The success rate of induction is higher when there is favourable cervix. (P <0.0001).

A study done on primigravida woman at term with un favourable cervix by Elliot 54 and colleagues[21] , and has compared the effects of different dosages of oral mifepristone like 50 mg and 200 mg with placebo on cervical ripening and induction of labor. At a higher dosage like 200 mg, mifepristone resulted in a favorable cervix and spontaneous labor more often than in placebo group .In this study Bishops score in study group ,at 0^{th} hour is having with mean 3.62 ,and in control group with mean 2.18 .After 24 hours ,Bishops score in study group is having with mean 7.97 ,which is higher than in control group with mean 7.88.

There are other studies comparing mifepristone with placebo. A comparison study done by Wing DA 64 et al [15] who has observed that, women who has received 200 mg mifepristone daily for two consecutive days went into labor within 72 hours in 54 %,while comparing in placebo group only 18.2 percent of women had went in to labor.

In another Randomised control trial study done by Berkane 26 et al [21] has shown that treatment was successful in about 52.7% of the patients with assessable for efficacy with no significant difference among the groups (P=0.73), comparing between mifepristone and placebo.

A similar study done by Karl et al [15] stated that mifepristone treated group was successful in 52.7% of patients when compared with placebo. Another randomized control trial done by Giacalone et al[17] from France also shown that 23 (76%) nulliparous women had favorable improvement in bishop score, proving that mifepristone is effective for cervical ripening and reducing the time to delivery when

compared with placebo.

A study done by Nadia et al[26] on 17 (85 %) parous woman, had shown that the relationship between parity and success rate was close to significance (P = 0.053). This is comparable to the study done by Berkane et al[10] which stated that the rate of vaginal delivery increases with parity.

The rate of vaginal delivery is more in multiparous woman, stating that relation ship between parity and rate of vaginal delivery.

The mean interval between induction to active stage is 10.53 hours in the mifepristone along with dinoprostone gel treated group when compared to dinoprostone alone treated group was 17.21. Subjects in the mifepristone along with dinoprostone gel group has taken less induction to active stage time duration when compared to woman in dinoprostone alone group is 10.53, which is statistically significant with P value (P=0.001).

Mean induction to delivery interval is 15.100 in mifepristone along with dinoprostone gel group while in dinoprostone group was 22.100. Woman in the in mifeprisone and dinoprostone group is progressed to delivery fast when compared to woman in dinoprostone group, which is statistically significant.

A Cochrane review 2009 [38], said that compared to placebo mifepristone treated women were less likely to have an unfavorable cervix at 48 hours (RR – 0.39) or at 96 hours (RR- 0.39). Further the review stated that mifepristone treated women were more likely have delivery within 48 and 96 hours of treatment than with the placebo treated group.

The mean time interval between the induction and the onset of labor is significantly shorter in the mifepristone treated group, according to the study done by Frydman 10 et al [25].

A study done comparing dosage of mifepristone with time interval between the onset of labor and, the treatment to delivery was significantly shorter with 600 mg of Mifepristone when compared to placebo, according to Berkane et al study [15].

A study done by Josie et al [58] stated that women treated with mifepristone are more likely to have a favorable cervix within 48 to 96 hours when compared with placebo.

A study done by Zhonghua et al from Beijing[62] stated that the cervical ripening ratio was 100% in the mifepristone treated group.

Another study from department of women and child health says that the median time taken from the onset of labor into delivery is relatively lower in women treated with mifepristone than the women in the control group, this study done in Sweden [59].

A similar French study done on comparing the onset of labor stated that it was one day earlier in the mifepristone treated group when compared with placebo.

A comparison study done on mode of delivery by an RCT by Wing et al [18] who stated that 87.5% women in the mifepristone treated group were delivered vaginally 48 hours after the start of treatment than 70% in the placebo treated group.

Another study done on comparing mode of delivery by Zhonghua et Al [16] from Beijing stated that the incidence of vaginal delivery was more with 80.8% in the mifepristone treated group. The rate of caesarean deliveries (28.3%) was comparably less in the mifepristone treated group than the prostaglandin treated group (46.6%).

A Cochrane review in 2009 said that the mode of delivery by caesarean section was less in mifepristone treated women (RR -0.71). Another prospective study done by Mcgill et al United Kingdom showed that the rate of caesarean section

was significantly lower among women induced with mifepristone alone.

A similar comparison study done by Josie et al [25]on the basis of indication for caesarean section , stated that the fetal distress was less likely in mifepristone treated women with 2 (4 %) of cases . Among the 14 (28%) of placebo treated woman,8(16%) cases were done for fetal Distress, 6 (12%) cases were for failed induction, In a study by Wing et al[61] where meconium passage was 9.1% in the mifepristone treated group.

A Cochrane review 2009 stated that the rate of abnormal FHR pattern was higher in the mifepristone treated group. Another study by Wing et al [20] stated that the rate of fetal distress was higher in the mifepristone treated group.

In this study the difference in Apgar score at 1 min and at 5 min is statistically significant between the study and control group. 4 (8%) infants in the study group and 8(16%) infant in the control group required admission in NICU.

A Cochrane review in 2009 studied on neonatal complications said that the incidence of neonatal hypoglycemia might be more common after exposure to mifepristone (it antagonizes the action of glucocorticoids as well as the action of progesterone).

Another study done by Karl et al [38] stated that there was no difference in fetal tolerability and the rate of fetal distress. A study done by clamart et al [29] from France says that mifepristone appears safe and useful with no adverse effects on the fetus or mother.

Another study by Wing et al[61] also stated that there were no adverse uterine abnormalities or maternal complications observed in the mifepristone treated groups.

The need for re induction with dinoprostone gel is 23.1 % with mifepristone treated groups.

The need for augmentation with oxytocin is less in mifepristone along with dinoprostone group (75.4 %) when compared to dinoprostone gel group (84%).

