PROSTAGLANDINS WITH ESTRADIOL VERSUS PROSTAGLANDINS ALONE FOR INDUCTION OF LABOUR IN UNFAVOURABLE CERVIX - ONE YEAR RANDOMIZED CONTROL TRIAL AT KLES DR.PRABHAKAR KORE CHARITABLE HOSPITAL, BELAGAVI

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LIST OF ABBREVIATIONS USED

WHO	World Health Organization
RDS	Respiratory Distress Syndrome
IOL	Induction of Labour
IUGR	Intrauterine Growth Restriction
MAS	Meconium aspiration syndrome
PGs	Prostaglandins
EP receptors	G protein coupled receptors
GAGs	Glycosaminoglycans
PGE2	Prostaglandin E2 (dinoprostone)
NOS	Nitrate Oxide Synthase
CS	Cesarean Section
PROM	Premature Rupture of Membranes
PPROM	Preterm Premature Rupture of Membranes
FHR	Fetal Heart Rate
NICU	Neonatal Intensive Care Unit
LMP	Last Menstrual Period
IUGR	Intrauterine Fetal Retardation
IUFD	Intrauterine Fetal Death
LSCS	Lower segment caesarean section
CTG	Cardiotocography
RCT	Randomized Controlled Trail
EDFL	End Diastolic Fibre Length
EDD	Expected Date of Delivery
IL- 8	Interleukin - 8

CRH	Corticotropin Releasing Hormone
C -19	Carbon number 19
SOGC	Society of Obstetricians and Gynaecologists of Canada
ACOG	American College Of Obstetrics and Gynecology
MSAF	Meconium Stained Aspiration Syndrome

ABSTRACT

Introduction: Induction of labour (IOL) is defined as the process of artificially stimulating the uterus to start labor. Over the past few decades, induction incidence has increased due to increase in detection of high risks pregnancies. Prostaglandins have become one of the most effective pharmacological agents in inducing labour in an unfavorable cervix. However estrogen is a hormone involved in ripening of cervix, it increases the release of local hormones (prostaglandins) which help to ripen the cervix. So there is need to the study if addition of vaginal estradiol to prostaglandins would hasten the process of delivery interval without risks to both the mother and the fetus.

Objective: Primary objective: To evaluate the efficacy of addition of vaginal estradiol with prostaglandins in induction of labor in an unfavourable cervix. Secondary objective: to assess maternal and fetal outcome.

Methodology:

Design: Randomized controlled study.

Setting: KLE University's Dr. Prabhakar Kore Hospital and Medical Research Center, Attached to Jawaharlal Nehru Medical College, Belagavi.

Subjects: A prospective study of 120 pregnant women with unfavorable cervix fulfilling the eligibility criteria admitted in labour room within period between May 2015 to April 2016 were included in the study. Inclusion criteria: gestational age ≥ 36 weeks, singleton pregnancy, cephalic presentation, Bishop's score ≤ 4, intact membrane. Exclusion criteria**:** previous LSCS or any scar on uterus, premature rupture of membrane, placenta previa.

Intervention:

An informed consent was taken and by simple randomisation using opaque sealed envelope, they were allotted either with prostaglandins (dinoprostone, PGE2 gel) intaracervically alone group Or, using prostaglandins (dinoprostone, PGE2 gel) intaracervically with 50mcg vaginal estradiol tablet in the first dose followed by prostaglandins alone in the subsequent next two doses, sixth hourly of maximum 3 doses till cervical ripening is achieved. Preinduction cervical evaluation was assessed using Bishop's score before each induction and earlier whenever warranted. The following outcome measures were noted in both the groups: 1) Interval from initiation of induction to cervical ripening (a score ≤ 6 was taken as unfavourable and favourable when Bishop's score ≥ 8 at the end of 18 hours after initial induction). 2) Interval from induction to establishment of active labour (in primigravida >3cm with >80% effacement and in multipara > 4cm). 3) Induction to delivery interval. 4) Number of doses of prostaglandins required in each group.

Results: Main indications were postdated pregnancies (26.67%) and pre-eclampsia. In this study there is significantly longer mean interval time noted for induction to cervical ripening (12.88 ±4.91 vs. 8.92 ± 5.07; p <0.001), induction to active labour (16.97 ±4.93 vs. 11.02 ± 4.72; p <0.001) and induction to delivery time (21.97 ± 3.83 vs. 13.14 ± 4.98; p <0.001) in PGE2 group compared to combined PGE2 and estradiol group.It was noted that mean number of doses of PGE2 gel required was less in combined prostaglandins and estradiol group than prostaglandins group alone (p <0.001).Fetal outcome in both the groups were not statistically significant and hence were comparable.

Conclusion: Estradiol along with prostaglandins acts as a potentiating inducing agent in cervical ripening process and induction of labour than prostaglandins alone. Also the number of doses of prostaglandins required was more prostaglandins alone group compared to combined prostaglandins and vaginal estradiol group. The fetal outcome showed similar beneficial outcome in both the groups.

Key words: Estradiol, Induction, Labour, Prostaglandin.

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INTRODUCTION

Obstetrics and gynecology is that branch of medicine concerned with the study of women's health and reproduction. The aim of obstetrics in a pregnancy is to achieve a healthy baby and a healthy mother. Usually in majority of the women labour starts spontaneously and it results in vaginal delivery at or when the term is near. Induction of labour for cervical ripening is necessary if there are any medical or obstetric complications of pregnancy. Induction of labor is necessary when the benefits of delivery to either the mother or fetus outweigh than those who plan to continue their pregnancy.[1]

Induction of labour (IOL) is a process where labour is initiated artificially before its spontaneous onset for the purpose of achieving delivery of fetoplacental unit by mechanical or pharmacologic methods.[2] Even though induction is required in medical or obstetrical complications of pregnancy there are circumstances like non-medical or social reasons that warrants inductions. [3]Induction of labour is like a rapier or a double edged sword wherein one edge of the blade is always towards the user's neck. In other words, the more interference with the normal spontaneous onset of labour the higher chances that they may land up having risks like increased cesarean sections, fetal distress, more instrumental deliveries, chorioamnionitis, psychological disturbances.

Over the past few decades, the induction rates have been rising steadily. This has been attributed to physician and patient factors and also increases in high risk pregnancies. Also there is increase in elective cesarean disproportionately, accounting for 10 to 30% of inductions in some countries.[4]In UK, induction rate accounts for approximately 20% and in Canada 23.7% of deliveries. Unpublished data from World

Health Organization (WHO) Global Survey on Maternal and Perinatal Health where 373 health care facilities in 24 countries and nearly 3, 00,000 deliveries were involved showed that 9.6 % of the deliveries were induced. Here, Africans tend to have lower rate of induction (1.4%) than Asians and Latin American countries, and Srilanka the highest rate (35.5%).

When a women's care provider decides that labour induction is essential, the next step is to choose for the most appropriate method of induction. There are various factors that may influence the choice of labour induction method such as parity, cervical and membrane status and patient and provider preference.[2]

Numerous techniques have been attempted for induction of labour to ripen the unfavorable cervix and enhance the changes necessary for labour in the lower uterine segment like intravenous infusion of oxytocin, intravaginal or intracervical administration of prostaglandins and intracervical Foley's balloon catheter insertion.[6]

Induction of labour is very common in obstetric practice and it is not without risks. [5] WHO has recommended that IOL is performed with a clear medical indications and when expected benefits of delivery outweighs than potential harms. Indications that are common for labour induction include postdated pregnancy, oligohydramnios, hypertensive disorders, chorioamnionitis, intrauterine growth restiction, premature rupture of membranes (PROM), maternal medical problems, fetal demise, and Rh isoimmunisation etc. The chief contraindications to labour induction are vaginal bleeding, multiple pregnancy, placenta praevia, malpresentation, prolapsed umbilical cord, scarred uterus, and pelvic structural deformities.

Success of labour induction largely depends on cervical status; cervix that is unripe conveys a lower likelihood of vaginal delivery.[7] When pregnant women of

gestational age more than 41 weeks is induced, it is associated with a small reduction in perinatal deaths and meconium aspiration syndrome (MAS).[8] Induction following PROM shows reduction in chorioamnionitis, endometritis, and neonatal ICU (NICU) admissions.[9]

Before a regimen is selected, cervical ripening or preparedness for induction of labour should be assessed. Several methods have been implemented to assess the cervical status and this process has been described as pre-induction cervical ripening. Prostaglandins (PGs) and misoprostol are main pharmacologic agents that are available for labour induction and cervical ripening.

Since late 1960s, local application of Prostaglandin E_2 (PGE_2 or Dinoprostone) has been used for the cervical ripening. The outcome of local application of PGE_2 softens the cervix by a number of different mechanisms.[12] PGE_2 is administered intravaginally or intracervically, improves Bishop's score and induction to delivery time interval. In addition, it provides good acceptability and efficacy for the parturient. By the mid-1980s prostaglandins had become an established effective pharmacological agents for inducing labour when the cervix was unripe.[13, 14] For its clinical use in cervical ripening and labor induction they have been vastly studied, especially the PGE2.[14, 15] Uterine tachysystole and fetal distress were reported following administration of PGE_2 in 1 to 5% of women.

During the past 15 years the course of misoprostol (PGE_1) which, unlike PGE_2, is stable at room temperature and is effective when taken orally, is much cheaper than the alternative PGs. With these advantages, it has become a focus of attention for labor induction.

Cervical 'ripening' is a physiological process that occur in the later weeks of pregnancy and is completed with the onset of labor.[16] When cervix has not ripened and delivery is essential and, or has failed, this natural process has to be initiated. Augmentation of labour (WHO definition) refers to increasing the frequency and the intensity of already existing uterine contractions in a pregnant women with true labour but progressing inadequately, in order to achieve vaginal delivery.

Human cervical ripening is characterized by: oedema, leukocyte infiltration, dispersion of the collagen networks that results mainly from collagen degradation caused by leukocyte-released matrix - metalloproteinase, and also there is increase in total glycosaminoglycans (GAGs). The changes in the composition of the cervical connective tissue after PGE_2-induced cervical ripening are similar to those occurring in spontaneous cervical ripening [2]. Indeed, PGE_2 increases human cervical collagenolytic activity and GAGs synthesis, induces vasodilatation of human cervical arteries and thus promotes subsequent edema and leukocyte infiltration.[16-18]

PGE_2 transduces its signal via seven-transmembrane receptors, G protein-coupled receptors, called EP receptors.[13, 53] Ligand-binding studies have expressed the presence of these receptors in pregnant human cervical tissues. The prostaglandin E2 receptors (EP) family has been further classified into four subtypes (EP_1, EP_2, EP_3 and EP_4), differing in their structure, ligand-binding affinities and signal transduction pathways.[53] EP_1 and EP_3 receptors cause smooth muscle contraction, while EP_2 and EP_4 induce relaxation [of] smooth muscle.[13,53]Up-regulation of contractile EP_3 and/or down-regulation of relaxant EP_2 receptor mRNA have been demonstrated in the myometrium of parturient women .The changes in EP receptor associated with labour suggest that EP receptor expression is hormonally regulated at the time of labor by the changes in progesterone and estrogens during parturition .[14]

Furthermore, EP receptors are present within cervical tissues and predominantly expressed in blood vessels. When given estradiol, EP_1 and EP_3 receptor protein expressed in the blood vessels and longitudinal muscle layer of ovariectomised ewes are decreased. These changes would favor PGE_2-induced vasodilatation, leukocyte infiltration, and oedema and further facilitates smooth muscle relaxation during the cervical ripening process. In addition, estradiol administration results in perinuclear expression of the EP_3 receptor in the longitudinal muscle layer. This finding suggests that EP receptor locations are not only regulated by estradiol at the tissue level, but also at the cellular level, and that PGE_2 may control smooth muscle contraction and regulate ovine cervical dilatation in an intracrine manner via EP_3 receptors.

As the pregnancy reaches term, there is increasing concentrations of estrogen in the maternal circulation, the idea that if addition of estrogen to the prostaglandins could potentiate spontaneous onset of labor has led to this study in exploring the role and efficacy of vaginal estradiol with PGE2 combination for induction of labour in unfavorable cervix and to assess the safety of the fetal outcome. Also there is not enough literature to show the true effect of efficacy of vaginal estrogen along with prostaglandins for cervical ripening and labour induction.

The route of administration of estradiol gel can be given as endocervically, vaginally, extra-amniotically, or estradiol intramuscularly. There is some improved cervical favorability with mild myometrial stimulation when estriol gel is used extra-amniotically.

During cervical ripening, PGE_2 is generally considered to act mainly as an inducer of stromal extra cellular matrix protein and glycoprotein alteration. PGE_2 exerts its effects on blood vessels through multiple counterbalanced signaling

pathways in vascular smooth muscle cells thus acting as an important modulator of cervical vascular tone. EP_1 and EP_3 receptors induce vasoconstriction whereas EP_2 and EP_4 receptors provoke vasodilatation. Any modification of the contractile/relaxant EP receptor ratio will affect the ability of PGE_2 to provoke either vasoconstriction or vasodilatation.

EP_1 and EP_3 receptor protein expression were both significantly decreased in the blood vessel media of estradiol-replaced ovariectomized ewes compared with control tissues (by 23 and 31 % respectively). Estradiol concentrations rise in ovine maternal plasma at parturition and prostaglandins mediate premature delivery, induced by estradiol in pregnant sheep and goats. Estradiol, by decreasing EP_1 and EP_3 receptor expression, would facilitate EP_2 and EP_4 receptor-dependent vasodilator effects of PGE_2 and thus promote cervical ripening. Even modest variation in cervical EP receptor expression might be sufficient to provoke physiological alterations in the vascular response to PGE_2. Both in vitro and in vivo studies suggest an important role for EP_4 receptor in mediating PGE_2 ripening effects. PGE_2 induces GAG synthesis by human cervical fibroblasts via EP_4 receptors. Therefore, the significantly decreased expression of EP_1 and EP_3 receptors in the cervical stroma after estradiol replacement might play a role by altering the balance of positive and negative influences. As a result, the activation of EP_4 receptors by PGE_2 in this tissue compartment would represent a second mechanism for estradiol to promote cervical ripening.

In addition to the changes in EP_1 and EP_3 receptor tissue distribution, estradiol alters cellular EP receptor localization, demonstrated by perinuclear localization of EP receptors in porcine cerebral microvascular endothelial cells, in human embryonic kidney cells and in human myometrium.[19, 21]

Activation of pig peri-nuclear EP receptors by PGE_2 modulates intranuclear calcium transients and transcription of genes such as inducible nitric oxide synthase (NOS) and endothelial NOS.[21, 22] Therefore, PGE_2 might increase NO synthesis and facilitate cervical dilatation during parturition in an intracrine manner via the activation of perinuclear EP_3 receptor in the longitudinal muscle layer. Finally, estradiol-dependent expression of perinuclear EP_3 receptor might represent a novel indirect pathway for estradiol to regulate gene expression.

Bishop's score is a quantitative means to assess cervical status prior to induction and also to assess the response to induction process. It is a better predictor of time interval from induction to delivery. A score of ≥ 8 indicates favourable cervix (i.e., the probability of vaginal delivery is the same when labor is spontaneous or induced), while score of ≤ 6 indicates an unfavourable cervix (i.e., the probability of vaginal delivery is lower if labour is induced.

Over the past few decades, efforts have been made to avoid prolonged labour as it is an important cause of maternal and perinatal mortality and morbidity. So its main aim was to accelerate the process of onset of labour. While few interventions of methods of inductions maybe beneficial, their inappropriate use can cause side effects like uterine rupture, uterine hyperstimulation, shivering, uterine tachysystole, fluid retention etc or may lead to increased number of cesarean sections rate. Also induction is considered as failure if the induction- delivery interval goes beyond the limited time. So it was necessary to find an appropriate method of induction to enhance the process of cervical ripening and to have good maternal and fetal outcome. One recent study indicates that labour inductions at term or post-term reduces the rate of caesarean section by 12%, and also decrease fetal death. Furthermore, there is not enough literature to show the true effect of efficacy of combined vaginal estrogen

along with intracervical prostaglandins. This prompted us to know the efficacy of combined vaginal estradiol with intracervical prostaglandins in induction of labour in unfavourable cervix.

OBJECTIVES

Primary objective: to evaluate the efficacy of combined prostaglandins and vaginal estradiol compared to prostaglandin alone in labour induction and cervical ripening in unfavourable cervix.

Secondary objective: to assess for the maternal and fetal outcome.

REVIEW OF LITERATURE

Fetus at term is on a springboard ready to leap into the rough sea of tough humanity. The first journey of life, which is meant to be the shortest journey, may prove to be the most precarious journey ever undertaken.

For centuries, the need to deliver the fetus on time has been very essential. Cervical 'ripening' is a physiological process that occur throughout the later weeks of pregnancy and is completed with the onset of labour.[19]

When delivery is necessary and ripening has not occurred or has failed to be initiated, this natural process has to be accelerated.

