

**ROLE OF PHOSPHORYLATED INSULIN-LIKE GROWTH
FACTOR BINDING PROTEIN-1 AS PREDICTOR OF
SUCCESSFUL LABOR INDUCTION IN FULL TERM
PREGNANCY - A CROSS SECTIONAL STUDY**

By

DR. KOLAKOTLA AJITHA, MBBS



**DISSERTATION SUBMITTED TO SRI DEVRAJ URS ACADEMY
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KARNATAKA**

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

MASTER OF SURGERY

IN

OBSTETRICS AND GYNAECOLOGY

Under the Guidance of

Dr. SHEELA S R

Professor

Department of Obstetrics & Gynaecology

Co-Guide

Dr. SHASHIDHAR K N

Professor

Department of Biochemistry



**DEPARTMENT OF OBSTETRICS & GYNAECOLOGY
SRI DEVRAJ URS MEDICAL COLLEGE
TAMAKA, KOLAR – 563101**

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Date:

Place: Kolar

Dr. Kolakotla Ajitha

Post Graduate Student

Department of OBG

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Dr. SHEELA S R

Professor

Department of OBG

Sri Devraj Urs Medical College,

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Date:

Place: Kolar

Dr. SHASHIDHAR K N

Professor

Department of Biochemistry

Sri Devraj Urs Medical College,

Tamaka, Kolar – 563101

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Dr. MUNIKRISHNA M
Associate Professor &
Head of Department
Department of OBG
Sri Devraj Urs Medical College
Tamaka, Kolar

Dr. K. PRABHAKAR
Principal
Sri Devraj Urs Medical College
Tamaka, Kolar

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PHOSPHORYLATION INSULIN LIKE GROWTH FACTOR BINDING PROTEIN-1 AS A PREDICTOR OF SUCCESSFUL LABOR INDUCTION IN FULL TERM PREGNANCY-A CROSS SECTIONAL STUDY
ABSTRACT BACKGROUND: Induction of labor is the artificial initiation of uterine contractions before its spontaneous onset to deliver the fetus-placental unit. Induction of labor is one of the most important part of obstetrics, as we can interfere and induce labor as a lifesaving procedure for mother or fetus or both. The frequency of inducing labor to reduce the gestational period due to various indications has increased. Hence pre induction biomarkers are necessary to predict the successful induction of labor and mode of delivery. In this study Phosphorylated Insulin-like growth factor binding protein-1 (phIGFBP-1), an emerging pre-induction biomarker, is used to predict the successful labor induction. **AIMS:** To detect the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) in patients undergoing induction of labor using Actin nuchus test and to evaluate the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) among the patients with and without successful induction of labor. **MATERIALS & METHODS:** All the consenting eligible pregnant women who were hospitalized to the labour room were recruited for the study. Cervicovaginal swab from the women who are undergoing labor induction is taken and tested for presence Insulin-like growth factor binding protein-1 (IGFBP1), using Actin nuchus test. Then assessment will be made about mode of delivery in patients with and without phosphorylated insulin like growth factor binding protein-1 positive. **RESULTS:** The present study included 58 pregnant women who were over 37 weeks pregnant and were scheduled for induction. The findings showed that approximately half were primigravida mothers, followed by gravida 2 (29.3%) and 3 (22.4%). Most of the patients had a gestational age of more than 40 weeks (50%). Foleys's + Misoprostol + Oxytocin was the most common induction method used (32.8%), followed by Foleys's + Misoprostol (22.4%) and misoprostol only (22.4%). Most of the patients had a vaginal delivery (77.6%), while 22.4% had LSCS. Overall, the labor induction was successful among 93.1% of pregnant women. In the present study, the Actin nuchus test was positive in 79% of the cases. Most pregnant women scored a BISHOP score of 5 and above (70.7%), whereas 29.3% scored lower than 5. The presence of phIGFBP-1 in the cervicovaginal fluid is identified as a significant factor in predicting labor. The sensitivity, specificity, PPV, NPV and accuracy of the phIGFBP-1 in predicting successful labor induction were 85.2%, 100%, 100%, 33.3%, and 86.2%, respectively. **CONCLUSION:** Phosphorylated Insulin-like growth factor binding protein-1 (phIGFBP-1) was able to predict the success of induction of labor, with both sensitivity and specificity. **II INTRODUCTION** Induction of labour is the artificial initiation of uterine contractions before its spontaneous onset to deliver the fetus-placental unit. Induction of labour is one of the most important part of obstetrics, as we can interfere and induce labour as a lifesaving procedure for mother or fetus or both. The procedure is often carried either by physically rupturing the amniotic membranes, mechanical or pharmacological methods. Frequency of inducing labour to reduce gestational period has increased during last several decades. One in four births in developed nations result in a child being born at term after labour induction. 2.3 Data from the WHO Global survey on maternal and Perinatal Health, which included 373 health-care facilities in 24 countries and nearly 300,000 deliveries, showed that 9.6% of the deliveries require labour induction. An extended gestation period is linked to a higher chance of meconium stained liquor, meconium aspiration syndrome, low newborn of APGAR, fetal macrosomia, trauma during birth, and stillbirth. 5 With increase in gestational age increases, there could be greater chance of maternal problems such as dystocia of labor, third and fourth degree perineal tears (which are linked to fetal macrosomia), and increase in incidence of caesarean birth. 6,7 Cervical favorability before induction was traditionally evaluated using the Bishop score (BS) and measurement of transvaginal cervical length (TVL). Positive predictive value would be diminished by intra- and inter-observer variability. Phosphorylated Insulin-like growth factor binding protein-1 (IGFBP1) is an emerging preinduction biomarker with both unphosphorylated isoform which is found in amniotic fluid and phosphorylated isoform which is found in decidua, secretory endometrium uterus, liver and hepatoma cell line. Precise mode of action is uncertain, it act by binding to both IGF 1 and II receptors. 8 Decidual cells generate phosphorylated isoforms of Insulin-like growth factor binding protein-1, which is different from that seen in amniotic fluid. It appear in the cervical secretions of women whose membranes are still intact, due to disruption of chorio-decidual interface. The decidua and chorion will separate as the cervix ages, allowing proteins to seep into the cervical canal. 9,10 Various studies have been done to establish the significance of Phosphorylated Insulin-like growth factor binding protein-1 in preterm labor. The effectiveness of labor induction can be predicted by a bedside test for phosphorylated insulin-like growth factor binding protein-1. A commercially available strip test from Medix Biochemica, is being used to identify phIGFBP-1 in cervicovaginal samples. If two blue lines show up, the test is deemed positive; it is based on the principle of immunochromatography. Studies on phosphorylated IGFBP-1 and success of labor induction are limited in India. Hence, this study has been undertaken. **AIMS & OBJECTIVES** 1. To detect the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) in patients undergoing induction of labor using Actin nuchus test. 2. To evaluate the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) among the patients with and without successful induction of labor. 3. **REVIEW OF LITERATURE INDUCTION OF LABOR** The procedure of artificially stimulating the uterus to initiate labor is known as induction of labor (IOL). 11 The global goal of the World Health Organisation (WHO) is to ensure that all pregnant women and newborns have access to high-quality healthcare throughout their entire journey, from conception to the postnatal period. "Therefore, according to the World Health Organisation, IOL should only be done when there is a strong medical reason and the benefits outweigh the hazards. 12 A number of professional groups have released guidelines pertaining to the clinical indications and IOL procedures. 13,14 Nevertheless, in spite of the official guidelines, mothers are requesting an increasing number of medically unnecessary inductions to abbreviate their pregnancy or facilitate an elective birth at a certain time. 15 Since IOL disrupts the natural progression of pregnancy and labour, it is not surprising that it is associated with a higher frequency of certain complications including haemorrhage, caesarean deliveries, uterine hyperstimulation or rupture, and terrible the outcomes of newborns. 16 **HISTORY OF INDUCTION OF LABOUR** When Hippocrates first described mechanically dilating the cervical canal and stimulating the mammary glands, it was the beginning of labour induction. 77 Artificial membrane rupture was one of the methods used by Soranus in the second century AD to bring about labour. Cais developed a number of devices that could dilate the cervix, and Moshion was the first to describe the process manually.

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Dr. KOLAKOTLA AJITHA

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LIST OF ABBREVIATIONS

phIGFBP-1	Phosphorylated insulin-like growth factor-binding protein-1
IGFBP-1	Insulin-like growth factor-binding protein-1
IOL	Induction of labor
IGF	Insulin-like growth factor
PGE	Prostaglandin E2
PGF _{2a}	Prostaglandin $F_{2\alpha}$
PGH ₂	Prostaglandin H2
ROC	Receiver operating characteristic curve
Bpm	Beats per minute
FP	Prostaglandin F receptors
LR	Likelihood ratio
AOR	Adjusted odds ratio
WHO	World Health Organization
BS	BISHOP Score
TVL	Transvaginal length
TVUS	Transvaginal ultrasound
LSCS	Lower segment caesarean section

HIV	Human immunodeficiency viruses
NSAID'S	Non-steroidal anti-inflammatory drugs
FDA	Food and drug administration
PPV	Positive predictive value
NPV	Negative predictive value
RR	Relative risk
OR	Odds ratio
IL	Interleukin
MMP	Matrix metalloproteinases
ACOG	American college of obstetricians and gynaecologists
NICE	National institute for health and care and excellence
SOGC	Society of obstetricians and gynaecologists of canada

ABSTRACT

BACKGROUND: Induction of labor is the artificial initiation of uterine contractions before its spontaneous onset to deliver the feto-placental unit. Induction of labor is one of the most important part of obstetrics, as we can interfere and induce labor as a lifesaving procedure for mother or fetus or both. The frequency of inducing labor to reduce the gestational period due to various indications has increased. Hence pre induction biomarkers are necessary to predict the successful induction of labor and mode of delivery. In this study Phosphorylated Insulin-like growth factor binding protein 1 (phIGFBP-1), an emerging pre-induction biomarker is used to predict the successful labor induction.

AIM: To detect the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) in patients undergoing induction of labor using Actim partus test and to evaluate the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) among the patients with and without successful induction of labor.

MATERIALS & METHODS: All the consenting eligible pregnant women who were hospitalized to the labor room were recruited for the study. Cervicovaginal swab from the women who are undergoing labor induction is taken and tested for presence Insulin-like growth factor binding protein 1 (IGFBP1), using Actim partus test. Then assessment will be made about mode of delivery in patients with and without phosphorylated insulin like growth factor binding protein 1 positive.

RESULTS: This study included 58 pregnant women who were over 37 weeks pregnant and were scheduled for induction. The findings showed that approximately half were primigravida mothers, followed by gravida 2 (29.3%) and 3 (22.4%). Most of the patients had a gestational age of more than 40 weeks (50%). Foleys's + Misoprostol + Oxytocin was the most common induction method used (32.8%), followed by Foleys's +Misoprostol (22.4%) and misoprostol

only (22.4%). Most of the patients had a vaginal delivery (77.6%), while 22.4% had LSCS. Overall, the labor induction was successful among 93.1% of pregnant women.

In this study, the Actim partus test was positive in 79% of the cases. Most pregnant women scored a BISHOP score of 5 and above (70.7%), whereas 29.3% scored lower than 5. The presence of phIGFBP-1 in the cervicovaginal fluid is identified as a significant factor in predicting labor.

The sensitivity, specificity, PPV, NPV, and accuracy of the phIGFBP-1 in predicting successful labor induction were 85.2%, 100%, 100%, 33.3%, and 86.2%, respectively.

CONCLUSION: Phosphorylated Insulin-like growth factor binding protein 1 (phIGFBP-1) was able to predict the success of induction of labor, with both sensitivity and specificity.

INTRODUCTION

Induction of labor is the artificial initiation of uterine contractions before its spontaneous onset to deliver the feto-placental unit. Induction of labor is one of the most important part of obstetrics, as we can interfere and induce labor as a lifesaving procedure for mother or fetus or both. The procedure is often carried either by physically rupturing the amniotic membranes, mechanical or pharmacological methods.

Frequency of inducing labor to reduce gestational period has increased during last several decades. One in four births in developed nations result in a child being born at term after labor induction.^{2,3} Data from the WHO Global survey on maternal and Perinatal Health, which included 373 health-care facilities in 24 countries and nearly 300 000 deliveries, showed that 9.6% of the deliveries require labor induction.¹

An extended gestation period is linked to a higher chance of meconium stained liquor, meconium aspiration syndrome, low newborn of APGAR, fetal macrosomia, trauma during birth, and stillbirth.⁵ With increase in gestational age increases, there could be greater chance of maternal problems such as dystocia of labor, third and fourth degree perineal tears (which are linked to fetal macrosomia), and increase in incidence of caesarean birth.^{6,7}

Cervical favourability before induction was traditionally evaluated using the Bishop score (BS) and measurement of transvaginal cervical length (TVL). Positive predictive value would be diminished by intra- and inter-observer variability.

Phosphorylated Insulin-like growth factor binding protein 1, is an emerging preinduction biomarker with both unphosphorylated isoform which if found in amniotic fluid and phosphorylated isoform which is found in decidua, secretory endometrium uterus, liver and hepatoma cell line. Precise mode of action is uncertain, it act by binding to both IGF I and II receptors.⁸ Decidual cells generate phosphorylated isoforms of Insulin-like growth factor

binding protein 1, which is different from that seen in amniotic fluid . It appears in the cervical secretions of women whose membranes are still intact, due to disruption of chorio-decidual interface. The decidua and chorion will separate as the cervix ages, allowing proteins to seep into the cervical canal.^{9,10} Various studies have been done to establish the significance of Phosphorylated Insulin-like growth factor binding protein 1 in preterm labor .

The effectiveness of labor induction can be predicted by a bedside test for phosphorylated insulin-like growth factor binding protein-1. A commercially available strip test from Medix Biochemica, is being used to identify phIGFBP-1 in cervicovaginal samples. If two blue lines show up, the test is deemed positive; it is based on the principle of immunochromatography.

Studies on phosphorylated IGFBP-1 and success of labor induction are limited in India. Hence, this study has been undertaken.

AIMS & OBJECTIVES

1. To detect the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) in patients undergoing induction of labor using Actim partus test.
2. To evaluate the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) among the patients with and without successful induction of labor.

