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COMPARISON OF OUTCOME OF ORAL VERSUS VAGINAL ADMINISTRATION OF MISOPROSTOL FOR INDUCTION OF LABOUR AT TERM

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ABSTRACT

Introduction: Induction of labor before its spontaneous onset is often necessary in everyday practice. There is no single, clear best practice with respect to the choice of agent used for cervical ripening: both mechanical and pharmacologic agents are acceptable options, in general. The rationale of the study is that limited data is available comparing the outcome of misoprostol when used orally versus when used through vaginal route. The route with better induction of labor and easy to use will be recommended to other obstetricians. **Objective:** To compare the outcome of oral versus vaginal administration of misoprostol for induction of labour at term (gestational age >37 weeks). **Study Setting:** The study was conducted in Obstetrics & Gynecology Department, Shaikh Zayed Hospital, Lahore. **Duration of Study:** January 11, 2023 to July 10, 2023. **Study Design:** Randomized controlled trial. **Subjects & Methods:** Total 180(90 in each group) patients were enrolled. The women randomized to group-A received 50 microgram oral misoprostol 6 hourly orally up to a maximum of 4 doses. The women randomized to group B received 50 microgram misoprostol vaginally and repeated at 6 hours interval up to a maximum of 4 doses. Successful induction of labor was noted. Patient who successfully delivered the newborn vaginally were noted in each group. Data was entered and analyzed using SPSS v25.0. Post-stratification, Chi-square test was applied to see the effect on outcome taking p-value ≤0.05 as significant. **Results:** Age range in this study was from 18 to 40 years. The mean age of patients in group-A was 27.67±6.012 year and in group-B was 28.52±6.088 year. In group-A, mean gestational age was 38.28±4.37 weeks and 38.15±4.41 weeks in group-B. In group-A, mean number of doses was 2.7±1.3 and 2.3±1.2 in group-B. In Oral misoprostol group, 63(70.0%) had successful labour induction and 79(87.8%) had successful labour induction in Vaginal misoprostol group. In Oral misoprostol group, 62(68.9%) had vaginal delivery and 78(86.7%) had vaginal delivery in Vaginal misoprostol group with a p-value 0.004, which is statistically significant. **Conclusion:** There is difference in the outcome of oral versus vaginal administration of misoprostol in terms of successful induction of labour at term and vaginal delivery. Compared with vaginal misoprostol, oral misoprostol may be associated with increased risk of cesarean delivery and lesser labour induction.

KEYWORDS: *Induction of Labour, Cervical Ripening, Vaginal Misoprostol, Oral Misoprostol.*

INTRODUCTION

Induction of labour is a well-established obstetric concept since ancient times. Induction of labour is one of the most common procedures in obstetrics. In modern obstetrics, induction is indicated when benefits to either the mother and/or the foetus outweigh the risks in continuing the pregnancy. It could be elective or emergency induction of labour. In modern times, 1 out of 4 obstetric cases require induction of labour. Induction of labour is defined as iatrogenic stimulation of uterine contraction to accomplish delivery prior to the onset of spontaneous labour by using mechanical or pharmacological methods.[1-2,12-13]

Over the past several decades, the incidence of labour induction has continued to rise. In developed countries, the proportion of infants delivered at term following induction of labour, is as high as one in four deliveries.[3]

Induction is widely carried out all over the world, in cases where continuation of pregnancy is considered hazardous to both the mother or to the fetus or both.[4] Labour induction is considered as successful when patients enters the active phase of labour after 24 hours of the prostaglandin administration and plus minus 12 hours of oxytocin administration.[12]

There are many predictive factors for successful induction of labour i.e. parity, cervical status, maternal age, fetal weight birth etc.[5,13] Misoprostol is a prostaglandin E_1 analogue, a methyl-ester of prostaglandin E_1 additionally methylated at C-16. Misoprostol is an effective myometrial stimulant of pregnant uterus, selectively binding to prostanoid receptors.[6] Mariani-Neto et al, first reported using oral misoprostol (400µg four hourly), for the induction of labour following IUFD.[7] Many subsequent studies have shown that misoprostol is effective, easy to use and a cheap drug for induction of labour in women with IUFD.[8]

However, the preferred route of administration of misoprostol is still uncertain. Misoprostol is rapidly absorbed orally and vaginally.[9] Misoprostol is relatively cheap drug in Pakistan and available as 200 micro gram tablet. It is heat stable and there is no need to maintain cold chain.[14] In a study, in vaginal misoprostol group, induction delivery interval was significantly less (9.79±2.5 vs. 16.47±4.3 hours), vaginal delivery (90.4% vs. 74.5%) and successful induction was significantly higher (90.38% vs. 74.51%) than oral group, within 24 hours of induction.[10]

In another study, in oral misoprostol group, induction delivery interval was less but insignificantly (9.58±4.9 vs. 10.5±4.03 hours) than vaginal group, vaginal delivery (72% vs. 76%) and successful induction was same (100% vs. 100%), within 24 hours of induction.[11] The rationale of the study is that limited data is available comparing the outcome of misoprostol when used orally versus when used through vaginal route.

As oral administration of drug is easy to use with no expertise required, I have designed this study to compare the outcome of oral versus vaginal administration of misoprostol for induction of labour at term. The route with better induction of labor and easy to use will be recommended to other obstetricians.

REVIEW OF LITERATURE

For expecting mothers, the onset of labor is a highly-anticipated process; however, close to 25% of women will have their labor induced. In fact, the rate of induction of labor doubled between 1990 and 2006 and has continued to trend upwards. Regardless of whether labor is induced or spontaneously occurs, the goal is vaginal birth.[15]

INDICATIONS

Indications for labor induction include both maternal and fetal conditions. These medical indications are not absolute and factors such as gestational age, patient and provider preferences are important considerations. In addition to maternal and fetal conditions, non-medical or "elective" indications for labor induction also exist. In general, these indications are the exception rather than the rule. For example, the patient may live far away from hospital and/or have transportation issues.[16]

There may be other psychosocial or logistical reasons such as prior history of rapid labor as well. In these situations, the gestational age should be greater than or equal to 39 weeks. Additionally, particularly in nulliparous women, the cervix should be favorable (Bishop score 8 or greater). Regardless of the indication, risks and benefits of labor induction must be weighed against the benefits of pregnancy prolongation.[17]

Furthermore, correct determination of gestational age is critical. Criteria for determining a term gestation include an early ultrasound prior to 20 weeks gestation that supports current gestational age at or above 39 weeks, fetal heart tones documented via Doppler for 30 weeks or 36 weeks since positive pregnancy test.[15]

CONTRAINDICATIONS

The contraindications for induction are the same as the contraindications for a vaginal delivery. Examples include, vasa previa, placenta previa, myomectomy with entry into uterine cavity, previous classical hysterotomy, active genital herpes outbreak, umbilical cord prolapse, or transverse fetal lie.[15]

CERVICAL RIPENING AND INDUCTION OF LABOR

Cervical ripening is an important first component to labor induction. Prior to spontaneous labor, the cervix first begins to soften over time, and then before contractions ensue, the connective tissue components of the cervix are extensively remodeled, which is also known as cervical ripening. In the setting of labor induction, mechanical or pharmacological agents can be used to cause cervical ripening.

Ripening often stimulates labor. If not, further pharmacologic agents (i.e. oxytocin) can be used for induction. Generally, cervical ripening and induction of labor are on a continuum and not all women undergoing induction of labor need cervical ripening. The Bishop scoring system can be used to determine if the cervix is favorable or unfavorable.

If the cervix is deemed unfavorable, usually defined as Bishop score less than or equal to 6, cervical ripening is indicated. There are 5 components to the Bishop scoring: dilation, position of cervix, effacement, station (based on -2 to +3 scale), and cervical consistency, which are then scored from 0 to 3.[15,18]

MECHANICAL AGENTS FOR CERVICAL RIPENING

There are several mechanical methods for cervical ripening, including osmotic dilators, transcervical Foley and double balloon catheters. Mechanical methods work by directly causing cervical dilation and also by releasing endogenous prostaglandins and oxytocin.

Notably, when placing a mechanical device for cervical ripening in the presence of a low-lying placenta (edge within 2cm of internal os), there is a risk for potential hemorrhage and disruption of the placenta; thus, mechanical methods should be carefully considered in the setting of a low-lying placenta.[19-20]

Osmotic Dilators

Osmotic dilators include seaweed (Laminaria) and synthetic compounds (Lamicel and Dilapan). The dilators are hydrophilic such that they absorb water and enlarge, which in turn causes the cervix to dilate. Data regarding the efficacy of these dilators for induction of labor are mixed. Additionally, studies have shown an increased risk of infection with Laminaria use, resulting in chorioamnionitis, endometritis and neonatal sepsis.[19]

Extra-amniotic Saline Infusion

A catheter is used to infuse saline into the space between the uterine wall and the amnion. This results in additional prostaglandin release. Rates are commonly 30-40 mL per hour. The Cochrane review on mechanical methods for induction of labor cited no evidence to support use of extra-amniotic infusion. There was not a shorter time from induction to delivery.[20]

Transcervical Foley Catheter

A Foley catheter is placed just above the internal cervical os when used for mechanical cervical ripening. Most commonly, the catheter is inserted through the cervical canal with the aid of forceps during a sterile speculum exam. Other times, the Foley catheter can be placed during a digital exam. The catheter is then inflated and placed on traction such that it sits just above internal os, applying pressure.

Some leave the Foley catheter in until it is spontaneously expelled, while others remove catheter after a specific time interval. In general, transcervical Foley catheters may safely remain in place for more than 24 hours. Following catheter removal, most women require further induction of labor with oxytocin and/or amniotomy.