Labor induction is not without its risks for the mother and particularly for the fetus. Failed attempts at induction are more common now than 20 years ago probably because of the belief that any attempt at inducing labor should not persist beyond a few hours. The problems of fluid and electrolyte imbalance that sometimes accompanies prolonged syntocinon infusions in unfavourable cases are not seen now. Uterine hyperstimulation remains an infrequent but serious complication and can occur using any oxytocic agent, the consequences of this if unrecognized, can be very serious to the fetus. The search for an induction method that changes the unfavourable to favourable cervix without stimulating uterine contractions and improves the ultimate outcome of labour without risk to the fetus and mother remains the Holy Grail.

The law of nature which governs uterine smooth muscles is Frank Starling's Law – which states that force of contraction of smooth muscle is directly proportional to End Diastolic Fibre Length (EDFL). Myometrial smooth muscle is inherently a

contractile tissue; which is evident when isolated strips of myometrium when placed in isotonic water bath contract rhythmically without stimuli even in the presence of PG synthetase inhibitor.[19]

Cellular and Biochemical Events in cervical Ripening

Ripening of the cervix is complex, and therefore the understanding of physiologic mechanisms involved in cervical ripening is essential. Cellular aspects of cervical maturation include presence of collagen, smooth muscle and ground substance or connective tissue. Changes which take place in collagen and in the connective tissue matrix appear to be the primary factors in cervical ripening. Enzymes, hormones, and collagen breakdown by-products control the changes. Various hormones have been implicated in physiology of cervical ripening, while prostaglandins appear to play an important role.

Danforth et al.[20] were the first to identify that changes in the structure and biochemistry of connective tissue are key elements of cervical ripening. The collagen is embedded in a ground substance comprised of large molecular weight proteoglycan complexes containing a variety of substances called glycosaminoglycans.[21] They explained that during cervical ripening, the ground substance becomes more prominent, and the collagen fibrils arranged previously in an orderly fashion breaks up. Chemically, GAGs are long and negatively charged disaccharides that contain one uronic acid (glucuronic or iduronic) and one hexosamine (glucosamine or galactosamine). The structure of collagen is a helix of three collagen chains, approximately of 1, 00,000 MW each.[21]

Different types of glycosaminoglycans are described like heparan sulfate, chondroitin sulfate and dermatan. In the cervix, collagen fibrils of proteoglycans are linked by their protein core to GAG side chains and thus the mechanical strength of the cervix is maintained.[21]

Even though there is an increase in the total collagen content of cervix at term, the collagen concentration is reduced by 30-50% compared with the non-pregnant cervix. Metalloproteinese-l enzymes or collagenase are responsible for collagen breakdown. Fibroblasts, macrophages, leukocytes, polymorphs, and eosinophils produce this enzymes.[21]

Also as pregnancy progresses, there are alterations in the cervical GAGs and proteoglycans. The concentration of hyaluronic acid increases 12-fold with cervical dilatation of 2-3 cm. Hyaluronic acid binds water, increases the tissue hydration, and decreases rigidity in the cervix. It occurs simultaneously with a decrease in tissue level of two predominant proteoglycans, i.e. chondroitin and dermatan sulfate. The changes in the process of cervical ripening is the result of biochemical changes, which include an increase in water content, a reduction in collagen concentration, and changes in proteoglycan /glycosaminoglycan composition.[21]

The factors that control cervical ripening are complex and often not completely understood. It is speculated that especially in preterm cervical dilatation, inflammatory mediators play a part in cervical ripening. Also, the fibroblasts produce certain cytokines, i.e. interleukin- 8 (IL-8), and it can induce cervical ripening in human as well as in animal models. In animal studies, cervical ripening has been found effective with other cytokines like interleukin 1b and tumor necrosis factor-α (TNF- α).[21]

It is also been demonstrated that nitrous oxide, which is a known inflammatory mediator, may play a role in the tissue remodeling that occurs during cervical ripening. It has been suggested that programmed cell death (apoptosis) also have a significant role in cervical ripening. Undeniably, natural and synthetic prostaglandins (PGs) play a role in cervical ripening. PGE_2, PGI_2, and to a lesser extent PGF_2 are the major prostaglandins produced by the cervix. [21]

Lately misoprostol, a prostaglandin E_1 analogue, used for prevention and treatment of gastric and duodenal ulcer has now achieved its importance as a highly effective cervical ripening agent. Earlier, Prostaglandin E_2-mediates cervical ripening which may be due to the breakdown of collagen tissue, alteration in GAGs or proteoglycan content, /increased hyaluronic acid concentration, and cervical hydration.[21]

Clinically, estrogens like estradiol have been used to produce cervical ripening. The ripening effects of estrogen on the cervix are possibly related to the induction of prostaglandin synthesis by estradiol that results in an influx of protease-producing leukocytes, which may be responsible for promoting cervical ripening. Unlike estrogen, progesterone appears to hinder collagens activity and also acts as a potent anti-inflammatory agent.[21]

Estradiol (E2), or **17β-estradiol**, also known as estra-1, 3, 5(10)-

Triene-3,17β-estradiol is a steroid and estrogen-female sex hormone.

It is essential for the development and maintenance of female reproductive tissues but has an important effect in reproductive system. It is derived from *estra-*, Gk. *οἶστρος* (oistros, literally meaning "verve or inspiration") and *-diol*, a chemical name and suffix indicating that this form of steroid and sex hormone is a type of alcohol bearing two hydroxyl groups.). Estradiol is biosynthesized from progesterone (derived in two steps from cholesterol, via intermediate pregnenolone. It is produced especially within the follicles of the female ovaries, but also in other endocrine (i.e., hormone-producing) and non-endocrine tissues (e.g., including fat, liver, adrenal, breast). The different formulations are oral, gel form, transdermal patches, ointments, injections, topical spray, vaginal ring, spray, tablets. Side effects include nausea, vomiting, fluid retention and headache. It is contraindicated in deep vein thrombosis, pulmonary embolism or arterial thromboembolic disease or if there is presence of history of breast cancer.

Prostaglandins (dinoprostone): it has important effects in IOL (softening the cervix and causing uterine contraction). It is available as two formulations:

a) Cervidil: To be inserted in the posterior fornix and remove at the onset of active labor or after 12 hours.

b) Prepidil gel: 2.5 ml (0.5 mg) in cervical canal using syringe and catheter; may repeat after 6 hours, maximum cumulative dose 1.5 mg/24 hours.

Its side effect includes uterine rupture, hyperstimulation, nausea etc.

Human and animal studies support the observation that antiprogesterone agents helps in cervical ripening, induce neutrophil influx in cervical tissue, and stimulate PG synthesis. It has been postulated that relaxin, a 6-KD dimeric peptide hormone plays a role in cervical maturation.[21]

It has been proposed that relaxin increases collagenase activity in humans via a mitotic effect on fibroblasts. While the specific role of relaxin in human pregnancy is not clearly understood, there is evidence to support its role in cervical maturation and ripening.[21]

Pregnancy is maintained by

(1) Cervical factors and (2) Uterine factors

1. Cervical factors[22]

During pregnancy, the cervix is an important facor in maintaining uterine stability. To achieve this, the cervical shape and consistency has to be maintained. Cervical 'ripening' is a physiological process that occur throughout the later weeks of pregnancy and is completed with the beginning of labour. When delivery is necessary and ripening has not taken place, or has failed to be initiated, this natural process has to be initiated.

The cervix has its unique anatomy to enable it to perform its various roles. It consists predominantly of a stroma of connective tissue which can be subdivided into a superficial loose zone and a deeper dense stromal zone.

The main components of this connective tissue are collagen along with a small component of elastic tissue and an even smaller amount of muscle fibers. The collagen is possessed of dense regular fibrils arranged in parallel bundles, held together by cross-links with a few interspersed other cellular elements and mast cells. The ground substance is composed of proteoglycan complexes, which consist of GAGs side chains on core proteins linked to a hyaluronic acid chain binding it tightly. Dermatan sulphate and chondroitin sulphate are important GAGs in the cervix both of

which contain hyaluronic acid. It has got additional hydrophilic and binding strength properties.

Fibroblasts of plenty long cytoplasmic processes branch out from one cell body to another, possibly similar to myometrial gap junctions infiltrate the ground substance. Along with the advance of pregnancy, there is increased vascularity. The fibroblasts become secretory, the macrophages and white cells migrate out of vessel walls into the cervical stroma with an increase in water content. There is a decrease in collagen content and a certain rise in the glucuronic acid-containing heparan sulphate that contribute the collagen to bind much less strongly. Enzymatic breakdown of collagen fibrils by collagenases/matrix metalloproteinases produced by fibroblasts and polymorphonuclear leukocytes along with leukocyte elastase, which catabolises elastin, leads to increased cervical compliance. The precise mechanisms remain unproven. However, there has been close implications between the PGs and their synthase inhibitors as pregnancy advances. It is clear that the process of cervical ripening will occur without any detectable uterine contractions being stimulated. Cytokines, notably monocyte chemotactic protein-1 (MCP-1), and IL-8, or platelet activating factor (PAF), have been proposed as possible interactants in the remodeling process involved in cervical ripening, as nitric oxide, synthesized by macrophages, myometrium, and the cervix.

2. Uterine factors[23]

Uterus is maintained in quiescence stage throughout pregnancy probably due to following factors:

- Action of progesterone and estrogen via intracellular receptors.
- Myometrial cell plasma membrane receptor mediated increase in cAMP.

- Generation of cGMP.
- Modification of myometrial cell ion channel.

A few independent pathways maintain phase 'O' or quiescence phase. Any defect in these pathways may trigger the onset of labour.

The precise role for these agents in this physiological process remains to be elucidated.

A switch from contractions which are low frequency and low intensity but long lasting to contractions which are more frequent, with high intensity occurs before progressive cervical effacement and dilatation and regular uterine contraction.

The exact trigger for the onset of labour is unknown.

Possible causes for onset of labour are[24]

Following theories were postulated:

Hormonal factors

- Estrogen theory:
    - During pregnancy, most of the estrogens are present in a binding form. During the last trimester, more free estrogen appears, increasing the excitability of the myometrium and prostaglandins synthesis.
- Progesterone withdrawal theory:
    - Before labour, there is a drop in progesterone synthesis leading to predominance of the excitatory action of estrogens.
- Prostaglandins theory:

- Prostaglandins E_2 and $F_{2\alpha}$ are powerful stimulators of uterine muscle activity. $PGF_{2\alpha}$ was found to be increased in maternal and fetal blood as well as the amniotic fluid late in pregnancy and during labour.

- Oxytocin theory:
    - Although oxytocin is a powerful stimulator of uterine contraction, its natural role in onset of labour is doubtful. The secretion of oxytocinase enzyme from the placenta is decreased near term due to placental ischemia leading to predominance of oxytocin's action.
- Fetal cortisol theory:
    - Increased cortisol production from the fetal adrenal gland before labour may influence its onset by increasing estrogen production from the placenta.

Mechanical factors

- Uterine distension theory:
    - Uterus, like any hollow organ in the body when distended to a certain limit, it starts contracting so as to expel out its contents. This explains the preterm labour in case of multiple pregnancy and polyhydramnios.
- Stretching of the lower uterine segment:
    - By the presenting part nearing term.

Most probable sequence of events is

1. Uterine stretch receptors and parturition[23]

Considerable evidence is accumulating to support this hypothesis that fetal growth is an important component in activation of onset of labour.

Fetal growth and amniotic fluid pressure acts as a common activation pathway of stretch receptors on myometrium, which in turn induces specific contractions, increase in gap junction of associated protein and oxytocin receptors.

This makes the uterus more responsive to uterotonics which appear late at the time of labour.

2. Action of fetal cortisol on parturation[25]

At term, fetal adrenal glands produce 100 to 200 mg/day of steroids, which weigh the same as those in adults. Fetal cortisol level increases during last week of gestation leading to increase production of DHEA-S.

CRH is synthesized in maternal / fetal hypothalamus but identical CRH is synthesized in placenta in relatively large amount at term and this CRH is proposed to;

1. Fetal cortisol production, positive feedback, and CRH production.
2. High levels of cortisol modulate myometrial contractility by stimulating the membrane to increase PG synthesis.
2. CRH stimulate C-19 steroid synthesis leading to increased substrate for placental aromatization, resulting in shift in estrogen to progesterone ratio leading to loss of quiescence secondary to expression of contractile proteins.

There are instances where this natural spontaneous onset of labour need to be interfered artificially in maternal or fetal interest, a procedure called induction of labour.

The history of the induction of labor was limited by the failure of midwives and physicians to recognize the need or the desirability for it. Back in 1595, a Reverend Maister Alexis of Piemont was advocating a long list of medicaments said to stimulate the uterus. These included juniper berries, cinnamon, castor oil, and amber in white wine. In 1735, Dr. Henry Bracken suggested that in order to procure an early labor an unctuous application, such as oil of sweet almonds, should be applied warm using a bunch of feathers to "the privities and vagina." In mid 19th century the works of Aristotle was altered and it is stated that the midwife should let the waters break on their own. The contributions of Denman of the Middlesex Hospital to the induction of labor at the end of the 18th century lay not so much in his advocacy of artificial rupture of the membranes as such, but for his ability to recognize the need for it and for his effort thereby to forestall disproportion and secure an easier delivery with a smaller and more premature head.[26] Denman's method has stood the test of time. They followed in the course of the last century a series of more ruthless physical attacks upon the genital tract of the expectant mother, which persisted until the 1930s. Induction protocol has undergone a dramatic change after the advent of inducing agents like oxytocin, prostaglandins, and our understanding of mechanism of labour.

A retrospective study concluded that elective induction should be discouraged in the nulliparous woman, since the Caesarean rate of delivery is increased with elective induction.[27]

A case control study did not find elective induction itself to be predictive of Caesarean delivery.[28]

However, a meta-analysis of early trials concluded that there is no benefit to elective induction and there is no place for it in term pregnancy.[29]

The American College of Obstetricians and Gynecologists suggests that labour may be induced for logistic reasons, including risk of rapid labour, distance from hospital, and psychosocial reasons.[30]

Rate of induction of labor in increasing all throughout the world and accounts for 20% of women undergoing labour.[31]

Recommendations[32]

- The indication for induction should be documented, and discussion should include the method of induction used, reason for induction, associated risks, including failure to achieve labour and foresee possible increased risk of Caesarean section.
- If induction of labour is has failed, the indication and method of induction should be re-evaluated.
- Inductions should not be performed solely for suspected fetal macrosomia.
- Inductions should not be performed solely because of patient or care provider preference.
- Bishop's score used for assessing the cervix should be practiced by health care providers to acknowledge the likelihood of success and further proceed to select the appropriate method of induction.
- The Bishop's score should be documented.
- Care providers need to be aware of the fact that that there is higher failure rate in induction in women with an unfavorable cervix with a nulliparous women and thereby higher Caesarean section rate in nulliparous.

- Every woman should ideally have an ultrasound, preferably in the first trimester, to confirm gestational age.
- Institutions should have quality assurance programs and induction policies, including safety tools such as checklists, to ensure that inductions are performed only for acceptable indications.
- Women should be offered induction of labour between 41+0 and 42+0 weeks as this intervention may reduce meconium aspiration syndrome and perinatal mortality without increasing the Caesarean section rate.
- Women who desire to delay induction > 41+0 weeks should undergo twice-weekly assessment for fetal well-being.
- Intracervical Foley's catheters are acceptable agents that are safe both in the setting of a vaginal birth after Caesarean section and in the outpatient setting.
- Double lumen catheters may be considered a second-line alternative.
- Prostaglandins E_2 (cervical and vaginal) and misoprostol should not be used in the setting of vaginal birth after caesarean section as there is increased risk of uterine rupture.
- In case of ruptured membranes at term, vaginal prostaglandins E_2 may be considered.
- Misoprostol can be considered as an effective agent and safe for labour induction with intact membranes and on an inpatient basis.

Indications for induction

Induction is indicated when the risk of continuing the pregnancy, for the mother or the fetus, exceeds the risk associated with induced labour and delivery. The indication must be convincing, compelling, consented to, and documented. Based on

the recent SOGC Clinical Practice Guidelines on induction of labour, following are the indications for IOL[32]

High Priority

- Suspected fetal compromise
- Chorioamnionitis
- Preeclampsia ≥ 37 weeks
- Significant maternal disease not responding to treatment
- Significant but stable antepartum hemorrhage

Other indications

- Postdates (> 41+0 weeks) or post-term (> 42+0 weeks) pregnancy
- Uncomplicated twin pregnancy ≥ 38 weeks
- Diabetes mellitus (sugar if not controlled may indicate urgency)
- Alloimmune disease at or near term
- Intrauterine growth restriction (IUGR)
- Oligohydramnios
- Gestational hypertension ≥ 38 weeks
- Intrauterine fetal death (IUFD)
- PROM at or near term, GBS negative
- Logistical problems (history of rapid labour, distance to hospital)
- Intrauterine death in a prior pregnancy (Induction may be performed to alleviate parental anxiety, but there is no known medical or outcome advantage for mother or baby.)