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REVIEW OF LITERATURE

INDUCTION OF LABOR

The procedure of artificially stimulating the uterus to initiate labor is known as induction of labor (IOL).¹¹ The global goal of the World Health Organisation (WHO) is to ensure that all pregnant women and newborns have access to high-quality healthcare throughout their entire journey, from conception to the postnatal period. "Therefore, according to the World Health Organisation, IOL should only be done when there is a strong medical reason and the benefits outweigh the hazards."¹² A number of professional groups have released guidelines pertaining to the clinical indications and IOL procedures.^{13,14} Nevertheless, in spite of the official guidelines, mothers are requesting an increasing number of medically unnecessary inductions to abbreviate their pregnancy or facilitate an elective birth at a certain time.¹⁵ Since IOL disrupts the natural progression of pregnancy and labor, it is not surprising that it is associated with a higher frequency of certain complications including haemorrhage, caesarean deliveries, uterine hyperstimulation or rupture, and terrible the outcomes of newborns¹⁶

HISTORY OF INDUCTION OF LABOR

When Hippocrates first described mechanically dilating the cervical canal and stimulating the mammary glands, it was the beginning of labor induction.⁷⁷

Artificial membrane rupture was one of the methods used by Soranus in the second century AD to bring about labor.

Casis developed a number of devices that could dilate the cervix, and Moshion was the first to describe the process manually. Patients suffering from uterine haemorrhage were treated by Paré in the middle of the 16th century using a method that combined internal podalic version with manual cervical dilatation.⁷⁸

The technique was carried on by Bourgeois, a follower of Paré, who also used forceful enemas and combinations of several folk remedies to induce and enhance labor.⁷⁹

James used amniotomy to bring about early labor in 1810. Mechanical means of inducing labor, such as amniotomy, were the norm until the 20th century.⁸⁰

Dale noted in 1906 that myometrial contractions were brought on by extracts from the infundibular lobe of the pituitary gland. Bell documented the first instance of using a pituitary extract to induce labor three years down the road. As more and more reports of uterine rupture emerged, pituitary extract started to lose credibility in many medical facilities.⁸¹

Synthetic oxytocin has been used since 1955, after the discovery of its structural formula in 1953.

Karim and colleagues first reported using prostaglandins to induce labor in 1968. Since then, prostaglandins have been a regular means of inducing labor via various formulations of administration.⁸²

Misoprostol, a synthetic prostaglandin analogue, has lately been widely recognised as a safe and effective way to induce labor.

INCIDENCE

The practice of inducing labor to reduce the gestational period has been more common during the last few decades. Term births after induction of labor may occur in as many as one-quarter of babies in industrialised nations. Twenty percent of pregnancies end in the induction of labor.⁸³

The causes for the rising rates of induction of labor are complex and multifactorial.⁸⁴ some of them are:

- Widespread availability of cervical ripening agents.

- Improved knowledge of methods and indications for induction.
- More relaxed attitudes towards marginal/elective indications, both of the physician and the patient.
- Litigation constraints

INDICATIONS/CAUSES

The causes for a patient's late preterm, early term, late-term, or post-term delivery date might vary according on their obstetric and medical history. Results will be better with intrauterine oxygenation (IOL) when it is felt that it will help the woman, the foetus, or both, compared to expectant management, which is reserved for when labor naturally begins.¹⁸

IOL is often advised in light of the usual indications to prevent an extended pregnancy. A number of risk variables, such as carrying a male fetus, nulliparity, and maternal obesity, have been linked to post-term pregnancies.^{19,20} The rates of unfavourable outcomes have been linked to deliveries made after 42 weeks of gestation. Furthermore, according to the WHO, in most cases of pregnancies, IOL is advised for women who may be positively certain of having reached 41 weeks of gestation. Ultrasonography should be used for proper dating in each instance. The WHO advised routinely using one ultrasound scan before the 24 gestational weeks in 2016.¹ Putting this advice into practice may aid in determining the precise gestational age, which will aid in the WHO guidelines' acceptance even more. There are a number of alternatives for fetal monitoring in post-term pregnancies, including the modified biophysical profile, contraction stress test, nonstress test, and biophysical profile.²¹ A Cochrane review of foetal monitoring in more than three thousand high-risk pregnancies found no differences in perinatal death or Apgar scores below 7 at 5 minutes between the groups who underwent biophysical profiling and those that did not.²² That being said, not enough information is available to establish the optimal testing kind or frequency. Despite the lack of guidance from the World Health Organisation (WHO), several organisations have offered recommendations regarding antepartum surveillance. For example, ACOG suggests beginning the monitoring at or after 41 weeks gestation, SOGC suggests assessing the foetal well-being twice weekly after

41 weeks gestation, and NICE recommends starting the monitoring at 42 weeks of gestation and continuing it at least twice weekly.¹⁷

IOL at 39 gestational weeks in low-risk nulliparous women did not substantially reduce the incidence of a composite unfavourable perinatal outcome, but it did considerably reduce the frequency of cesarean birth, according to Grobman et al (2018) study including over 6000 pregnant women.²³ According to a Practice Advisory from ACOG, low-risk nulliparous women may be offered elective IOLs at 39 weeks of gestation, as long as the choice is communicated between the woman and her obstetric physician and resources are considered. The only official suggestion available at the moment is the ACOG Practice Advisory, as all guidelines were published prior to the ARRIVE study.¹⁷

A relevant Cochrane review includes 30 randomised controlled trials and 12,479 pregnant women who were at or beyond term. When compared to expectant management, IOL strategy was associated with a decrease in stillbirths (RR, 0.33;) and perinatal deaths (RR, 0.33). The induction group had a slightly higher rate of operative vaginal births (RR,1.07) but fewer caesarean deliveries (RR,0.92;) than the expectant management group. The induction group also had lower incidence of neonatal critical care unit admissions (RR,0.88) and Apgar scores of less than 7 at five minutes compared to the expectant management group (RR, 0.70).²⁴ No recommendations have ever advocated for IOL due to advanced maternal age. A randomised controlled trial found that among primigravid women who were 35 years old or older, there were no negative short-term effects on maternal or neonatal outcomes, and there was no significant effect on the rates of caesarean delivery when IOL was administered at 39 weeks of gestation compared to expectant management.²⁵

Conflicting advice for premature rupture of membranes at term are presented in existing guidelines. Although some guidelines suggest giving women the choice between IOL and expectant management, others state that IOL should be recommended (in the next 24 hours or as soon as possible). Some guidelines differentiate between pregnant women who test

positive for group B streptococcus and those who test negative. According to this, women who test positive should be induced "as soon as feasible," namely within 24 hours, 73 or 6 hours, and they should have an IOL sooner than those who do not.²⁶

When it comes to scheduling, the relevant standards suggest that women who are expecting simple twins (i.e., first twin cephalic) have a scheduled birth. Without distinguishing between monochorionic and dichorionic pregnancies, some suggestions propose IOL at 37 weeks, 38 weeks, or in the period between 37 and 38 weeks.

Multiple guidelines suggest that, in the absence of additional indicators, suspected macrosomia is not a suitable justification for IOL.²⁶ In situations of "proven" macrosomia, mechanical methods (IOLs) are recommended by the World Health Organisation (WHO), the Queensland Health, and the Canberra Hospital recommendations. When macrosomia is suspected, an ultrasound may be conducted to assess the estimated foetal weight, according to two of these recommendations. After 36 weeks, 3700 weeks, or 3900 weeks, the predicted weight should be 3500 g, 3700 g, or 3900 g, respectively, according to these criteria, before the recommended 39 weeks.²⁶

All recommendations suggest that, depending on the clinical situation, a woman's IOL may be indicated in connection to decreasing fetal movements. The findings of testing for fetal welfare should guide the scheduling, and expectant treatment may need to include additional fetal observation. There is just one recommendation for a time that is >38 weeks or sooner if it is indicated.²⁶

METHODS OF INDUCTION

Collagen makes up the majority of the cervix and smooth muscle makes up the majority of the body of the uterus. There are a number of dynamic changes that occur to the cervix throughout pregnancy and delivery, including constriction, dilatation, and thinning. Inducing labor by mechanical or pharmacological means might cause these physiological changes to

occur in the cervical region.¹¹ Using prostaglandins, such as dinoprostone given intracervically or vaginally, misoprostol given orally, intracervically, or vaginally, and intravenous oxytocin are examples of pharmacological techniques. Not every woman is a good candidate for pharmacological labor induction techniques. Women with high parity should have lower prostaglandin levels, and women who have had a prior cesarean section shouldn't utilize prostaglandins. The risks of uterine rupture, hyperstimulation, extended labor, and fetal and maternal compromise are increased with pharmacological induction of labor. The WHO advises against leaving women receiving a pharmaceutical induction of labor unattended since this might lead to an increase in medical expenses.²⁷

A planned rupture of the amniotic membrane, or amniotomy, is one surgical technique that may be used to induce labor.⁷ Umbilical cord prolapse may occur during an amniotomy if the foetal section that is visible is not positioned in the pelvis. It increases the risk of infection for the mother and the foetus; hence it is not recommended for women who are HIV positive. Mechanical procedures were among the first ways of inducing labor that were recorded. The cervix's favourability, as measured by the Bishops score, is the main indicator of labor induction success. Methods of mechanical induction of labor include ripening and dilating the cervix with manual manipulation, which allows for the spontaneous onset of labor.²⁸ The use of an intracervical Foley catheter and membrane sweeping, often known as "stripping" or "stretch and sweep," are examples of mechanical techniques.²⁷

MEMBRANE SWEEPING

All standards recommend membrane sweeping or stripping as a simple method to reduce the need for further IOL procedures.^{13,14} At the 40-and 41-week prenatal visits, women who are not expecting a child should have their membranes swept; at the 41-week antenatal visit, ladies who are expecting multiple children should have their membranes swept. A finger is inserted beyond the internal os and then wrapped three times around it to separate the membranes from the lower segment; this process is called membrane sweeping.¹⁴ An increase

in phospholipase A2 activity and PGF2a levels occurs as a consequence of this intervention, which decreases the need for additional methods of induction and increases the likelihood of spontaneous labor beginning within 48 hours. A Cochrane analysis that compared expectant treatment with membrane sweeping showed that sweeping was linked to a 40 percent lower probability of formal IOL (RR, 0.60).²⁹ Additionally, the likelihood of not going into labor or giving birth within 48 hours was reduced by 23 percent (RR, 0.77;).²⁹ When sweeping the membranes during vaginal inspection, there was a higher risk of vaginal hemorrhage and pain compared to expectant management. Interestingly, there is not enough data to support the use of herbal supplements, acupuncture, homeopathy, breast stimulation, or other such techniques for IOL.²⁶

During a vaginal examination, a membrane sweep is carried out with agreement.³⁰ The doctor has to insert one or two fingers into the woman's cervix and rotate them in a circular motion to separate the lower uterine segment from the inferior pole of the membrane. If the cervical os is closed, one alternative is to massage the cervix. Membrane sweeping is an easy process that may be done many times and used either alone or in conjunction with other induction techniques. By releasing localized prostaglandins F2 α , phospholipase A2, and cytokines from the intrauterine tissues, membrane sweeping is utilized to encourage the usual physiological commencement of labor. These hormones stimulate cervical ripening, which may lead to uterine contractions, by acting on the cervix. Stretching the cervical spine may help initiate the Ferguson reaction because it stimulates the uterus and releases the relaxin hormone. The technique aims to soften and ripen the cervix, increase cervical favorability, and stimulate uterine activity in order to reduce the need for a formal induction of labor and to induce spontaneous uterine contractions that may start labor.²⁷

AMNIOTOMY

The process by which an obstetrician intentionally breaks the amniotic sac is known as an amniotomy. It is sometimes called artificial rupture of membranes or, more colloquially,

"breaking the water." As a standard part of labor management, obstetricians have been doing this procedure for at least a few hundred years. There are many reasons why the amniotic sac may be purposefully ruptured during childbirth, some of which are to affect the rate of labor, to enable more precise monitoring of the fetal condition, and to qualitatively evaluate the amniotic fluid.³¹

The most common causes for artificial membrane rupture during pregnancy include inducing or speeding up labor, or to facilitate the insertion of intrauterine monitoring equipment that allow for direct assessment of foetal health. It is easy to monitor the foetal heart rate and uterine activity with the use of external monitoring devices. On occasion, nevertheless, a more exact measurement of the uterine activity or foetal heart rate is required during labor. In order to implant a foetal scalp electrode or an intrauterine pressure catheter, this kind of monitoring physically requires rupturing the amniotic membrane.^{32,33}

Hooks made specifically to grip and tear the amniotic membrane make amniotomy a simple procedure. The two gadgets that are most often used are a finger cot with a hook on the end and a rod that is about 10 inches long. Using either gadget, the medical professional performs a sterile digital exam to measure cervical dilation first. Simultaneously, the fetal presenting component is assessed to make sure it is, in fact, the fetal head and to determine whether or not it is firmly engaged in the pelvis. An artificial rupture of the membranes may be performed by the practitioner after the fetal presentation and engagement have been confirmed.^{31,34}

While using the rod-hook technique, it is common practice to use the non-dominant hand to grasp the end of the rod that is still outside the vagina. Two fingers are used to cover the rod while it is inserted into the vagina. Once the practitioner has a firm grasp on the presenting part and the amniotic membrane, they may advance the hook to the membrane using their non-dominant hand. After catching the amniotic membrane with the hook, gentle traction in a superior direction is used to tear it. A successful rupture of the membrane is usually

indicated by the rapid return of vaginal amniotic fluid. Typically, this liquid does not have any scent and is see-through. On rare occasions, however, the liquid may contain meconium or have a bloodstain in it. It is critical to note the colour of the fluid close to the area of rupture. It is recommended that the practitioner refrains from removing their hand from the vagina immediately after an artificial membrane rupture. This is because the risk of cord prolapse is highest at this period, and it may be noticed while the amniotic fluid continues to drain. It is possible to withdraw the vaginal hand if the amniotic fluid stops flowing quickly and the vaginal chord is no longer felt.³¹

MECHANICAL METHODS

While NICE warns against routinely utilising mechanical therapies, ACOG, SOGC, and WHO all support their use of balloon catheters for induction of labor (IOL). The WHO also suggests using oxytocin with a balloon catheter combination as a backup induction technique in cases when prostaglandins are unavailable or not advised. The use of a balloon catheter during cervical ripening is associated with a roughly 10% overall risk of intrapartum maternal infection, according to a meta-analysis of 43 studies.³⁵ A Cochrane review evaluated the efficacy of mechanical methods for IOL or cervical ripening during the third trimester to that of placebo, no treatment, prostaglandins, and oxytocin. The proportion of mothers who were unable to give birth vaginally within 24 hours did not vary significantly between mechanical methods and vaginal PGE2 (RR, 1.72;).³⁶