Different size catheters (ranging from 14 to 26 French) and different amounts of balloon catheter inflation volume (25 to 80 mL of sterile saline or water) are used. A randomized trial compared 30mL to 80mL balloon inflation volumes. There was no difference in multiparous women.[20]

However, in nulliparous women who received the 80mL balloon inflation volume, they had greater cervical dilation, faster labor, and decreased oxytocin augmentation requirement compared to nulliparous women who were ripened with 30mL balloon inflation volume.[21] In general, 30 to 50mL is most commonly used.[19]

A transcervical Foley catheter remains an option for women with premature rupture of membranes. Data does not indicate an increased risk of infection with this mechanical method. However, some providers chose other options in the setting of premature rupture of membranes, but this decision is at the discretion of the provider.[22-23] Generally, transcervical Foley catheter cervical ripening is done while the patient is hospitalized; however, there have been a few preliminary studies regarding outpatient regimens that have shown promising results. A randomized trial comparing transcervical Foley catheter ripening in an outpatient versus inpatient setting found the efficacy to be similar across settings with no adverse maternal or neonatal outcomes.[24]

The transcervical Foley catheter cervical ripening method overall has a very safe profile. Premature rupture of membranes, bleeding, displacement of presenting part and chorioamnionitis/endometritis have been associated infrequently with this form of cervical ripening.[19]

The transcervical Foley catheter has been shown to be as effective as other methods of cervical ripening. The Bishop score changes on average between 3 and 5 points. Furthermore, uterine tachysystole is uncommon with transcervical Foley catheter ripening, and if this method is poorly tolerated by patient and/or fetus, it can easily be removed. Because of these reasons as well as its low cost and room temperature stability, it is a strong option for cervical ripening, especially in low resource settings.[25]

Double Balloon Catheter

The double balloon catheter is similar to the transcervical Foley catheter method but has an additional second balloon that sits just below the external os. Thus, the double balloon catheter is able to apply pressure to both the internal and external os. The double balloon catheter is significantly more expensive than the single Foley balloon catheter method. A randomized control trial comparing single to double balloon catheters showed equal efficacy for labor induction.[25]

PHARMACOLOGIC METHODS FOR CERVICAL RIPENING AND INDUCTION OF LABOR

Prostaglandins

During spontaneous labor, prostaglandins produced in the myometrium and decidua result in uterine contractions. Synthetic prostaglandins can be given for cervical ripening and labor induction.[18]

Prostaglandins are associated with increased risk of uterine rupture with a scarred uterus and thus should not

be used in patients desiring trial of labor after cesarean delivery.[26]

When prostaglandins are given, fetal heart rate and uterine contractions should be monitored continuously initially and the patient should lie down for at least 30 minutes.[15]

PGE1 misoprostol (Cytotec)

The typical dose for intravaginal misoprostol is 25 micrograms every 3 to 6 hours. A randomized control trial comparing 25 and 50 mcg doses found the 50mcg dose was slightly more effective but was associated with a higher incidence of uterine tachysystole and neonatal cord pH less than 7.16. In addition to intravaginal, misoprostol can also be administered orally, bucally and sublingually.[27]

Sublingual misoprostol is as effective as oral misoprostol at the same dose, but larger research studies are needed before routine use of buccal or sublingual administration.[28] The typical corresponding oral dose of misoprostol is 100mcg. A randomized trial compared intra-vaginal 25 mcg of misoprostol to oral 100mcg and found similar efficacy for cervical ripening and labor induction.[29-30]

Misoprostol remains an appropriate option in women with premature rupture of membranes.[31] No studies have demonstrated long-term adverse fetal outcomes related to in-utero exposure to misoprostol in absence of fetal distress.[15]

PGE_2 dinoprostone

Synthetic prostaglandin E_2, dinoprostone, comes in two forms: a gel in a 2.5mL syringe containing 0.5 mg or a vaginal insert containing 10mg. The insert releases prostaglandin more slowly than the gel. There is some data regarding outpatient use of dinoprostone, but additional studies are needed before this becomes routine practice.[15]

PGE_1 vs. PGE_2

In a randomized trial, intra-vaginal misoprostol was compared to dinoprostone intracervical gel. The time from induction to vaginal delivery was shorter on average with misoprostol. There was not a difference in the delivery route between the two groups. The incidence of uterine tachysystole was similar between the two groups. Additionally, misoprostol is significantly less expensive than dinoprostone.[32]

Oxytocin

Synthetic oxytocin is the most common method for labor induction. It mimics natural endogenous oxytocin produced during spontaneous labor and similarly stimulates uterine contractions. Contractions begin after 3 to 5 minutes, and oxytocin reaches a steady level in plasma by 40 minutes. Oxytocin side effects include uterine tachysystole and fetal heart rate abnormalities.[15] Fetal heart rate and contractions should be monitored during oxytocin administration.[18]

Most commonly Oxytocin is administered intravenously and can be titrated based on contraction frequency and strength. There are various regimens for oxytocin administration. A Cochrane review compared the effectiveness of low versus highdose oxytocin for induction of labor. There was no difference in time to delivery or cesarean delivery rate between the two groups.

There was a significant increase in uterine tachysystole in the high-dose group, but the consequences of this were not clearly identified. The review was unable to recommend either a low or high-dose protocol over the other. An oxytocin checklist was developed for oxytocin administration focusing on uterine contractions and fetal heart rate rather than specific infusion rates or dosing.[33]

Outcomes were compared before and after initiation of the checklist protocol. The maximum infusion rate of oxytocin was lower in the checklist protocol group. There was no difference in time in labor between groups. Furthermore, the cesarean delivery rate was lower and newborn outcomes improved in the checklist protocol group.[34]

NON-PHARMACOLOGIC METHODS FOR CERVICAL RIPENING OR INDUCTION OF LABOR

Non-pharmacologic methods for cervical ripening and induction of labor exist and offer an alternate and inexpensive approach for patients.

Nipple Stimulation

Breast stimulation stimulates uterine contractions, likely by increasing oxytocin levels. A Cochrane review found that when compared to no intervention, more women entered labor by 72 hours with nipple stimulation; however, this was only significant for women who had a favorable cervix initially.

Additionally, there was a decrease in post-partum hemorrhage among women who performed nipple stimulation. There were no cases of uterine tachysystole. However, a trend towards an increase in perinatal death amongst women who used nipple stimulation was noted. More information is needed regarding the safety of this method before recommendations about its use can be endorsed.[35]

Membrane Stripping

Membrane stripping releases endogenous prostaglandins, which can induce labor, and by doing so, eliminate the need for formal induction. To perform membrane stripping, the clinician performs a vaginal exam and places a finger into cervical os in a circular movement to separate the inferior portion of membranes from the lower uterine segment.

A Cochrane review found that membrane stripping results in an increased number of women entering spontaneous labor within 48 hours and decreases the need for induction. There was no difference in risk of maternal or neonatal infection. Potential side effects include patient discomfort during the procedure, vaginal bleeding, rupture of membranes and contractions following the procedure.[36]

Amniotomy

The amniotic membranes can be ruptured artificially to induce labor. It is difficult to know the time interval from amniotomy to delivery, and with increasing time from amniotomy to delivery, there is an increasing risk for infection. A Cochrane review found that there was not sufficient data regarding amniotomy as a method for labor induction to draw a conclusion on its safety and efficacy.[37]

COMPARISON AND COMBINATIONS OF METHODS FOR CERVICAL RIPENING AND INDUCTION OF LABOR

There is no clear consensus on what method is the best for cervical ripening and induction of labor. There have been multiple studies comparing individual methods as well as combinations of various methods.

Of note, the obstetric care consensus on the safe prevention of the primary cesarean delivery made the recommendation for cervical ripening methods to be implemented in women undergoing induction of labor with an unfavorable cervix. The obstetric care consensus is a joint statement from both the American College of Obstetricians and Gynecologist and the Society for Maternal Fetal Medicine.[38]

Misoprostol versus Transcervical Foley Catheter

A randomized controlled trial compared induction of labor with misoprostol to transcervical Foley catheter. There was no difference in cesarean delivery rate or time from induction to delivery between groups. Additionally, there was no difference in maternal or neonatal infections.[23]

A Cochrane review comparing prostaglandins with mechanical methods found no difference in cesarean delivery rate. Additionally, it was noted that there was less uterine tachysystole with fetal heart rate changes with mechanical methods compared to prostaglandins.[20]

Misoprostol versus Oxytocin

A randomized controlled trial compared induction of labor with misoprostol to oxytocin. All women included started with an unfavorable cervix. There was no difference in cesarean delivery rates, maternal complications or neonatal outcomes between groups. However, the time from induction to delivery was shorter in the oxytocin group.[39]

Transcervical Foley Catheter versus Oxytocin

A Cochrane review found reduction in cesarean delivery rate when transcervical Foley catheter was used versus oxytocin. Uterine tachysystole with fetal heart rate changes was not reported. There was no difference in maternal complications but neonatal morbidity was not reported.[20]

Transcervical Foley Catheter with Oxytocin versus Misoprostol

A randomized control trial compared induction of labor in nulliparous women with an unfavorable cervix using transcervical Foley catheter with oxytocin versus misoprostol. There was no difference in cesarean delivery rates, maternal complications or neonatal outcomes between groups. The time from induction to delivery was shorter in the transcervical Foley catheter and oxytocin group.[40]

Transcervical Foley Catheter with Misoprostol versus Misoprostol

A randomized control trial compared induction of labor with transcervical Foley catheter plus misoprostol to misoprostol alone. There was no difference in cesarean delivery rates nor maternal complications or neonatal outcomes between groups. The time from induction to delivery was shorter in the transcervical Foley catheter with misoprostol group.[41]

Transcervical Foley Catheter with Oxytocin versus Transcervical Foley Catheter

A randomized control trial compared induction of labor with transcervical Foley catheter with oxytocin to transcervical Foley catheter alone. There was no difference in cesarean delivery rates or time from induction to delivery between the two groups.[42]

CRITERIA FOR FAILED INDUCTION OF LABOR AND PREVENTING THE FIRST CESAREAN DELIVERY

Induction of labor for nulliparous women with an unfavorable cervix has a two-fold increased risk of cesarean delivery. Thus, first ensuring the induction of labor is indicated is very important.[38]

A prospective study examined induction outcomes after institution of a standardized protocol for the diagnosis of a failed induction of labor. A cesarean delivery could not be performed for a failed induction of labor before reaching the active phase of labor until after at least 12 hours of oxytocin administration after membrane rupture. Active phase of labor was defined as 4cm dilated and 90% effaced or 5cm dilated.