Unacceptable indications

- Care provider or patient convenience
- Suspected fetal macrosomia (estimated fetal weight > 4000 gm) in non-diabetic women is an unacceptable indication because there is no reduction in the incidence of shoulder dystocia but twice the risk of CS.

Contra-indications[32]

Induction should be avoided if there is any danger hampering to labour or vaginal delivery. They include, but are not limited to the following:

- Prior classical or inverted T uterine incision
- Placenta or vasa previa or cord presentation
- Previous uterine rupture
- Abnormal fetal lie or presentation (e.g. transverse lie or footling breech)
- Significant prior uterine surgery (e.g. full thickness myomectomy)
- Pelvic structural deformities
- Active genital herpes
- Invasive cervical carcinoma

Whenever possible, for patients with prior uterine incision or surgery, the operative report or the opinion of the surgeon should be obtained and reviewed. Induction of labour using various methods may be associated with an increased risk of:

- Failure to achieve labour
- Operative vaginal delivery
- Caesarean section (CS)
- Cord prolapse with ARM

- Tachysystole with or without FHR changes
- Chorioamnionitis
- Inadvertent delivery of preterm infant in the case of inadequate dating
- Uterine rupture in scarred and unscarred uteri recommendations.

Pre-induction assessment

The goal of labour induction is to reduce the delivery time interval and to achieve a successful vaginal delivery, although induction exposes women to a higher risk of a CS than spontaneous labour. Before induction, there are several clinical elements that need to be considered to estimate the success of induction and minimize the risk of CS. Factors that have been shown to influence success rates of induction include the Bishop's score, parity (previous vaginal delivery), BMI, maternal age, estimated fetal weight, and diabetes.[32]

Bishop's score

The Bishop's score was developed in 1964 as a predictor of success for an elective induction. The initial scoring system used five determinants (dilatation, effacement, station, position, and consistency) that attributed a value of 0 to 2 or 3 points each (for a maximum score of 13). Bishop showed that women who had Bishop's score of > 9 were equally likely to deliver vaginally or if allowed to labour spontaneously or induced.[33]

In 1966, Burnett modified the scoring scheme (still in use and still known as the Bishop's score) so that each variable was assigned a maximum value of 2 points (for a maximum score of 10). [34]

A favourable pre-induction Bishop's score of >6 are predictive of a successful vaginal delivery. Initial studies were limited to parous women, but the score was later found also to be applicable to nulliparous women.[32]

Modified Bishop's Scoring System Used for Assessment of Inducibility[34]

Factor	Score		
	0	1	2
Dilatation (cms)	0	1-2	3-4
Length (cms)	>3	1-3	<1
Consistency	Firm	Medium	Soft
Position	Posterior	Mid	Anterior
Station	-3 or above	-2	Sp -1 or 0

Assessment of cervical status is fundamental for the clinician to estimate the likelihood of a successful vaginal delivery. Of the Bishop's score criteria for predicting successful induction, the most important is cervical dilatation, followed by effacement, station, and position, with the least important being consistency.[35, 36]

Several studies have shown an increased rate of failed induction and CS when women are induced with an unfavourable cervix.[37 - 40]

Xenakis's prospective study of 597 pregnancies stratified by low (4 to 6) and very low (0 to 3) Bishop's scores found the highest risk of CS in both nulliparous and parous women with scores of 0 to 3 versus those with a Bishop's score > 3. Even women with a score of 4 to 6 had a significantly higher risk of CS than those with spontaneous labour. The rate of failed induction was higher for women with a very low Bishop's score (0 to 3) in both nulliparous and parous women.[41]

The clinician may consider other non-modifiable factors in the pre-induction counseling period with the woman. Elevated BMI (> 40 kg/m^2), [37-39] maternal age > 35 years, [38,39] estimated fetal weight >4 kg, [37] and diabetes mellitus [37] have been shown to increase the CS rate when labour is induced. The presence of these negative predictive factors for a successful induction may play a role in the mutual decision to delay intervention and to allow for the opportunity of a spontaneous labour. These factors should not be used as a deterrent to vaginal delivery. In studies of women with a favourable cervix, the CS rate of induced pregnancies was equivalent to those managed expectantly.[42-44]

Several studies have compared the ability of the Bishop's score to predict successful labour induction with ultrasound assessment of the cervix with conflicting results.

Peregrine ET al.[45] reported cervical length > 1 cm to be a predictor for CS with induction of labour. In contrast, Hatfield et al.[46] found that cervical length was not predictive of successful labour induction, and Rozenberg et al.[47] reported that the Bishop's score was a better predictor of time interval from induction to delivery.

Using ultrasound to assess cervical ripeness, Bartha et al.[48] found that fewer women were induced with PG with no difference in outcomes. Fetal fibronectin and transvaginal ultrasound have been shown to predict successful induction, but neither has been shown to be superior to the Bishop's score.[32]

- Health care providers should assess the cervix (using the Bishop's score) to determine the likelihood of success and to select the appropriate method of induction.

- The Bishop score should be documented.

- Care providers need to consider that induction of women with an unfavourable cervix is associated with a higher failure rate in nulliparous patients and a higher Caesarean section rate in nulliparous and parous patients.

Cervical ripening

The success of induction depends largely on the consistency, compliance, and configuration of the cervix. The unripe cervix thus remains a well-recognized impedent to the successful induction of labour. Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected. Many methods have been devised to ripen the cervix and this process has been described as pre-induction cervical ripening.[21, 32]

Methods of cervical ripening and labor induction[21]

- Nipple stimulation, castor oil, herbs like blue/black choosy, evening primrose oil, red raspberyleaves, and homeopathic solutions like caulophyllum, cimicifuga, pulsatilla were used as methods for induction. Enemas, acupuncture, sweeping or stripping of the membranes, amniotomy were administered later. Few of them adopt mechanical dilatation like balloon catheters laminaria japonica, synthetic osmotic dilators for induction of labour. Pharmacologic hormonal preparations like prostaglandin E_2 (Cervidil, Prepidil, hospital-compounded gels), misoprostol (prostaglandin E_1 analogue [cytotec], mifepristone (RU-486), relaxin etc are being used now. Oxytocin is added for induction and augmentation of labour.

Considering cervical characteristics different methods have been used to improve its conditions prior to labor induction. It could be divided into biochemical or mechanical, respectively corresponding to the use of pharmacological substances through which different administration or to the use of devices crossing the cervical canal.

Prostaglandins

Many studies has tried to identify the role of prostaglandins (PGs) in the uterus, cervix and which of them would cause effects similar to physiological processes. As a result, it has been determined that PgE_2 would be the one causing cervical changes more similar to physiological ones.[24] Afterwards with the development of PgE_2 in form of a gel for cervical use, it became the choice Pg for cervical ripening and labor induction in developed countries. In practice, clinical use in developing countries has never been consistent, because of the high cost and thermoliability making commercialization and storage difficult.

Prostaglandins in general, specially the PgE2, have been vastly studied for clinical use, for cervical ripening and labor induction.[22,25,26] Nevertheless both the synthetic and natural ones, although they have been determined to be efficacious and safe, do have some inconveniences, such as stimulating uterine contractility when the initial aim is restricted to cervical change, use cannot be interrupted even in the occurrence of an undesirable effect, are associated to hyper stimulation of the uterus are not readily accessible in Brazil and are contraindicated in women with prior C-Section scars.

Prostaglandins act on cervix by dissolution of collagen fibrils and an increase in water content of the cervix. Furthermore, prostaglandins increase intracellular calcium levels, causing myometrial contractions. Prostaglandins are already found in the myometrium, deciduas and fetal membranes and increases during pregnancy. Earlier it was given by intramuscular and oral routes, nowadays its application is by locally, vaginally or intracervically. These routes are preferred because of patient acceptability with fewer side effects. The intracervical approach was found to be more effective than intravaginal route with less maternal side effects and intrapartum complications. As for undesirable effects, it includes fever, chills, vomiting and diarrhea, etc.

Overall, induction with prostaglandins was associated with an increase in successful vaginal delivery within 24 hours, a reduction rate of cesarean delivery but an increase in the risk of uterine tachysystole with FHR changes.[27] Prostaglandins should not be used in women with a myomectomy or prior cesarean delivery due to increased risk of uterine rupture.[28] After administration of prostaglandins for cervical ripening, monitoring FHR and uterine activity should be adopted[7].

Misoprostol, a methyl analogue PGE_1 has become the choice prostaglandin of more recent studies, for many reasons: easy to store because of thermo stability, lost effective, easy to administer, can be used in many ways with efficacy. Though the side effects include uterus hyper stimulation, the use of low doses (25 mcg) every four to six hours has been proved to be safe, reducing this effect.[27-29.] Furthermore, this is the only prostaglandin readily available in the domestic market.

Misoprostol is a PGE1 analogue, acts primarily by producing uterine contraction, can be administered orally and vaginally. Its advantage is its cheap, needs

no refrigeration. Studies at Wing el have determined that the safest regimen involves intravaginal administration of 25µg of misoprostol.WHO suggest that dosage of oral misoprostol of 25mcg every 2 hourly, and vaginal misoprostol of 25mcg every six hourly, show moderate degree evidence with strong recommendations for oral analogue of the drug, whereas it has weak recommendations for vaginal analogue. Some authors presume that because of 'First Pass Effect 'of misoprostol, misoprostol when administered vaginally, was more effective than orally route when same dosage was use. So that the dose of oral route of misoprostol was increased to overcome the bioavailability differences in vaginal versus oral preparations. Also in intracervical route the dose required for the misoprostol was less as it reaches the target organ directly, thus maximizing the local effect and systemic absorption is reduced. Even though misoprostol has risk factor like uterine e hyper stimulation and tachysystole and require monitoring, those risks were less as reported by Wing et al. Study.

Estrogen is a hormone in the ripening of cervix. A variety of estrogen preparations have been used (such as tablets, gels, creams and infusions).Most studies have natural estrogen analogues such as estradiol. Estradiol has direct effect on the cervix causing the cervix to soften without painful contractions which could be due to increased collagenolytic enzymes activity as they are required for softening if cervix. Such effect on cervix has been demonstrated in few studies. It could also o be due to increase level of estradiol in systemic circulation that could lead to increase in number of gap junctions in the myometrium or could be by direct oxytocic effect.

Oxytocin: Du Vigneud synthesized Syntocinon from the nano–peptide oxytocin in the 1950. It is used in induction and augmentation of labour by intravenous infusions. It is more frequently used as an adjunct with prostaglandins

when cervix is unfavourable. In favourable cervix most obstetricians perform low amniotomy followed by oxytocin immediately or within an hour, or after 4- 6 hours in a titrated infusion dose.

Amniotomy: a procedure involving puncturing of membranes and release of amniotic fluid below the presenting part of fetus in the maternal pelvis. It evokes posterior pituitary to release oxytocin via Ferguson reflex which later release prostaglandins into uterine vein, enhancing uterine activity.

In a study conducted by Ellora Dasgupta and Gurneesh Singh 2012,.they reported that doses of misoprostol required for cervical ripening ($p=0.017$), time required for cervical ripening ($p=0.042$), time required for vaginal delivery cases ($p = 0.047$) were significantly less in combined misoprostol and estradiol group than misoprostol only group. Hence, combination of misoprostol with vaginally administered estradiol seems to be safe, well effective for cervical ripening and induction of labour

In 2004, endocrinology study both in vitro and in vivo suggest important role for EP4 receptor in mediating prostaglandin ripening effects. Prostaglandin induces glycoaminoglycans (GAGs) synthesis by human cervical fibroblasts via EP4 receptors.

In Cochrane review 2008, estrogen alone was used as an inducing agent and compared with prostaglandins. There were insufficient data to make any meaningful conclusions when comparing estrogens alone with prostaglandins and to assess if estrogen alone was effective in inducing labour. So they should only be used as a part of randomized control trials as there are alternative effective options for inducing labour.

In a study done by M Raksha andArun Rao showed that there was significant reduction in the number of misoprostol doses required in cervical ripening in combined misoprostol and vaginal estradiol than misoprostol group alone. There was also significant reduction in the time interval required for cervical ripening in the combined group than misoprostol alone and it was statistically significant ($p < 0.001$).[3]

Luther ER conducted a double-blind, randomized study to evaluate if estrogen "priming" of the unripe cervix followed by prostaglandin induction of labor would have an addictive effect on cervical ripening for induction of labour and if it would benefit the success rate of induction. It involved 100 near-term women with (Bishop's score ≤ 4) who received an intramuscular injection of either 10 mg of estradiol valerate or a placebo 48 hours prior to induction of labor with oral prostaglandin E1. The serial changes in Bishop Scores were very identical in both groups. The success induction rate in the study group (69.8%) versus the control group (61.9%) was statistically insignificant.

The duration interval of labor in the study group was 9.9 +/- 4.1 hours was statistically not significant with control group being 9.1 +/- 3.7 hours. This study concluded that 10 mg of estradiol valerate had no deleterious effect on the unripe cervix near term and did not show a synergistic effect with prostaglandins during induction of labor.[2]

Limitations: There is insufficient data to quantify the safety and effectiveness of vaginal estradiol tablet and intracervical prostaglandins combinations as an inducing agent in labour induction. Till date, limited number of studies has compared combination of prostaglandins with vaginal estradiol and prostaglandins alone. Also the vaginal tablet estradiol is expensive and not available in India. Dinoprostone drug requires refrigeration and is also costly.

MATERIALS AND METHODS

The present study was conducted in the department of Obstetrics and Gynaecology, KLES Dr.Prabhakar Kore Charitable Hospital, Belagavi during the period of May 2015 to April 2016.

Study Design

The study design was a Hospital based prospective randomized comparative study.

Study period and duration

The present study was conducted from May 2015 to April 2016.

Place

This study was conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi, a teaching hospital attached to Jawaharlal Nehru Medical College, Belagavi.

Source of data

Singleton pregnant women ≥ 36 weeks admitted in labour room at KLES Dr. Prabhakar Kore Charitable Hospital fulfilling inclusion criteria for induction of labour under the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi were involved.

Sample size

A total of 120 pregnant women with singleton pregnancy having ≥ 36 weeks of gestation, cephalic presentation, Bishop's score ≤ 4, intact membrane, history of no

previous Cesarean section eligible for my study for induction of labour were randomized into two groups of 60 each and studied.

Sampling procedure

The sample size was calculated by considering type I error rate $\alpha = 0.05$ and type error $\beta = 0.02$ and power of 120% sample size was determined based on the following formula.

$$n = \frac{2 (Z_\alpha + Z_\beta)^2 \times (S_1^2 \times S_2^2)}{(x_1 - x_2)^2}$$

Where: $Z_\alpha = 1.96$

$Z_\beta = 0.84$

x_1 (mean) $= 11.28$

x_2 (mean) $= 7.6$,

s_1 = {standard deviation (SD1)} = 4.2

s_2 = {standard deviation (SD2)} = 3,

Therefore,

$$n = \frac{2 (1.96 + 0.84)^2 \times (4.2^2 \times 3^2)}{(11.28 - 7.6)^2}$$

$n = 118.21 \sim 120$

Hence, sample size was taken as 60 in each group totaling a sum of 120 cases.120 pregnant women who fulfilled the selection criteria for induction of labour were randomized into 60 each belonging to either group of prostaglandins alone or combined prostaglandins and estradiol group.

Selection criteria

Inclusion

- Gestational age ≥36 weeks.
- Singleton pregnancy
- Cephalic presentation
- Bishop's score less than or equal to 4
- With intact membrane

Exclusion

Pregnant women with;

- Previous LSCS or any scar on uterus.
- PROM/ PPROM
- Placenta praevia

Ethical clearance

The study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Belagavi.

Consent form

Pregnant women fulfilling selection criteria at Department of Obstetrics and Gynaecology at KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi were briefed about the nature of the study, details of the treatment and a written informed consent was obtained after being explained about the risks and benefits of the study. They were given free will to withdraw at any time during the study if they desire to do so (Annexure I).

Data collection

Patients were interviewed for demographic characteristics and obstetric history. Data regarding age, obstetric history and period of gestation were noted. These women were evaluated for Preinduction cervical status based on modified Bishop's Score. If Preinduction Bishop's Score ≤ 4, they were included for the study and the findings were recorded on a predesigned and pretested proforma (Annexure II).

Randomisation

The selected women were randomized into two groups by simple randomisation using an opaque sealed envelope, into either without vaginal estradiol **Group A:** GROUP PGE2–Prostaglandin E2 gel intracervically alone group or **GROUP B:** PGE2+ E (Estradiol)- Combined Prostaglandin E2 gel intracervically and 50µg of estradiol tablet intravaginal group.

Group PGE2

In this group pregnant women underwent induction of labour using intracervical prostaglandin E2 gel only, every sixth hourly for a maximum of three doses of prostaglandin till cervical ripening is achieved.