A RCT done by Frydman et al [32] suggested that the need for oxytocin was much lesser in the mifepristone treated group when compared with placebo.

Another French [11] study stated that women treated with mifepristone had more spontaneous labor and lesser doses of augmentation.

Another study by Wing et al stated that the dose and amount of oxytocin required was lesser in the mifepristone treated group.

Mifepristone has proved very useful for medical abortion in the first and second trimester termination of pregnancy. It has an established role as an effective cervical priming agent. This effect is now utilized for cervical ripening in term pregnancies. Mifepristone is well tolerated by pregnant women and the efficacy which has been proved in many trials.

There are a few reports in the literature describing the effect of mifepristone as a pre induction cervical ripening agent for term pregnancies.

However available data shows that mifepristone along with dinoprostone is better than a dinoprostone alone at ripening the cervix or inducing labor.

In this study we found that mifepristone as a pre induction cervical ripening agent had better proven efficacy especially in multigravida women as similarly by various other earlier standard trials. The need for re induction/augmentation with other cervipriming agents/oxytocics were also reduced in the mifepristone treated groups.

Theoretically, mifepristone as a method of inducing agent in women with previous caesarean section, as it does not involve administering exogenous oxytocic drugs that have potential to over stimulate. There is evidence of a possible reduction

in the incidence of caesarean section following mifepristone treatment (compared to placebo) that would justify further trials quoted as per the reviews of Cochran 2009.

Maternal Complications are similar in both groups. This study aimed to assess the safety and efficacy of oral mifepristone along with dinoprostone as a pre induction cervical ripening agent in term pregnancies and to study its adverse effects on mother and fetus. The results are encouraging with no significant adverse effects on mother and fetus. Further efforts can be put on to prove the study further and prove the effectiveness of the drug and its efficacy.

Further studies can be done comparing 200 mg of mifepristone with 400 mg or even higher doses if found favorable. It promises to be a more compliant drug in near future.

SUMMARY

The present study is a Randomized control trial, conducted on 130 pregnant Women who were post dated pregnancy and having indication for induction.

All the pregnant woman were divided in two groups randomly :

Group A : Constituted 65 pregnant woman in whom 200mg mifepristone and intracervical dinoprostone gel is used depending upon the Bishops score.

Group B : 65patients received intracervical dinoprostone gel alone is used.

- The age range varied from < 20 years to > 30 years. Most common age group is > 20 years in study group with percentage of 36 %, and in control group is 20 - 24 years with percentage of 56 % .
- The mean age of mifepristone along with dinoprostone and dinoprostone alone group is 22.82 and 23.66 years respectively.
- In the present study we observed the number of multiparous women were higher than primiparous women. Multipaous and primiparous women are 52.3 % and 47.7% respectively in mifepristone along with dinoprostone and also in dinoprostone group.
- In this study comparison of Bishops score before induction in study group is higher with mean 3.62 and in control group was with mean 3.10, which is statistically significant with P value 0.001.
- In comparison of Bishops score after 24 hours in study group with mean 7.97 and control group with P value 7.87 which is not statistically significant with P value 0 .950 .
- In comparison of time taken from induction to active phase in study group is with mean 10.53 which is lower than in control group with mean 17.21 with P value 0.001, which is statistically significant.

- In comparison of time taken from induction to delivery in study group is with mean 15.100 which is lower than in control group with mean 22.100 which is statistically significant with P value 0.001.
- In comparison of requirement of oxytocin for augmentation of labor which is less in mifepristone along with dinoprostone group with percentage of 61.5%. In dinoprostone alone group is higher with percentage 75.4 %.
- In comparing mode of delivery, patients delivered vaginally in study group is with percentage 67.7% which is more than in control group with percentage of 63% with insignificant P value 0.4992.
- In comparison of Percentage of patients delivered by LSCS are with percentage 32.3 % in study group, which is less than in control group with 37 % with insignificant P value.
- In study group 23.3 % patients are required induction with dinoprostone along with mifepristone as a pre induction agent.
- Most common indication for lscs in both groups is fetal distress.
- Maternal complications are more in control group with percentage of 7.7 % with significant P value 0.0226.
- NICU admissions are more in mifepristone along with dinoprostone group with 18.5 %, and in dinoprostone alone group is 21.5 %.

CONCLUSION

There is insufficient information available from clinical trials to support the use of mifepristone to induce labor. How ever, this study reveals that oral mifepristone is safe and an effective drug for pre induction cervical ripening. It is cost effective when compared to dinoprostone. It is stable at room temperature and does not need refrigeration. Dinoprostone requires refrigeration. It has an added advantage of ease of administration, better patient compliance and acceptance, reduced oxytocin requirement, with less maternal complications. The drug has no untoward side effects on uterine contraction and no major maternal complications. This drug has safe neonatal outcome.

This drug is more effective in multigravida when compared to primigravida. Hence mifepristone offers advantages over PGE2 gel which is currently used for pre induction cervical ripening.

Recommendations :

Mifepristone is safe and effective drug, as it does not involve administering exogenous oxytocic drugs that have the potential to over –stimulate, and even rupture, the uterus, it can be used as method of inducing labor in woman with previous section, if it is deemed important .more work and further research studies can be done.