It is possible to introduce a Foley catheter via either the internal or external cervical os. The next step is to fill the balloon with normal saline, which typically ranges in volume from 30 to 80 mL. This aids in cervical dilatation by means of internal os pressure. A faster induction and reduced syntocinon need were seen with an 80 mL expanded volume compared to a 30 mL volume. One balloon applies pressure to the outside and one to the inside of the OS when a double-balloon is used. We may use varying amounts of regular saline to fill both balloons. In most cases, the use of a Cook or Foley catheter ends when the cervical dilatation

reaches three or four centimetres. Osmotic dilators are inserted into the cervical os and come in various diameters.^{11,13}

MISOPROSTOL

At room temperature, misoprostol, a synthetic analogue of PGE₁, is stable. It's used for cervical ripening, inducing labor, terminating the pregnancy, and controlling postpartum haemorrhage. Misoprostol provides a number of potential benefits over dinoprostone, including a longer shelf life, a much cheaper cost, and the absence of a refrigeration need. Oral, rectal, sublingual, and vaginal administration are among the ways misoprostol may be given; however, absorption varies. When taken orally, plasma concentrations increase swiftly, reach their peak between 12.5 and 60 minutes, and then begin a sharp decline by 120 minutes. When vaginal tablets are used, levels rise steadily to a peak in 60 to 120 minutes and then gradually decrease to around 60 percent of the peak level in 240 minutes. Misoprostol pills are not intended to be administered vaginally; therefore absorption can be irregular or sluggish.³⁷ Vaginal misoprostol has three times the bioavailability of oral misoprostol. Researchers Powers et al. found that nonpregnant women had mean half-lives of 37 minutes for oral misoprostol (200 mcg) and 44-50 minutes for vaginal misoprostol inserts (100-400 mcg).³⁸ It is not entirely known what the typical dose, regimen, and safety of misoprostol given using the buccal or sublingual routes are. As such, regular use of these methods of administration is not currently advised.³⁹

Dinoprostone and misoprostol enhance cervical extracellular collagen remodelling by increasing water content and promoting changes in glycosaminoglycan content. When these mechanisms work together, the cervix opens up, softens, and effaces. Nevertheless, the aforementioned differences in PGE₁ and PGE₂ biochemical activity, in addition to receptor activation and inhibition, may considerably affect the clinical effectiveness of dinoprostone and misoprostol.⁴⁰

Dinoprostone has been shown to minimize the time between induction and delivery, improve cervical effacement and dilatation, decrease the rate of unsuccessful inductions, utilize less oxytocin, and lower the rate of cesarean birth when compared to placebo or no therapy at all.³⁹ A Cochrane review of research comparing dinoprostone formulations indicated that PGE2 formulations were similarly helpful, and there were no differences in the incidence of caesarean deliveries.⁴¹ Several studies have shown that the effectiveness of dinoprostone gel is either equal to or inferior to that of misoprostol pills either orally or vaginally.⁴ Clinical trials and meta-analyses confirmed that the vaginal administration of misoprostol improved cervical ripening and reduced the rate of vaginal delivery failure.⁴² Vaginal misoprostol was more effective than other vaginal prostaglandins in facilitating vaginal delivery the same day and reducing the need for oxytocin augmentation. Another thing is that a Cochrane review of 76 trials found that oral misoprostol worked just as well as vaginal misoprostol. Last but not least, a metaanalysis including 96 randomized controlled studies revealed that although oral misoprostol was most successful in lowering the incidence of cesarean sections, vaginal dinoprostone was superior in lowering the number of vaginal births not completed within 24 hours.⁴²

PROSTAGLANDINS

Prostaglandins are eicosanoids that are produced when phospholipase A2 extracts arachidonic acid, a 20-carbon unsaturated fatty acid, from phospholipids in cell membranes. One or more prostaglandin G/ synthases, also known as cyclooxygenases 1 and 2 , convert arachidonic acid into prostaglandin H2 (PGH2) in a sequential fashion.⁴³ Prostacyclin (via prostaglandin I synthase), prostaglandin E2 (PGE2), prostaglandin F2 (PGF2), and prostaglandin E synthase all play a role in the conversion of labile PGH2 to active prostanoids.⁴⁴ ProIsozymes 1 and 2 of microsomal prostaglandin E synth and cyclooxygenases 2 form a preferred pairing. There are five primary types of prostaglandins: thromboxane A2, prostaglandin D2, prostaglandin I2, and prostaglandin F2a (PGF2a). During cervical ripening and parturition, PGE2 and PGF2a are the two primary prostaglandin

subtypes. While PGE2 primarily works on the prostaglandin type E prostanoid family of receptors, PGF2a primarily functions via prostaglandin FP receptors.⁴⁵ You may find PGE2 and PGF2a in many different parts of the reproductive system, including the cervix, uterus, placenta, and foetal membranes. In addition to the decidua and trophoblast, prostaglandin receptors have been found in the myometrium, cervix, and foetal membranes.^{45,46}

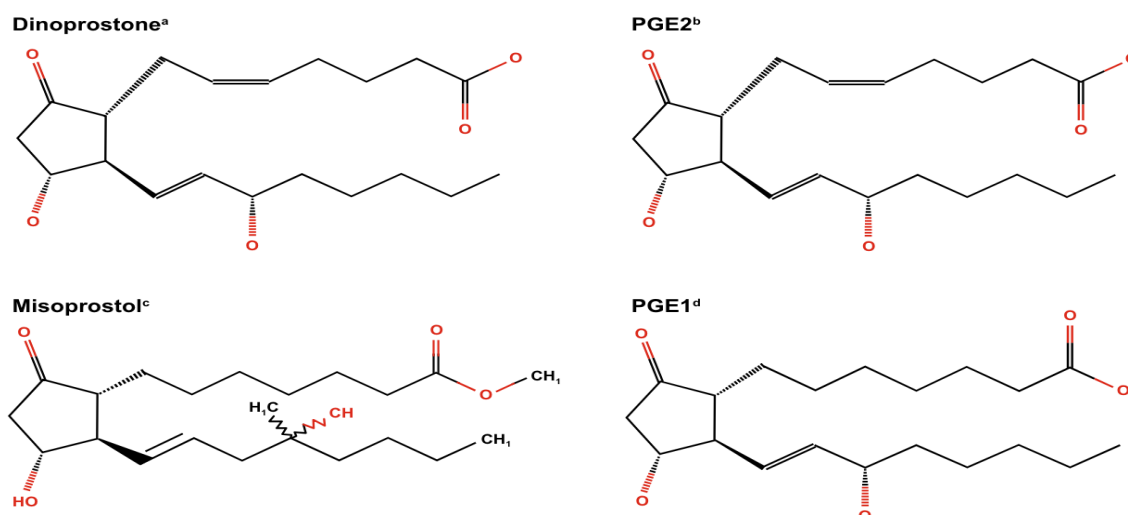


Figure1 : Misoprostol, PGE2, dinoprostone, and PGE1 structures⁴⁷

PGE2

Dinoprostone is a viable option for cervical ripening, according to the FDA. Cervidil is a vaginal implant and Prepidil is a cervical gel; both are analogues to the body's natural PGE2. The half-life of dinoprostone is around 2.5-5 minutes, and its onset and duration of action are controlled and maintained. To maintain the chemical stability of the drug, both formulations need cold storage.^{37,47}

MIFEPRISTONE

Progesterone and glucocorticoid receptors are the targets of mifepristone's action. Mifepristone acts as a selective progesterone antagonist at low dosages. It does this by establishing a connection with the progesterone receptor found in cells. Mifepristone blocks the action of cortisol at high doses by binding to the glucocorticoid receptor. This process

controls hyperglycemia in certain instances and increases blood cortisol levels by influencing the hypothalamic-pituitary-adrenal axis. In comparison to the glucocorticoid I receptor, the glucocorticoid II receptor is more affinitous to mifepristone.⁴⁸

Mifepristone has the potential to be used as a means of inducing labor in late pregnancy since it increases uterine contractility by antagonistically acting against progesterone and increases the uterus's sensitivity to prostaglandin activities. Rats have shown labor when exposed to mifepristone due to its ability to counteract progesterone-induced oxytocin receptor inhibition and increase prostaglandin production. Additionally, premature birth in mice has been shown to be induced by mifepristone and is linked to an increase in prostaglandins and cytokines. Curiously, a randomised controlled trial on beef heifers found that women given mifepristone had a 43-hour mean time to delivery compared to 182-hour mean time for women given a placebo, suggesting that retained placenta was a problem in the experimental group. In a macaque monkey model, mifepristone administration increased decidua prostaglandin F2alpha production but had no effect on amnion prostaglandin E2 synthesis.⁴⁹ Women who experience fetal mortality during a later pregnancy may also benefit from the use of mifepristone in conjunction with prostaglandins to induce labor. Based on evidence from women who had an early pregnancy termination, nulliparous women respond better to mifepristone.⁵⁰

OTHER METHODS

The American College of Obstetricians and Gynaecologists (ACOG) and the Society of Obstetricians and Gynaecologists (SOGC) both recommend oxytocin for inducing labor, and they recommend different dosage schemes. Low dose: 0.5-2 mU/min at baseline, 1-2 mU/min as dosage increases, and 15-40 minutes between doses. High dose: 4-6 mU/min at baseline, 3-6 mU/min as dosage increases, and 15-40 minutes between dosages. Despite a claim to the contrary by the National Institute for Health and Care Excellence, the World Health Organisation warns against relying only on intravenous oxytocin for IOL when

prostaglandins are not available. After oxytocin administration has started, it is recommended to monitor the uterus's reactivity, the foetal heart rate, and the pace of oxytocin infusion.^{13,26} A Cochrane analysis assessed the benefits of oxytocin monotherapy for IOL and third-trimester cervical ripening in contrast to alternative IOL techniques or placebo/no treatment. Compared to expectant management, oxytocin induction was linked to a decreased probability of vaginal delivery failure within 24 hours (8.4 percent vs. 53.8 percent; RR, 0.16).⁵¹

CONTRAINDICATIONS¹³

The following are examples of situations when IOL is not appropriate:

- Vasa previa or placenta previa
- Fetal presentation in the transverse orientation
- Prolapse of the umbilical cord
- An earlier instance of a traditional C-section's history
- Herpes infection that is active
- An endometrial cavity breach after a prior myomectomy (ACOG 107)

COMPLICATIONS & OUTCOMES

Prostaglandins and oxytocin may be responsible for uterine tachysystole, which may occur with or without abnormal foetal heart rate tracings. While nitroglycerin is an option that needs further research, the American College of Obstetricians and Gynaecologists (ACOG) suggests terbutaline or other tocolytics as potential alternatives.⁵² When standard methods of resolving the issue, such as removing prostaglandin from the vagina, moving the mother, administering extra oxygen, fluids, and reducing or stopping the oxytocin infusion, fail, a caesarean section may be considered. When it comes to uterine hyperstimulation during IOL, the World Health Organisation recommends betamimetics, however the National Institute for Health and Care Excellence (NICE) urges to consider tocolysis instead. In situations when foetal distress is suspected, a Cochrane review looked at how tocolytic treatment affected

perinatal, maternal, and foetal outcomes. Tocolytic therapy improved fetal heart rate abnormalities more than no treatment did (RR, 0.26;). When compared to magnesium sulfate, betimimetic treatment demonstrated a nonsignificant tendency of lowering uterine hyperactivity (RR, 0.07).⁵³

Depending on the circumstances, a caesarean section may not be necessary if the American College of Obstetricians and Gynaecologists suggests waiting 12 to 18 hours after latent labor begins before concluding that the induction attempted was ineffective.⁵⁴ (Simon) A higher rate of caesarean delivery and a higher failure rate in nulliparous patients are associated with inducing a woman with an unfavourable cervix, according to the "Canadian Society of Obstetricians and Gynaecologists." Healthcare providers should be aware of this fact regardless of their patient's pregnancy status. If induction is unsuccessful, NICE states that the next course of action should be a repeat induction attempt (the timing of which should be determined by the clinical state and the woman's preferences) or a caesarean²⁶ birth.

PREDICTORS FOR SUCCESSFUL INDUCTIONS

The Bishop score is one of many characteristics associated with successful inductions; obstetricians should also consider the unique characteristics of each woman waiting for the "main event" of labor. Vaginal birth rates may vary according to factors such as mother parity, age, medical comorbidities, and body mass index. Mode of delivery is affected by the expected weight and gestational age of the foetus, because larger foetuses may have difficulty passing their heads through the birth canal. Lastly, the likelihood of success could be impacted by the hospital's location, the provider's tolerance, and the decision to induce. To choose the best candidates and induction techniques, healthcare practitioners must weigh all these aspects in the office, along with the possible risks and advantages of induction vs expectant management.^{13,55}

In his groundbreaking research, Dr. Bishop established what is now known as "The Pelvic Score," which takes into account the cervix's dilatation, effacement, consistency,

position, and station of the presenting component. A score between zero and eleven was obtained by adding these components together. The main purpose of this score was to "determine the proximity to the spontaneous onset of labor." He argued that, because dating and foetal size estimates were "notoriously inaccurate" when he published his findings, the best way to induce labor (score of Z9) so that the baby wouldn't be born too early.⁵⁵ In addition to a Cochrane review, the Bishop score has been evaluated in a number of retrospective research. These articles found that women with a better Bishop score had a lower incidence of caesarean births, and they also found that vaginal deliveries were more common for both good and bad scores when inductions of labor were used instead of expectant care. Despite its limitations, the Bishop score remains a crucial variable in many studies that stratify women for induction of labor. All things considered, an induction should go well if a patient has a good Bishop score. Unfavourable scores, however, do not sufficiently distinguish individuals who choose not to deliver vaginally.^{5,56}

For a considerable amount of time, the effectiveness of inducing labor has been strongly correlated with maternal parity. The fact that multiparous patients had a better success rate with induction than nulliparous ones is not unexpected. Concerning "induction in the nulliparous patient, there still remains the crucial issue of why this should be done" due to the strong history of a prior vaginal birth, Dr. Bishop noted.⁵⁷

Any discussion of how gestational age at delivery and foetal size affect induction outcomes is convoluted due to the strong link between these variables. To illustrate the point, at what point in the pregnancy does a particular patient's foetus surpass a specific size threshold that is compatible with her pelvis? The mother's pelvis becomes involved, further complicating these considerations. Foetal weights between 4500 and 5000 g are associated with an increased risk of caesarean section and birth trauma according to recognised criteria; however, not all pregnant women will reach this weight limit. Thus, the success of inducing labor is often decreased as the fetal weight increases.⁵⁵