Group PGE2 and Estradiol(PGE2+ E)

In this group pregnant women underwent induction of labour using vaginal estradiol tablet 50µg with intracervical prostaglandin E2 gel in the first dose followed by prostaglandin E2 gel intracervically alone in the subsequent next two doses each dose after six hours apart, thereby maximum of total three doses till cervical ripening is achieved.

Induction of laborwas performed by the treating obstetrician.Pre-induction Bishop's score was assessed and women who had Bishop's score ≤ 4 were included.Clinical pelvic assessment was done to rule out cephalopelvic disproposition. Non stress test was taken for at least 20 minutes before and 30 minutes after the induction.After randomisation, they were either induced using group A protocol of prostaglandin gel (dinoprostone) alone, 0.5mg intracervically every sixth hourly of maximum three doses till cervical ripening was achieved or, group B protocol was followed using combined prostaglandin gel 0.5mg intracervically and estradiol 50µg tablet vaginally inserted in the posterior fornix in the first dose followed by prostaglandin gel 0.5mg intracervically in the subsequent next two doses every sixth hourly for total of maximum three doses till cervical ripening was achieved. Women were advised to be at bed for at least half an hour after induction.

Bishop's Score were assessed prior to every induction and whenever warranted if earlier. Pregnant women was considered to achieve established active labour if cervical dilatation more than 4 cm in primigravida and 3cm in multigravida and when there was 3-4 contractions lasting for 10 seconds in 10 minutes. If spontaneous rupture of membrane occurred before cervix had become favourable they were excluded. If rupture of membrane occurred spontaneously after active labour, colour of the liquor was noted. Meconium stained liquor (MSL) if present, was noted and continuous cardiotocography (CTG) was monitored. If there were any fetal distress due to pathological trace on CTG associated with MSL or late decelerations trace persisting for >45 minutes, patient was taken for Cesarean Section.

Side effects like hyperstimulation, uterine rupture, nausea, vomiting, MSL, fetal distress were monitored.In this study we have taken uterine hyperstimulation as

series of single contractions lasting for two minutes or more, or frequency of five or more contractions lasting for ten minutes for half an hour. If hyperstimulation occurred then further doses of prostaglandins were not given. Theneed for administration of oxytocin along with prostaglandins was also studied as oxytocin was used if adequate contractions were not achieved. Mode of delivery was noted. Failed induction was considered when pregnant women have not attained a Bishop's Score of ≥ 6 after eighteen hours of initial induction. Fetal outcome was monitored for birth asphyxia, Apgar score in 1 minute and 5minutes and requirement for NICU admission.

Intervention

Outcome variables

All the women were assessed for Bishop's score prior to every induction. Successful cervical ripening was considered if Bishop's Score was more than or equal to 8 after 3 doses of induction. Failed induction was considered when the women did not go into labour or the cervix has not ripen i.e., when Bishop's Score is ≤ 6 at the end of the chosen protocol and/or after 18 hours after administration of drug from first induction.

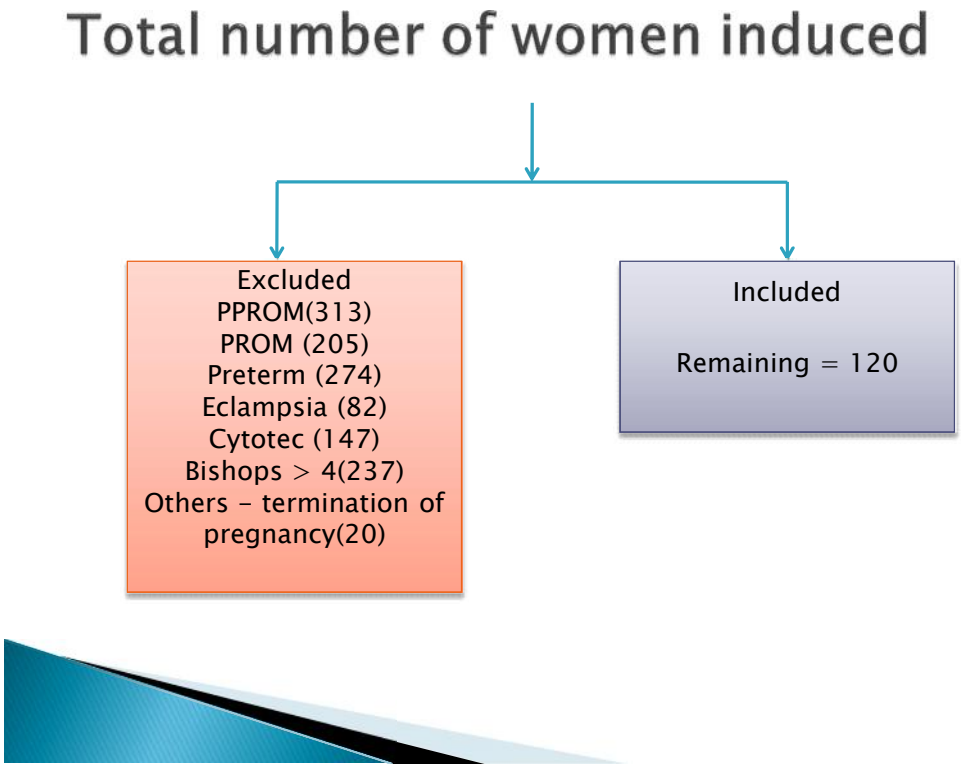
The pregnant women were assessed for following outcomes.

- Induction initiation to cervical ripening interval.
- Induction initiation to time taken for establishment of active labour
- Induction initiationto delivery interval
- Mode of delivery
- Indications for LSCS
- Side effects : hyperstimulation, uterine rupture, nausea, vomiting

- Fetal outcome
    - Birth weight of babies
    - Apgar score in one minute and after 5 minutes
    - NICU admission

Statistical analysis

Data obtained was coded and entered into the Microsoft Excel Spreadsheet. The data was analysed using statistical software SPSS 20. The categorical data was expressed in terms of frequencies and percentages while continuous data was expressed as mean ± standard deviation (SD). The two groups were compared using either chi-square test or Fishers exact test for categorical data and independent sample‘t’ test was used to compare the means of different parameters. A ‘p’ value of less than or equal to 0.05 at 95 Confidence interval was considered as statistically significant.


Total number of women induced
Excluded
PPROM(313)
PROM (205)
Preterm (274)
Eclampsia (82)
Cytotec (147)
Bishops > 4(237)
Others – termination of pregnancy(20)
Included
Remaining = 120

RESULTS

The present one year Hospital based prospective randomized comparative study was conducted from May 2015 to April 2016 in the department of Obstetrics and Gynaecology, in a tertiary care hospital, Belgaum. Pregnant women ≥ 36 weeks of gestations who fulfilled the eligibility criteria for induction of labour were enrolled and 120 women were randomized.

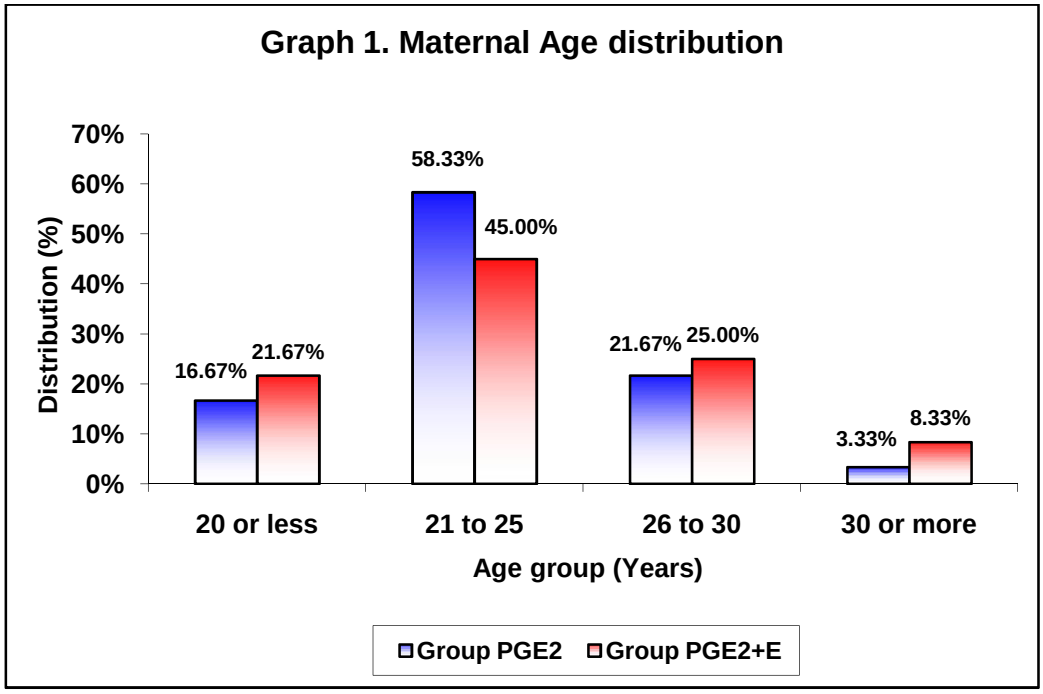
These women were randomised into two groups of 60 each, as Group PGE2 (induction with intracervical prostaglandin E2 gel only every 6^{th} hourly of maximum three doses) and Group PGE2 and vaginal estradiol (induction with 50µg estradiol tablet vaginally with intracervical prostaglandin E2 gel in the first dose followed by prostaglandin E2 gel intracervically alone in further next two doses, sixth hourly interval of maximum three doses in total till cervical ripening is achieved).

The data obtained was tabulated on excel spreadsheet and analysed using SPSS version 20.00 statistical software. The final results and observations were tabulated as below.

Table 1. Maternal Age distribution

Age group (Years)	Group PGE2 (n = 60)		Group PGE2+E (n = 60)	
	Number	**Percentage**	**Number**	**Percentage**
20 or less	10	16.67	13	21.67
21 to 25	35	58.33	27	45.00
26 to 30	13	21.67	15	25.00
30 or more	2	3.33	5	8.33
Total	**60**	**100.00**	**60**	**100.00**

p = 0.438



In the present study most of the women were aged between 21 to 25 years in group in PGE2 (58.33%) as well as in group PGE2 and estradiol (45%). However the age distribution in group PGE2 and group PGE2 and estradiol was comparable (p=0.438).

Table 2. Mean Maternal Age

Variables	Group PGE2 (n=60)		Group PGE2 + E (n=60)		p value
	Mean	SD	Mean	SD	
Age (Years)	23.67	3.05	24.53	3.98	0.206

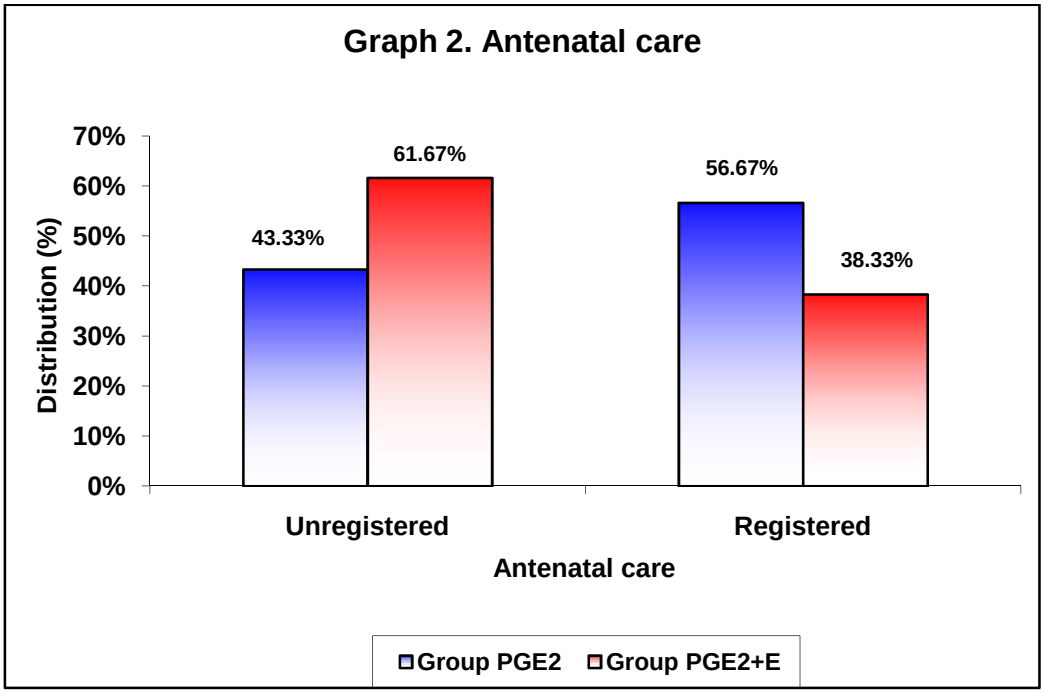
p = 0.206

In this study the mean maternal age in group PGE2 was 23.67 ± 3.05 years compared to 24.53 ± 3.98 years in group PGE2 and estradiol, however the difference observed was statistically not significant (p = 0.206)

Table 3. Antenatal care

Antenatal care	Group PGE2 (n = 60)		Group PGE2 + E(n = 60)	
	Number	**Percentage**	**Number**	**Percentage**
Unregistered	26	43.33	37	61.67
Registered	34	56.67	23	38.33
Total	**60**	**100.00**	**60**	**100.00**

p = 0.577

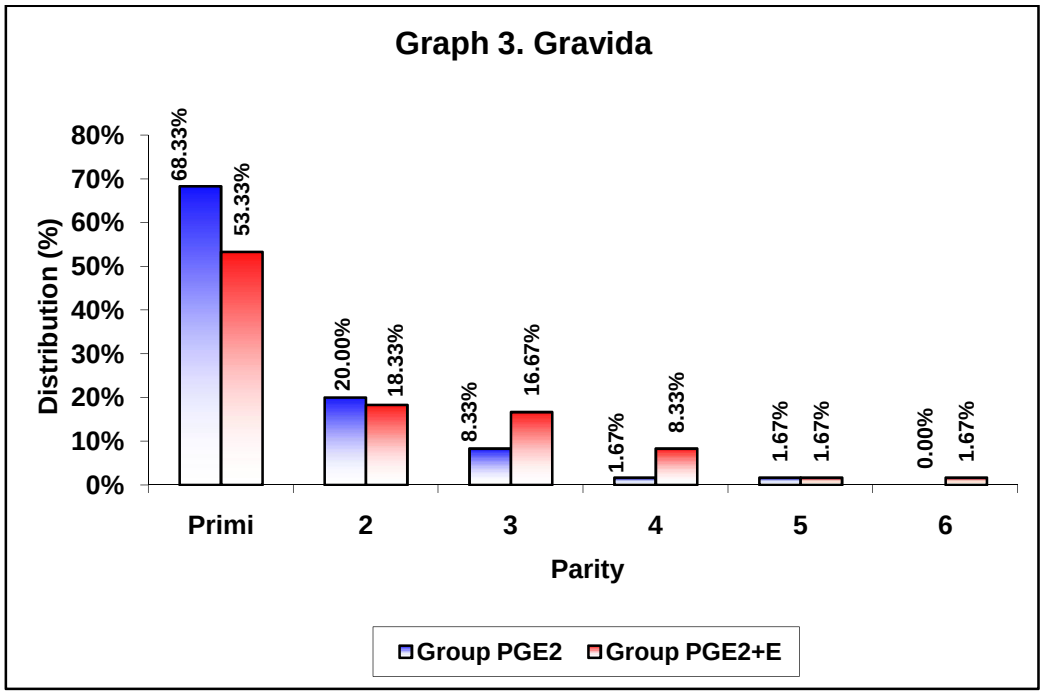


In the present study 56.67% of the women in group PGE2 and 38.33% in group PGE2 and estradiol was registered case for antenatal care. However both the groups were comparable in terms of antenatal care (p = 0.577).

Table 4. Gravida

Gravida	Group PGE2 (n=60)		Group PGE2 + E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Primi	41	68.33	32	53.33
2	12	20.00	11	18.33
3	5	8.33	10	16.67
4	1	1.67	5	8.33
5	1	1.67	1	1.67
6	0	0.00	1	1.67
Total	**60**	**100.00**	**60**	**100.00**

p= 0.210



In the present study most of the women in group PGE2 (68.33%) as well as PGE2 and estradiol (53.33%) were primigravida (p=0.210) and hence was comparable.