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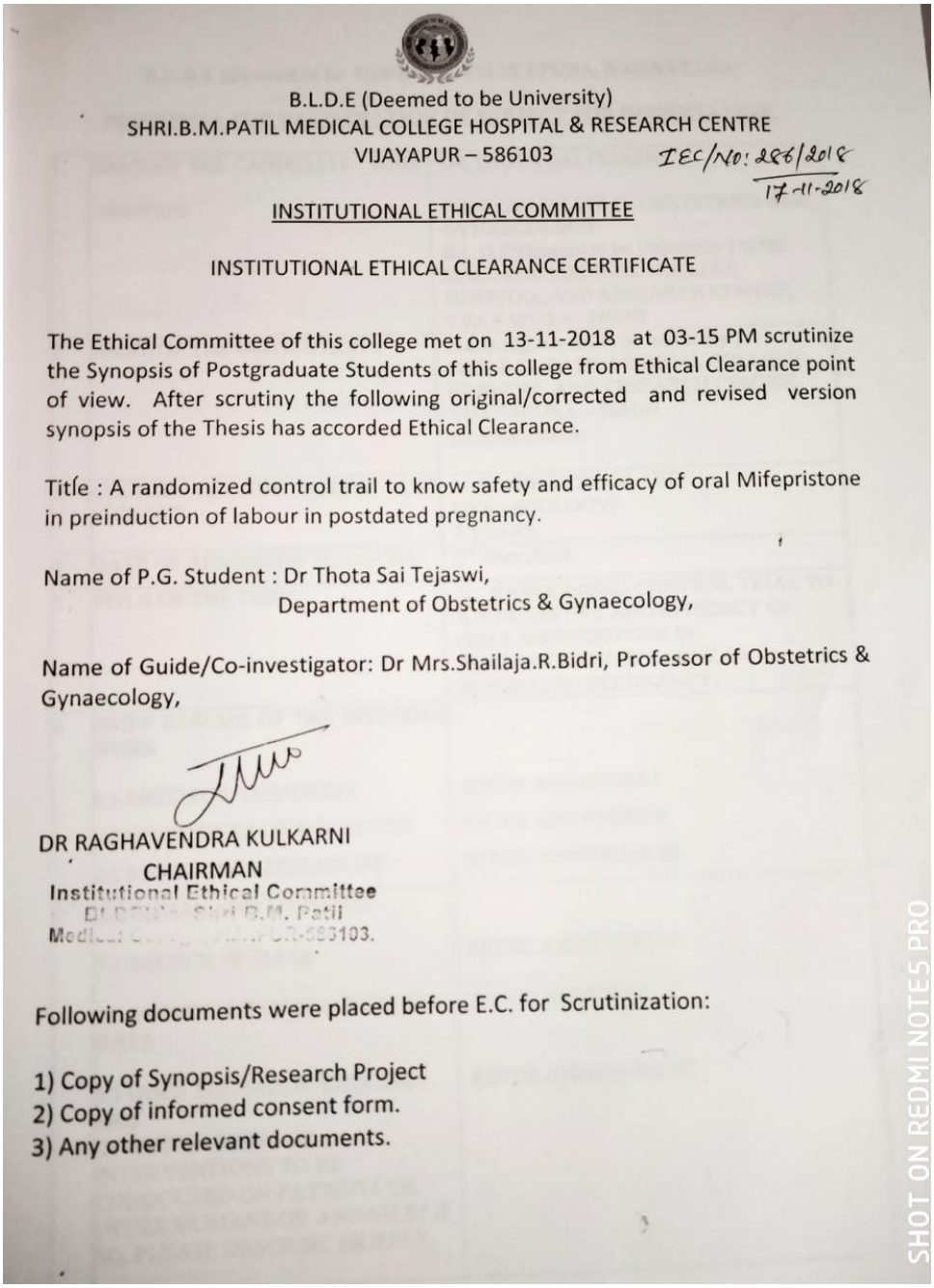
ANNEXURES

ETHICAL CLEARANCE CERTIFICATE



B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/NO: 286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : A randomized control trail to know safety and efficacy of oral Mifepristone in preinduction of labour in postdated pregnancy.

Name of P.G. Student : Dr Thota Sai Tejaswi,
Department of Obstetrics & Gynaecology,

Name of Guide/Co-investigator: Dr Mrs.Shailaja.R.Bidri, Professor of Obstetrics & Gynaecology,

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
[illegible] Shri B.M. Patil
Medical [illegible] 586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

SAMPLE INFORMED CONSENT FORM

TITLE OF THE TOPIC : "A RANDOMISED CONTROL TRIAL TO KNOW SAFETY AND EFFICACY OF ORAL MIFEPRISTON IN PRE INDUCTION OF LABOUR IN POST DATED PREGNANCY ''.

DURATION OF STUDY : FROM OCTOBER 2018 TO JUNE 2020

PRINCIPAL INVESTIGATOR : Dr. T.SAI TEJASWI

PG GUIDE NAME : Dr.S. R. BIDRI

PURPOSE OF RESEARCH :

To determine safety and efficacy of oral mifepristone and dinoprostone in pre induction of labor in post dated pregnancy .

PROCEDURE :

I understand that I will be a part of this study. My history and physical findings will be recorded and evaluated in a systematic way. I am giving oral mifepristone and intracervical dinoprostone as an inducing agent in women who have given consent for induction and fit for the study.

RISK AND DISCOMFORTS:

I understand that this procedure may involve complications like Maternal Nausea, vomiting, diarrhea, Headache, hyperthermia, fever, Abdominal cramps, Chorioamnionitis, puerperal sepsis, Uterine contraction abnormalities-Tachysystole ,hypertonus, Hyperstimulation.

Intrapartum Fetal Complications include Fetal heart rate abnormalities, Meconium passage-thin, thick.