If fetal heart rate tracing was not reassuring, then a cesarean delivery was performed for fetal indication rather than a failed induction of labor. No multiparous women underwent a cesarean delivery for failed induction of labor, and many nulliparous women were able to have a vaginal delivery after allowance of

additional time in the latent phase of labor induction rather than proceeding to cesarean delivery earlier.[43]

A subsequent observational study investigated induction of labor outcomes for nulliparous patients only. Active labor was similarly defined. The study found that allowing even up to 18 hours of induction prior to reaching active labor in nulliparous women allowed more women to have a vaginal delivery without increasing maternal or neonatal morbidity.[44]

The obstetric care consensus on the safe prevention of the primary cesarean delivery recommends that before proceeding with cesarean delivery for a failed induction of labor prior to reaching active phase of labor, oxytocin should be given for a least 12 to 18 hours after membrane rupture, as long as maternal and fetal status are reassuring. The latent phase of labor may last longer than 24 hours. A prolonged latent phase in itself is not an indication for cesarean delivery. The active phase was defined at 6cm dilated.[38]

The workshop summary on preventing the first cesarean delivery defined failed induction of labor as: "failure to generate regular (e.g. every 3 minutes) contractions and cervical change after at least 24 hours of oxytocin administration, with artificial rupture of membranes if feasible." The workshop was a collaboration between the Society for Maternal Fetal Medicine, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the American College of Obstetricians and Gynecologists.[17]

TRIAL OF LABOR AFTER CESAREAN DELIVERY

Women who are candidates for a trial of labor after cesarean delivery (TOLAC) should be offered one. It is necessary to have an extensive discussion between provider and patient regarding risks and benefits of TOLAC versus repeat cesarean.

Contraindications to TOLAC include any contraindication for a vaginal delivery, prior classical or T-incision of the uterus, and previous uterine rupture. Women with one or two previous cesarean deliveries are candidates for TOLAC, but data regarding TOLAC risk in women with more than two previous cesareans deliveries are limited.[45]

A vaginal birth after cesarean delivery (VBAC) offers a faster recovery, avoidance of abdominal surgery, and lower risk for complications such as infection and hemorrhage than a cesarean delivery. There is however the unlikely but potentially catastrophic event of uterine rupture. With a prior low transverse hysterotomy, the risk of uterine rupture is 0.5 to 0.9%. When uterine rupture occurs, there is an increased risk for maternal and neonatal morbidity and mortality.[45]

A repeat cesarean delivery avoids the risk of uterine rupture during TOLAC. However, every cesarean delivery has the increased risk of hemorrhage, infection, thromboembolism, bowel or bladder injury as well as a longer recovery compared to a vaginal delivery. It is imperative to consider future reproductive plans as well. Additional repeat cesareans carry more risk for intra-operative complications as a result of adhesions and furthermore the very morbid risk of abnormal placentation requiring cesarean hysterectomy.[45]

In summary, a successful VBAC has less risk for maternal morbidity and mortality than scheduled repeat cesarean delivery, which has less risk than cesarean delivery after a failed TOLAC. Similarly, neonatal morbidity is lower with VBAC than failed TOLAC. The trouble is it is not possible to know who will have a successful VBAC ahead of time. The overall likelihood of successful VBAC is 60-80%.[38,45]

There is a calculator that was developed to help to provide an estimated likelihood of successful VBAC. If a woman had a cesarean delivery for a recurring issue (such as arrest of labor or descent), she has a lower likelihood than a woman who had a cesarean delivery for a non-recurring issue such as fetal intolerance or breech presentation.

Factors that increase likelihood of successful VBAC include previous vaginal delivery and spontaneous labor. Factors that decrease likelihood of successful VBAC include older maternal age, obesity, non-white ethnicity, pre-eclampsia, short inter-pregnancy interval, late-term or post-term gestation, and increased birth weight.[45]

An induction of labor for women desiring TOLAC is not contraindicated. The likelihood of successful VBAC with induction of labor is slightly decreased and risk of uterine rupture is slightly increased when compared to VBAC with spontaneous labor.[45]

A transcervical Foley catheter is a great option for cervical ripening in women with prior cesarean delivery. Misoprostol is contraindicated for induction of labor in the third trimester in women with a prior uterine scar. Lastly, when performing a TOLAC, a physician capable of performing a cesarean delivery must be readily available.[45]

CERVICAL RIPENING

In pregnancy, the uterine cervix serves 2 major functions. First, it retains its physical integrity by remaining firm during pregnancy as the uterus dramatically enlarges. This physical integrity is critical so that the developing fetus can remain in the uterus until the appropriate time for delivery. Second, in preparation for labor and delivery, the cervix softens and becomes more distensible, a process called cervical ripening. These chemical and physical changes are required for cervical dilation, labor and delivery of a fetus.

UTERINE CHARACTERISTICS

The human uterus is composed of 2 basic parts, the fundus and the cervix. The fundus is composed of 2 layers: the myometrium and endometrium. The myometrium, which is predominantly smooth muscle cells, comprises the wall of the uterus and is the thickest layer. The endometrium, which lines the endometrial cavity, undergoes dramatic changes during the menstrual cycle.

In the absence of pregnancy, it sheds down to the basal layer at the end of the cycle during menses. The normal pregnant cervix is 3.5 cm or longer and is composed predominantly of connective tissue, mainly collagen. In contrast to the fundus, it has only 10-15% smooth muscle. It changes little during the menstrual cycle and pregnancy until the onset of cervical ripening.

The human cervix consists mainly of extracellular connective tissue. The predominant molecules of this extracellular matrix are type 1 and type 3 collagen, with a small amount of type 4 collagen at the basement membrane. Intercalated among the collagen molecules are glycosaminoglycans and proteoglycans, predominantly dermatan sulfate, hyaluronic acid, and heparin sulfate.

Fibronectin and elastin also run among the collagen fibers. The highest ratio of elastin to collagen is at the internal os. Both elastin and smooth muscle decrease from the internal to the external os of the cervix.

RIPENING OF THE CERVIX

Cervical ripening refers to the softening of the cervix that typically begins prior to the onset of labor contractions and is necessary for cervical dilation and the passage of the fetus. Cervical ripening results from a series of complex biochemical processes that ends with rearrangement and realignment of the collagen molecules. The cervix thins, softens, relaxes and dilates in response to uterine contractions, allowing the cervix to easily pass over the presenting fetal part during labor.

In late pregnancy, hyaluronic acid content increases in the cervix. This leads to an increase in water molecules that intercalate among the collagen fibers. The amount of dermatan sulfate decreases, leading to reduced bridging among the collagen fibers and a corresponding decrease in cervical firmness. Chondroitin sulfate also decreases.

Cervical ripening is associated with decreased collagen fiber alignment, decreased collagen fiber strength and diminished tensile strength of the extracellular cervical matrix. An associated change with the cervical ripening process is an increase in cervical decorin (dermatan sulfate proteoglycan 2), leading to collagen fiber separation. Together, these changes lead to softening of the cervix (ie, ripening).

With uterine contractions, the ripened cervix dilates as the presenting fetal part descends, leading to reorientation of the tissue fibers in the cervix in the direction of the stress. Under the effect of myometrial contractions, the cervix passively dilates and is pulled over the presenting fetal part. Evidence also indicates that the elastin component of the cervix behaves in a ratchet like manner so that dilation is maintained following the contraction.

In summary, cervical ripening is the result of realignment of collagen, degradation of collagen cross-linking due to proteolytic enzymes. Cervical dilation results from these processes plus uterine contractions. This is a complicated series of events in which many changes occur both simultaneously and sequentially. Research in this area is challenging due to both the difficulties inherent in human subjects research and the many differences existing between species.

ROLE OF VARIOUS HORMONES IN THE PROCESS OF CERVICAL RIPENING

A complex series of interactions occurs whereby various hormones stimulate the chemical reactions critical for cervical ripening. Associated with cervical ripening is an increase in the enzyme cyclooxygenase-2, leading to a local increase of prostaglandin E2 (PGE2) in the cervix. The increase in local PGE2 leads to a series of important changes associated with cervical ripening, including the following:

- Dilation of small vessels in the cervix
- Increase in collagen degradation
- Increase in hyaluronic acid
- Increase in chemotaxis for leukocytes, which causes increased collagen degradation
- Increase in stimulation of interleukin (IL)–8 release

Prostaglandin F2-alpha is also involved in the process via its ability to stimulate an increase in glycosaminoglycans. Cervical ripening is associated with increased activity of matrix metalloproteinases 2 and 9, enzymes that degrade extracellular matrix proteins.

Cervical collagenase (also called matrix metalloproteinase 1) and elastase also increase. Near term, collagen turnover increases and degradation of newly synthesized collagen increases, leading to decreased collagen content in the cervix.