Table 5. Parity

Parity	Group PGE2 (n=60)		Group PGE2 +E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Primigravida	41	68.33	32	53.33
Multigravida	19	31.66	28	46.66
Total	**60**	**100.00**	**60**	**100.00**

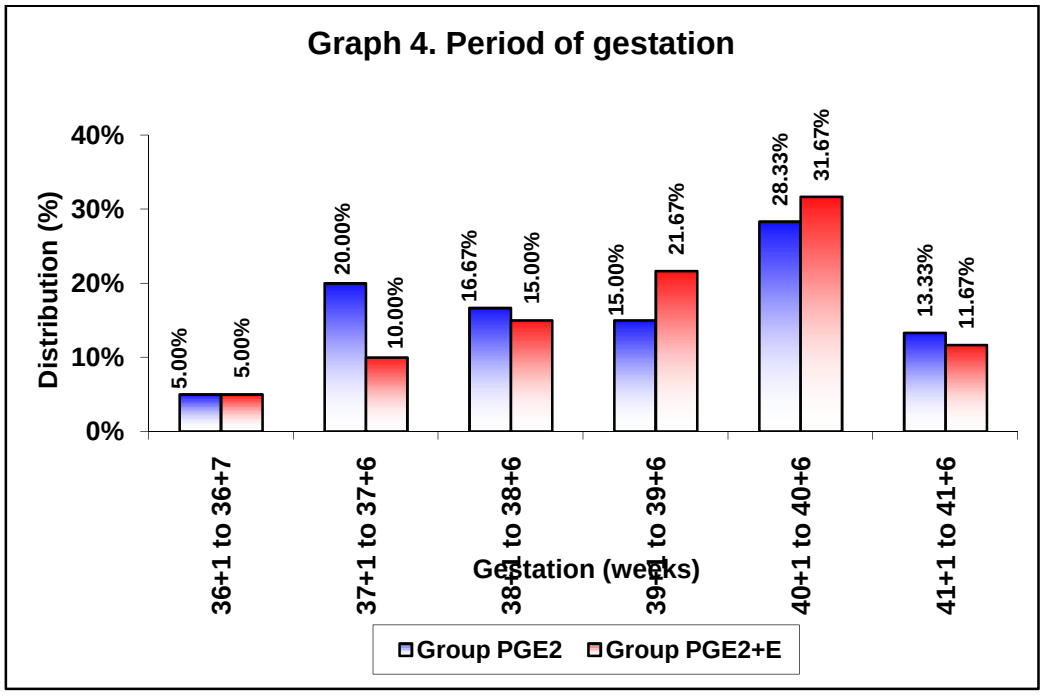
p = 0.092

Most of the women in both the groups belonged to primigravida group (73/120) Parity distribution was not significant. However they were comparable.

Table 6. Period of gestation

Gestation (weeks)	Group PGE2 (n=60)		Group PGE2 +E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
36+1 to 36+6	3	5.00	3	5.00
37+1 to 37+6	12	20.00	6	10.00
38+1 to 38+6	10	16.67	9	15.00
39+1 to39+6	9	15.00	13	21.67
40+1 to 40+6	17	28.33	19	31.67
41+1 to 41+6	9	13.33	10	11.67
Total	**60**	**100.00**	**60**	**100.00**

p = 0.659



In this study 28.33% of the women from group PGE2 and 31.67% from group PGE2 and estradiol had gestational age between 40+1 to 40+6 weeks (p=0.659) and hence were comparable.

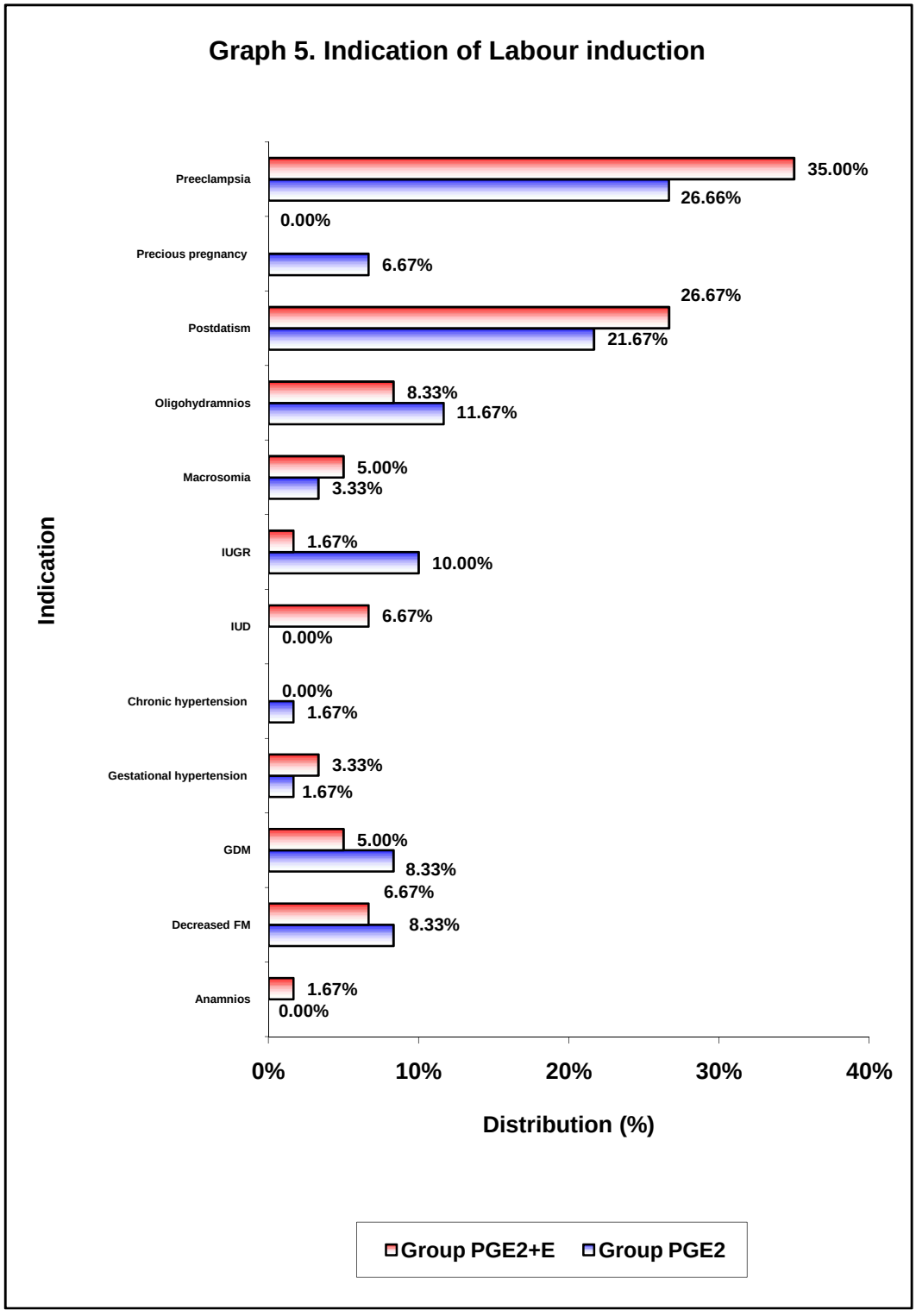
Table 7. Mean period of gestation

Variables	**Group PGE2 (n=60)**		**Group PGE2 +E (n=60)**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Period of gestation (weeks)	39.24	1.47	39.54	1.51	**0.252**

In this study the mean period of gestation in group PGE2 was 39.24 ± 1.47 weeks compared to 39.54 ± 1.51weeks in group PGE2 and estradiol but the difference observed was statistically not significant (p = 0.252).

Table 8. Indications for labour induction

Indications for labour induction	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Anamnios	0	0.00	1	1.67
Decreased Fetal Movement	5	8.33	4	6.67
GDM	5	8.33	3	5.00
Gestational Hypertension	1	1.67	2	3.33
Chronic Hypertension	1	1.67	0	0.00
IUFD	0	0.00	4	6.67
IUGR	6	10.00	1	1.67
Macrosomia	2	3.33	3	5.00
Oligohydramnios	7	11.67	5	8.33
Postdatism	13	21.67	16	26.67
Precious Pregnancy	4	6.67	0	0.00
Preeclampsia	16	26.66	21	35.00
Total	**60**	**100.00**	**60**	**100.00**

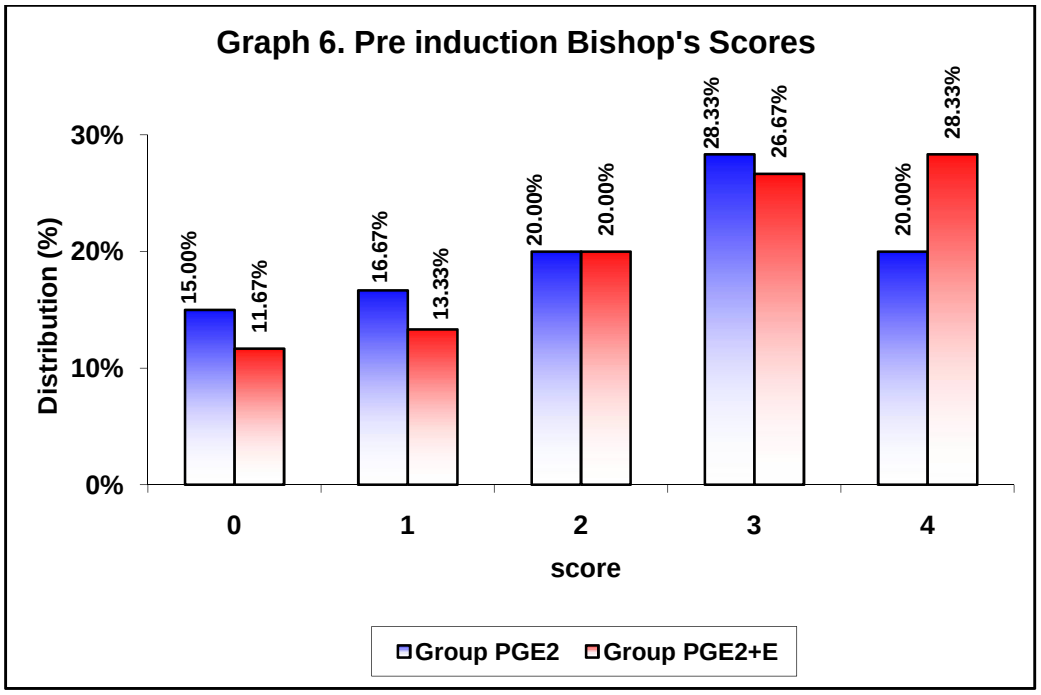


In the present study the commonest indication for induction of labour was preeclampsia in group PGE2 (26.66%) as well as group PGE2 and estradiol (35%) followed by postdatism. The other causes are as shown in Table 8 and graph 5.

Table 9. Pre induction Bishop's Scores

Score	Group PGE2 (n=60)		Group PGE2 +E(n=60)	
	Number	**Percentage**	**Number**	**Percentage**
0	9	15.00	7	11.67
1	10	16.67	8	13.33
2	12	20.00	12	20.00
3	17	28.33	16	26.67
4	12	20.00	17	28.33
Total	**60**	**100.00**	**60**	**100.00**

x^2 = 1.365 DF (degree of freedom) = 4 p = 0.850



In the present study preinduction Bishop's Score of 3 and 4 were noted maximum in both the groups i.e., 28.33% and 20% respectively in PGE2 group and in PGE2 and estradiol group as 26.67% and 28.33%. Preinduction Bishop's Score of 2 were similar in both study groups to be 20%. . Preinduction Bishop's Score of 1 was 16.67% in PGE2 group and 13.33% in combined group. Preinduction Bishop's Score of zero were least in both study groups as 15% and 11.67% in combined study group. However, the distribution of women based on preinduction Bishop's Scores was almost equal and was not significant ($p = 0.850$).

Table 10. Mean preinduction Bishop's Score

Variables	Group PGE2 (n=60)		Group PGE2+E (n=60)		p value
	Mean	SD	Mean	SD	
Bishop's Score	2.19	1.37	2.45	1.35	0.270

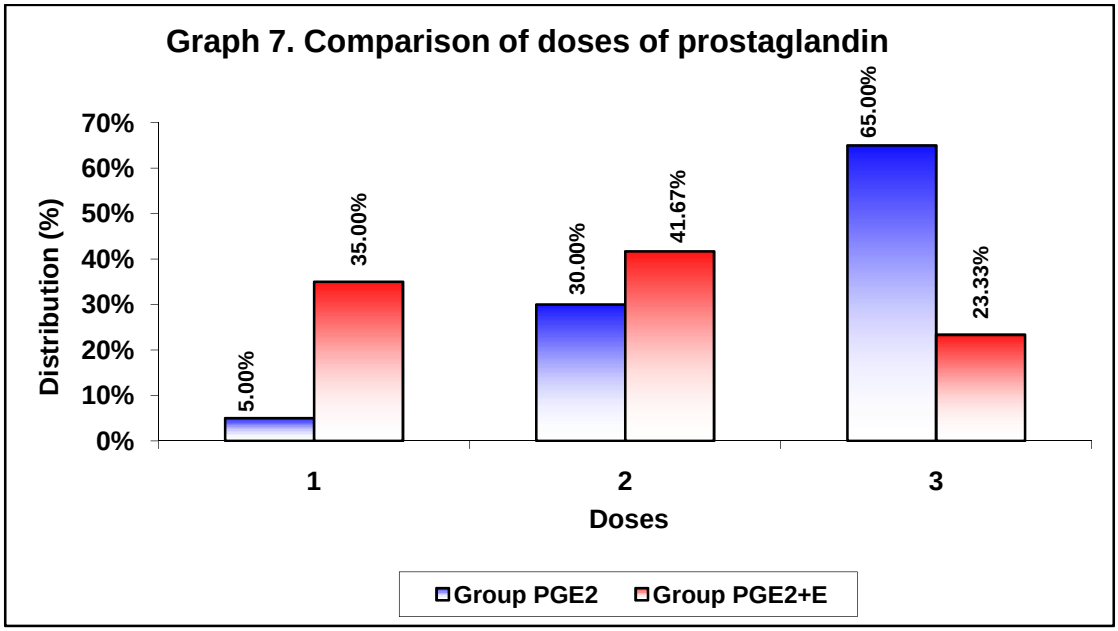
p = 0.270

In this study the mean preinduction Bishop's score in group PGE2 was 2.19 ± 1.37 compared to 2.45 ± 1.35 in group PGE2 and estradiol but the difference observed was statistically not significant (p = 0.270).

Table 11. Comparison of doses of prostaglandins

Doses	Group PGE2 (n=60)		Group PGE2 +E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
1	3	5.00	21	35.00
2	18	30.00	25	41.67
3	39	65.00	14	23.33
Total	**60**	**100.00**	**60**	**100.00**

x^2 =26.432 DF=2 p<0.001



In the present study 65% of the women in group PGE2 required three doses of prostaglandins compared to 23.33% in group PGE2 and estradiol for the cervix to become favourable. In group PGE2 and estradiol, most of the women (41.67%) received two doses of prostaglandins. Three pregnant women from group PGE2 required only one dose of prostaglandin while 21 pregnant women from combined group required only one dose of prostaglandin for the cervix to become favourable. This difference was statistically significant ($p < 0.001$).

Table 12. Mean number of doses of prostaglandins

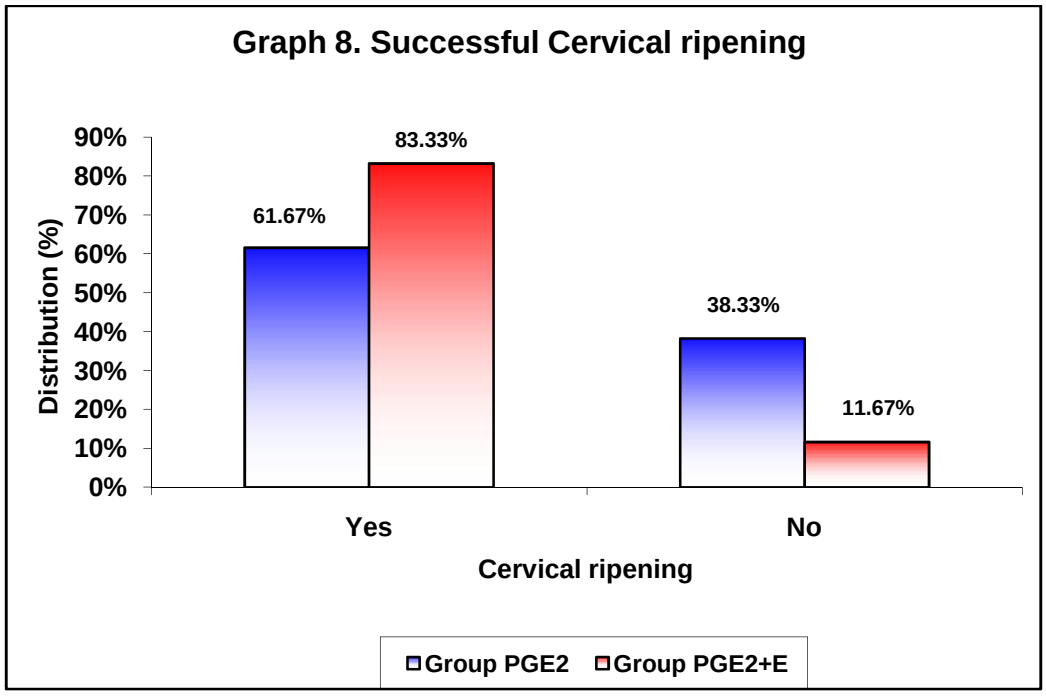
Variables	Group PGE2 (n=60)		Group PGE2 +E (n=60)		p value
	Mean	**SD**	**Mean**	**SD**	
Number of doses of prostaglandins	2.62	0.59	1.86	0.76	**< 0.001**

In this study the mean number of doses of prostaglandin administered were significantly higher in PGE2 group (2.62 ± 0.59) compared to that of combined PGE2 and estradiol group (1.86 ± 0.76) which was statistically significant ($p < 0.001$).