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that Dr. Thota .sai tejaswi of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases. Further Dr. T.SAI TEJASWI informed me that he/she is conducting dissertation/research titled "A Randomized control trial to know safety and efficacy of Oral Mifepristone in Pre-induction Cervical Ripening and Induction of Labour in Postdated Pregnancy." under the guidance of Dr. S. R. BIDRI requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place :

PROFORMA FOR STUDY

Case No. :

Name :

Age /Sex :

I P NO :

Date of admission :

Date of study :

Date of discharge :

Occupation :

Residence :

Married life :

Obstetrics score : G P L A

Menstrual history :

LMP : According to 1 st trimester scan

EDD : EDD :

POG : POG :

Past History :
Family History :

Personal History :

General Physical Examination :

PR: BP:

Per Abdomen :

Fundal Height [GA]

Presentation :

Symphysio Fundal height : [cm]

Obstetrics examination :

Per vagina:

Bishops preinduction cervical scoring system : at 0 hrs

PARAMETERS		SCORE		
CERVIX	0	1	2	3
DILATATION (cm)				
Effacement (%)				
Consistency				
Position				
HEAD : station				
Cervical length (cm)				

BISHOP Score at the end of 24 hours :

Parameters		Score		
Cervix	0	1	2	3
DILATATION (cm)				
Effacement (%)				
Consistency				
Position				
HEAD : station				
Cervical length (cm)				

Spontaneous labour within 24 hours:

Spontaneous labour within 48 hours:

Spontaneous labour within 72 hours:

Time interval between induction of labor to active stage of labor (min):

Time interval between induction of labor to delivery (min) :

Mode of delivery:

Vaginal delivery within 24 hours :

Vaginal delivery between 24 and 48 hours:

Instrumental :

LSCS :

INTRAPARTUM :

1) Premature rupture of membranes : YES /NO

2) Meconium stained amniotic fluid : YES/NO

3) Oxytocin for augmentation : YES/NO

4) Episiotomy / perineal laceration : YES//NO

5) Abnormal fetal heart rate patterns: YES/NO

Adverse effects in mother :

1) Tachysystole :

2) Hyper systole :

3) Hyper stimulation syndrome :

PERINATAL OUTCOME :

Birth weight :

Apgar score :

Gestational age :

NICU admission : YES / NO

Neonatal complications:

Neonatal Mortality:

KEY TO MASTER CHART

PP – Prolonged pregnancy

GHTN – Gestational hypertension

ABN DOP – Abnormal Doppler

MASTER CHART

S.NO	Name	Age in Years	IP.NO	OBS score	Gestational age	Indication	Bishops score		Gel used or not	Oxytocin	Induction to active phase	Induction to delivery	Mode of delivery	Indication for LSCS	Complications		B.WT	AP GAR score		NICU admission
							0 Hour	24 HOURS							Maternal	Fetal		1 min	5 min	
1	Vani kalyani	27	13648	primi	40 WEEKS	PP	2	6	yes	NO	NO	30 HOURS	LSCS			Fetal distress	2.9 kg	6	7	yes
2	Tejaswini Kulloli	24	15003	PRIMI	40 WEEKS 5 DAYS	PP	3	6	YES	YES	28 HOURS	30 HOURS	FTVD				3.1 KG	7	8	NO
3	Bhagya Diddali	20	15440	PRIMI	37 WEEK 1 DAY	IUGR	2	6	YES	YES	30 HOURS	34 HOURS	FTVD				2.6 KG	6	7	NO
4	Geeta Zaleki	28	1139	G4P3L2D1	40 WEEK	PP	2	4	NO	YES	17 HOUR	26 HOURS	LSCS	MALPRESENTATION-BROW			2.8 KG	6	7	NO
5	Kalpana Ramadevi	26	10037	G4P3L3	40 WEEK 2 DAYS	PP	4	12	NO	YES	6.5 HOUR	8.5 HOURS	FTVD				2.9 KG	7	8	NO
6	AMRUTHA SATHA	25	9122	G2P1L1	41 WEEKS	PP	3	8	YES	YES	30 HOURS	34 HOURS	FTVD				3 KG	6	7	YES
7	GAYATHRI PAWAR	20	8730	PRIMI	37 WEEKS	ABN D	3	5	NO	NO		26 HOURS	LSCS	FETAL DISTRESS			3.2 KG	7	8	YES
8	RESHMA RATHOD	19	8842	PRIMI	39 WEEKS 2 DAYS	GHTN	3	8	NO	YES	23 HOURS	28 HOURS	FTVD				2.24 KG	6	8	NO
9	KEERTI PATIL	19	5766	PRIMI	40 WEEKS	IUGR	3	6	NO	NO		11 HOURS	LSCS	IUGR MSL FD			2.1 KG	6	7	YES
10	POOJA PATIL	27	17422	G2P1L1	40 WEEKS	PP	3	8	NO	YES	14 HOURS	20.5 HOURS	FTVD				2.8 KG	7	9	NO
11	KASHIBHAI	19	4014	PRIMI	38 WEEKS	IUGR	4	10	NO	YES	20 HOURS	28 HOURS	FTVD				2.72 KG	7	8	NO
12	MATABHAI	19	3949	G3P2L2	39 WEEKS	GHTN	6	12	NO	YES	7 HOURS	11.5 HOURS	FTVD				3.2 KG	7	8	NO
13	BHAGHYASHREE	19	3856	G2P1L1	36 Weeks	GHTN	6	10	NO	YES	18 HOURS	24.5 HOURS	FTVD				2.32 KG	7	9	NO
14	AMRUTH BEMANNA	19	3941	PRIMI	40 WEEKS 2 DAYS	PP	6	10	NO	YES	16 HOURS	25.5 HOURS	FTVD				3.15 KG	6	8	NO
15	LAXMI RAGHAVENDRA	19	18234	G2P1L1	40 WEEKS 5 DAYS	PP	3	12	NO	YES	16 HOURS	26 HOURS	FTVD				3.06 KG	6	8	NO
16	LAXMI	19	19081	PRIMI	38 WEEKS 2 DAYS	GHTN	3	10	NO	YES	18 HOURS	26.5 HOURS	FTVD				3.16 KG	7	8	NO
17	SAVITHA METRI	29	5869	G3P2L2	41 WEEKS 4 DAYA	PP	4	10	NO	YES	18 HOURS	21 HOURS	FTVD				2.8 KG	7	7	NO