In animal studies, sex steroids have been demonstrated to be involved in cervical ripening. In the rat cervix, increasing estrogen leads to increased collagenase activity, cervical cell apoptosis, and eosinophil infiltration. Animal models also exhibit a decrease in receptor-mediated progesterone activity, but whether this is involved in cervical ripening is unclear.

The role of inflammatory agents in cervical ripening has also been studied. IL-8 can lead to neutrophil chemotaxis, which is associated with collagenase activity

and cervical ripening. These inflammatory agents may be particularly important as mediators of cervical ripening associated with preterm labor.

Recent study has focused on the nitric oxide synthase (NOS)/nitric oxide (NO) system. The NOS/NO system has been postulated to have a regulatory role in the myometrium and cervix during pregnancy and parturition. In rat studies, NO and increased NOS activity are associated with uterine quiescence. NOS activity is higher prior to labor and decreases during labor, thereby playing a role in the onset of uterine contractions associated with labor.

In rat studies, NO levels and NOS activity behave in an opposite fashion in the cervix. Prior to cervical ripening, NOS activity is low and then increases at the time of labor, associated with cervical ripening. NOS activity leading to NO production is the final pathway in inducing chemical changes associated with cervical ripening. In the human cervix, ripening is associated with an increase in induced NOS (iNOS) and brain NOS expression in the cervix.

Resident and migrating inflammatory cells can cause the increase in iNOS activity. Indeed, in the primate, cervical ripening has many aspects of an inflammatory process—tissue remodeling and breakage of chemical bridges between collagen fibers. Inflammatory agents such as IL-1, tumor necrosis factor-alpha, and IL-8 seem to be involved in cervical ripening.

NO also appears to play a role in this process because animal studies show that increased cervical NO leads to an increase in metalloproteinase activity, cellular apoptosis in the cervix, and glycosaminoglycan synthesis in the cervix. All of these changes are associated with the cervical ripening process.

NO also could play a role in premature cervical ripening associated with preterm labor, particularly in preterm labor triggered by infection. Inflammatory cells are rich in iNOS activity, leading to a dramatic increase in NO in the cervix, which stimulates the chemical changes associated with cervical ripening and leads to preterm labor and delivery. Human and animal studies support a role for NO in the process of cervical ripening. NO donors, when applied to the cervix, induce cervical ripening.

To stop preterm labor successfully, both uterine contractions and cervical ripening must be halted. Speculating that this requires blockage of prostaglandin synthesis in the uterine fundus and cervix (and local NO synthesis in the cervix) is tempting. The role that inflammatory agents play in the cervical ripening process could explain the explosive nature of the cervical changes that occur in preterm labor, particularly when associated with uterine infections.

EVALUATION OF CERVICAL RIPENING

A variety of techniques have been developed to quantify cervical ripening in order to predict the timing of labor and delivery. This quantification is useful for patients at risk for preterm labor and for helping predict which patients will respond to induction of labor for medical reasons or for postdate pregnancy.

The most commonly used methodology to evaluate cervical ripening is the Bishop score because it is simple and has the most predictive value. This score uses cervical dilation, effacement, consistency, position, and the station of the presenting part. Other methods that have been described in the literature, generally for gauging the risk of preterm labor, include ultrasound assessment of the cervix and detection of fetal fibronectin in cervicovaginal secretions.

A Bishop score of 5 or more is considered significant for cervical ripening and favorable for induction of labor. Bishop score is calculated as follows:

Dilation

- For 0 cm, 0 points are scored.
- For 1-2 cm, 1 point is scored.
- For 3-4 cm, 2 points are scored.
- For 5-6 cm, 3 points are scored.

Effacement

- For 0-30%, 0 points are scored.
- For 40-50%, 1 point is scored.
- For 60-70%, 2 points are scored.
- For 80%, 3 points are scored.

Station

- For -3 station, 0 points are scored.
- For -2 station, 1 point is scored.
- For -1 and 0 station, 2 points are scored.
- For +1 to +2 station, 3 points are scored.

Consistency

- For firm consistency, 0 points are scored.
- For medium consistency, 1 point is scored.
- For soft consistency, 2 points are scored.

Position

- For posterior position, 0 points are scored.
- For mid position, 1 point is scored.
- For anterior position, 2 points are scored.

A recent study examining over 5,600 nulliparous women undergoing induction of labor found that a simplified Bishop score, including only cervical dilation, effacement, and station, was equally as predictive as the traditional Bishop score in predicting vaginal delivery.[46]

Emerging evidence suggests that ultrasound assessment of the cervix helps distinguish patients at increased risk of preterm labor. In meta-analysis, Crane and Hutchens evaluated more than 300 studies, including 14 articles involving more than 2200 women in their final analysis.

They found that ultrasound is a strong predictor of preterm birth among asymptomatic women at less than 35 weeks' gestation.[47]

Detection of fetal fibronectin in cervicovaginal secretions has also been used. Fetal fibronectin is a glycoprotein found in amniotic fluid and at the chorionic decidual interface. The absence of this protein in cervicovaginal secretions predicts prolongation of pregnancy.

Fetal fibronectin is also predictive of response to prostaglandin application to the cervix at term in order to induce cervical ripening and labor. Currently, evaluation of fetal fibronectin is used predominantly in the assessment and triage of patients for preterm labor.

INDUCTION OF CERVICAL RIPENING

Bishop scores are somewhat subjective, but a score of less than 5 suggests further ripening is needed, while a score of 9 or greater suggests ripening is completed. No maximum has been determined for the number of doses of a cervical ripening agent that can be given.

Indeed, if the patient has no pressing indication for delivery and if fetal well-being parameters are reassuring, the patient can even be discharged, to return in a few days for another attempt at induction. Good clinical judgment is indispensable. A variety of methods have been developed to induce cervical ripening in the preparation of the cervix for labor and delivery.[48]

Prostaglandins

Two forms of PGE2 (dinoprostone) are available commercially. In randomized trials, the 2 forms are equivalent in efficacy. The first is Prepidil, which is formulated as a gel and is placed inside the cervix, but not above the internal os. The application (3 g gel/0.5 mg dinoprostone) can be repeated in 6 hours, not to exceed 3 doses in 24 hours.

The second is Cervidil, which contains 10 mg of dinoprostone embedded in a mesh and is placed in the posterior fornix of the vagina. This allows for controlled release of dinoprostone over 12 hours, after which it is removed.

Comparison between the use of intravenous oxytocin alone with a combination of oxytocin and either vaginal or intracervical PGE2 demonstrate that prostaglandins result in a significantly lower cesarean delivery rate and an increased proportion of vaginal deliveries within 24 hours.

However, patients with ruptured membranes the time of labor induction had an increased rate of chorioamnionitis among those receiving vaginal or intra-cervical PGE2.[49]

Prostaglandin E1 analog (misoprostol) use has been described in a series of articles. This is a synthetic prostaglandin, which is marketed as an antiulcer agent under the trade name Cytotec. One quarter of a tablet (25 mcg), which can be crushed and placed on the cervix, has been shown in many studies to be quite effective in inducing cervical ripening and labor. The application of the medication can be repeated every 4 hours.

Two meta-analyses comparing randomized trials of vaginal misoprostol with dinoprostone found an increased rate of vaginal delivery within 24 hours and similar cesarean delivery rates in the misoprostol groups and hence conclude that misoprostol is the more effective agent.[50-51]

Misoprostol has also been administered orally (50-100 mcg, which can be repeated every 4 h), but vaginal administration seems to be more efficacious. Vaginally administered misoprostol has been used for cervical ripening and labor induction in pregnancies complicated by oligohydramnios.

In these patients, the risk for adverse perinatal outcomes was not increased compared with patients with normal amniotic fluid volumes. Note that the US Food and Drug Administration classifies Cytotec as a pregnancy category X drug. The manufacturer has been ambivalent about this off-label use of the medication, and the Food and Drug Administration only acknowledges that misoprostol is being used in pregnancy.

The American College of Obstetrics and Gynecology (ACOG) Committee on Obstetrics Practice recommends that misoprostol not be used in induction of labor after previous cesarean section or major uterine surgery, due to a significant risk of uterine rupture.[52]

The major risk of the above prostaglandin preparations is uterine hyper-stimulation. The woman and fetus must be monitored for contractions, fetal well-being, and changes in the cervical Bishop score. Finally, Christensen et al demonstrate that the combination of oxytocin induction, preceded by a dinoprostone insert is safe, and this significantly shortens induction-to-delivery times.[53]

The exception to this appears to be women with prior cesarean deliveries. The ACOG Committee on Obstetric Practice, in its review of pertinent literature, notes that the sequential use of prostaglandins and oxytocin appears to increase the risk of uterine rupture in women with previous cesarean section.[52]

A randomized controlled trial by Al-Ibraheemi et al that randomized 200 patients into a cervical ripening using misoprostol and a transcervical Foley bulb simultaneously group and a misoprostol alone group reported that the combined group showed shorter time to delivery (15.0 hours vs 19.0 hours in the misoprostol-only group [P=.001]).[54]

Balloon catheter

A 30-mL to 50-mL Foley catheter filled with saline is effective in inducing cervical ripening and dilation. The catheter is placed in the uterus, and the balloon is filled. Direct pressure is then applied to the lower segment of the uterus and the cervix. This direct pressure causes stress in the lower uterine segment and probably the local production of prostaglandins.