Table 13. Successful cervical ripening

Successful cervical ripening	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	37	61.67	53	88.33
No	23	38.33	7	11.67
Total	**60**	**100.00**	**60**	**100.00**

x2 = 11.378 **DF=1** **p = 0.001**



In the present study the significantly higher number of women had successful cervical ripening in group PGE2 and estradiol (83.33%) compared to group PGE2 (61.67%) which was statistically significant (p=0.001). 38.33% (30/120) of women in both the groups had failed cervical ripening

Table 14. Mean time interval

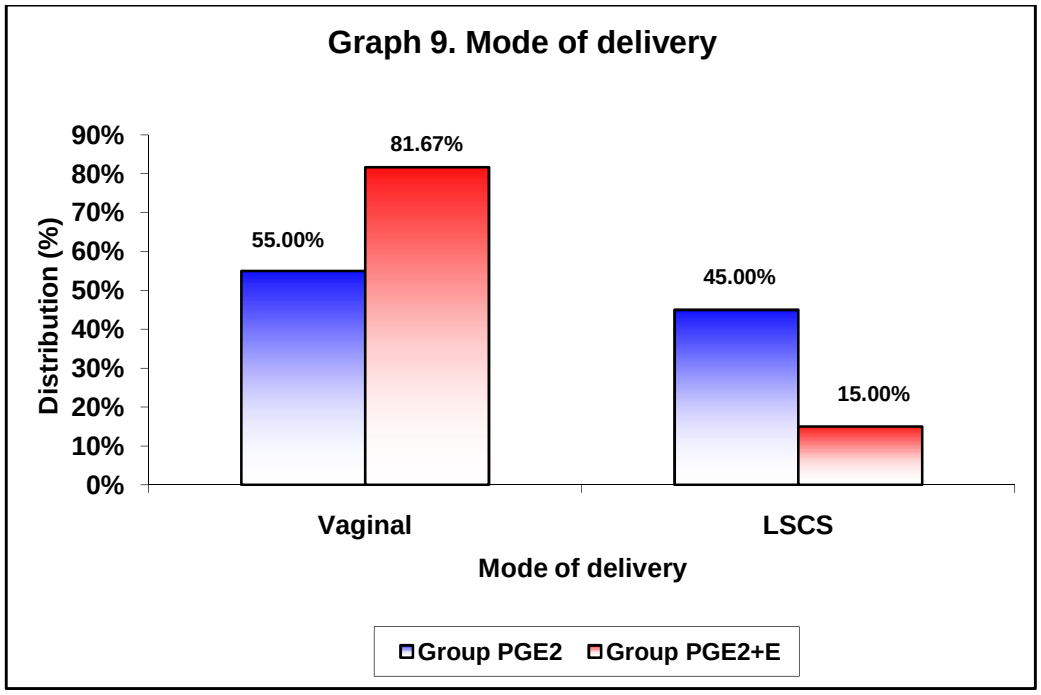
Variables	Group PGE2 (n=60)		Group PGE2+E (n=60)		p value
	Mean	**SD**	**Mean**	**SD**	
Induction to cervical ripening interval (hours)	12.88	4.91	8.92	5.07	**<0.001**
Induction to active labour interval (hours)	16.97	4.93	11.02	4.72	**<0.001**
Time for from induction to delivery (Hours)	21.97	3.83	13.14	4.98	**<0.001**

In this study there is significantly longer mean interval time noted for induction to cervical ripening (12.88 ±4.91 vs. 8.92 ± 5.07; p<0.001), induction to active labour (16.97 ±4.93 vs. 11.02 ± 4.72; p<0.001) and induction to delivery time (21.97 ± 3.83 vs. 13.14 ± 4.98; p<0.001) in group PGE2 compared to combined PGE2 and estradiol group. Hence they were statistically significant in each time interval.

Table 15. Mode of delivery

Mode of delivery	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Vaginal	33	55.00	51	81.67
LSCS	27	45.00	9	15.00
Total	**60**	**100.00**	**60**	**96.67**

x^2 = 12.1 DF = 2 p = 0.001

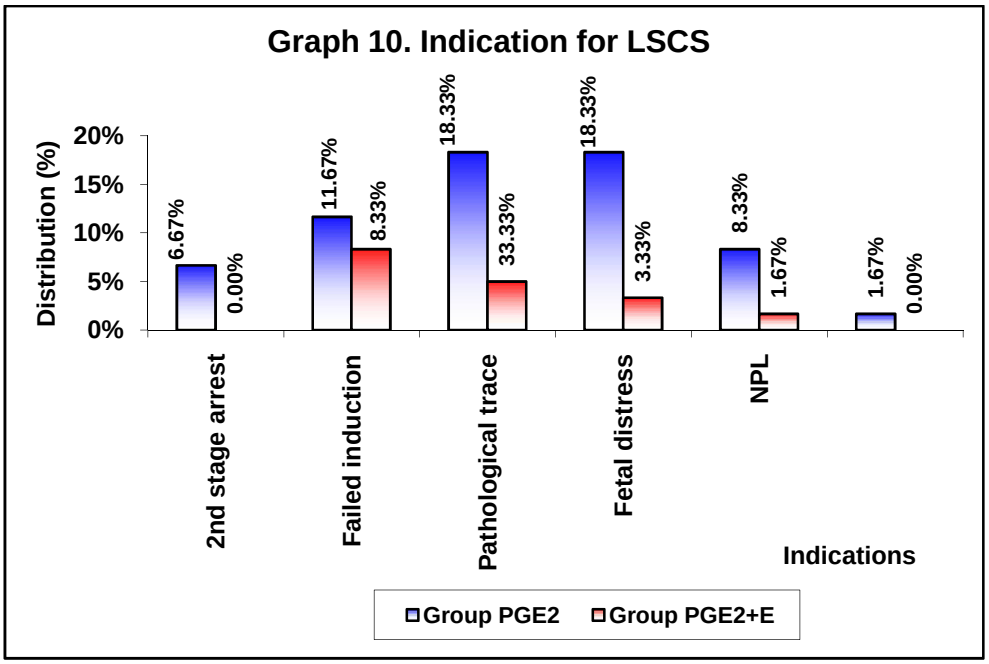


In the present study higher number of vaginal deliveries were noted in PGE2 and vaginal estradiol group significantly compared to PGE2 alone group (81.67% vs. 55%) and hence was statistically significant (p = 0.001).

Table 16. Indication for LSCS

Indications	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
2nd stage arrest	4	14.81	0	0.00
Failed induction	13	48.14	5	55.55
Pathological trace	5	18.51	3	33.33
Non progress of labour	5	18.51	1	11.11
Total	**27**	**100.00**	**9**	**100.00**

x^2 = 2.30 **DF = 3** **p = 0.513**

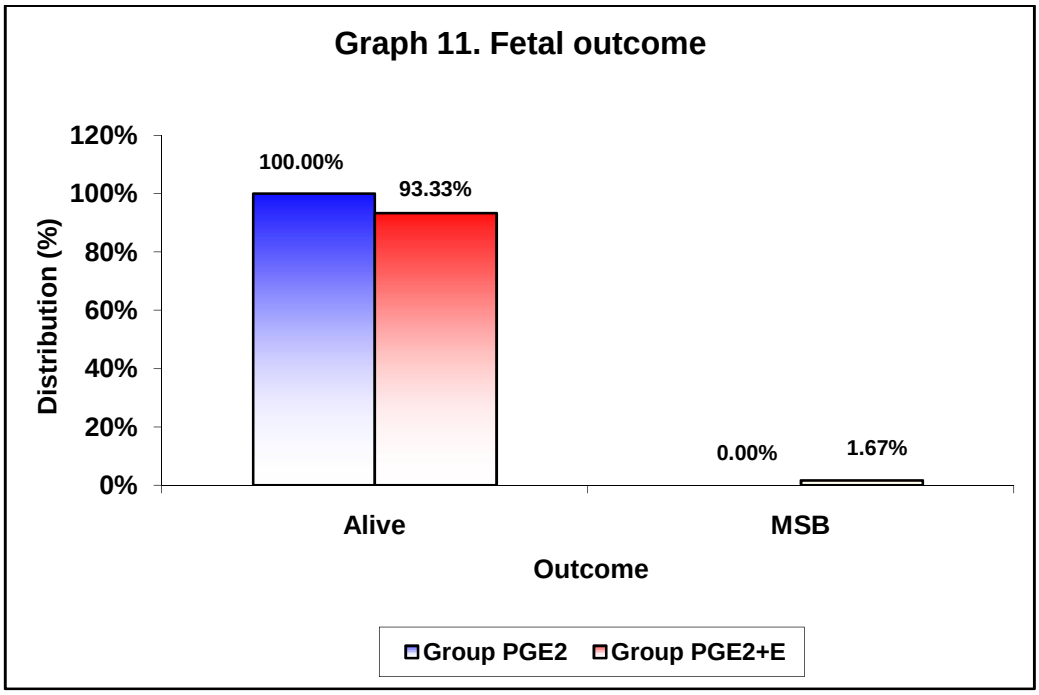


In this study commonest indication for LSCS was failed induction (total number = 18) in both the groups. PGE2 had (13/27) failed induction while in combined group it was (5/9). However this difference was statistically not significant (p=0.513).

Table 17. Fetal Outcome

Fetal outcome	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Alive	60	100.00	56	93.33
MSB (macerated still birth)	0	0.00	4	6.67
Total	**60**	**100.00**	**60**	**100.00**

p = 0.042

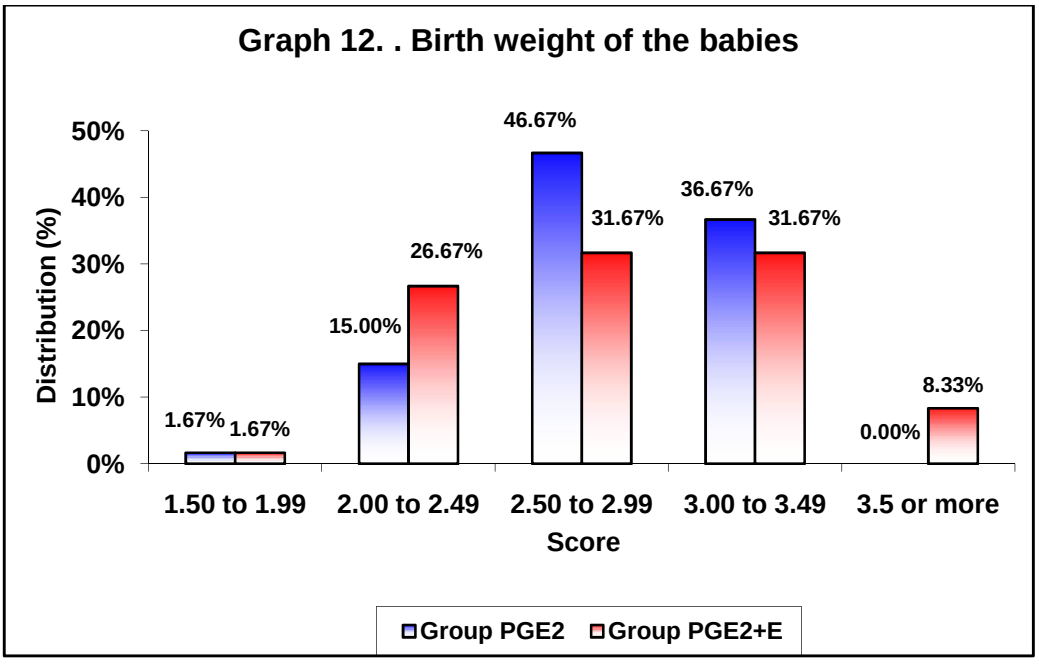


In the present study with regard to fetal outcome, all the women had live birth babies excluding four intrauterine death (MSB) babies which were 1.67%

Table 18. Birth weight of the babies

Birth weight (Kgs)	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	Percentage	Number	Percentage
1.50 to 1.99	1	1.67	1	1.67
2.00 to 2.49	9	15.00	16	26.67
2.50 to 2.99	28	46.67	19	31.67
3.00 to 3.49	22	36.67	19	31.67
3.5 or more	0	0.00	5	8.33
Total	**60**	**100.00**	**60**	**100.00**

p = 0.042



In these study babies of birth weight of babies between 2.50 to 2.99 kg was noted maximum with 46.67% in group PGE2 compared to 31.67% in group PGE2 and estradiol. This difference was statistically significant (p = 0.042).

Table 19. Mean birth weight of babies

Variables	Group PGE2 (n=60)		Group PGE2+E (n=60)		p value
	Mean	**SD**	**Mean**	**SD**	
Birth weight (kgs)	2.88	0.38	2.89	0.46	0.823

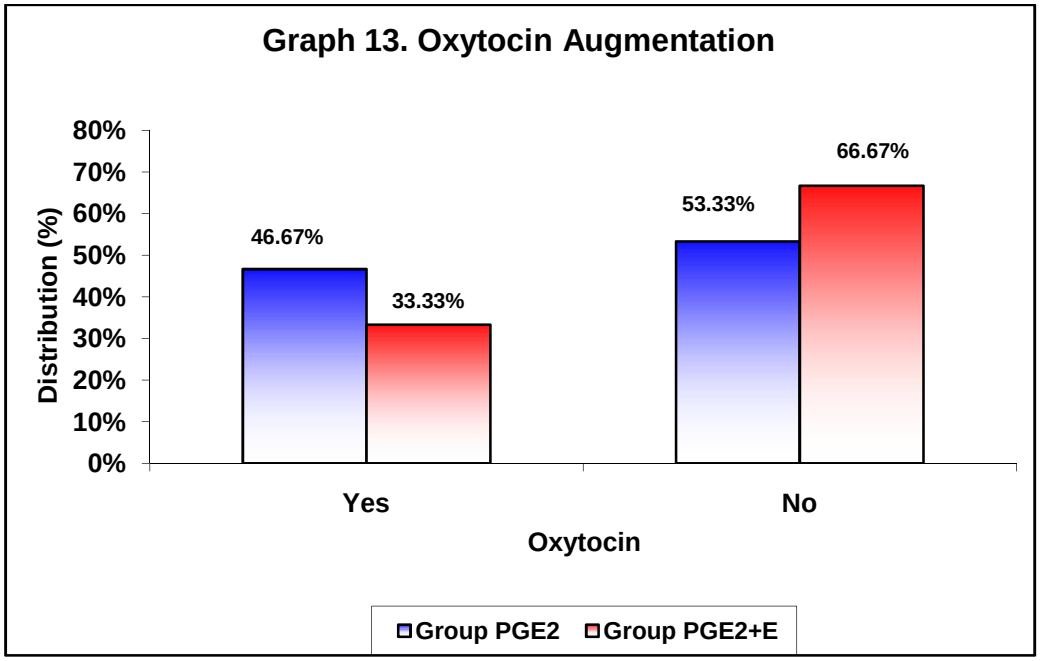
p = 0.0823

In this study the mean birth weight of babies was comparable in group PGE2 (2.88 ± 0.38) and in group PGE2 and estradiol (2.89 ± 0.46) (p = 0.823).