18	POOJA ANIL	27	6278	PRIMI	37 WEEKS 3 DAYS	GHTN	3	6	NO	YES	19 HOURS	23 HOURS	LSCS	FETAL DISTRESS			2.6 KG	6	8	YES
19	NAGARATNA	19	5964	PRIMI	40 WEEKS	PP	3	8	NO	YES	26 HOURS	32 HOURS	FTVD			MSL	3.0 KG	6	8	YES
20	BORAMMA	19	6684	G2P1L1	40WEEKS 5 DAYS	PP	3	10	NO	YES	22 HOURS	26 HOURS	FTVD			MSL	2.71 KG	7	9	YES
21	ANNAPURNA	19	4499	G3P2L2	41 WEEKS 1 DAY	PP	3	6	NO	YES	19 HOURS	27 HOURS	FTVD				2,9 KG	7	9	
22	VAISHALI	24	22686	PRIMI	40 WEEKS	PP	3	6	NO	NO	16 HOURS	23 HOURS	LSCS	NON REASSURING NST			3.2 KG	7	9	
23	YASMIN	23	20855	PRIMI	39 WEEKS	IUGR	4	12	NO	YES	17 HOURS	23.5 HOURS	FTVD			MSL	2 KG	8	9	
24	JYOTHI	28	19982	PRIMI	40WEEKS 2 DAYS	PP	4	4	NO	NO		10 HOURS	LSCS	NON REASSURING NST		MSL	2 KS	8	9	YES
25	SAVITRI BOMANALLI	22	24678	PRIMI	40 WEEKS 3 DAYS	PP	4	8	NO	YES	20 HOURS	28 HOURS	FTVD				3.3 KG	7	8	NO
26	MADINA BALLAD	19	17389	PRIMI	40 WEEKS	PP	4	6	YES	NO		32 HOURS	LSCS	FAILED INDUCTION			2.9 KG	7	9	
27	REKHA DEVARAJ	19	17353	G3P2L2	40 WEEKS 1 DAY	PP	4	6	YES	YES	24 HOURS	34 HOURS	FTD				3.2 KG	6	7	
28	RENUKA MAJJAGI	24	14797	G4P3L2D 1	37 WEEKS 3 DAYS	GHTN	5	12	NO	YES	4 HOURS	6 HOURS	FTVD				3 KG	8	9	NO
29	NASRIN	19	15573	G3P2L2	40 WEEKS	PP	5	12	NO	YES	10 HOURS	18 HOURS	FTVD				2.9 KG	8	9	NO
30	SARASWATHI	19	43738	PRIMI	40 WEEKS	PP	2	12	NO	NO		20 HOURS	FTVD			MSL	2.8 KG	7	8	NO
31	RENUKA BAJANTRI	19	40655	G2A1	38 WEEKS 2 DAYS	PP	4	10	NO	YES	10 HOURS	18 HOURS	FTVD				3 KG	8	9	NO
32	DEEPA MUTTU	19	19	PRIMI	42 WEEKS 3 DAYS	PP	4	10	NO	YES	20 HOURS	28 HOURS	LSCS	MSL WITH FD			2.8 KG	7	8	NO
33	MALLAMMA	19	9642	G2P1L1	38 WEEKS 2 DAYS	IUGR	3	12	NO	YES	8 HOURS	11 HOURS	FTVD				3.1 KG	8	9	NO
34	ANJUM	19	12414	PRIMI	40 WEEKS	PP	3	6	NO	NO	18 HOURS	20 HOURS	LSCS	MSL WITH FD			3.2 KG	6	7	NO
35	GOURI POOJA	19	14084	PRIMI	40 WEEKS 2 DAYS	PP	2	10	NO	NO	16 HOURS	22 HOURS	LSCS	MSL WITH FD		FD	3.2 KG	5	6	YES
36	RESHMA	19	12533	G3P2L2	41 WEEKS	PP	4	10	NO	YES	14 HOURS	18 HOURS	FTVD				3.2 KG	6	7	YES
37	DANAMMA	19	13909	PRIMI	38 WEEKS 4 DAYA	GHTN	4	8	NO	YES	21 HOURS	28 HOURS	FTVD				2.4 KG	7	8	YES
38	BHAGHYASHREE	27	4849	G3P2L2	42 WEEKS	PP	2	6	YES	YES	28 HOURS	32 HOIURS	FTVD				3.4 KG	7	8	NO
39	ASHA BANDIWAL	19	4816	G2P1L1	40 WEEKS	PP	8	12	NO	YES	9 HOURS	17 HOURS	FTVD				3.2 KG	7	9	NO
40	TARABHAI	25	12323	PRIMI	40 WEEKS 6 DAYS	PP	8	14	NO	YES	8 HOURS	13 HOURS	FTVD				2 KG	7	9	NO

41	PRIYANKA	19	5790	PRIMI	40 WEEKS 2 DAYS	PP	4	10	YES	YES	28	32	FTVD				3.2 KG	6	7	YES
42	BHAGHYASHREE	21	13483	G2A1	40 WEEKS 5 DAYS	PP	4	12	YES	YES	20 HOURS	25 HOURS	FTVD			FD	2.3 KG	6	7	YES
43	SUVARNA KATURI	24	13494	G3P1L1A1	38 WEEKS 5 DAYS	GHTN	3	3	NO	NO		16 HOURS	LSCS	NPOL			3.1 KG	7	8	NO
44	SHAINAZ	28	13498	G3P2L1D1	38 WEEKS 1 DAY	GHTN	4	12	YES	YES	18 HOURS	23 HOURS	FTVD				3 KG	7	8	YES
45	DEEPA APTIL	23	13524	PRIMI	40 WEEKS	PP	3	3	NO	NO		16 HOURS	LSCS	OLIGOHYDRAMNIOS			2.8 KG	6	7	NO
46	PRABHAVATHI	32	13562	G4P2L2A1	40 WEEKS	PP	4	8	NO	YES	10 HOURS	18 HOURS	FTVD				2.6 KG	7	8	NO
47	LAXMI BANDAR	29	13547	G4P3L2D1	38 WEEKS 4 DAYS	IUGR	5	8	NO	YES	14 HOURS	17 HOURS	LSCS	MSL WITH FD			2.9 KG	6	7	NO
48	BIBIFATIMA	21	13588	G2A1	37 WEEKS 6 DAYS	ABN D	4	6	NO	NO		16 HOURS	LSCS			MSL	3 KG	7	8	NO
49	REHANA	24	13654	G2P1L1	41 WEEKS	PP	4		YES	YES	26	30	FTVD				2.8 KG	7	8	NO
50	SHREEDEVI PATIL	23	13683	G2P1L1	40 WEEKS 5 DAYS	PP	3	5	NO	YES	14 HOURS	18 HOURS	LSCS	FD			2.76 KG	7	8	NO
51	RENUKA SINDAGI	22	13760	G2A1	40 WEEKS 3 DAYS	PP	4	5	NO	NO	8 HOURS	16 HOURS	LSCS				3 KG	8	9	NO
52	KHAJABI	22	13757	PRIMI	41 WEEKS 5 DAYS	PP	2	4	NO	NO		14 HOURS	LSCS	POOR BISHOPS SCORE			3.2 KG	6	8	NO
53	SMITHA MAHAYAT	28	13791	PRIMI	40 WEEKS	PP	2	4	YES	YES	18 HOURS	22 HOURS	LSCS	NON RASSURING NST			2.9 KG	7	8	NO
54	VANDANA	31	13793	G3P2L2	40 WEEKS	PP	2	4	NO	YES		10 HOURS	LSCS	FETAL DISTRESS			2.5 KG	7	8	NO
55	SONALI	26	13818	PRIMI	39 WEEKS 1 DAY	GHTN	2	4	NO	YES	22 HOURS	26 HOURS	LSCS				2.9 KG	7	8	NO
56	MANJULA	25	13863	G4P2L2A1	40 WEEKS	PP	4	8	YES	YES	28	32	FTVD				3.2 KG	8	9	NO
57	REKHA JEGGALI	22	13842	G2P1L1	40 WEEKS 3 DAYS	PP	3	8	NO	YES	18 HOURS	24 HOURS	FTVD				2.7 KG	6	7	NO
58	RENUKA CHAWADI	23	13884	G2P1L1	40 WEEKS 5 DAYS	PP	4	8	NO	YES	16 HOURS	22 HOURS	FTVD				2.6 KG	8	9	NO
59	SHWETHA	26	13404	PRIMI	40 WEEKS 4 DAYS	PP	3	5	NO	NO		22 HOURS	LSCS	POOR BISHOPS SCORE			3.3 KG	6	8	NO
60	SWETHA KALLAMA	22	13902	PRIMI	40 WEEKS	PP	4	8	YES	YES	26	30	FTVD				3.4 KG	7	9	NO
61	MAHANANDA	30	13976	G3P2L2	38 WEEKS 6 DAYS	GHTN	4	8	NO	YES	16 HOURS	24 HOURS	FTVD				3.0 KG	8	9	NO
62	SHOBHA	26	13980	G3P1L1A1	38 WEEKS 6 DAYS	GHTN	2	4	No	No		18 HOURS	LSCS	FETAL DISTRESS			2.6 KG	6	7	NO

63	HUSSAINBHE	22	14047	PRIMI	38 WEEKS	IUGR	4	6	NO	YES		20 HOURS	LSCS	POOR BISHOPS SCORE			2.8 KG	7	8	NO
64	HARADHA	25	14065	G2P1L1	40 WEEKS	PP	4	8	NO	YES	16 HOURS	20 HOURS	FTVD				2.9 KG	7	6	NO
65	DIVYA RATHOD	26	14123	PRIMI	40 WEEKS 4 DAYS	PP	4	10	yes	YES	28	32	FTVD				2.5 KG	8	7	NO

S.NO	NAME	AGE	IP.NO	OBS SCORE	POG	INDICATION FOR INDUCTION	0 HOURS	BISHOPS SCORE	NO OF GELS USED	OXYTOCIN	INDUCTION TO ACTIVE PHASE	INDUCTION TO DELIVERY	MODE OF DELIVERY	INDICATION FOR LSCS	COMPLICATIONS		B.WT	APGAR SCORE		NICU
															MATERNAL	FETAL		1 MIN	5 MIN	
1	NIRMALA	24	2326	PRIMI	38 WEEKS 6 DAYS	GHTN	1	8	2	YES	16 HOURS	22 HOURS	FTVD				3.1 KG	6	7	
2	DEEPIKA	25	2282	G4P3L3	38 WEEKS 3 DAYS	GHTN	3	8	1	YES	10 HOURS	18 HOURS	FTVD				2.8 KG	7	8	
3	SHAKUNTALA	21	5931	PRIMI	41 WEEKS 4 DAYS	PP	0	3	3	NO		24 HOURS	LSCS	FAILED INDUCTION	FEVER	FD	3.0 KG	5	6	YES
4	SUNITA	24	13297	G2P1L1	40 WEEKS 3 DAYS	PP	3	10	1	YES	7 HOURS	11 HOURS	FTVD				3.1 KG	7	8	
5	BHAGYASHREE	25	12091	G2P1L1	38 WEEKS 2 DAYS	GHTN	3	12	1	YES	6.5 HOURS	8 HOURS	FTVD				2.8 KG	7	8	
6	SUNANDA	22	13181	G2P1L1	40 WEEKS 5 DAYS	PP	2	8	2	YES	10 HOURS	14 HOURS	FTVD				2.9 KG	6	7	
7	SAVITRI	22	10755	PRIMI	39 WEEKS 4 DAYS	GHTN	1	8	2	YES	11 HOURS	17 HOURS	FTVD				3.2 KG	6	7	
8	BHAYA	18	11291	G2A1	41 WEEKS 2 DAYS	PP	2	6	2	YES	13 HOURS	17.5 HOURS	FTVD				3.2 KG	7	9	
9	JAYASHREE	20	11781	PRIMI	39 WEEKS 4 DAYS	IUGR	2	4	2	YES	10 HOURS	12 HOURS	LSCS	MSL WITH FD			3.1 KG	5	6	YES
10	SATYAWWA	28	11623	G4P1L1A2	38 WEEK	GHTN	2	10	2	YES	6 HOURS	10.5 HOURS	FTVD				2.08 KG	7	8	
11	SUKANYA	23	14565	G2A1	40 WEEKS 1 DAY	PP	1	8	2	YES	13 HOURS	18 HOURS	FTVD				3.26 KG	7	8	
12	KALAVATHI	20	14715	G2A1	40 WEEKS	PP	2	6	1	YES	8 HOURS	10 HOURS	FTVD				3.7 KG	7	8	
13	CHANAMMA	19	23541	PRIMI	40 WEEKS 4 DAYS	PP	1	10	3	YES	20 HOURS	24 HOURS	FTVD			MAS	2.8 KG	6	7	YES
14	RESHMA	18	28683	PRIMI	40 WEEKS 4 DAYS	PP	1	4	3	NO		22 HOURS	LSCS	FAILED INDUCTION			3.0 KG	6	7	
15	POOJA	21	15591	PRIMI	41 WEEKS 4 DAYS	PP	1	6	1	YES	10 HOURS	14 HOURS	FTVD				3.2 KG	7	8	
16	LAVANYA	20	15328	PRIMI	41 WEEKS	PP	1	8	2	YES	10 HOURS	16 HOURS	FTVD				2.1 KG	7	8	
17	FARIDA	30	31365	G4P2L2A1	39 WEEKS 3 DAYS	GHTN	2	4	3	NO		16 HOURS	LSCS	FAILED INDUCTION	PPH		3.6 KG	6	7	
18	VIDYASHREE	30	22953	G3P2L2	40 WEEKS 4 DAYS	PP	3	12	1	YES	5 HOURS	8.5 HOURS	FTVD				3.9 KG	7	8	