In some studies, the catheter is combined with a saline solution as an extra-amniotic infusion. No evidence suggests that extra-amniotic saline infusion (EASI) increases the risk of chorioamnionitis. A meta-analysis involving 27 studies and 3532 patients found that no difference between Foley balloon and PGE2 use in cesarean delivery rate.[55-56]

This study was hampered by significant heterogeneity of the studies and subgroup analysis suggested that Foley balloon in combination with oxytocin and EASI may indeed have a higher vaginal delivery rate and lower rate of tachysystole.[57]

The PROBAAT trial compared the effectiveness and safety of induction of labor using a Foley catheter with induction using vaginal prostaglandin E2 gel. They found that in women with an unfavorable cervix at term, the outcomes were similar, with fewer maternal and neonatal side-effects associated with Foley catheter use.[58]

Low-dose oxytocin infusion

In this method, a low-dose oxytocin infusion is performed, with an increase in dose from 1 to 4 mU/min. Ferguson et al showed this method to be comparable to intravaginal misoprostol for cervical priming. Because of the ease of turning off the oxytocin infusion, they suggested that this method may have a preferential role in high-risk patients whose fetuses are at increased risk for intolerance of labor.[59]

Anti-progesterone

Mifepristone (formerly known as RU 486) is an effective anti-progesterone and antiglucocorticoid that works by binding to progesterone and glucocorticoid receptors. Although individual randomized trials have shown favorable results for its use in inducing labor, a Cochrane Database review concluded that data were insufficient to support its use in labor induction. This review did note a decreased rate of cesarean delivery with mifepristone use, suggesting potential future areas of research.[60]

Hygroscopic dilators

Several products are available that can be placed in the cervix and dilated by water absorption. Laminaria are made from dried seaweed. Commercial products, Dilapan and Lamicel, are produced from synthetic hygroscopic material. Several dilators are inserted in the cervix as many as will fit and they expand over 12-24 hours as they absorb water.

Absorption of water leads to expansion of the dilators and opening of the cervix. They probably work much the same as the balloon catheter. Women do not need prophylactic antibiotics for the balloon catheter or hygroscopic dilators, unless specific indications exist such as need for sub-acute bacterial endocarditis (SBE) prophylaxis.

Membrane stripping

Manual separation of the amniotic membranes from the cervix is thought to induce cervical ripening and the onset of labor. The mechanism is unknown, but mechanical disruption of this tissue has been postulated to cause an increase in local prostaglandins by the induction of phospholipase A2 in the cervical and membrane tissues.

Such a postulation is certainly consistent with the known stimulation of cervical ripening by prostaglandins. However, there is no strong evidence at this time that membrane stripping significantly shortens the duration of pregnancy. Authors of a Cochrane Database review on this topic concluded that this practice provides no clinically important benefits.[61]

Nitric oxide donors

Studies are being conducted on the use of nitric oxide donors for cervical ripening with conflicting results. Preliminary small studies evaluating isosorbide mononitrate (40 mg) and glyceryl trinitrate had encouraging results. However, randomized controlled trials comparing misoprostol with and without isosorbide mononitrate have demonstrated contradictory results.

Furthermore, a Cochrane Database review of 8 studies consisting of 718 patients evaluating the use of nitric oxide donors for cervical ripening in first trimester surgical abortion found them to be inferior to prostaglandins and associated with more side effects.[62-64]

A randomized, double-blind, placebo-controlled study by Schmitz et al also cast doubt on the use of nitric oxide donors in cervical ripening, finding them to be no more effective than placebo in reducing the rate of cesarean sections in nulliparous women with prolonged pregnancy. The study, of nulliparous women at 41 weeks' gestation, included 678 patients who received vaginal isosorbide mononitrate and 684 women who received placebo, all on an outpatient basis.

The investigators found that the cesarean delivery rate in the isosorbide mononitrate and placebo groups were nearly identical (27.3% vs. 27.2%, respectively) and that side effects occurred more frequently in the women treated with the nitric oxide donor than in the other patients (78.8% vs. 27.9%, respectively).[65]

Relaxin

Because of the results from a series of animal studies, relaxin has been predicted to have effects on cervical ripening in humans. The findings that porcine relaxin induces cervical ripening in humans supports this conclusion.

Paradoxically, human relaxin has no effect on the human cervix, and relaxin is not currently used in cervical ripening or induction of labor. The reason for the species difference is unknown and calls into question the role of human relaxin in human parturition.

In addition, animal research suggests that supplemental hyaluronidase may shorten labor leading to improved induction success. Future research in these areas, and others, may lead to improved cervical ripening and labor induction methods.[66]

Summary of induction of cervical ripening

Induction of cervical ripening is critical to successful induction of labor in a pregnant patient whose cervix has not gone through the ripening process. Cervical ripening allows the uterine contractions to effectively dilate the cervix. The amount of uterine pressure required to dilate a ripe cervix is thought to be approximately 1600 mm Hg, while the pressure to dilatate an unripe cervix is estimated to be greater than 5 times that, or 10,000 mm Hg.

ECONOMIC BURDEN OF MISTIMED CERVICAL RIPENING

Preterm and early term labor and delivery

Accurate dating of pregnancy using early prenatal care and ultrasonography is advised before cervical ripening and induction of labor. Mistimed cervical ripening and induction can result in unplanned iatrogenic preterm birth and recent evidence documents increased neonatal morbidity in babies born prior to 39 weeks' gestation but after 37 weeks' gestation.

Current ACOG guidelines recommend against elective induction of labor before 39 completed weeks of pregnancy, unless medical indications for earlier delivery are noted. Elective inductions account for about half of all inductions and 10% of deliveries.

The ACOG recommends that dating be confirmed with at least one of the following

- Ultrasonography dating at less than 20 weeks' gestation is consistent with gestational age of 39 weeks or more
- Fetal heart tones have been documented in the patient's medical records for at least 30 weeks by Doppler ultrasonography
- 36 weeks have passed since a positive urine or serum pregnancy test for human chorionic gonadotropin.

In the United States, the national cost for preterm labor, undelivered, exceeds $360 million in total expenditures per year. Preterm labor hospitalization costs are in excess of $820 million. However, the direct economic cost is only a fraction of the ultimate cost of delivery of children who are preterm.

The cost of immediate newborn care for preterm infants has been estimated at $5 billion annually, and long-term health costs are also very high. Several studies have shown significant morbidity among children born prematurely. A 5-year follow-up evaluation of children born before 32 weeks' gestation showed significant language difficulties.

Of children born weighing less than 1500 g, one fourth had severe or multiple psychological problems, with a significant decrease in intelligence quotient and school learning and an increase in discipline problems. A 10-year follow-up evaluation of children born before 29 weeks' gestation showed a significant increase in behavioral disorders in school and performance below grade level.

The great successes in neonatal nurseries and intensive care units have dramatically increased the ability of children who are significantly preterm to survive. However, the learning disabilities and behavioral disorders in this group are quite significant, creating an ongoing challenge for their parents, the schools, and society as a whole.

Post-term pregnancy

Postdate labor induction in a woman with an unripe cervix is also associated with difficulties. Although research has demonstrated a higher cesarean delivery rate when labor is included in the absence of a ripened cervix, once pregnancies go beyond 41 weeks' gestation, induction of labor may provide benefits.

In a meta-analysis of studies examining induction of labor versus expectant management of low-risk pregnancies, Sanchez-Ramos et al found that induction of labor at 41 weeks' gestation resulted in a lower cesarean delivery rate (20.1%) than those expectantly managed (22%) with no significant differences in perinatal morbidity. Therefore, cervical ripening is advised prior to inducting labor in women with an "unfavorable" or un-ripened cervix.[67]

CONTRAINDICATIONS TO CERVICAL RIPENING

Contraindications to cervical ripening include, but are not limited to, the following:

- Active herpes
- Fetal malpresentation
- Non-reassuring fetal surveillance
- History of prior traumatic delivery
- Regular contractions
- Unexplained vaginal bleeding

- Placenta previa
- Vasa previa
- Prior uterine myomectomy involving the endometrial cavity or classical cesarean delivery

Previously, a history of a prior low transverse cesarean delivery was considered a contraindication to induction of labor. According to the ACOG Practice Bulletin on Vaginal Birth After Previous Cesarean Delivery, induction of labor is not contraindicated in women with a prior low transverse cesarean delivery; however, use of prostaglandins should be avoided in these patients due to a significantly increased risk of uterine rupture.[68]

A relative contraindication to cervical ripening is ruptured membranes. At this time, no evidence shows that cervical ripening followed by delayed induction of labor reduces the rate of cesarean delivery.[69]

MISOPROSTOL

Misoprostol is a synthetic analogue of PGE1. Its chemical name is 15-deoxy-16hdroxy-16-methyl-9-oxoprost-13 E-en-1-oate. It was mainly used for the treatment of gastric and duodenal ulcers caused by the use of non-steroidal anti-inflammatory drugs. It has been approved by United States for this particular use. In obstetrics, misoprostol is used for first and second trimester abortions and for cervical ripening before induction of labour.

Misoprostol has not been approved by the Food and Drug Administration for any of its usage in obstetrics. It is manufactured by G.D Searle and Co. (now Pfizer) for the treatment of peptic ulcer and is marketed under the trade name 'Cytotec' in more than 70 countries. Compared to other prostaglandins, misoprostol is cheap, stable at room temperature and has fewer side effects.

STRUCTURE AND CHEMISTRY OF MISOPROSTOL

The naturally occurring Prostaglandin E was found to reduce the gastric acid secretion and was used for the treatment of gastric ulcers.

The drawbacks of natural prostaglandins are

(1) Rapid metabolism resulting in a lack of oral activity and short duration of action when given parenterally.
(2) Numerous side effects.
(3) Chemical instability leading to short shelf life.

Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather at C-15. The methyl ester at C-1 increases its anti-secretory potency and duration of action of misoprostol, while the movement of hydroxyl group from C-15 to C-16 and the addition of methyl group at C-16 improves oral activity, increases duration of action and improves the safety profile of the drug.

PHARMACOKINETICS OF MISOPROSTOL

Misoprostol tablets were initially developed to be used orally. Other routes of administration are also possible like sub-lingual, vaginal, buccal and rectal. Many studies looked at its pharmacokinetic properties through these routes. The three factors studied widely were peak concentration, time to peak concentration and the area under serum concentration versus time curve.

The Cmax or peak concentration denotes how well the drug can be absorbed. Tmax or time to peak concentration denotes how rapidly the drug can be absorbed and the AUC denotes the total exposure to the drug. Misoprostol is extensively absorbed and rapidly undergoes de-esterification to its active form misoprostol acid which is responsible for its clinical actions.

Misoprostol-acid is readily detectable in the plasma unlike its parent compound. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

ORAL ROUTE

Following oral administration misoprostol is rapidly absorbed and has a Tmax of 12±3 minutes. The mean plasma value of misoprostol after an oral route of administration has a linear relationship with the dose taken. Cmax of misoprostol acid diminishes when the dose is taken with food or antacids. Cmax when taken on an empty stomach and with breakfast was 811±317 pg/ml and 303±176 pg/ml respectively while Tmax was 14±8 minutes and 64±79 minutes respectively which were statistically significant.

Less than 90% binds to serum protein. After oral administration of radiolabelled misoprostol, about 80% is detected in the urine. Oral route had a quicker onset of action of 8 minutes and a higher serum peak concentration compared to vaginal route. The duration of action of oral misoprostol is approximately 2 hours. The AUC after oral administration was only 54% of that after sublingual administration due to the first-pass metabolism of oral drug through the liver. Within 1 hour of administration misoprostol acid is secreted in the colostrum.[70-71]

VAGINAL ROUTE

Zeimen et al. studied the pharmacokinetics between oral and vaginal misoprostol. When administered vaginally, misoprostol has a slower absorption but a longer duration of action. The time to peak concentration between oral and vaginal drug was 34±17 minutes compared to 80±27 minutes which was statistically significant. The plasma levels gradually reach a peak within 70-80 minutes and then slowly declines with the drug still detectable up to 6 hours.[72]

The vaginal absorption of misoprostol is inconsistent and depends on the amount and pH of the vaginal secretions

and is therefore different for every woman. Sometimes the tablet would be seen to be persistently present in the vagina after several hours of administration denoting its incomplete and variable absorption. Many people moisten the tablet with water before administration but evidence has proved that to be non-beneficial in increasing its bioavailability.[70]

PHARMACODYNAMICS

As misoprostol was initially used for protection against the ulcerogenic effect of NSAID's on the gastric mucosa, its anti-secretory and mucosal protective actions were noticed as the main effects while its action on the uterus and cervix were considered to be its side effects. Later the drug was widely studied on pregnant and non-pregnant women. At term the number of prostaglandin receptors on the uterus increases. Misoprostol acts on these receptors and causes its action on the uterus and cervix.

USES OF MISOPROSTOL

Even though misoprostol has not been approved by the FDA, it has been used widely in the field of obstetrics and gynecology. But human experiments to determine its appropriate dosage and safety are lacking. Animal studies have shown no evidence of fetotoxic, teratogenic or carcinogenic effects. Early studies of misoprostol on the pregnant uterus have shown that results from animal studies cannot be extrapolated to determine its effects on the pregnant human uterus.

Animal studies have shown that at the dose used for anti-ulcer treatment, misoprostol had no effect on the uterus. But human studies done by Rabe et al has shown that 200 mcg or 400 mcg of misoprostol used in the first trimester resulted in vaginal bleeding, abdominal pain and softening of the cervix. The effect of misoprostol as an abortifacient is significantly amplified when pretreated with mifepristone.[73] Uninterrupted pregnancies following the use of misoprostol either alone or as an additional agent for termination in the first trimester, are known to be associated with anomalies in the fetus. The most logical etiology for the teratogenic effect of misoprostol is disruption of the developing vascular system caused by uterine contractions, resulting in orofacial and limb defects termed as Mobius syndrome. This occurs when the fetus is exposed to this agent between 5-8 weeks of gestation.[74]

Therefore misoprostol is better avoided in pregnant women who intend to continue their pregnancies to term. Subsequent studies have shown that intravaginal misoprostol can terminate first and second trimester pregnancies and was as effective as PGE2 and also had the advantage of being less costly and easy to store and administer.[75]

Use of misoprostol in the third trimester has been associated with increased incidence of uterine hyperstimulation irrespective of the dose used. This occurs due to the accumulative effect of misoprostol. Use of higher doses of misoprostol is associated with higher incidence of hyperstimulation, meconium passage and even cesarean section rate for fetal distress but many studies have failed to demonstrate any change in the cesarean delivery rate with the use of this drug.[76]

Wing et al compared a 3 hourly schedule of 25 mcg vaginally administered misoprostol with that of a 6 hourly schedule. The 6 hourly schedules had lesser hyperstimulation and meconium passage but the difference did not reach statistical significance. Women who received the drug every 3 hourly had shorter labor duration from the time of induction and also required less oxytocin augmentation.[77]

Myometrial stimulation by misoprostol is probably dose related but optimal dosing of intra-vaginal misoprostol for cervical ripening and labour induction is yet to be determined. As per WHO recommendations low dose vaginal misoprostol of 25 mcg every 6 hourly is suggested for induction of labor. Misoprostol administered orally at a dose of 50 mcg every 4 hours was found to be as effective and safe as vaginally or intracervically administered prostaglandins.[78]

The frequency of gastrointestinal side effects with oral misoprostol is less compared to orally administered dinoprostone. In women with pre-labor rupture of membranes, oral misoprostol was found to be useful for improving the cervical score and also for reducing the incidence of oxytocin infusion for labor induction and a decrease in the induction – delivery interval.[79]

A double blinded randomized controlled trial was done by Dodd et al between 20 mcg of oral misoprostol administered every 2 hourly and vaginal dinoprostone gel given six hourly which found no difference between the two arms in terms of vaginal birth achieved in 24 hours from induction. There was no significant difference between maternal and neonatal adverse outcomes.[80]

Adair et al conducted a double blind placebo controlled randomized trial between 200 mcg of oral misoprostol and 50 mcg of vaginal misoprostol repeated every 6 hourly and have shown similar efficacy between the two in terms of total length of labor and cesarean delivery rate. Oral misoprostol at this dose decreased the interval to the onset of uterine contractions but caused uterine hyperstimulation and tachysystole.[81] Toppozada et al compared 100 mcg of misoprostol administered either orally or vaginally every 3 hourly. Vaginal misoprostol had shorter time interval to delivery but was associated with more abnormal FHR tracings and uterine hyperstimulation.[82]

Another study done by Hall et al comparing 100 mcg of oral misoprostol and 25 mcg of vaginal misoprostol showed no difference between the delivery time or the

rate of tachysystole between the two arms and they concluded that in a well-equipped hospital setting, oral misoprostol could be used as safely and effectively as its vaginal analogue.[83]

Bennett et al studied 50 mcg of misoprostol administered every 4 hourly by oral or vaginal route and concluded that though oral misoprostol had a longer duration from induction to delivery compared to vaginal misoprostol, the incidence of cesarean section rate was similar between the two groups. There was a higher incidence of fetal heart rate changes in the vaginal misoprostol group. They suggested that until the optimal dosing interval for vaginal use is determined, the preferred route of misoprostol administration should be oral.[84]

Shetty et al like Bennett et al studied 50 mcg of misoprostol by oral or vaginal route every 4 hourly for a maximum of 5 doses. They found that the vaginal route initiates labor faster but had a higher frequency of uterine hyperstimulation and higher intervention rate for fetal distress.[85]

A randomized comparison of 100 mcg of oral misoprostol and 25 mcg of vaginal misoprostol given every 4 hourly done by Wing et al showed an increase in the need for oxytocin requirement, cesarean section rate and NICU admissions in the vaginal misoprostol group with no statistical significance. Though the induction delivery interval was less in the oral misoprostol group, the incidence of uterine hyperstimulation and tachysystole was higher but with no statistical significance.[86]

Wing et al also studied a lower dose of oral misoprostol i.e. 50 mcg every four hourly and 25 mcg vaginal misoprostol at the same frequency. They found that oral misoprostol at this dosage was less effective for cervical ripening though there was lesser hyperstimulation and cesarean section rate compared to vaginal misoprostol.[87]

50 mcg of misoprostol by oral or vaginal route every 4 hourly was evaluated by Bano et al who concluded that misoprostol at this dose was as safe and effective as compared with vaginal misoprostol. There was no statistical difference between the induction – to –delivery interval, oxytocin requirement, cesarean section rate or meconium staining in both these groups.[88]

Rasheed et al also studied between the same dose of 50 mcg misoprostol by oral or vaginal route administered every 4 – 6 hourly and found that the induction delivery interval was much higher in the oral misoprostol group (20.6 hours versus 13.5 hours, $p < 0.01$) compared to the vaginal misoprostol group.[89]

Kwon et al randomized women to receive 50 mcg of misoprostol orally or vaginally and every 6 hourly till the cervix was favorable for amniotomy, spontaneous rupture of membranes or active labor occurred and found that vaginal misoprostol resulted in shorter induction to delivery interval with fewer doses required per patient but oral misoprostol was associated with lesser cesarean section rate and higher rate of hyperstimulation and oxytocin requirement.[90]

50 mcg of oral misoprostol every 3 hourly and 50 mcg of vaginal misoprostol every 6 hourly for labor induction was studied by Fisher et al. Vaginal misoprostol every 6 hourly was more effective in achieving vaginal delivery faster than oral misoprostol at the same dose but shorter frequency of administration. Uterine hyperstimulation was higher in the vaginal misoprostol group.[91]

The safety and efficacy of misoprostol orally and vaginally was assessed in a randomized controlled trial by Carlan et al in 1004 women at a dose of 200 mcg oral misoprostol with increase in dose to 300 mcg at subsequent dose and 50 mcg of vaginal misoprostol with increment to 100 mcg at subsequent dose.

The induction to delivery interval was similar in both the groups thereby proving the similarity in the efficacy between oral and vaginal misoprostol at this dosage. But the oral misoprostol at this high dose was associated with higher incidence of uterine hyperstimulation and intervention.[92]

Misoprostol in titrated doses was evaluated in two studies by Cheng et al and Colon et al. In the study done by Cheng et al patients were randomized to receive oral or vaginal misoprostol. The patients in the oral misoprostol group received 20 ml of a 1mcg/ml solution of misoprostol every 1 hourly for 4 hours and patients in the vaginal misoprostol group received 25 mcg every 4 hourly.

The median interval from the first dose of misoprostol to delivery in the oral group was 8.2 hours and in the vaginal group it was 17.6 hours ($p<0.01$). The requirement for oxytocin was much lesser in the oral group where only 10.9% required and 53.8% required in the vaginal group ($p<0.01$). Uterine hyperstimulation was absent in the oral group while 11% of patients in the vaginal group developed hyperstimulation ($p<0.01$).

Cesarean section rate was also higher in the vaginal group (4% in the oral and 17% in the vaginal group) ($p<0.01$). 5.7 % of neonates from the vaginal group required NICU admission while non from the oral group required ($p=0.16$). This study proves that titrated oral misoprostol is associated with lesser cesarean section rate and is highly safe and efficacious compared to vaginal misoprostol.[93]

In the randomized clinical trial done by Colon et al patients in the oral misoprostol group received 50 mcg of misoprostol initially and the dose was increased to 100 mcg after 4 hours. The patients in the vaginal misoprostol group received 25 mcg every 4 hourly for a

maximum of 4 doses. There was no statistical significance between the induction- to – delivery interval, need for oxytocin administration, uterine hyperstimulation and meconium stained amniotic fluid.

The incidence of cesarean section rate was lower in the oral misoprostol group 19.4% vs. 32.4% which was statistically significant ($p<0.05$). The NICU admissions were more in the oral misoprostol group. Serious maternal outcome of death probably due to amniotic fluid embolism occurred in one study but the dose of misoprostol used was not mentioned. Two maternal morbidities consisting of atonic postpartum hemorrhage requiring cesarean hysterectomies were reported.[94]

They concluded that though misoprostol was effective than the other conventional methods used, its safety was not established and they recommended larger studies to exclude this possibility. Windrim et al also concluded that oral misoprostol appears to be no less effective or safe than the available and accepted regimens for induction of labor at term and that it is well tolerated.

A drawback with the use of oral misoprostol is that if hyperstimulation with or without fetal heart rate changes occurred after oral misoprostol, intravenous tocolytic agent or even cesarean section must be resorted to. Lavage or removal of the tablet remnant, an option in vaginal misoprostol use is not possible.

OBJECTIVE

To compare the outcome of oral versus vaginal administration of misoprostol for induction of labour at term (gestational age >37 weeks).

OPERATIONAL DEFINITIONS

Outcome in terms of successful induction

Induction of labour is used to bring an end to pregnancy when the benefits of giving birth at that time outweigh the risks of the induction process. Any patient at term with cervical dilation of more than 4 cm was labeled as successful induction of labor.

Vaginal delivery

Any pregnancy terminated with the delivery of newborn through the vagina, is labeled as vaginal delivery.

Indication of labor induction

1. Oligohydramnios
2. Fetal intrauterine growth restriction IUGR, with no abnormal doppler
3. Gestational hypertension at term
4. Pre-gestational diabetes well-controlled, with the timing at 39 0/7 to 39 6/7 weeks of gestation
5. Gestational diabetes (GDM), diet, or exercise controlled, with the timing at 39 0/7 to 40 6/7 weeks of gestation
6. Abruptio placentae
7. Intrauterine fetal demise (IUFD)

HYPOTHESIS

There is difference in the outcome of oral versus vaginal administration of misoprostol in terms of successful induction of labour at term and vaginal delivery.

MATERIALS AND METHODS

Study Setting

The study was conducted in Obstetrics & Gynecology Department, Shaikh Zayed Hospital, Lahore.

Duration of the Study: January 11, 2023 to July 10, 2023.

Study Design

Randomized controlled trial **Sampling Technique**
Non-probability consecutive sampling **Sample Size**

The sample size of 180(90 in each group) is estimated by using 95% confidence level with 80% power of test and taking an expected percentage of successful induction as 74.51% with oral misoprostol and 90.38% with vaginal misoprostol.[10]

SAMPLE SELECTION

Inclusion Criteria

- Singleton pregnancy
- Patients ages between 18-40 years
- Patients at term (between 37 to 42 weeks of gestation)
- Patients parity either nulliparous or multiparous with cephalic presentation
- Decision regarding the induction of labour taken by an unbiased consultant obstetrician blinded to the studied

Exclusion Criteria

- Vasa previa or placenta previa (on history, examination and record evaluation)
- Transverse fetal presentation (on history, examination)
- Umbilical cord prolapse (on history, examination)
- History of a prior classical cesarean section (on history, examination and record evaluation)
- Active herpes infection(on history, examination and record evaluation)
- A previous myomectomy breaching the endometrial cavity (on history, examination and record evaluation)
- Grand multiparty - greater than or equal to 5 live births or stillbirths (on history, examination and record evaluation)
- Preterm premature rupture of membranes (on history, examination and record
- evaluation)
- History of fetal anomalies (on history, examination and record evaluation)
- Contraindication to misoprostol (history of allergy to prostaglandins, (on history, examination and record evaluation)

DATA COLLECTION PROCEDURE

After approval from hospital ethical committee and taking written informed consent from guardians, all 180(90 in each group) patients were enrolled. Demographic information (including name, age and gender) was also recorded. Patients were divided into two groups randomly by using lottery method; each group consisted of ninety patients.

The women randomized to group-A received 50 microgram oral misoprostol 6 hourly orally up to a maximum of 4 doses. The women randomized to group B received 50 microgram misoprostol vaginally and repeated at 6 hours interval up to a maximum of 4 doses. Oral misoprostol is available in the form of 200µg tablets. All patients received steroid injections before 24 hours for the fetal lung maturity.

Patients meeting the operational definition of successful induction of labor were noted. Patients who progressed to active labour were transferred to labour ward and managed accordingly. Patient who successfully delivered the newborn vaginally were noted in each group. All the data was collected through a pre-designed proforma (attached). Gestational age was calculated from the first day of last normal menstrual period.

DATA ANALYSIS PLAN

Data was entered and analyzed using SPSS v25.0. Frequencies and percentages were expressed for qualitative variables like successful induction and vaginal delivery.

Quantitative variables like age and gestational age were expressed by Mean±S.D. Data was stratified for age, gestational age, parity to deal and total number of doses with effect modifiers. Post-stratification, Chi-square test was applied to see the effect on outcome taking p-value ≤0.05 as significant.

RESULTS

Total 180 patients undergoing induction of labor were enrolled in this study. Patients were divided in two groups i.e. Group-A (Oral misoprostol) and Group-B (Vaginal misoprostol).

Age range in this study was from 18 to 40 years. The mean age of patients in group-A was 27.67±6.012 year and in group-B was 28.52±6.088 year. In group-A, 38(42.2%) were in 18-30 years age group, while 52(57.8%) were in 31-40 years age group, while in group-B, 39(43.3%) were in 18-30 years age group, while 51(56.7%) were in 31-40 years age group **(Table-1)**.

In group-A, mean gestational age was 38.28±4.37 weeks and 38.15±4.41 weeks in group-B. In group-A, 51(56.7%) had gestational age between 37-39 weeks and 39(43.3%) had between 40-42 weeks, while in group-B, 48(53.3%) had gestational age between 37-39 weeks and 42(46.7%) had between 40-42 weeks **(Table-2)**.

In group-A, 40(44.4%) were nulliparous/primiparous and 50(55.6%) were multiparous, while in group-B, 46(51.1%) were nulliparous/primiparous and 44(48.9%) were multiparous **(Table-3)**.

In group-A, mean number of doses was 2.7±1.3 and 2.3±1.2 in group-B. In group-A, 67(74.4%) had single dose and 23(25.6%) had multiple doses, while in group-B, 63(70.0%) had single dose and 27(30.0%) had multiple doses **(Table-4)**.

In Oral misoprostol group, 63(70.0%) had successful labour induction and 79(87.8%) had successful labour induction in Vaginal misoprostol group with a p-value 0.003, which is statistically significant **(Table-5)**.

In Oral misoprostol group, 62(68.9%) had vaginal delivery and 78(86.7%) had vaginal delivery in Vaginal misoprostol group with a p-value 0.004, which is statistically significant **(Table-6)**.

According to stratification of successful labour induction between group with respect to different variables, statistically significant difference was noted in successful labour induction ($p<0.05$) **(Table-7 to 10)**.

According to stratification of vaginal delivery between group with respect to different variables, statistically significant difference was noted in vaginal delivery ($p<0.05$) **(Table-11 to 14)**.

Table 1: Comparison of age groups distribution between groups.

Age groups	Groups		Total
	Oral misoprostol	Vaginal misoprostol	
18-30 years	38	39	77
	42.2%	43.3%	42.8%
31-40 years	52	51	103
	57.8%	56.7%	57.2%
Total	90	90	180
	100.0%	100.0%	100.0%

Table 2: Comparison of gestational age distribution between groups.

Gestational age	Groups		Total
	Oral misoprostol	Vaginal misoprostol	
37-39 weeks	51	48	99
	56.7%	53.3%	55.0%
40-42 weeks	39	42	81
	43.3%	46.7%	45.0%
Total	90	90	180
	100.0%	100.0%	100.0%

Table 3: Comparison of parity distribution between groups.

Parity	Groups		Total
	Oral misoprostol	Vaginal misoprostol	
Nulli/Primiparous	40	46	86
	44.4%	51.1%	47.8%
Multiparous	50	44	94
	55.6%	48.9%	52.2%
Total	90	90	180
	100.0%	100.0%	100.0%

Table4: Comparison of number of doses distribution between groups

Number of doses	Groups		Total
	Oral misoprostol	Vaginal misoprostol	
Single dose	67	63	130
	74.4%	70.0%	72.2%
Multiple doses	23	27	50
	25.6%	30.0%	27.8%
Total	90	90	180
	100.0%	100.0%	100.0%

Table 5: Comparison of successful induction between groups.

Successful induction	Groups		Total	p-value
	Oral misoprostol	Vaginal misoprostol		
Yes	63	79	142	0.003
	70.0%	87.8%	78.9%	
No	27	11	38	
	30.0%	12.2%	21.1%	
Total	90	90	180	
	100.0%	100.0%	100.0%	

Table 6: Comparison of vaginal delivery between groups.

Vaginal delivery	Groups		Total	p-value
	Oral misoprostol	Vaginal misoprostol		
Yes	62	78	140	0.004
	68.9%	86.7%	77.8%	
No	28	12	40	
	31.1%	13.3%	22.2%	
Total	90	90	180	
	100.0%	100.0%	100.0%	

Table 7: Successful induction between groups with respect to age.

Age groups	Successful Induction	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
18-30 years	Yes	23	35	58	0.003
		60.5%	89.7%	75.3%	
	No	15	4	19	
		39.5%	10.3%	24.7%	
	Total	38	39	77	
		100.0%	100.0%	100.0%	
31-40 years	Yes	40	44	84	0.043
		76.9%	86.3%	81.6%	
	No	12	7	19	
		23.1%	13.7%	18.4%	
	Total	52	51	103	
		100.0%	100.0%	100.0%	

Table 8: Successful induction gestational age.

Gestational age	Successful induction	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
37-39 weeks	Yes	36	45	81	0.003
		70.5%	93.8%	81.8%	
	No	15	3	18	
		29.4%	6.3%	18.2%	
	Total	51	48	99	
		100.0%	100.0%	100.0%	
40-42 weeks	Yes	27	34	61	0.042
		69.2%	81.0%	75.3%	
	No	12	8	20	
		30.8%	19.0%	24.7%	
	Total	39	42	81	
		100.0%	100.0%	100.0%	

Table 9: Successful induction between groups with respect to parity.

Parity	Successful induction	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
Nulli/Primiparous	Yes	26	42	68	0.003
		65.0%	91.3%	79.1%	
	No	14	4	18	
		35.0%	8.7%	20.9%	
	Total	40	46	86	
		100.0%	100.0%	100.0%	
Multiparous	Yes	37	37	74	0.043
		74.0%	84.1%	78.7%	
	No	13	7	20	
		26.0%	15.9%	21.3%	
	Total	50	44	94	
		100.0%	100.0%	100.0%	

Table 10: Successful induction number of doses.

Number of doses	Successful induction	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
Single dose	Yes	46	56	102	0.005
		68.7%	88.9%	78.5%	
	No	21	7	28	

		31.3%	11.1%	21.5%	
	Total	67	63	130	
		100.0%	100.0%	100.0%	
Multiple doses	Yes	17	23	40	0.041
		73.9%	85.2%	80.0%	
	No	6	4	10	
		26.1%	14.8%	20.0%	
	Total	23	27	50	
		100.0%	100.0%	100.0%	

Table 11: Vaginal delivery between groups with respect to age.

Age groups	Vaginal delivery	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
18-30 years	Yes	23	34	57	0.008
		60.5%	87.2%	74.0%	
	No	15	5	20	
		39.5%	12.8%	26.0%	
	Total	38	39	77	
		100.0%	100.0%	100.0%	
31-40 years	Yes	39	44	83	0.048
		75.0%	86.3%	80.6%	
	No	13	7	20	
		25.0%	13.7%	19.4%	
	Total	52	51	103	
		100.0%	100.0%	100.0%	

Table 12: Vaginal delivery gestational age.

Gestational age	Vaginal delivery	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
37-39 weeks	Yes	33	41	74	0.018
		64.7%	85.4%	74.7%	
	No	18	7	25	
		35.3%	14.6%	25.3%	
	Total	51	48	99	
		100.0%	100.0%	100.0%	
40-42 weeks	Yes	29	37	66	0.042
		74.4%	88.1%	81.5%	
	No	10	5	15	
		25.6%	11.9%	18.5%	
	Total	39	42	81	
		100.0%	100.0%	100.0%	

Table 13: Vaginal Delivery Between Groups With Respect To Parity.

Parity	Vaginal delivery	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
Nulli/Primiparous	Yes	24	39	63	0.010
		60.0%	84.8%	73.3%	
	No	16	7	23	
		40.0%	15.2%	26.7%	
	Total	40	46	86	
		100.0%	100.0%	100.0%	
Multiparous	Yes	38	39	77	0.042
		76.0%	88.6%	81.9%	
	No	12	5	17	
		24.0%	11.4%	18.1%	
	Total	50	44	94	
		100.0%	100.0%	100.0%	

Table 14: Vaginal Delivery number of doses.

Number of doses	Vaginal delivery	Groups		Total	p-value
		Oral misoprostol	Vaginal misoprostol		
Single dose	Yes	46	54	100	0.021
		68.7%	85.7%	76.9%	
	No	21	9	30	
		31.3%	14.3%	23.1%	
	Total	67	63	130	
		100.0%	100.0%	100.0%	
Multiple doses	Yes	16	24	40	0.049
		69.6%	88.9%	80.0%	
	No	7	3	10	
		30.4%	11.1%	20.0%	
	Total	23	27	50	
		100.0%	100.0%	100.0%	

DISCUSSION

Misoprostol is, a cost effective treatment, being increasingly used for induction of labour since past few years. There have been different published reports of misoprostol use through different routes (oral, vaginal and rectal) and in varying doses (25 µg to 200 µg). In the present study, baseline characteristics such as age, parity and gestational age were distributed equally across the treatment arms. This is the impact of randomization which distributes known and unknown confounders across treatment groups.

In this study, 50 microgram oral misoprostol 6 hourly orally up to a maximum of 4 doses and 50 microgram misoprostol vaginally and repeated at 6 hours interval up to a maximum of 4 doses. Jindal *et al* used same dose of misoprostol via oral and vaginal route and found that vaginal route was more effective for inducing labour successfully as compared to oral route and their findings were similar to results of our study where vaginal route was found to be more effective.[10]

In our study, successful induction with 50 µg vaginal misoprostol was higher (87.8 vs. 70%). Shetty et al. reported lower failure (2.4 vs. 6.76%) with 50 µg vaginal misoprostol as compared to oral and at the same time reported shorter induction delivery interval by 10.1 hour.[95] Even Latika et al. observed 100% success rate with 50µg vaginal misoprostol and 100 µg oral misoprostol.[96-97] While comparing 50 µg vaginal misoprostol with Foley's catheter/oxytocin, successful induction was 90.61 vs. 78.44% and induction delivery interval shorter by 7.87 h in vaginal misoprostol group.[98]

As vaginal misoprostol is absorbed rapidly and eliminated slowly from body making it available to act for a longer time as compare to oral resulting in rapid progression of labor leading to greater number of women delivering within 24 h of induction (69.5 vs. 56.4%).[99,95] In our study, more women (86.7 vs. 68.9%) delivered within 24 hour in vaginal group. Cesarean section rate in group-A was 31.1% as compared to 13.3% (p=0.004) in group-B. Darney *et al* reported (4% and 17%) and Kambhampati *et al* reported (6% and 14%) in both groups.[100-101]

In another study by Ratnakhatri *et al*, the rates of operative delivery in both groups were 14% and 30% which were similar in comparison to our study.[102] In contrast, other studies reported that no difference in the rate of cesarean delivery in oral vs. vaginal misoprostol. The proportion of cesarean delivery in oral group was 41% and vaginal group was 42% (p=0.63).[103-106] In a study by Sultana *et al* need for cesarean section in oral misoprostol was 30% as compared to 34% in vaginal misoprostol (p=0.78).[106]

In a study, in vaginal misoprostol group, induction delivery interval was significantly less (9.79±2.5 vs. 16.47±4.3 hours), vaginal delivery (90.4% vs. 74.5%) and successful induction was significantly higher (90.38% vs. 74.51%) than oral group, within 24 hours of induction.[10] In another study, in oral misoprostol group, induction delivery interval was less but insignificantly (9.58±4.9 vs. 10.5±4.03 hours) than vaginal group, vaginal delivery (72% vs. 76%) and successful induction was same (100% vs. 100%), within 24 hours of induction.[11]

Misoprostol effectively induces labour, with the vaginal route of administration and has a faster action than with the oral route in equivalent doses. More trials are needed to find the right oral dosage that combines efficacy with safety. Misoprostol is especially relevant for Pakistan where economic resources are scarce and high temperatures prevail.

This drug is cheap as compared to other prostaglandins licensed for pregnancy termination, induction of labour and treatment and prevention of post-partum hemorrhage. It is heat stable so is easily stored at room temperatures and it had few systemic side effects. Although formulated for oral usage, but rapidly absorbable via sublingual, vaginal and per rectal route.

CONCLUSION

There is difference in the outcome of oral versus vaginal administration of misoprostol in terms of successful induction of labour at term and vaginal delivery. Compared with vaginal misoprostol, oral misoprostol may be associated with increased risk of cesarean delivery and lesser labour induction.

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