Table 20. Need for Oxytocin Augmentation

Oxytocin Augmentation	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	28	46.67	20	33.33
No	32	53.33	40	66.67
Total	**60**	**100.00**	**60**	**100.00**

x^2 = 2.22 **DF = 1** **p = 0.136**

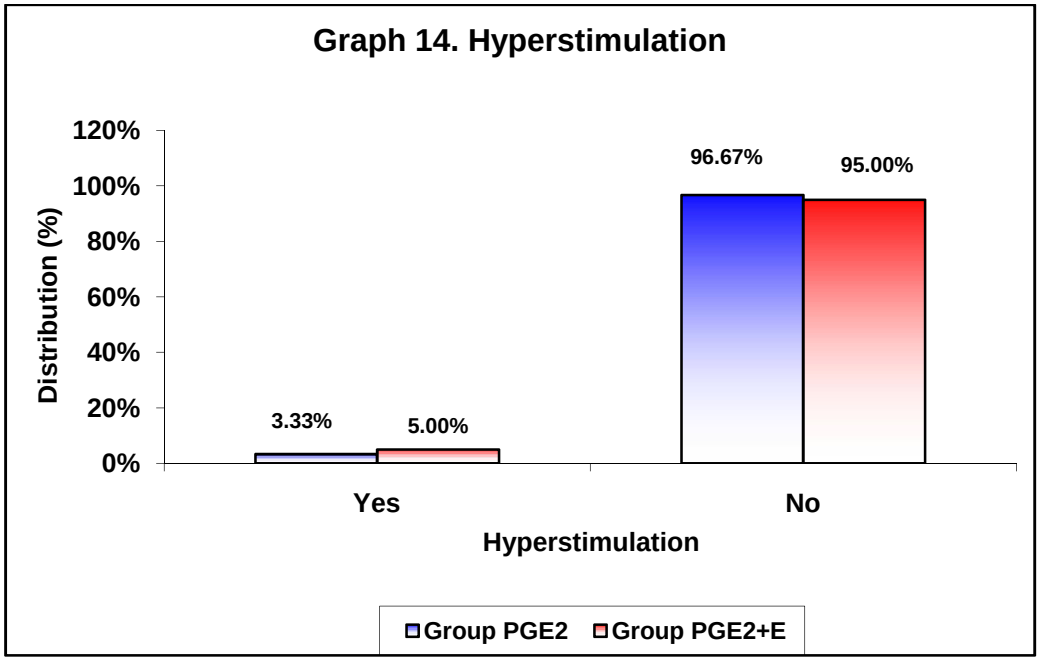


In the present study 46.67% of the pregnant women in group PGE2 had oxytocin augmentation compared to 33.33% in group PGE2 and estradiol but this difference was statistically not significant (p = 0.136).

Table 21. Hyperstimulation

Hyperstimulation	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	2	3.33	3	5.00
No	58	96.67	57	95.00
Total	**60**	**100.00**	**60**	**100.00**

x^2 = 0.209 DF=1 p = 0.500

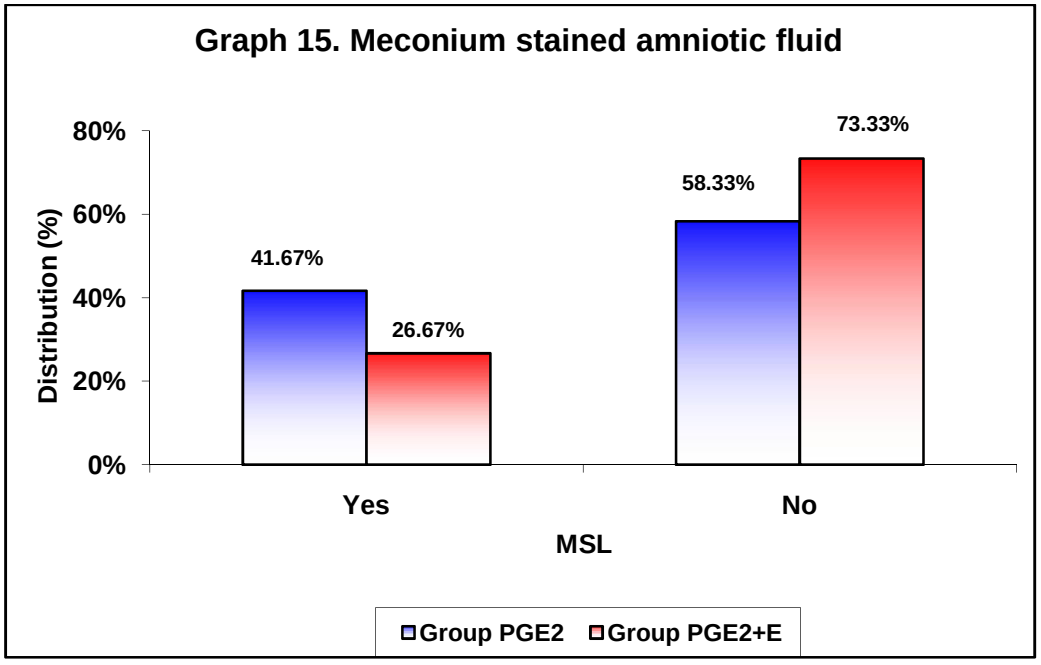


In this study hyperstimulation was noted in 3.33% of the women in group PGE2 compared to 5% in group PGE2 and estradiol (p = 0.500)

Table 22. Meconium stained amniotic fluid (MSAF)

MSAF	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	25	41.67	16	26.67
No	35	58.33	44	73.33
Total	**60**	**100.00**	**60**	**100.00**

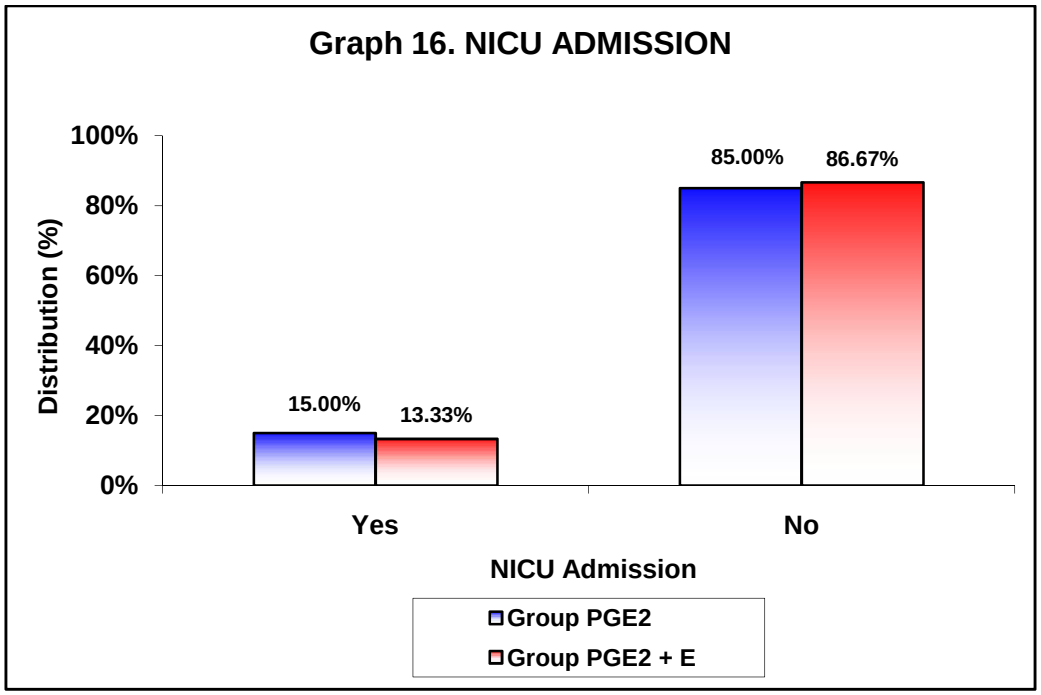
x^2 = 3.001 DF = 1 p = 0.083



In this study, meconium stained amniotic fluid was noted in 41.67% with group PGE2 compared to 26.67% in group PGE2 and estradiol. But this difference was statistically not significant (p = 0.083).

Table 23. NICU ADMISSION

NICU Admission	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	9	15.00	8	13.33
No	51	85.00	52	86.67
Total	**60**	**100.00**	**60**	**100.00**
			p =	0.343

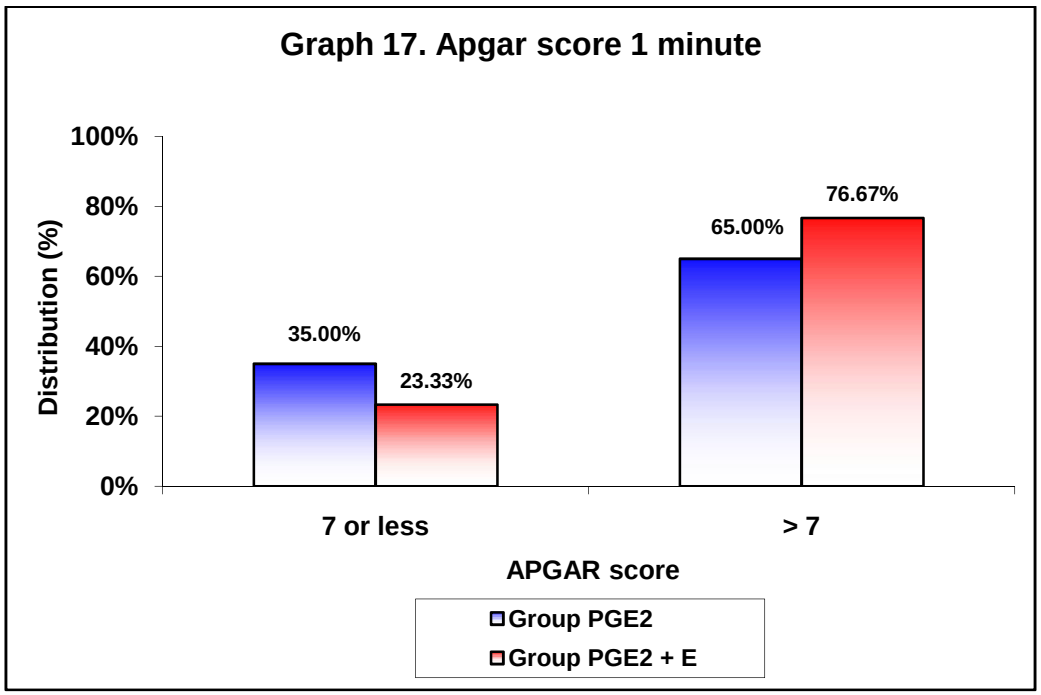


There were nine NICU admissions after delivery in PGE2 group while in combined group eight babies were admitted in NICU. However the NICU admissions in both the groups were statistically not significant (p = 0.343).

Table 24. APGAR score 1 minute

APGAR score	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
≤ 6	14	23.00	9	12.33
≥ 8	46	76.67	51	86.67
Total	**60**	**100.00**	**60**	**100.00**

p =0.160

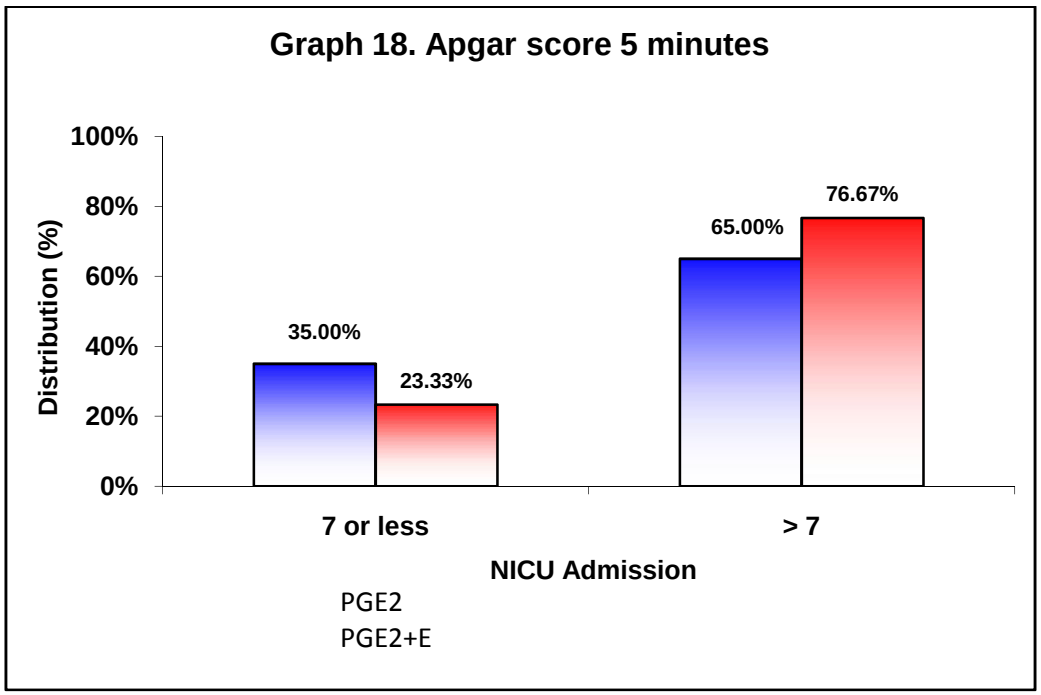


Apgar score of the babies in both the groups after one minute was not statistically significant (p =0.160).

Table 25. APGAR score 5 minutes

APGAR SCORE	Group PGE2 (n=60)		Group PGE2+E (n=60)	
	Number	**Percentage**	**Number**	**Percentage**
≤ 6	8	11.33	4	6.67
≥ 8	42	66.67	46	76.67
Total	**60**	**100.00**	**60**	**100.00**

p =0.152



Apgar score of the babies in both the groups after five minutes was not statistically significant (p =0.152).

DISCUSSION

The incidence of labour induction has increased over the last decade [1]. Labour induction may be indicated in medical or obstetrical complications of pregnancy but it may be chosen for non-medical or social reasons. When a care provider of women decides that labour induction is desired, they must next choose an appropriate method of induction. Several factors may influence the choice of method for induction of labour including cervical and membrane status, parity, and patient and provider preference. In this paper we review the evidence for effectiveness of pharmacologic, mechanical, investigational and complementary and alternative medicine means in third trimester labour induction.

Around 20% of all deliveries are preceded by labor induction. In the last 50–60 years, prolonged pregnancy and maternal hypertensive disorders were the major indications. The 'other' indications include antepartum hemorrhage, diabetes mellitus, red-cell alloimmunisation, demonstrable placental insufficiency and previous unexplained still birth at term etc. In our study, prolonged pregnancy and maternal hypertensive disorders accounted for (29/120) and (41/120) cases respectively. The recent analysis by Kirby et al.[26] data on induction of labor in the United States from 1990 to 2002 reported increased induction rate from around 5–10 % in 1990 to about 17–21 % in 2002. In our study, 30% (36/120) women underwent cesarean section.

This one year Hospital based prospective randomized comparative study was done in labour room from May 2015 to April 2016 under the department of Obstetrics and Gynecology in a tertiary care Hospital. A total of 120 pregnant women with gestational age of ≥ 36 weeks, who fulfilled the inclusion criteria were randomised into two groups of 60 each as Group A - induction with prostaglandin E2 gel

intracervically every sixth hourly of maximum three doses or Group B - PGE2 and vaginal estradiol (induction with PGE2 gel 0.5mg intracervically and estradiol tablet 50µg vaginally in first dose followed by PGE2 gel 0.5mg intracervically alone in next second and third dose sixth hours apart of maximum three doses) till cervical ripening is achieved.

In the present study, commonest age group was between 21 to 25 years in group PGE2 (58.33%) as well as combined PGE2 and estradiol group (45%). However the age distribution in group PGE2 and combined group was comparable (p=0.438). The mean maternal age in PGE2 group was 23.67±3.05 years when compared to 24.53±3.98 years in combined PGE2 and estradiol group (p=0.206). In a prospective double blind study by Dasgupta E and Singh G, the mean maternal age was 21.67 ± 1.15 years in women who underwent induction of labour with misoprostol compared to women who underwent induction of labour with misoprostol + estradiol had mean age of 22.33 ± 2.58 years (p=0.121).[13] The mean maternal age observed in the present study was slightly higher in both the groups compared to the study by Dasgupta E and Singh G but was comparable in both the groups.[13] In this study nearly half of the women in group PGE2 (56.67%) and more than one third (38.33%) in group PGE2 and estradiol were registered for antenatal care (p=0.577).

With regard to parity, most of the women in group PGE2 (68.33%) as well as combined PGE2 and estradiol group(53.33%) were primigravida (73/120) (p=0.210). 28.33% of the women from group PGE2 and 31.67% from group PGE2 and estradiol group had gestational age between 40+1 to 40+6 weeks (p=0.659). The mean period of gestational age in group PGE2 was 39.24 ± 1.47 weeks compared to 39.54±1.51

weeks in PGE2 and estradiol combined group but the difference observed was statistically not significant (p=0.252).

Most women in this study belonged to preinduction Bishop's score of 3 and 4 in group PGE2, i.e. 28.33% and 20% respectively while in group PGE2 and estradiol had 26.67% and 28.33% respectively (p=0.850).Women with preinduction Bishop's score of 2 were similar in both the groups (20%) while Bishop's score of 0 and 1 in PGE2 were 15% and 16.67% and in combined PGE2 and estradiol 11.67% and 13.33% respectively. The mean preinduction Bishop's score in group PGE2 was 2.19 ± 1.37 compared to 2.45 ± 1.35 in group PGE2 and estradiol. The distribution of women based on preinduction Bishop's score observed was almost equal and statistically not significant (p=0.270) and hence comparable in both the groups which was in accordance with M.Raksha, Arun Rao study.[53]

The commonest indication for induction of labour was preeclampsia in PGE2 (26.66%) as well as in group PGE2 and estradiol (35%) and also postdatism (21.6% in PGE2 and 26.67% PGE2 and estradiol) respectively. These findings suggest that preinduction characteristics in group PGE2 and combined group were comparable in terms of maternal age, antenatal care, Bishop's Score and gestational age which rule out the possible bias in the study results.