19	VIJAYALAXMI	21	22849	PRIMI	40 WEEKS 5 DAYS	PP	2	6	3	NO	NO	16 HOURS	LSCS	FD			2.5 KG	6	7	YES
20	LAXMICHAVAN	23	22866	PRIMI	42 WEEKS	PP	4	12	1	YES	6 HOURS	11.5 HOURS	FTVD				2.5 KG	7	8	
21	GIRIJA BIRADAR	26	28880	PRIMI	38 WEEKS	ABN D	2	2	1	NO	NO	5.5 HOURS	LSCS	UTERINE HYPERSTIMULATION SYNDROME	HYPERSTIMULATION		3 KG	7	8	
22	NIRMALA	28	26483	G2P1L1	40WEEKS 1 DAY	PP	3	8	1	YES	9 HOURS	14 HOURS	FTVD				3.4 KG	7	8	
23	NETRA KOLI	26	17840	G2P1L1	40 WEEKS 5 DAYS	PP	2	12	2	YES	11 HOURS	15 HOURS	FTVD				3.3 KG	7	8	
24	RUKMINI	30	28063	PRIMI	40 WEEKS	PP	1	3	3	NO	NO	23 HOURS	LSCS	FAILED INDUCTION			2.5 KG	6	7	
25	AISHWARYA MOTI	25	26922	PRIMI	40 WEEKS 6 DAYS	PP	2	4	1	NO	NO	6 HOURS	LSCS	FD		FD	2.9 KG	7	8	
26	NANDINI PAWAR	20	26889	PRIMI	41 WEEKS 6 DAYS	PP	2	4	1	NO	NO	5 HOURS	LSCS	FD		FD	2.8 KG	6	7	YES
27	MAHALAXMI	21	38073	PRIMI	41 WEEKS 4 DAYS	PP	2	10	2	YES	11 HOURS	15 HOURS	FTVD				2.9 KG	7	9	
28	SUNANDA KUMBAR	28	18177	PRIMI	40 WEEKS 2 DAYS	PP	3	4	2	NO	NO	18.5 HOURS	LSCS	FAILED INDUCTION		FD	3.2 KG	6	7	YES
29	RIYANA	20	19122	PRIMI	40 WEEKS 6 DAYS	PP	3	10	2	YES	18 HOURS	24 HOURS	FTVD				2.5 KG	7	8	
30	SUMITRA RATHOD	24	17012	G2P1L1	40 WEEKS 3 DAYS	PP	2	6	3	YES	15 HOURS	28 HOURS	FTVD				2.7 KG	7	8	
31	SNEHA AJAY	20	28739	PRIMI	39 WEEKS 6 DAYS	GTHN	3	12	1	YES	6 HOURS	9 HOURS	FTVD				.4 KG	7	8	
32	SAVITHA PUJERI	23	37602	G2A1	39 WEEKS 6 DAYS	GHTN	2	3	2	NO	NO	17 HOURS	LSCS	FAILED INDUCTION			3 KG	6	7	
33	SHILPA HACHAD	19	29802	PRIMI	40 WEEKS 2 DAYS	PP	3	8	1	YES	6.5 HOURS	13.5 HOURS	FTVD				3.18 KG	7	8	
34	TASLIM SHAIKH	24	32368	G3P2L2	40 WEEKS	PP	1	12	1	YES	5 HOURS	8 HOURS	FTVD				3.1 KG	7	8	
35	BHAGIRATHI	22	6641	G2P1L1	40 WEEKS	PP	4	10	1	YES	6.5 HOURS	9 HOURS	FTVD				2.76 KG	7	8	
36	NIKITHA	20	9766	PRIMI	38 WEEKS 5 DAYS	IUGR	3		1	NO	NO	4 HOURS	LSCS	FD			3.7 KG	6	7	
37	ZULEKHA	20	10680	G2P1L1	41 WEEKS 1 DAY	PP	2	8	1	YES	7 HOURS	12 HOURS	FTVD				3.18 KG	6	7	
38	SHRUTHI BIRADAR	28	38651	PRIMI	36 WEEKS 5 DAYS	GHTN	1		3	NO	NO	20 HOURS	LSCS	NPOL WITH FD			2.4 KG	6	7	YES
39	SAVITHA SHIVOOR	24	3567	G4P1L1A2	40 WEEKS 2 DAYS	PP	3		1	YES	10 HOURS	14 HOURS	FTVD				2.8 KG	7	8	
40	LAXMI DAYADEEP	29	6458	G3P2L2	38 WEEKS 6 DAYS	ABN D	2		1	YES		7 HOURS	LSCS	FD			3.2 KG	6	7	
41	ASHA AWATHI	26	7325	PRIMI	41 WEEKS 2 DAYS	PP	3	6	1	YES	7 HOURS	12 HOURS	LSCS	MSL WITH FD			2.89 KG	6	7	YES
42	LAXMI ALABEL	22	4141	G3P2L2	39 WEEKS 6 DAYS	GHTN	3		3	YES	18 HOURS	21.5 HOURS	FTVD				3.4 KG	7	8	

43	AASMA	20	6634	PRIMI	40 WEEKS 3 DAYS	PP	2		3	YES	16.5 HOURS	23 HOURS	LSCS	FAILED INDUCTION			3.4 KG	7	8	YES
44	MAHANADA	26	5380	G2P1L1	40 WEEKS 3 DAYS	PP	2	10	1	YES	8 HOURS	10 HOURS	FTVD				2.6 KG	7	8	
45	LAXMI MINAJAGI	28	5394	G3P2L2	41 WEEKS 4 DAYS	PP	3	8	1	YES	9 HOURS	14 HOURS	FTVD				3.2 KG	7	8	
46	SAVITA SHIVANANDA	28	3678	G4P1L1A2	39 WEEKS 4 DAYS	GHTN	3	8	2	YES	14 HOURS	18 HOURS	FTVD							
47	ASHWINI BAJANALI	22	33442	PRIMI	40 WEEKS	PP	3	8	2	YES	16 HOURS	20.5 HOURS	FTVD				3.6 KG	7	8	
48	PREMALATHA	25	12677	G5P2L2A2	37 WEEKS 1 DAY	GHTN	2	12	1	YES	6 HOURS	10 HOURS	FTVD				3.1 KG	7	8	
49	BHAGAMMA	20	43776	PRIMI	39 WEEKS 1 DAY	GHTN	1	4	3	YES	16 HOURS	27 HOURS	LSCS		FEVER		2.36 KG	7	8	YES
50	SHANTA BIRADAR	21	31925	PRIMI	40 WEEKS 1 DAY	PP	4	10	1	YES	10 HOURS	13.5 HOURS	FTVD				3.1 KG	7	8	
51	MAHADEVI VIMALAKA	24	41833	G3P2L2	41 WEEKS	PP	2	8	1	YES	7 HOURS	15 HOURS	FTVD				2.8 KG	7	8	
52	HEENA KOUSAR	21	39949	G2A1	40 WEEKS 3 DAYS	PP	2	10	2	YES	10 HOURS	19 HOURS	FTVD				2.5 KG	7	8	
53	UMA VALTHAR	20	40522	PRIMI	38 WEEKS 3 DAYS	IUGR	3	8	2	YES	10 HOURS	14.5 HOURS	FTVD				3.15 KG	7	8	
54	AMBIKA JAMBAGI	30	644	G3P2L2	41 WEEKS 5 DAYS	PP	2	12	2	YES	9 HOURS	13.5 HOURS	FTVD				3.38 KG	7	8	
55	RADHA DEVI	27	39514	G4P1L1A2	38 WEEKS 4 DAYS	IUGR	2	10	2	YES	10 HOURS	17 HOURS	FTVD				2.8 KG	7	8	
56	SHAHERA	20	39362	PRIMI	40 WEEKS 3 DAYS	PP	2		1	NO		7 HOURS	LSCS	MSL		MAS	3.1 KG	6	7	YES
57	NAGAMMA	20	19072	PRIMI	40 WEEKS 3 DAYS	PP	2	8	2	YES	10 HOURS	18 HOURS	FTVD				2.7 KG	7	8	
58	BHARATI HIKIMALL	23	42006	PRIMI	40 WEEKS 3 DAYS	PP	2	4	2	NO	14 HOURS	18.5 HOURS	LSCS	MSL		FD	3.61 KG	6	7	
59	GURUBASAWWA	25	10828	PRIMI	40 WEEKS 6 DAYS	PP	2		1	NO	6 HOURS	6.5 HOURS	LSCS	MSL		FD	2.8 KG	6	7	
60	HASEENA	24	14132	G2A1	40 WEEKS 3 DAYS	PP	1		3	NO	20 HOURS	22 HOURS	LSCS	FAILED INDUCTION	FEVER		3.2 KG	7	8	
61	GAYATRI	32	979	G3P2L2	42 WEEKS 1 DAY	PP	2	8	2	YES	15 HOURS	20 HOURS	FTVD				2.9 KG	6	7	
62	SAVITHA	24	3567	G4P1L1A2	39 WEEKS 4 DAYS	GHTN	3	8	1	YES	7 HOURS	14 HOURS	FTVD				3.3 KG	7	8	
63	SHASHIKALA	24	17600	G3P1L1A1	36 WEEKS 4 DAYS	ABN D	4	12	1	YES	8 HOURS	12 HOURS	FTVD				2.4 KG	7	8	
64	GURUSIDAMMA	27	14679	G6P3L3A2	39 WEEKS 5 DAYS	GHTN	2	10	2	YES	14 HOURS	20 HOURS	FTVD				2.9 KG	6	7	
65	DUNDAWWA	28	14607	G3P1L1A1	40 WEEKS 6 DAYS	PP	2	8	3	YES	18 HOURS	24 HOURS	FTVD			FD	4.0 KG	6	7	YES