It is difficult to distinguish the contributions of maternal age and parity to a successful induction of labor since they are linked factors that interact. These concerns are especially important since older women are more likely to have expectant management risks, including stillbirth.⁵⁸ The independent link between maternal age and successful inductions has been the subject of a small number of studies. Labor lasted longer for older mothers, regardless of whether they had children or not, according to previous research.⁵⁵ Zaki examined labor trends, correcting for induction, by mother age and parity using a more recent obstetric cohort. Their findings showed that total labor durations decreased dramatically with increasing maternal age up to 40 years of age [7.8 hours for women in the 20-29 age range compared to 7.4 hours for women in the 30-39 age range for nulliparous women and 7.5, 6.7, and 6.5 hours for multiparous women depending on their age].⁵⁹

PHOSPHORYLATED INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN-1

Placental protein 12 is another name for Insulin-like growth factor-binding protein 1 (IGFBP-1), which is a member of the IGFBP family. The cysteine content is high in all members of the superfamily IGFBP. The protein family is composed of high-affinity insulin-like growth factor (IGF) binding proteins (IGFBPs) and low-affinity binding proteins of comparable types. Among IGFBP's functions is the regulation of IGF I and II, which it does by changing the half-lives of these growth factors and by amplifying or dampening their effects on cell proliferation. The hypothalamic factor growth hormone releasing hormone regulates the anterior pituitary gland's secretion of growth hormone. Through insulin-like growth factor-1 (IGF 1), growth hormone operates.^{60,61}

The insulin-like growth factor (IGF) system facilitates development and differentiation via the use of low molecular weight peptides. The six high-affinity versions of IGFBP, numbered 1–6, have been identified, and they bind to IGFs in various organs and the blood. Theories suggest that these IGFBPs regulate the endocrine effects of blood IGFs and lengthen

their half-life. The presence of IGFBP-1 is believed to be crucial for the physiologically active form of IGF-I because of the inverse link between the free fraction of IGF-I and IGFBP-1 (2). Excessive levels of non-phosphorylated IGFBP-1 may be utilised to diagnose preterm pre-labor rupture of membranes because this protein seeps through the cervix. Amniotic fluid has quantities of non-phosphorylated IGFBP-1 that are 100-1000 times greater than serum levels. Preterm delivery is predicted in labouring women by higher levels of phosphorylated IGFBP-1 (phIGFBP1) in cervical secretions. In addition, research has shown that cervical softening at term is accompanied with higher phIGFBP-1 levels in cervical secretions.⁶²⁻⁶⁴ The proteins that bind to insulin-like growth factors are essential for the development and growth of the placenta and the foetus. One important protein that is generated in decidualized endometrial cells during pregnancy is called phIGFBP-1. phIGFBP-1 may seep into cervical secretions as a consequence of tissue damage at the choriodecidual interface brought on by uterine contractions.

ROLE IN PREGNANCY

Kurkinen-Räty et al. discovered that symptomatic women at risk of preterm birth may be identified by high levels of phIGFBP-1 in cervical secretions. Afterwards, several studies have shown that cervical phIGFBP-1 has multiple advantages over cervicovaginal foetal fibronectin and may accurately predict when a woman will give birth prematurely if her membranes are still intact during a preterm labor episode. In particular, findings are unaffected by a history of sexual activity, urine contamination, reduced expenses, and quicker testing. That being said, several publications have questioned the test's prognostic power for premature delivery.^{65,66}

PREDICTING PRE-TERM DELIVERIES

In asymptomatic women, the cervical phIGFBP-1 test had a poor predictive accuracy for preterm birth at 37, 34, and 32 weeks of gestation, with pooled sensitivity and specificities, summary positive and negative likelihood ratios ranging from 14-47 percent, 76-93 percent, 1.5-4.4, and 0.6-1.0, respectively. The test had a low ability to predict when a baby would be born prematurely at 34 or 37 weeks of gestation, when the baby would be born within 7 or 14 days of the test, and when the test was administered to both the mother and the baby. Among women who went through preterm labor, the summary positive and negative likelihood ratios ranged from 60 to 68 percent, 77 to 81 percent, 2.7 to 3.5, and 0.4 to 0.5, respectively. The accuracy of identifying women who are not at risk of giving birth within the next 48 hours was found to be low to moderate, with a total negative probability ratio of 0.28 for all women and 0.23 for women with singleton gestations. This was seen in women suffering an episode of premature labor. Patients experiencing an episode of preterm labor who are unable to give birth within 48 hours may find relief via the discovery of cervical phIGFBP-1. Having said that, its ability to forecast whether a woman will have a preterm birth, whether she is experiencing symptoms or not, is limited.⁶⁶

ACTIM PARTUS TEST

Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) leaking into cervical secretions and the commencement of foetal membrane separation from the decidua parietalis are prelabour events. Actim Partus is a bedside kit created by Medix Biochemica of Finland to detect phIGFBP-1 in these secretions. To obtain an endocervical sample for the Actim Partus test, a sterile Dacron swab was spun in the external cervical os for 10 to 15 seconds. After dipping the swab into 0.5 ml of the extraction buffer (included in the Actim Partus kit) and giving it a good swirl for 20 seconds, the specimen was thoroughly rinsed. We then removed the swab and, for five minutes, immersed the Actim Partus dipstick into the buffer solution tube to detect the presence of phIGFBP-1. To identify phIGFBP-1, this

immune-enzymatic test made use of the monoclonal antibody 6303. The outcome was recorded when the dipstick was removed. Two blue lines signified a successful test result. A single blue line signified a poor outcome.⁶⁷

SIMILAR STUDIES IN THE PAST ON THE ROLE OF phIGFBP IN THE INDUCTION OF LABOR SUCCESS

It was examined and compared by Rathore et al. the levels of cervical phIGFBP-1 in primigravida's who had long pregnancies, with and without effective induction of labor (IOL). Hospital conducted a diagnostic study (cross-sectional research design) on 84 first-time mothers who were at least 41 weeks along in an uncomplicated singleton pregnancy between 2016 and 2018. The values of phIGFBP-1, transvaginal cervical length, and Bishop score were 3.0, 3.5, and 7.8 cm, respectively. The sensitivity, specificity, PPV, NPV, + LR, and - LR values for phIGFBP-1 ($> 7.8 \mu\text{g/l}$) were 0.87, 0.89, 0.85, 6.76, and 0.15, respectively. It was discovered that phIGFBP-1 was the most reliable indicator of a successful IOL (OR 44.200) using logistic regression analysis. In primigravida's with protracted pregnancies, phIGFBP-1 is a significant independent predictor of successful IOL compared to TVL and BS.⁸

Researchers Vallikannu et al. evaluated the safety of cervical IGFBP-1 and its potential to predict a successful induction of labor using the Bishop score and TVUS cervical length as reference points. Although TVUS is not as widely used as bedside IGFBP-1 testing, it is more tolerable than the Bishop score. After adjusting for factors such as cervical length (≤ 29 or ≤ 27 mm), Bishop score (≥ 4 or ≥ 5), and other significant characteristics, IGFBP-1 continued to predict vaginal delivery (adjusted odds ratio, AOR 5.5;) and vaginal delivery within 24 hours of induction (AOR 4.9). When it comes to vaginal birth, IGFBP-1 is 81% sensitive, 59% specific, 82% positive predictive, and 58.2% negative predictive, with likelihood ratios of 2.0 and 0.3, respectively. IGFBP-1 may assist inform decisions about labor induction for nulliparous women because it predicted vaginal birth more accurately than BS or TVUS.⁶⁸

Kruit et al. chose 35 women who had never given birth before, were carrying a single, healthy baby, and had a cephalic presentation at 40 weeks or more gestation to undergo labor induction. They took serial cervical swab samples throughout induction. They looked at the levels of the following proteins: IG.

FBP-1, pHIGFBP-1, MMP-8, MMP-2, and MMP-9. Both IGFBP-1 and pHIGFBP-1 concentrations increased during the induced cervical ripening. However, levels of matrix metalloproteinases-8 and -9 decreased. But since they couldn't predict how the labor induction would turn out, these adjustments didn't appear to be suitable for clinical application.⁶⁹

By analysing insulin-like growth factor binding protein-1 (IGFBP-1) levels in cervical secretions, Dogl et al. sought to see whether these levels may predict the success of induction efforts as well as the spontaneous onset of labor in later stages of pregnancy. When expectant management was used to predict the commencement of spontaneous labor and delivery within 72 hours, IGFBP-1 and the Bishop score both demonstrated low sensitivity (0.24, 0.92) and excellent specificity (0.45 and 0.80, respectively). The cervical length was more sensitive (0.67, 0.58). With a low sensitivity and a decent specificity, IGFBP-1 predicted successful induction within 24 hours based on the Bishop score (0.06, 1.00) and cervical length (0.45, 0.76). Parity enhanced successful induction. Both the success of labor induction after a full-term pregnancy and the commencement of labor on one's own are predicted by IGFBP-1. The levels of performance for both the bishop score and cervical length were comparable. In a study conducted by Setiyorini et al., preeclamptic women who were induced into labor had their IGFBP-1 levels and Bishop Score changes examined.

The average Bishop score for 66 patients was 2.5 ± 1.81 for women who gave birth after 24 hours of labor and 2.6 ± 1.8 for those who were in labor for 12 hours or longer. Despite the higher bishop score for the successful labor group, there was no obvious difference between the two groups. At the median, the IGFBP-1 value was 10.8 mcg/L, with a range of 8.29 ± 5.033 mcg/L. Successful induction was linked to noticeably higher levels of IGFBP-1, as shown by

an area-under-the-curve (AUC) of 0.76 and a cutoff value of 8.145. A possible indicator of successful labor induction in patients of preeclampsia during a full-term pregnancy is an IGFBP-1 level more than 8.145.⁷⁰

The purpose of the study by Kosinska-Kaczynska et al. was to identify any potential correlation between the presence of phosphorylated IGFBP-1 (phIGFBP-1) in cervical secretions during term and post-term pregnancies and the occurrence of spontaneous labor or vaginal birth. In 32.5% of cases, uterine contractions happened suddenly. Of women who gave birth, 67.5 percent did so vaginally and 32.5 percent had a cesarean section. A successful vaginal birth (0.67, 0.48) and the spontaneous commencement of labor (sensitivity 0.69, specificity 0.42) were predicted by the phIGFBP-1 test. When it came to predicting whether or not a vaginal birth would be successful, all three tests were just as sensitive as the phIBFBP-1 and the ultrasound cervical examination. There was a significant reduction in the time it took for women whose phIGFBP-1 tests came back positive to go from preinduction to the spontaneous start of delivery. A test for phIGFBP1 could be another way to predict whether a post-term pregnancy will have a successful vaginal birth or whether labor will start spontaneously.⁷¹

To forecast the result of induction, Cheung et al. evaluated biochemical alterations in the cervix, pre-induction sonography, and digital inspection. The prediction of the induction result was better when the cervix's sonographic evaluation and maternal features were combined, as opposed to using only BS or cervical length. The induction result was not further improved by including the presence or absence of phIGFBP-1.⁷²

Clinical, biophysical, and molecular features were examined by Riboni et al. to forecast the efficacy of prostaglandin-induced labor induction. At the ROC curves, the best cervical length cut-off was 22 mm, IL-6 was 5 mg/dl, and IL-8 was 20,237 mg/dl. At univariate analysis, there was a considerable correlation between the commencement of the active phase and all success predictors except IL-6. Using multivariate analysis, we found that the Bishop

score (OR 2.3), phIGFBP-1 test (OR 11.2), and IL-8 (OR 6.6) were independent variables that, when combined, helped to predict the success of labor induction. In combination with the Bishop score and IL-8, the phIGFBP-1 is a fast and easy test that may predict the effectiveness of labor induction using prostaglandins.⁷³

Nuutila et al. looked at the isoforms of insulin-like growth factor binding protein-1 (IGFBP-1) in cervical secretion to see whether those isoforms might be utilised to forecast cervical ripeness at term. Assay 2 revealed a greater IGFBP-1 content in all cervical samples than assay 1, whereas assay 1 revealed the reverse effect in all samples. Initially, the median IGFBP-1 concentration was almost four times greater in ripe cervixes (Bishop scores 6 or above; n = 29) compared to immature cervixes (Bishop scores 5 or less; n = 35). A doubling of cervical IGFBP-1 values occurred eight hours after the first PGE₂ administration. Different from those in amniotic fluid, phosphorylated versions of IGFBP-1 are secreted by women who have intact foetal membranes; these isoforms signal cervical ripeness. A bedside test for certain isoforms of IGFBP-1 might help predict whether a patient is amenable to inducing labor.⁹

MATERIALS AND METHODS

Study site: Department of Obstetrics and Gynaecology , R.L. Jalappa Hospital & Research Centre, which is affiliated with Sri Devaraj Urs Medical College and is run by SDUAHER, is located in Tamaka, Kolar.

Study population: All Pregnant women >37 weeks gestational age who are getting admitted and are planned for induction at RLJH and research centre, Tamaka who fulfill inclusion and exclusion criteria.

Study design: Cross sectional study

Study period: September 2022 to December 2023

Sampling method: Using convenient sampling, all eligible respondents were recruited into the research in a sequential fashion until the sample size was attained.

Inclusion criteria:

- Intrauterine pregnancy with gestational age ≥ 37 week
- Singleton pregnancy.
- Cephalic presentation.
- Pregnant woman not in labor.

Exclusion criteria:

- Conditions where vaginal delivery is contraindicated.
- Premature rupture of membranes.

Sample size:

Based on the research by Ibrahim A et al., which found that 81.4% of participants tested positive for IGFBP-1 following induction of labor in patients older than 37 weeks, the sample size was determined using the formula.

$$\text{Sample Size} = \frac{Z_{1-\alpha/2}^2 P (1-P)}{d^2}$$

$$d^2$$

$Z_{1-\alpha/2}$ = is standard normal variate (at 5% type 1 error ($P < 0.05$) it is 1.96 and at 1% type 1 error ($P < 0.01$) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.

P = Expected proportion in population based on previous studies or pilot studies

d = Absolute error or precision

P = 81.4% or 0.814

q = 18.6% or 0.186

d = 10% or 0.10

A minimum of 58 people will be included in the research based on the above-mentioned data at a 95% confidence level.

Ethical considerations: The consent was granted by the institutional review board. In order to ensure that only those who were willing to participate in the research actually did so, we obtained their signed, informed permission. Participants were informed of the potential advantages and dangers of the research, as well as the fact that their participation was entirely voluntary, before their agreement was obtained. Everyone involved in the research was able to keep their identities secret.

Data collection tools: All the relevant parameters were collected and documented in a structured study proforma.

Methodology:

- After the written informed consent, patient fulfilling the inclusion criteria will be included in the study.
- Detection of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) in cervical secretions will be done by Actim partus test.

- The patient will be placed in the lithotomy position. A sterile Cusco speculum will be insert into the vagina.
- A sterile polyester swab will be inserted into the cervical os. The swab will be left in the cervical os for 10–15 s to allow it to absorb the secretions.
- The specimen will be extracted immediately from the swab by swirling the swab vigorously in the extraction solution for 10–15 s.
- In the dipstick the yellow dip area will be placed into the extraction sample and held until the liquid front entering the result area is seen. The dipstick from the solution is removed and placed in a horizontal position.
- Interpretation of the results: If the test line and control line appear, the test result was positive. If one blue line, the control line, appears, the test result was negative. When control line did not appear, the test was invalid.
- Labor induction was done according to the standard guidelines.
- prostaglandin E1 (misoprostol) will be started for unfavourable cervix.
- Initial dose of 25 mcg vaginal tablet will be given. Reassessment will be done 4 h after the initial dose unless clinical condition indicates earlier assessment.
- If no cervical ripening occurred after four doses of misoprostol, at 4-hour interval the procedure will be considered failure and the patient will be delivered by Caesarean section.
- If there is cervical ripening, Oxytocin infusion was started by 5 U or 2.5U in 500 ml of normal saline or Ringer solution in 6 h following the last dose of misoprostol, and is titrated.
- During the period of induction, the fetal heart rate will be monitored continuously by means of electronic fetal heart rate monitoring (cardiotocography). Maternal monitoring will be done including blood pressure measurements every 2 h and frequent clinical evaluation.
- The fetal heart rate will considered reassuring if stable baseline rate was between 110 and 160 bpm with a short-term and long-term variability (>5 bpm) and No deceleration.

- Accelerations are considered with more than 15 bpm for more than 15 s, with fetal movement and with contractions.
- If the fetal heart rate patterns are non-reassuring or maternal contractile abnormalities are present prompt delivery was performed by Caesarean section.
- Caesarean section will be done in the following situations: persistent non reassuring or abnormal fetal heart pattern , failed induction of labor and persistent contractile abnormalities .
- Then assessment will be made about mode of delivery in patients with and without phosphorylated insulin like growth factor binding protein 1 positive.

Statistical Methods:

We will use SPSS 22 version software to analyse the data that has been put into a Microsoft Excel data sheet. Frequencies and proportions will be used to represent categorical data.

As a significance test, chi-square will be used. The mean and standard deviation will be used to describe continuous data. In order to determine the difference in means, a significance test called an independent t test will be used. Statistical significance will be determined if the P value is less than 0.05.

RESULTS

There were 58 patients included in the study

Table 1: Table showing age wise distribution of patients

AGE	Frequency	Percent
< 20 YEARS	10	17.2
21-25 YEARS	20	34.5
26-30 YEARS	21	36.2
>30 YEARS	7	12.1
Total	58	100.0

Figure 2: Graph showing age wise distribution of patients

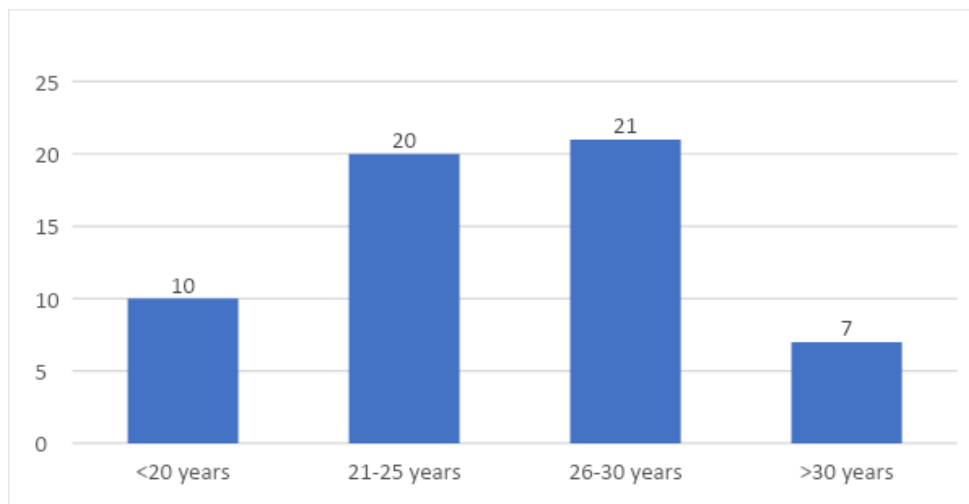


Table 1 and Figure 2: Majority of the patients were in the age group between 26 and 30 years (36.2%), followed by 21-25 years (34.5%), while 17.2% and 12.1% of the patients were <20 years and >30 years, respectively.

Table 2: Table showing patients as per gravida

GRAVIDA	Frequency	Percent
PRIMIGRAVIDA	26	44.8
GRAVIDA 2	17	29.3
GRAVIDA 3	13	22.4
GRAVIDA 4	2	3.4
Total	58	100.0

Figure 3: Graph showing patients as per gravida

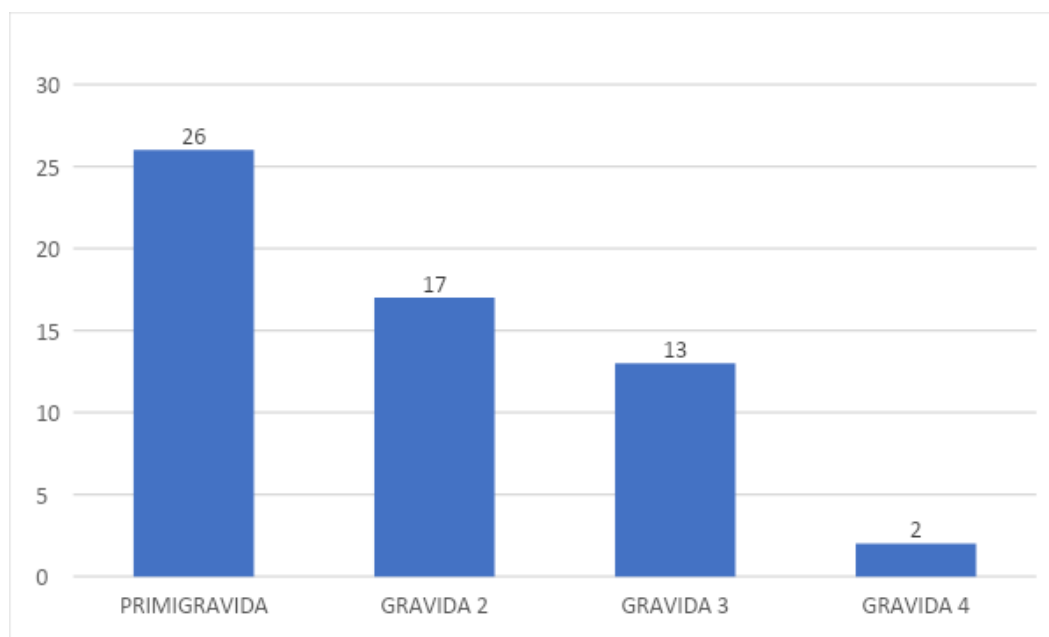


Table 2 and Figure 3: Most of the women were primigravida (44.8%), followed by gravida 2 (29.3%) and 3 (22.4%)

Table 3: Table showing patients as per gestational age

GESTATIONAL AGE	Frequency	Percent
37-38+6	13	22.4
39-39+6	16	27.6
≥ 40	29	50.0
Total	58	100.0

Figure 4: Graph showing patients as per gestational age

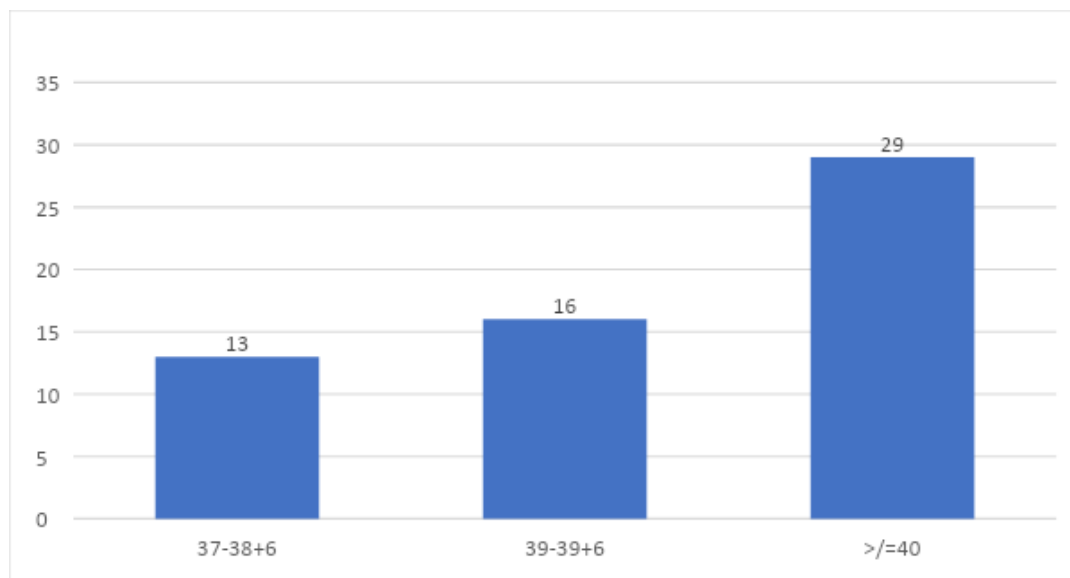


Table 3 and Figure 4: Majority of the patients were with gestational age of more than 40 weeks (50%).

Table 4: Table showing patients as actim partus test status

ACTIM PARTUS TEST	Frequency	Percent
POSITIVE	46	79.3
NEGATIVE	12	20.7
Total	58	100.0

Figure 5: Pie chart showing patients as actim partus test status

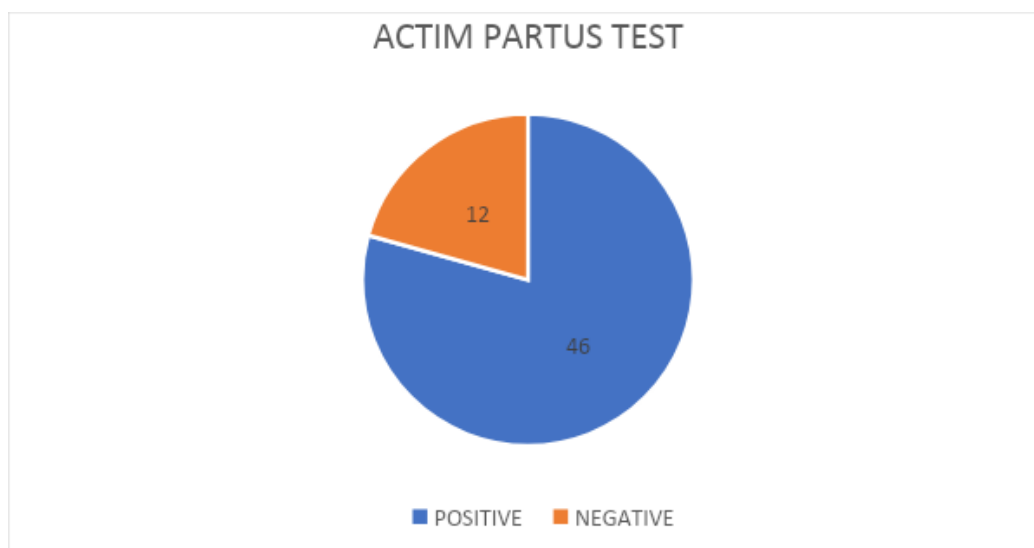


Table 4 and Figure 5: Actim partus test is positive in 79.3 % of pregnant women and is negative in 20.7 % .

Table 5: Table showing Bishop score distribution of patients

BISHOP SCORE	Frequency	Percent
<5	17	29.3
5	41	70.7
Total	58	100.0

Figure 6: Pie chart showing Bishop score distribution of patients

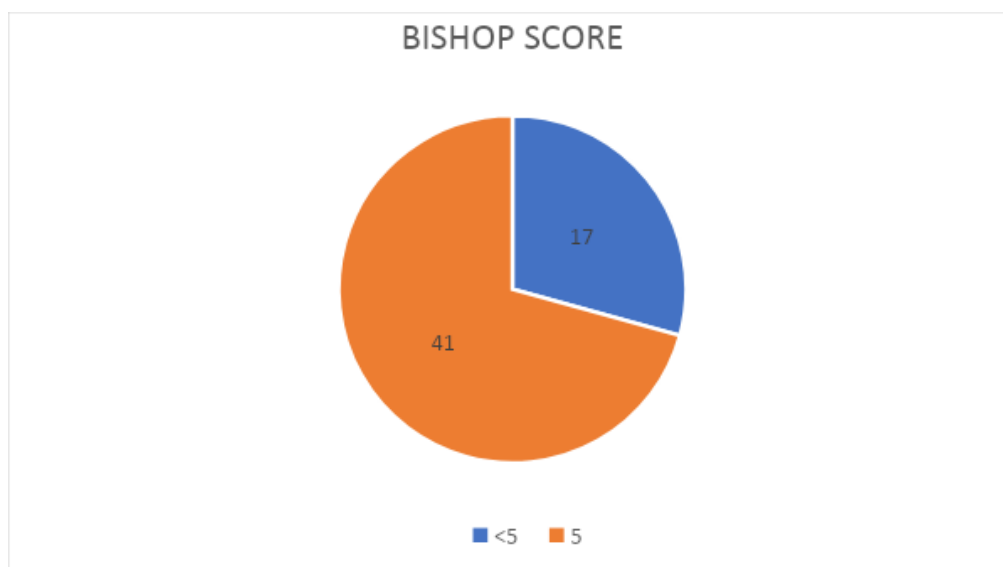


Table 5 and Figure 6: Most of pregnant women had a BISHOP score of 5 (70.7%), while 29.3% had less than 5.

Table 6: Table showing method of induction among patients

METHOD OF INDUCTION	Frequency	Percent
FOLEYS'S +MISOPROSTOL+OXYTOCIN	19	32.8
FOLEYS'S +MISOPROSTOL	13	22.4
FOLEYS'S +OXYTOCIN	5	8.6
MISOPROSTOL+OXYTOCIN	8	13.8
MISOPROSTOL	13	22.4
Total	58	100.0

Figure 7: Graph showing method of induction among patients

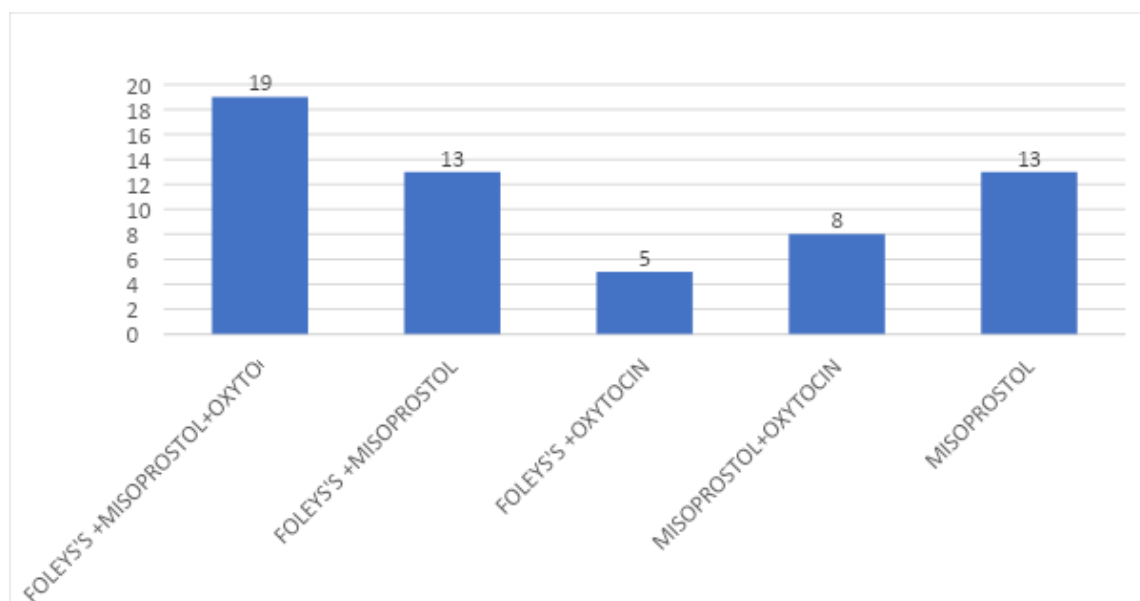


Table 6 and Figure 7: Foleys's +Misoprostol + Oxytocin was the most common induction method used (32.8%), followed by Foleys's +Misoprostol (22.4%) and misoprostol only (22.4%)

Table 7: Table showing mode of delivery among patients

MODE OF DELIVERY	Frequency	Percent
VAGINAL DELIVERY	45	77.6
LSCS	13	22.4
Total	58	100.0

Figure 8: Pie chart showing mode of delivery among patients

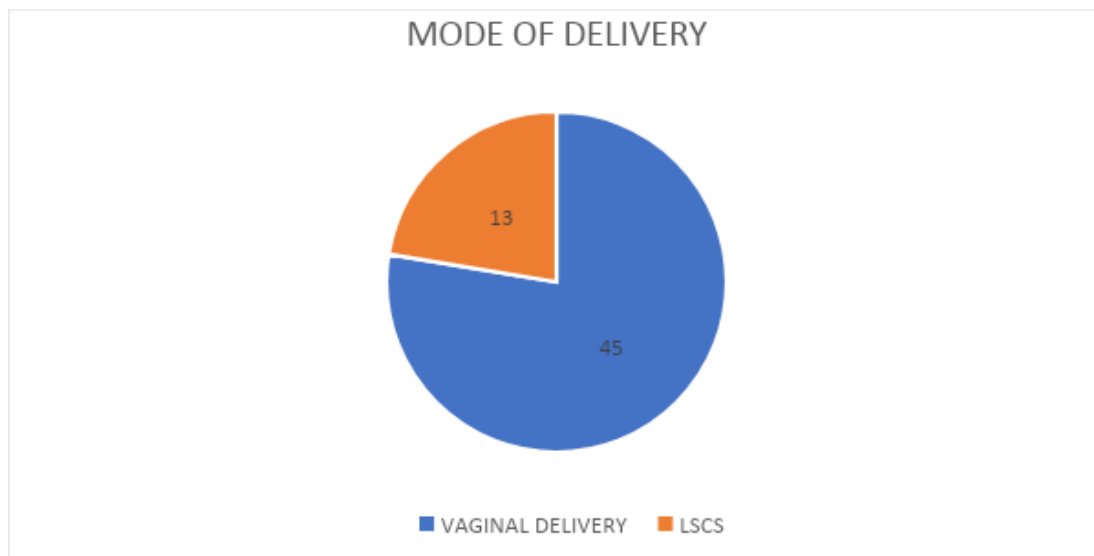


Table 7 and Figure 8: Majority of the patients had vaginal delivery (77.6%), while 22.4% had LSCS.

Table 8: Table showing indications of LSCS in patients

INDUCTION OF LABOR	Frequency	Percent
FAILED INDUCTION	4	30.8
NON-PROGRESSION OF LABOR	4	30.8
FETAL DISTRESS	4	30.8
DEEP TRANSVERSE ARREST	1	7.7
Total	13	100.0

Figure 9: Graph showing indications of LSCS in patients

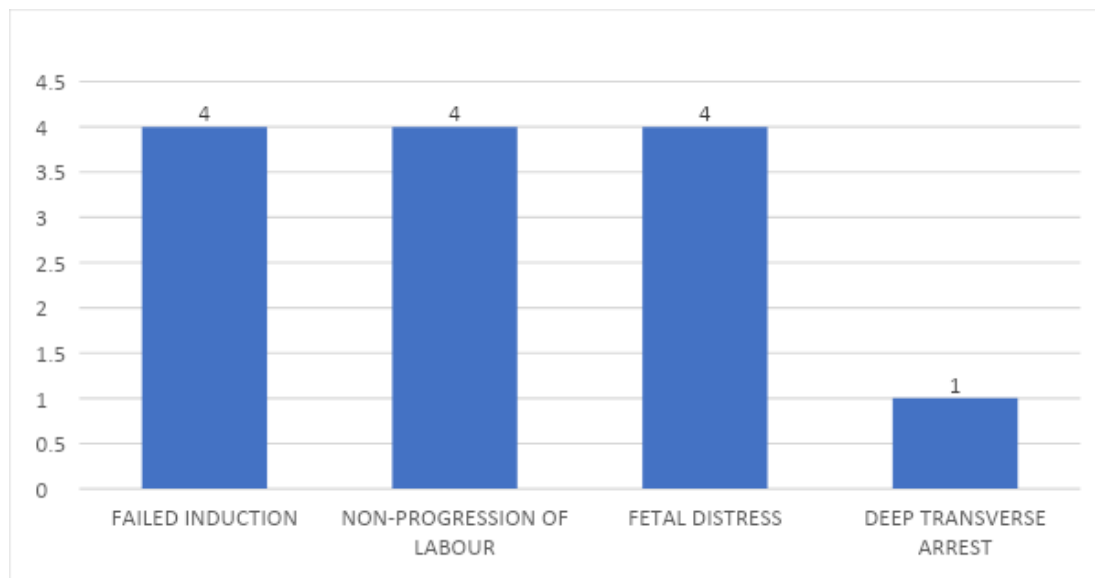


Table 8 and Figure 9: Foetal distress (30.8%), non-progression labor (30.8%), and failed induction (30.8%) were the most prevalent reasons for the LSCS.

Table 9: Table showing the outcome of labor induction

INDUCTION OF LABOR	Frequency	Percent
Success	54	93.1
Failed	4	6.9
Total	58	100.0

Figure 10: Pie chart showing the outcome of labor induction

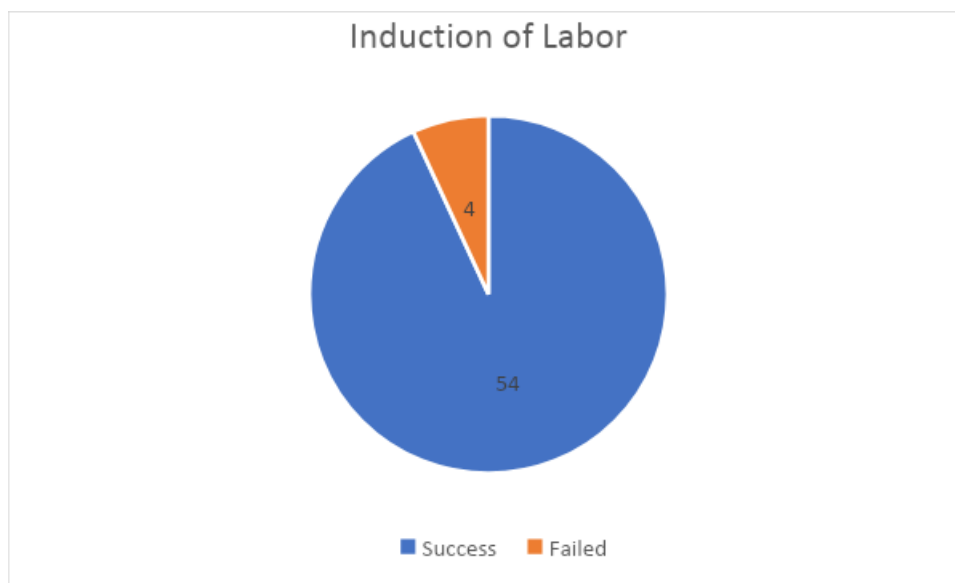


Table 9 and Figure 10: Overall induction of labor was successful among 93.1% of the pregnant women

Table 10: Table showing relationship of induction of labor with actim partus test results

Induction of Labor * Actim partus test					
			ACTIM PARTUS TEST		P value
			Positive	Negative	
Induction of Labor	Success	Frequency	46	8	<0.001
		Percentage	100.0%	66.7%	
	Failed	Frequency	0	4	
		Percentage	0.0%	33.3%	
Total		Frequency	46	12	
		Percentage	100.0%	100.0%	

Figure 11 : Graph showing relationship of induction of labor with actim partus test results

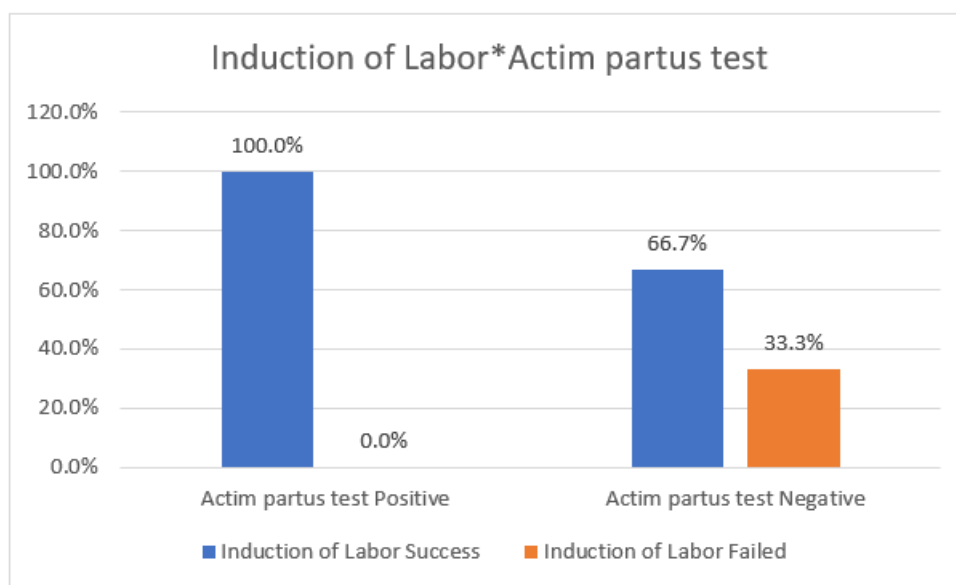


Table 10 and Figure 11: The ability to induce labor successfully was significantly correlated with the presence of phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1).

Table 11: Table showing diagnostic validity measures of PhIGFBP-1 in predicting successful induction of labor

Sensitivity	85.2
Specificity	100
PPV	100
NPV	33.3
Accuracy	86.21

Figure 12: Graph showing diagnostic validity measures of phIGFBP-1 in predicting successful induction of labor

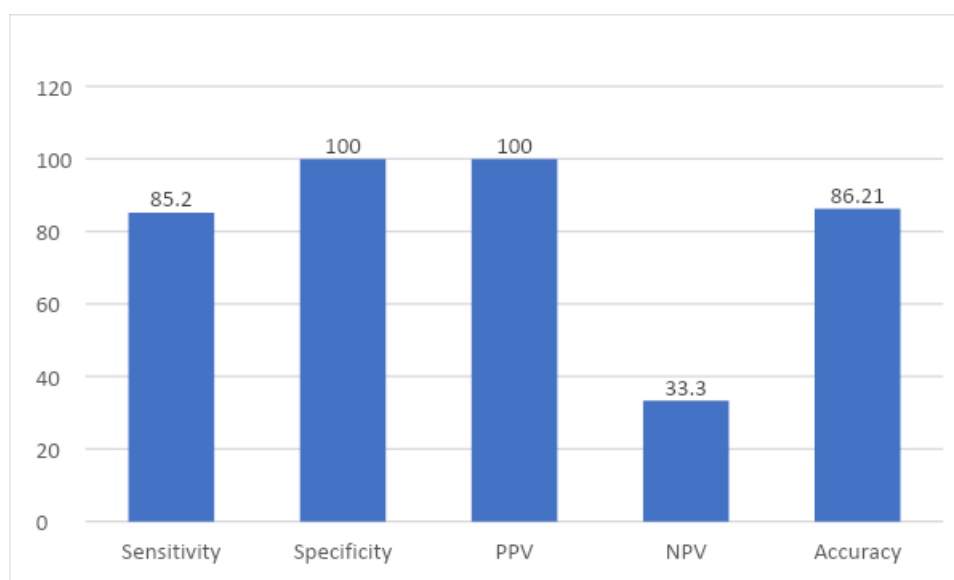


Table 11 and Figure 12: Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) diagnostic accuracy for predicting labor induction success in inducing labor was predicted with an accuracy rate of 86.2%, a sensitivity rate of 85.2%, a specificity rate of 100%, a positive predictive value of 100%, and a negative predictive value of 33.3% by the phIGFBP-1.

DISCUSSION

The present study included 58 pregnant women who were over 37 weeks pregnant and were scheduled for induction. The findings showed that approximately half were primigravida mothers, followed by gravida 2 (29.3%) and 3 (22.4%). Most of the patients had a gestational age of more than 40 weeks (50%). Foleys's + Misoprostol + Oxytocin was the most common induction method used (32.8%), followed by Foleys's + Misoprostol (22.4%) and misoprostol only (22.4%). Most of the patients had a vaginal delivery (77.6%), while 22.4% had LSCS. Overall, the labor induction was successful among 93.1% of pregnant women.

The majority of the patients (79% in this research) tested positive for Actim partus. While 29.3% of pregnant women had a score below 5, the majority (70.7%) got a score of 5 or above on the BISHOP. Cervicovaginal fluid pHIGFBP-1 levels are considered an important indicator of impending labor. With an accuracy of 86.2%, a sensitivity of 85.2%, a specificity of 100%, a PPV of 100%, and an NPV of 33.3%, the pHIGFBP-1 was a reliable predictor of a successful labor induction.

DEMOGRAPHY

Rathore et al.⁸ studied 84 primigravida mothers with uncomplicated singleton pregnancies, all 41 weeks or more pregnant. **Kruit et al.**⁶⁹ studied 35 primigravida women with intact amniotic sacs. They included the women in gestational weeks for more than 40 weeks, and 80% were more than 42 weeks. Fetal induction was failed in 33%. The fetal induction was successful in 93% of our study in comparison.

Kosinska-Kaczynska et al. recruited 167 pregnant women who had either a singleton or a postterm pregnancy for a prospective cohort study. They estimated pHIGFBP-1 in cervix secretions in predicting labor progression. Among them, 67.5% delivered vaginally, while the remaining 32.5% underwent cesarean deliveries. In the present study, labor induction was

successful among 93.1% of pregnant women. 22% of the study population underwent cesarean section, which is lower than that of the compared study.⁷¹

Cheung et al. included 460 pregnant women who were measured for cervix length, angle, and baby's head position between weeks 37 and 41 of gestation. Following induction, women gave birth vaginally in 74% of cases. Compared to that, 22% of the women in this research had a caesarean section, while the remaining 78% had a vaginal birth.⁷²

BISHOP SCORE AND PHIGFBP-1 COMPARISON

Riboni et al.⁷³ carried out a study across multiple centers to examine the differences in clinical, biophysical, and molecular factors that can help predict the effectiveness of labor induction using prostaglandins. They included 115 pregnant women at term. The BS was more than four in 43% of cases. In the present study, the cut-off of BS was five, and 71% of women were above five BS.

In the study by **Rathore et al.**, BS and the threshold for phIGFBP-1 were set at 3 cm and 7.8 µg/l, respectively. Women with phIGFBP-1 levels exceeding 7.8 µg/l exhibited specific characteristics, with 87% sensitivity, 89% specificity, and 89% positive predictive value (PPV). We found that 71% of pregnant women in our study had a BS score of five or above, which is higher than the results reported by Rathore et al. This difference in accuracy is likely due to the fact that we included pregnant women beyond 37 weeks of gestation in our study, whereas Rathore et al. concentrated on simple first-trimester pregnancies beyond 41 weeks of gestation.⁸

Vallikannu et al. predicted IGFBP-1 independently in vaginal delivery following induction. However, when adjusting to BS, it was not predictive. When it came to forecasting labor, IGFBP-1 had a sensitivity of 81%, specificity of 59%, positive predictive values of 82%, and negative predictive values of 58%. The accuracy was higher in our study in comparison, probably because of pregnant women with multiparas, while Vallikannu et al. included only

nulliparous women in predicting labor. The difference in accuracy might also be due to the larger sample size (193).⁶⁸

In Kruit et al. study, out of 35 women, 17 (50%) had a BS score of less than three, while in our study, the cutoff for BS was five, and 70% had a BS score exceeding five in the present study. This discrepancy might be attributed to the fact that the study by Kruit et al. only included nulliparous women, while the present study included gravida 2 (29.3%) and 3 (22.4%) among the study participants.⁶⁹

Dogl et al. found IGFBP-1 to have 45% sensitivity, 80% specificity, 62% PPV, and 67% NPV in predicting labor. They found that the IGFBP-1 test is a valid technique for assessing labor induction. The research also indicated that BS has a sensitivity of 24% and a specificity of 92%. The diagnosis accuracy was greater in the current research in comparison, perhaps because of the various study designs utilised by Dogl et al., i.e., cohort study, whereas the present investigation used a cross-sectional design. In addition, Dogl et al. included only post-term pregnant women, while the present study included those with pregnancy 37 weeks and above.¹⁰

Setiyorini et al. looked into the variations in IGFBP-1 levels and the Bishop Score in preeclamptic women undergoing induction of labor. Participants in the research had to have preeclampsia and be 37 weeks along in their pregnancy. In our research, 93.1% of pregnant women had a successful labor induction, while the study only recorded 77% of successful inductions. The lower successful induction in Setiyorini et al. could be due to the inclusion of preeclampsia cases. Both studies have demonstrated that IGFBP-1 predicts spontaneous labor progress.⁷⁰

The mean BS was 5.3 ± 2.4 at admission and increased significantly to 9.3 after removing the Foley catheter in **Kosinska-Kaczynska et al. study results**. In the study, phIGFBP-1 was found to have 69% sensitivity and 42% specificity for predicting the spontaneous onset of labor. When it came to predicting successful labor induction, phIGFBP-

1 showed 85% sensitivity, 100% specificity, PPV, and 33% NPV. However, the current study found that it had higher sensitivity and specificity than before when it came to predicting successful labor induction. Also,, the study of estimated that the accuracy of BS and phIGFBP-1 does not differ, significantly and serve serves a predictors predictor. ⁷¹

Cheung et al. study showed 75% specificity for BS in predicting vaginal delivery. The study concluded that the ultrasound was superior in predicting the labor compared to BS. Also, the phIGFBP-1 did not significantly affect the prediction. However, the present study independently assessed the prediction of phIGFBP-1 in labor, showing 100% specificity, which is higher than that of the compared study, which assessed the BS. ⁷²

Brik et al. ⁷⁴ carried out a prospective observational research including 276 pregnant women carrying a singleton from week 24 to week 34. Similar to the current research, 58% of those participants were not pregnant. For those delivered within 32 weeks, the sensitivity was between 73% and 76%. A somewhat faster indicator of labor than IGFBP-1, phIGFBP-1 in cervical secretions has recently emerged as an important indicator of labor. The lower accuracy in the study of Brik et al was due to the inclusion of women with gestational weeks less than 34 weeks, while we included those with more than 37 weeks.

Nuutila et al. examined the IGFBP-1 in cervical fluid for labor prediction. In the beginning, they discovered that labor prediction services had an average IGFBP-1 level that was almost four times higher than the general population. There was an eightfold rise in cervix IGFBP-1 levels eight hours after the initial PGE2 injection. ⁹

The risk of LSCS during induction of labor is higher among post-term pregnancy, which varied from 10 to 37%. The present study, which included pre- and post-term, had 22% LSCS. Since LSCS for induction of labor has complications, including excessive blood loss, it is essential to have a sensitive tool to predict labor onset. Since the fetal complications and death rate is higher with increase in gestational age, it is important to predict the spontaneous labor. ⁷⁵

In the observational study, the results of **Vankayalapati et al.**⁷⁶ included 125 nulliparous and 63 parous women with average gestational days of 294 days. Among nulliparous women, 55% underwent induced for labor, and 19% were induced among parous women. Their study found that the length of the cervical canal is a strong predictor of when labor will begin in pregnant women, regardless of their gestational age. We also found that the presence of phIGFBP-1 in the cervical secretion is associated with both spontaneous labor starting and a successful vaginal birth. Up until now, researchers have mostly used the Bishop score and cervical length assessment to make these predictions.

SUMMARY

- Pharmacological, surgical, and mechanical techniques may all be used to induce labor.
- The effectiveness of labor induction may be predicted by a bedside test for phosphorylated isoforms of insulin-like growth factor binding protein-1 (IGFBP-1).
- A cross-sectional study was conducted in 58 Pregnant women >37 weeks gestational age to evaluate the presence of Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) among the patients with and without successful induction of labor.
- The study was conducted between September 2022-December 2023
- Majority of the patients were in the age group between 26 and 30 years (36.2%), followed by 21-25 years (34.5%)
- Most of the women were primigravida (44.8%). Majority of the patients were with gestational age of more than 40 weeks (50%).
- Actim partus test was found to be positive among 79.3% of the women
- Foleys's +Misoprostol+Oxytocin was the most common induction method used (32.8%).
- Overall induction of labor was successful among 93.1% of the pregnant women
- Significantly higher of patients with Phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) positivity had successful induction of labor
- The most common indications for the LSCS were failed induction (30.8%), non-progression labor (30.8%) and fetal distress (30.8%).
- The sensitivity, specificity, PPV, NPV and accuracy of the phIGFBP-1 in predicting successful induction of labor were 85.2%, 100%, 100%, 33.3% and 86.2%, respectively.

CONCLUSION

Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) was able to accurately predict the successful induction of labor, with both high sensitivity and specificity. Presence of Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervicovaginal secretions correlate strongly with the successful labor induction. These findings support the incorporation of phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) assessment into routine prenatal care, offering a valuable tool for optimizing labor management and ensuring safe labor.

LIMITATIONS

- It is a study based at a single centre with limited sample size.
- Because this research is cross-sectional, proving cause-and-effect relationships is difficult. The assessment of phIGFBP-1 doesn't measure the specific other independent confounders that cause the labor prediction.
- Additionally, unlike randomized controlled trials (RCTs), this study didn't compare two groups to examine the effects of phIGFBP-1. The lack of a comparative method restricts the ability to identify, factors impact on predicting labor. It's crucial to recognize that without a control group or the manipulation of variables through experiments, it's difficult to solely attribute the differences seen to labor prediction.

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ANNEXURE I

PATIENT CONSENT FORM

“Role of phosphorylated Insulin-like Growth Factor Binding Protein-1 as Predictor of Successful Labor Induction in Full Term Pregnancy - A CROSS SECTIONAL STUDY”

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I have understood that I have the right to refuse consent or withdraw it at any time during the study and this will not affect my treatment in any way. I consent voluntarily to participate in this study

Name of Participant_____

Signature/ thumb print of Participant_____

Date_____

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant and to the best of my ability made sure that the participant understands that the following will be done: A sterile Cusco speculum will be inserted into vagina, cervix is visualized and swab will be taken from cervical os and is tested for presence of **Phosphorylated insulin-like growth factor-binding protein-1**(phIGFBP-1).

I confirm that the participant was given an opportunity to ask questions about the study and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of Researcher/person taking the consent: Dr. KOLAKOTLA AJITHA

Signature of Researcher /person taking the consent: _____

Date _____

Name and Address of Principal Investigator:

Dr. KOLAKOTLA AJITHA

R.L Jalappa Hospital

Tamaka, Kolar.

ರೋಗಿಯ ಒಪ್ಪಿಗೆ ನಮೂನೆ

"ಪೂರ್ಣ ಅವಧಿಯ ಗರ್ಭಾವಸ್ಥೆಯಲ್ಲಿ ಯಶಸ್ವಿ ಕಾರ್ಮಿಕ ಪ್ರೇರಣೆಯ ಮುನ್ನೂಚಕವಾಗಿ ಫಾಸ್ಫೊರಿಲೇಟೆಡ್ ಇನ್ಸುಲಿನ್ ತರಹದ ಬೆಳವಣಿಗೆಯ ಅಂಶ ಬೈಂಡಿಂಗ್ ಪ್ರೋಟೀನ್-1 ಪಾತ್ರ - ಒಂದು ಅಡ್ಡ ವಿಭಾಗದ ಅಧ್ಯಯನ"

ನಾನು ಮೇಲಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿದ್ದೇನೆ ಅಥವಾ ಅದನ್ನು ನನಗೆ ಓದಿದ್ದೇನೆ. ಅದರ ಬಗ್ಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶವಿದೆ ಮತ್ತು ನಾನು ಕೇಳಿದ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ. ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಒಪ್ಪಿಗೆಯನ್ನು ನಿರಾಕರಿಸುವ ಅಥವಾ ಅದನ್ನು ಹಿಂತೆಗೆದುಕೊಳ್ಳುವ ಹಕ್ಕನ್ನು ನಾನು ಹೊಂದಿದ್ದೇನೆ ಮತ್ತು ಇದು ನನ್ನ ಚಿಕಿತ್ಸೆಯ ಮೇಲೆ ಯಾವುದೇ ರೀತಿಯಲ್ಲಿ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಾನು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಸಮ್ಮತಿಸುತ್ತೇನೆ

ಭಾಗವಹಿಸುವವರ ಹೆಸರು:

ಭಾಗವಹಿಸುವವರ ಸಹಿ/ಹೆಬ್ಬರಳಿನ ಮುದ್ರೆ:

ದಿನಾಂಕ:

ಒಪ್ಪಿಗೆಯನ್ನು ತೆಗೆದುಕೊಳ್ಳುವ ಸಂಶೋಧಕ/ವ್ಯಕ್ತಿಯ ಹೆಳಿಕೆ:

ಸಂಭಾವ್ಯ ಭಾಗವಹಿಸುವವರಿಗೆ ನಾನು ಮಾಹಿತಿ ಹಾಳೆಯನ್ನು ನಿಖರವಾಗಿ ಓದಿದ್ದೇನೆ ಮತ್ತು ನನ್ನ ಸಾಮರ್ಥ್ಯಕ್ಕೆ ತಕ್ಕಂತೆ ಈ ಕೆಳಗಿನವುಗಳನ್ನು ಮಾಡಲಾಗುತ್ತದೆ ಎಂದು ಭಾಗವಹಿಸುವವರು ಅರ್ಥ ಮಾಡಿಕೊಂಡಿದ್ದಾರೆ ಎಂದು ಖಚಿತ ಪಡಿಸಿಕೊಂಡಿದ್ದೇನೆ: ಸ್ಟೆರೈಲ್ ಕುಸ್ತೋ ಸೈಕ್ಯುಲಮ್ ಅನ್ನು ಯೋನಿಯೊಳಗೆ ಸೇರಿಸಲಾಗುತ್ತದೆ, ಗರ್ಭ ಕಂಠವನ್ನು ದೃಢೀಕರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಸ್ವಾಬ್ ತೆಗೆದುಕೊಳ್ಳಲಾಗುತ್ತದೆ. ಗರ್ಭ ಕಂಠದ ಓಎಸ್ ನಿಂದ ಮತ್ತು ಫಾಸ್ಫೊರಿಲೇಟೆಡ್ ಇನ್ಸುಲಿನ್ ತರಹದ ಬೆಳವಣಿಗೆಯ ಅಂಶ-ಬಂಧಿಸುವ ಪ್ರೋಟೀನ್-1 (PHIGFBP-1) ಇರುವಿಕೆಯನ್ನು ಪರೀಕ್ಷಿಸಲಾಗುತ್ತದೆ. ಭಾಗವಹಿಸುವವರಿಗೆ ಅಧ್ಯಯನದ ಕುರಿತು ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶವನ್ನು ನೀಡಲಾಗಿದೆ ಮತ್ತು ಭಾಗವಹಿಸುವವರು ಕೇಳಿದ ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳಿಗೆ ಸರಿಯಾಗಿ ಮತ್ತು ನನ್ನ ಸಾಮರ್ಥ್ಯಕ್ಕೆ ತಕ್ಕಂತೆ ಉತ್ತರಿಸಲಾಗಿದೆ. ಎಂದು ನಾನು ದೃಢೀಕರಿಸುತ್ತೇನೆ. ವ್ಯಕ್ತಿಯನ್ನು ಸಮ್ಮತಿಯನ್ನು ನೀಡುವಂತೆ ಒತ್ತಾಯಿಸಲಾಗಿಲ್ಲ ಮತ್ತು ಒಪ್ಪಿಗೆಯನ್ನು ಮುಕ್ತವಾಗಿ ಮತ್ತು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ನೀಡಲಾಗಿದೆ. ಎಂದು ನಾನು ದೃಢೀಕರಿಸುತ್ತೇನೆ.

ಸಂಶೋಧಕರ/ಸಮ್ಮತಿಯನ್ನು ತೆಗೆದುಕೊಳ್ಳುವ ವ್ಯಕ್ತಿಯ ಹೆಸರು: ಕೋಲಕೋಟ್ಟ ಅಜಿತ

ಒಪ್ಪಿಗೆಯನ್ನು ತೆಗೆದುಕೊಳ್ಳುವ ಸಂಶೋಧಕರ/ವ್ಯಕ್ತಿಯ ಸಹಿ

ದಿನಾಂಕ

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು ಮತ್ತು ವಿಳಾಸ:

ಡಾ.ಕೋಲಕೋಟ್ಟ ಅಜಿತ

ಆರ್.ಎಲ್ ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಟಮಕ, ಕೋಲಾರ.

ANNEXURE II

PATIENT INFORMATION SHEET

STUDY TITLE: “Role of phosphorylated Insulin-like Growth Factor Binding Protein-1 as Predictor of Successful Labor Induction in Full Term Pregnancy-A CROSS SECTIONAL STUDY”

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that I will be needing a swab from the cervicovaginal region for the testing of presence of Phosphorylated insulin-like growth factor-binding protein-1(phIGFBP-1). The entire finance of the tests will be borne by me alone and you will not be required to pay for anything outside of your regular treatment.

We are conducting this study to predict successful labor induction in women who are planned for induction of labor. If you are willing to be enrolled in this study, you will be required to give a swab from the cervicovaginal region for the tests. You will receive the standard care pre- and post-delivery or operatively irrespective of whether you choose to opt for the study or not.

You are free to opt-out of the study at any time if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are part of the study. In case of any complication during surgery patient will be treated accordingly.

Your identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact Dr. KOLAKOTLA AJITHA or any other member of the above research team for any doubt or clarification you have.

Dr. KOLAKOTLA AJITHA

Mobile no: 9553044877

E-mail id: ajithakoakotla@gmail.com

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: "ಫಾಸ್ಫೊರಿಲೇಟೆಡ್ ಇನ್ಸುಲಿನ್ ತರಹದ ಬೆಳವಣಿಗೆಯ ಪಾತ್ರ ಅಂಶ ಪೂರ್ಣವಾಗಿ ಯಶಸ್ವಿ ಕಾರ್ಮಿಕ ಪ್ರೇರಣೆಯ ಮುನ್ನೂಚಕವಾಗಿ ಪ್ರೋಟೀನ್-1 ಅನ್ನು ಬಂಧಿಸುವುದು ಅವಧಿ ಪ್ರೆಗ್ನಿನ್-ಎ ಕ್ರಾಸ್ ಸೆಕ್ಷನಲ್ ಸ್ಪಡಿ "

ಸ್ಪಡಿ ಸೈಟ್: ಆರ್.ಎಲ್ ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ಟಮಕ, ಕೋಲಾರ.

ಉಪ ಸ್ಥಿತಿಯ ಪರೀಕ್ಷೆಗಾಗಿ ನನಗೆ ಗರ್ಭಕಂಠದ ಪ್ರದೇಶದಿಂದ ಸ್ವಾಬ್ ಅಗತ್ಯವಿದೆ ಎಂದು ನಿಮಗೆ ತಿಳಿಸಲು ಇದುಫಾಸ್ಫೊರಿಲೇಟೆಡ್ ಇನ್ಸುಲಿನ್ ತರಹದ ಬೆಳವಣಿಗೆಯ ಅಂಶ-ಬಂಧಿಸುವ ಪ್ರೋಟೀನ್-1(PhIGFBP-1). ಪರೀಕ್ಷೆಗಳ ಸಂಪೂರ್ಣ ಹಣವನ್ನು ನಾನು ಮಾತ್ರ ಭರಿಸುತ್ತೇನೆ ಮತ್ತು ನಿಮ್ಮ ನಿಯಮಿತ ಚಿಕಿತ್ಸೆಯ ಹೊರತಾಗಿ ನೀವು ಏನನ್ನೂ ಪಾವತಿಸಬೇಕಾಗಿಲ್ಲ. ಕಾರ್ಮಿಕರ ಪ್ರಚೋದನೆಗೆ ಯೋಜಿಸಲಾದ ಮಹಿಳೆಯರಲ್ಲಿ ಯಶಸ್ವಿ ಕಾರ್ಮಿಕ ಪ್ರೇರಣೆಯನ್ನು ಉಹಿಸಲು ನಾವು ಈ ಅಧ್ಯಯನವನ್ನು ನಡೆಸುತ್ತಿದ್ದೇವೆ. ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ದಾಖಲಾಗಲು ಸಿದ್ಧರಿದ್ದರೆ, ಪರೀಕ್ಷೆಗಳಿಗಾಗಿ ನೀವು ಗರ್ಭಕಂಠದ ಪ್ರದೇಶದಿಂದ ಸ್ವಾಬ್ ಅನ್ನು ನೀಡಬೇಕಾಗುತ್ತದೆ. ನೀವು ಅಧ್ಯಯನಕ್ಕೆ ಆಯ್ಕೆ ಮಾಡಿಕೊಳ್ಳಬೇಕೆ ಅಥವಾ ಬೇಡವೇ ಎಂಬುದನ್ನು ಲೆಕ್ಕಿಸದೆಯೇ ಅಥವಾ ಪ್ರಸವಪೂರ್ವ ಮತ್ತು ನಂತರದ ಪ್ರಮಾಣಿತ ಆರೈಕೆಯನ್ನು ನೀವು ಸ್ವೀಕರಿಸುತ್ತೀರಿ. ಅಧ್ಯಯನದ ಭಾಗವಾಗಲು ನೀವು ತೃಪ್ತರಾಗಿದ್ದರೆ ಅಥವಾ ಭಯಪಡದಿದ್ದರೆ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹೊರಗುಳಿಯಲು ನೀವು ಸ್ವತಂತ್ರರಾಗಿದ್ದೀರಿ. ನೀವು ಅಧ್ಯಯನದ ಭಾಗವಾಗಲು ನಿರಾಕರಿಸಿದರೆ ನಿಮ್ಮ ಚಿಕಿತ್ಸೆ ಮತ್ತು ಕಾಳಜಿಗೆ ಧಕ್ಕೆಯಾಗುವುದಿಲ್ಲ. ನೀವು ಅಧ್ಯಯನದ ಭಾಗವಾಗಿದ್ದರೆ ಅಧ್ಯಯನವು ನಿಮಗೆ ಯಾವುದೇ ಅಪಾಯ ಅಥವಾ ಆರ್ಥಿಕ ಹೊರೆಯನ್ನು ಸೇರಿಸುವುದಿಲ್ಲ. ಶಸ್ತ್ರಚಿಕಿತ್ಸೆಯ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ತೊಡಕುಗಳ ಸಂದರ್ಭದಲ್ಲಿ ರೋಗಿಗೆ ಅನುಗುಣವಾಗಿ ಚಿಕಿತ್ಸೆ ನೀಡಲಾಗುತ್ತದೆ. ನಿಮ್ಮ ಗುರುತು ಮತ್ತು ಕ್ಲಿನಿಕಲ್ ವಿವರಗಳು ಗೌಪ್ಯವಾಗಿರುತ್ತವೆ. ಅಧ್ಯಯನದ ಭಾಗವಾಗಿರುವುದರಿಂದ ನೀವು ಯಾವುದೇ ಹಣಕಾಸಿನ ಪ್ರಯೋಜನವನ್ನು ಪಡೆಯುವುದಿಲ್ಲ. ನಿಮ್ಮಲ್ಲಿರುವ ಯಾವುದೇ ಸಂದೇಹ ಅಥವಾ ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ಡಾ. ಕೋಲಕೋಟ್ಟ ಅಜಿತ ಅಥವಾ ಮೇಲಿನ ಸಂಶೋಧನಾ ತಂಡದ ಇತರ ಸದಸ್ಯರನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ.

ಡಾ.ಕೋಲಕೋಟ್ಟ ಅಜಿತ

ಮೊಬೈಲ್ ಸಂಖ್ಯೆ: 9553044877

ಇ-ಮೇಲ್ ಐಡಿ: ajithakoakotla@gmail.com

ANNEXURE III

PROFORMA

NAME:

AGE:

ADDRESS:

UHID NO:

I.P NO:

DATE/ TIME OF ADMISSION:

DATE/ TIME OF DISCHARGE:

CHIEF COMPLAINTS:

OBSTETRICAL HISTORY:

Booked/ Un booked/ Referred

Married Life:

Consanguineous marriage: Yes/ No

Obstetrical Score:

MENSTRUAL HISTORY:

LMP:

EDD:

POG:

C EDD:

PAST HISTORY:

PERSONAL HISTORY:**FAMILY HISTORY:****GENERAL PHYSICAL EXAMINATION:**

Pallor/ Icterus/ Cyanosis/ Clubbing/ Lymphadenopathy/ Edema

PR: RR:

BP: TEMP:

CVS:

RS:

CNS:

PER ABDOMEN:

PER SPECULUM:

PER VAGINA:

PROVISIONAL DIAGNOSIS:

	POITIVE	NEGATIVE
ACTIM PARTUS TEST		

	VAGINAL DELIVERY	CESAREAN SECTION
MODE OF DELIVERY		

ANNEXURE IV

KEY TO MASTER CHART

KEYS			
A	AGE	<20	1
		21-25	2
		26-30	3
		>30	4
B	GRAVIDA	PRIMIGRAVIDA	1
		GRAVIDA 2	2
		GRAVIDA 3	3
		GRAVIDA 4	4
C	GESTATIONAL AGE	37-38+6	1
		39-39+6	2
		>=40	3
D	ACTIM PARTUS TEST	POSITIVE	1
		NEGATIVE	2
E	BISHOP SCORE	<5	1
		5	2
F	METHOD OF INDUCTION	FOLEYS'S +MISOPROSTOL+OXYTOCIN	1
		FOLEYS'S +MISOPROSTOL	2
		FOLEYS'S +OXYTOCIN	3
		MISOPROSTOL+OXYTOCIN	4
		MISOPROSTOL	5
G	MODE OF DELIVERY	VAGINAL DELIVERY	1
		LSCS	2
H	INDICATION FOR LSCS	FAILED INDUCTION	1
		NON PROGRESSION OF LABOUR	2
		FETAL DISTRESS	3
		DEEP TRANSVERSE ARREST	4

ANNEXURE V

MASTER CHART

S.NO	UHID	A	B	C	D	E	F	G	H
1	220507	2	1	2	1	1	5	1	
2	229736	3	2	2	1	2	4	1	
3	194979	3	3	1	1	2	4	1	
4	258623	3	1	1	2	2	2	2	1
5	263924	1	1	2	1	2	1	1	
6	226925	3	1	3	2	2	2	2	2
7	51310	4	4	1	1	2	4	1	
8	258567	3	1	2	2	2	2	2	2
9	242250	2	1	1	1	2	1	1	
10	268469	3	1	3	1	1	4	1	
11	264877	2	2	2	2	2	1	1	
12	232234	2	1	1	1	1	1	1	
13	262702	2	2	3	1	2	1	1	
14	275351	3	1	2	1	2	5	1	
15	275922	2	1	3	1	1	3	1	
16	198493	2	2	1	1	2	5	1	
17	274355	1	1	3	1	1	2	2	3
18	283733	3	4	3	1	2	3	1	
19	200097	2	2	2	2	2	1	1	
20	286957	2	1	3	1	1	5	1	
21	287767	3	2	2	1	1	3	1	
22	302072	1	2	2	2	1	5	2	1
23	303554	4	2	2	1	2	1	1	
24	287170	4	1	3	1	2	1	2	3
25	243349	3	2	3	1	1	1	1	
26	306850	3	1	3	1	2	3	2	4
27	311722	2	2	2	1	2	2	1	
28	313240	4	3	2	1	2	1	1	
29	303941	3	1	3	2	1	2	2	2
30	315300	3	3	1	1	2	5	1	
31	316911	2	1	3	1	2	5	1	
32	235235	2	3	3	1	1	1	1	
33	321296	2	2	3	2	1	2	1	
34	312935	1	2	2	2	2	2	2	1
35	307707	3	3	2	1	2	2	1	
36	134193	3	3	1	1	1	5	1	
37	331706	2	1	3	1	2	1	2	3
38	156258	2	3	3	1	2	1	1	
39	328033	3	2	3	2	2	2	1	
40	242246	1	1	3	1	2	2	1	

41	343334	3	3	1	1	2	5	1	
42	349855	3	3	3	1	1	5	1	
43	351730	2	1	3	1	2	1	1	
44	355863	1	1	3	1	2	1	1	
45	365801	2	1	3	2	1	4	1	
46	355120	1	1	1	1	2	2	1	
47	349743	2	2	1	1	2	4	1	
48	385520	2	1	3	2	1	5	2	1
49	271002	1	1	3	1	2	5	2	3
50	373129	3	2	2	1	2	4	1	
51	374805	2	1	1	1	2	4	1	
52	361100	4	3	3	1	2	1	1	
53	331954	3	3	1	1	2	2	1	
54	190387	1	2	3	1	1	1	1	
55	191269	3	3	3	1	2	5	1	
56	201264	4	3	3	1	2	3	1	
57	184995	1	1	2	1	2	1	2	2
58	202816	4	2	3	1	2	1	1	