In the present study majority of the women in group PGE2 received three doses of prostaglandin gel (65%) compared to 23.33% in combined group. In combined PGE2 and vaginal estradiol group, most of the women (41.67%) received lesser number of two doses of prostaglandins than PGE2 alone group. This difference was statistically significant (p<0.001). The mean number of doses of prostaglandins administered were significantly higher in PGE2 only group compared to PGE2 and

estradiol combined group (2.62 ± 0.59 vs. 1.86 ± 0.75; p<0.001). These findings suggest that, induction of labour with intracervical prostaglandin E2 gel requires significantly higher number of doses compared to combined intravaginal estradiol tablet and prostaglandin E2 gel. On an average, 4–5 doses of misoprostol were required in a study by Dasgupta E and Singh G. for cervical ripening or initiation of active labor which is similar to other studies also, however doses required in combined group was significantly less ($p = 0.017$)[13] which was also similar with M.Raksha and Arun Rao study.[53] In study by Dasgupta E and Singh G., in misoprostol only group, duration of interval between induction initiation to cervical ripening , induction initiation to active labor and initiation and induction initiation to delivery were 12.67 ± 3.21, 15.33 ± 3.76 and 18.25 ± 6.13 h, respectively.[13]

In this study, more significant number of women had cervical ripening in combined PGE2 and vaginal estradiol group (83.33%) compared to group PGE2 (61.67%) (p=0.001). The mean time for cervical ripening to occur was significantly higher in group PGE2 compared to combined study group (12.88 ±4.91 vs. 8.92 ± 5.07; p<0.001). Also mean time interval for establishment of active labour was significantly increased in group PGE2 compared to PGE2 and vaginal estradiol group (16.97 ±4.93 vs. 11.02 ± 4.72; p<0.001) and mean induction to delivery time was significantly more in group PGE2 compared to group PGE2 and vaginal estradiol (21.97±3.83 vs. 13.14±4.98; p<0.001).

These findings suggest that, induction of labour with combined vaginal estradiol tablet and intracervical prostaglandin E2 gel offers higher success rate of cervical ripening along with minimum duration of time for active labour and induction to delivery time interval compared to only prostaglandin alone group.

According to M.Raksha and Arun Rao study, [53] when vaginal misoprostol was combined with vaginal estradiol the mean time interval from induction to cervical ripening had shown to be 7.62 hours which are in slightly similar to our study, it took 8.92 hours for combined prostaglandins and vaginal estradiol group for cervix to ripen after initial induction. In a systemic review study by JMC Crane and B Butler, there was a higher rate of vaginal deliveries with misoprostol compared to PGE2 (RR =1.22, 95% CI = 0.96-1.55) and lower rate of oxytocin administered in misoprostol group when compared to PGE2 group (46.4% vs. 62.4%).[49-52] Various studies have found induction delivery interval with vaginal misoprostol in Dasgupta E and Singh G to be 16–20 hours, which is in agreement with our study (16.97 ±4.93).[13,53]In Dasgupta E and Singh G study and M.Raksha and Arun Rao study in combined misoprostol and vaginal estradiol ,the induction to delivery duration interval were reduced to 12.07 hours while in present study it took 13.14 hours in combined group as compared to prostaglandin alone group which was much more i.e., 21.97 hours.

Some studies have shown effect on cesarean section rate with misoprostol. In M.Raksha and Arun Rao study, they had 29 cesarean with misoprostol group and 10 with misoprostol and estradiol group.[53] In the present study significantly higher number of vaginal deliveries were noted in group PGE2 and estradiol (49/60) compared to group PGE2 (33/60) (80% vs. 51.67%; p=0.002) as similar to M.Raksha and Arun Rao. However, no such difference was found in Dasgupta E and Singh G study. The commonest indication for cesarean section LSCS was failed induction in both the groups (13 in PGE2 and 5 in PGE2 and estradiol). PGE2 group had five fetal distress (16.66%) for LSCS in 8.33% of the women. However this difference was statistically not significant (p = 0.513). These findings show that induction of labour with combined vaginal estradiol along with intracervical prostaglandin E2 gel have

higher tendency for vaginal delivery and thereby offers favourable maternal outcome when compared to intracervical prostaglandin E2 alone group.

In this study all babies were alive in the study except four macerated babies which were already present before the induction. Most of the babies belonged to birth weight between 2.50 to 2.99 kgs (46.67%) in group PGE2 and 31.67% in group PGE2 and estradiol. This difference was statistically significant (p=0.042). However, the mean birth weight was comparable in group PGE2 (2.88 ± 0.38) and in group PGE2 and estradiol (2.89 ± 0.46) (p=0.823). Two of the five suspected fetal macrosomia cases underwent cesarean section. Both the M.Raksha and Arun Rao study and the Dasgupta E and Singh study reported that, there were no significant adverse effects seen with use of vaginal 25μg misoprostol on either fetus or mother in both the groups.[13, 53]

In the present study 46.67% of the pregnant women required oxytocin administration compared to 33.33% in group PGE2 and estradiol but this difference was statistically not significant (p=0.136). In M.Raksha and Arun Rao study or Dasgupta studies, [13, 53] the role of oxytocin was not mentioned and there was no incidence of uterine hyperstimulation in both study groups. Hyperstimulation was noted in 3.33% of the women in group PGE2 compared to 5% in group PGE2 and estradiol (p=0.5). If women developed hyperstimulation, further induction was discontinued. However, there was no uterine rupture detected in both the protocols. In a systemic review study by JMC Crane and B Butler, the risk of uterine hyperstimulation and tachysystole were both higher with misoprostol than PGE2 group.[49]

Colour of the liquor was noted if spontaneous rupture of membrane occurred. Meconium stained liquor (MSL) was noted in 41.67% with group PGE2 compared to 26.67% in group PGE2 and estradiol. But this difference was statistically not significant (p=0.083). These findings suggest that, safety profile of induction of labour with combined vaginal estradiol along with intracervical prostaglandin E2 gel is comparable to that of intracervical prostaglandin E2 gel only.

There were nine NICU admissions in PGE2 group due to two birth asphyxia, three due to hyperbilirubinemia, three due to meconium aspiration syndrome, while one baby failed to attained normal oxygen saturation and four NICU admissions were present in the combined group due to low oxygen saturation of the babies and four babies had MAS and were kept under observation. However it was not statistically significant. Apgar score in one minute and Apgar score in five minutes in both the groups were not statistically significant.

Overall, the present study demonstrated that induction of labour with combined vaginal estradiol tablet along with intracervical prostaglandin E2 gel requires significantly lower number of doses of prostaglandins for cervical ripening, yields higher success rate of cervical ripening with lesser time for establishment of active labour and induction to delivery time and are safe for vaginal delivery and are more effective than that of intracervical prostaglandin E2 when used alone in induction of labour.

Estrogen is a hormone involved in the ripening of cervix. A variety of estrogen preparations have been used (such as tablets, gels, creams and infusions). Most studies have natural estrogen analogues such as estradiol. In M.Raksha and Arun Rao study, they concluded that estradiol acts synergistically with misoprostol vaginally

and significantly hastens the process of cervical ripening, initiation of active labor and vaginal delivery. There were insufficient data to quantify the safety and effectiveness of estrogen along with prostaglandins as an inducing agent. Till date only few literatures have compared prostaglandins with vaginal estradiol versus prostaglandins alone in induction of labour in unfavourable cervix. Hence a futher study on combined prostaglandins with vaginal estradiol for labour induction is warranted.

The findings observed in the present study were consistent with several other studies. However the present study findings were strongly in agreement with the study by Dasgupta E. and Singh G.

CONCLUSION

Based on the findings of this study it may be concluded that, induction of labour with combined vaginal estradiol along with intracervical prostaglandin E2 gel requires significantly lower number of doses of for prostaglandin E2 gel for cervical ripening, yields higher success rate of cervical ripening with lesser duration interval for establishment of active labour and induction to delivery time and is more effective that of intracervical prostaglandin E2 gel alone. Thus vaginal estradiol along with prostaglandins has the potential to induce labour and in to ripen cervical in an efficacious way. Fetal outcome when combined vaginal estradiol along with intracervical prostaglandin E2 or intracervical prostaglandin E2 gel alone was used was not statistically significant and hence had similar beneficial outcome.

SUMMARY

The present study was designed to determine the effectiveness and safety of vaginal estradiol and prostaglandins in cervical ripening and induction of labour in unfavourable cervix and also to assess mode of delivery and tostudy maternal outcome and fetal outcome.

This one year randomized controlled trial was conducted in the Department of Obstetrics and Gynecology, KLE University's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of May 2015 to April 2016. A total of 120 pregnant women who were admitted in the labour room fulfilling theinclusion criteria were included in the study. Based on the opaque sealed envelope, these women were randomized into two groups with 60 cases in each group. GROUP A was induced using prostaglandins alone intracervically every sixth hourly of maximum three doses till cervical ripening was achieved and Group B was induced using prostaglandin intracervically and estradiol tablet vaginally in the first dose followed by prostaglandins alone intracervically in subsequent next two doses till cervical ripening is achieved. Pre-induction Bishop's score was assessed prior to every induction or whenever warranted if earlier.

The outcomes assessed were time interval between induction to cervical ripening, induction to active labour and induction to delivery time interval. Furthermore, mode of delivery, number of doses of prostaglandins used birth weight of the babies, fetal birth asphyxia, NICU admissions, Apgar score at 1minute and 5 minutes were also asssessed.

Overall in the present study, the mean time for cervical ripening to occur was significantly higher in group PGE2 compared to combined study group (12.88 ±4.91 vs. 8.92 ± 5.07; p<0.001). Also mean time interval for active labour was significantly increased in group PGE2 compared to PGE2 and vaginal estradiol group (16.97 ±4.93 vs. 11.02 ± 4.72; p<0.001) and mean induction to delivery time was significantly more in group PGE2 compared to group PGE2 and vaginal estradiol (21.97±3.83 vs. 13.14±4.98; p<0.001) and was statistically significant in each time interval of outcomes measured. Fetal outcome in both the groups was not statistically significant and hence were comparable. Hyperstimulation in both the groups were comparable in both the groups.

Hence the combination of vaginal estradiol along with prostaglandins when compared to prostaglandin alone enhance the process of cervical ripening and induction of labour and has a beneficial effect to the mother and the fetus. Also the number of prostaglandins required for cervical ripening was less when combined vaginal estradiol used with prostaglandins. There was more successful vaginal delivery in combined group than prostaglandins alone when used in the study.

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ANNEXURE – I – ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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Ref: MDC/DOME/235 **Date: 19/11/2014**

To,

PG student in OBG,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"PROSTAGLANDINS WITH ESRTADIOL VERSUS PROSTAGLANDINS ALONE FOR INDUCTION OF LABOUR IN UNFAVOURABLE CERVIX – ONE YEAR RANDOMIZED CONTROL TRIAL AT KLE DR. PRABHAKAR KORE CHARITABLE HOSPITAL AND MRC, BELGAUM ",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr.Hema Dhumale)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr.Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

15

ANNEXURE – I I– CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

You are hereby requested to participate in study which we are conducting method of induction of labour in unfavourable cervix using prostaglandins i.e., cerviprime gel with vaginalestradiol conducted by Dr. _____, Post Graduate in M.S. Obstetrics And Gynecology under the guidance of Dr. _____ Professor, Department of Obstetrics And Gynecology, J.N. Medical College, Belagavi under KLE University, Belagavi. This may help in shortening time interval in the process of spontaneous onset of labour.

We request you to enrol yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide not to participate you are free to withdraw at any time.

The rate of labour induction has more than doubled. The goal of labour induction is to artificially stimulate uterine contractions so that pregnant women can deliver vaginally with shorter time interval along with healthy mother and healthy baby. The purpose of the study is to evaluate the effectiveness of vaginal estradiol combined with dinoprostone versus dinoprostone alone in induction of labour in unfavourable cervix and to assess fetal and maternal outcome.

Procedure Involved:

Once you consent to participate in the study some information will be collected from you and will be assigned randomly using an opaque sealed envelope containing either vaginal estradiol tablet or without vaginal estradiol tablet. Bishop's Score will be assessed and subjects re-examined before every induction and induction will be proceeded as per following protocol i.e. GROUP A: 3 doses of cerviprime alone intracervically at 6 hrs interval maximum of 3 doses, GROUP B: intracervical cerviprime with vaginal estradiol only in the first dose followed by intracervical cerviprime alone in next subsequent two doses at 6 hrs interval of maximum of 3 doses

The response to induction will be assessed by periodic Bishop's score at specified intervals and whenever warranted if earlier. Outcome of time intervals between a) Induction initiation- cervical ripening, b) Induction initiation - active labour, c) Induction initiation –deliveries, mode of deliveries and number of doses of cerviprime used will be assessed including fetal and maternal outcome.

Risks and Benefits:

This study may or may not help and directly benefit you, but findings of this study possibly help in managing pregnant women who require induction of labour with high risks which may shorten duration of delivery interval to achieve healthy mother and a healthy baby. Although the side effects of cerviprime include uterine hyperstimulation, tachysystole, uterine rupture etc and side effects of vaginal estradiol being deep vein thrombosis, nausea, vomiting etc., there are no additional risks to you or your baby due to this study.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E.S hospital.

Alternatives: Even if you decline the participation in the study, you will get the same standard of care as any other pregnant women of the hospital.

Privacy and Confidentiality:

The only people to know that you are a research subject are members of the research team which include Dr. _____ and Dr_____. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation:

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and the cost of the study will be borne by the investigator for estradiol vaginal tablets.

Compensation:

In the event of injury related to the study, treatment will be made available through funds in KLES Charitable Hospital, Belagavi. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Dr. _____, at Department of Obstetrics And Gynecology, KLES Hospital & MRC.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr._____., Department of Obstetrics And Gynecology, KLES Hospital and MRC. Dr. _____ Professor, Dept. Of Obstetrics and Gynecology, KLES Hospital and MRC, Belagavi.

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Prof. & Head of Pathology as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.0831 2473777 ext-1527 at J. N. Medical College, Belagavi or phone number: 9480275601.

CONSENT STATEMENT

Consent for participation in research trial I_____ voluntarily agree to participate as a subject for the study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read or explained in my own vernacular language, including the risks and the benefits and having all my questions answered.

Name of the Patient :

Signature or the Left Thumb Print of Subject:

Witness Name: Signature:

Investigator's Name: _____ Signature:

Place:

ANNEXURE – III– PROFORMA

PROSTAGLANDINS WITH ESTRADIOL VERSUS PROSTAGLANDINSALONE FOR INDUCTION OF LABOUR IN UNFAVOURABLE CERVIX- RANDOMIZED CONTROL TRIAL:

S.L.NO: ☐☐☐ DATE: ☐☐☐☐☐☐

TIME ☐☐

OP/IP NO: ☐☐☐☐☐☐ Registered/Unregistered: ☐

Patients Name: _____

Age: _____

Address: _____

_____

Contact No: _____

Obstetric History:

G ☐ P ☐ L ☐ A ☐ D ☐ / Primigravida

Menstrual History:

LMP: ☐☐☐☐☐☐

EDD: ☐☐☐☐☐☐

Period of Gestation: ☐

Induction using randomized group:

1. Dinoprostone gel 0.5mg intracervicallysixth maximum 3 doses.
2. Dinoprostone gel 0.5mg intracervicallywith 50mcg estradiol tablet vaginally only in the first dose followed by 0.5mg dinoprostone gel aloneintracervically alone in the subsequent next two doses every sixth hourly for amaximum of 3 doses.

Bishop's Score will be assessed before each inductionand if warrantsearlier in any intervention.

BISHOP'S SCORE:

DATE ANDTIME	Pre-Induction time	6hours	12hours	18hours	Active labour	Delivery Time
Cervix:						
Dilatation (cm)						
Length(cm)						
Consistency						
Position						
Head: Station						
Bishop's Score						

Augmentation with oxytocin: YES/NO ☐

Date and time of established active labour: ☐

Date and time of delivery: ☐

Mode of delivery:

Vaginal ☐

Ventouse ☐

Forceps ☐

C-section ☐

Indication for labour induction: _____

Indication for Cesarean section: _____

Results of Bishop's score:

- PG Induction-Cervical Ripening ☐

  Time Interval:

- PG Induction-Active labor ☐

  Time Interval:

- PG Induction-Delivery ☐

  Time Interval:

Fetal outcome:

MSB/FSB/LIVE BIRTH ☐

Time and date of delivery: ☐

Birth weight of baby: ☐ Sex: ☐

Apgar score: 1 minute ☐

5 minute ☐

Meconium stained liquor:Yes/No ☐

NICU Admission: Yes/No ☐

Maternal complications:

Uterine Rupture ☐

Uterine hyperstimulation: Yes/No ☐

Nausea / vomiting ☐

Prenatal diagnosis:

Postnatal diagnosis: