تأثير استخدام الميزوبروستول
في تحفيز الولادة على الأم والمولود

رسالة مقدمة
توطئة لنيل درجة الماجستير
في أمراض النساء والتوليد

مقدمة من
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كلية طب بنها - جامعة الزقازيق
2004
MATERNAL AND NEONATAL OUTCOME WITH MISOPROSTOL USE FOR LABOR INDUCTION

Thesis
Submitted in partial fulfillment for the Master degree (M.Sc) (Obstetrics and Gynecology)

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BENHA FACULTY OF MEDICINE
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2004
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AIM OF THE WORK

The aim of our work is to find out if the use of misoprostol for labor induction has any undesirable effects on the mother and/or the neonate.
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine mono – phosphate</td>
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<tr>
<td>Cm</td>
<td>Centimeter</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>COX – II</td>
<td>Cyclooxygenase isoenzymes PGH synthase – 2</td>
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<td>COX-I</td>
<td>Cyclooxygenase isoenzymes PGH synthase – 1</td>
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<td>CTG</td>
<td>Cardiotocography</td>
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<td>Fig</td>
<td>Figure</td>
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<td>gm</td>
<td>gram</td>
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<td>HDF</td>
<td>Human dermal fibroblasts</td>
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<td>HSF</td>
<td>Hypertrophic scare fibroblasts</td>
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<td>IL 6</td>
<td>Interleukin – type – 6</td>
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<tr>
<td>IL 8</td>
<td>Interleukin – type – 8</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IU</td>
<td>International unit</td>
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<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>Kgm</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L/S ratio</td>
<td>Lecithin / Sphingomyelin ratio</td>
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<td>MAS</td>
<td>Meconium aspiration syndrome</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
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<tr>
<td>MHZ</td>
<td>Mega hertez</td>
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<tr>
<td>min</td>
<td>Minute</td>
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<tr>
<td>mu</td>
<td>Millunit</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>NICU</td>
<td>Neonatal intensive care unit</td>
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<tr>
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<td>Number</td>
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<tr>
<td>NSAID</td>
<td>Non steroidal anti – inflammatory drugs</td>
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<td>°C</td>
<td>Centigrade</td>
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<tr>
<td>PG H2</td>
<td>Prostaglandin H2</td>
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<tr>
<td>PGE$_1$</td>
<td>Prostaglandin E$_1$</td>
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<td>PGE$_2$</td>
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<td>PGF$_{2\alpha}$</td>
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<tr>
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<td>Prostaglandins</td>
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<tr>
<td>PLA2</td>
<td>Phospholipase A2 Type</td>
</tr>
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<td>PROM</td>
<td>Premature rupture of membranes</td>
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<tr>
<td>PVCS</td>
<td>Premature ventricular contraction</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TGF</td>
<td>Transforming growth factor</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
<td>TXA2</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>USA</td>
<td>United states of America</td>
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<tr>
<td>g</td>
<td>Microgram</td>
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<tr>
<td>$\bar{x}$</td>
<td>Arithmetic mean</td>
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<tr>
<td>$x^2$</td>
<td>Chi – square test</td>
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<td>%</td>
<td>Percentage</td>
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<td>&amp;</td>
<td>And</td>
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<td>Symbol</td>
<td>Description</td>
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<td>&gt;</td>
<td>More than</td>
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<td>≤</td>
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<td>≥</td>
<td>Equal or more than</td>
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<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
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Induction of labor is undertaken when the advantages of delivery for the mother and/or the baby are considered to outweigh the disadvantages (Hofmeyer, 2003).

Induction of labor implies stimulation of uterine contractions before the spontaneous onset of labor, with or without ruptured membranes (Cunningham et al., 2001a).

Various techniques have been used for induction of labor. Induction of labor with prostaglandins has been considered the most common approach to induce a labor, and used above all by vaginal way in patients with unripe cervix. They stimulate the natural PG effects at the beginning of delivery and showed a great efficacy (Tinelli et al., 2003 and Tensor, 2003).

PGE$_2$ is the best method for cervical ripening and labor induction, but the widespread use of prostaglandin E2 in its currently approved form is limited because of its high cost and thermal instability, which leads to difficult storage (Egarter et al., 1990; Arias, 1993a and de Aquino and Cecatti, 2003).

Misoprostol a synthetic E1 methyl analogue prostaglandin, is at present receiving more attention as a cervical modifying agent and labor induction, as it has the advantages of low cost, thermal stability, easy handling and storage, and also easy administration.
(vaginal or endocervical). However, there is still a need for better establishing its safety so as to avoid hyperstimulation syndrome, which could result in undesirable consequences for the newborn (de Aquino and Cecatti, 2003).
INDUCTION OF LABOR

History of induction:

Induction of labor is a common obstetric instrument to employ when the potential risk to continue a pregnancy is higher than to terminate it (Tinelli et al., 2003).

In the past, many drugs had been tried but were found unsuitable as Cinnamon, Caffeine, Digitals and Sugar (Donald, 1972). The crude extract of ergot was tried in 1800 but was abandoned, being dangerous for mother and fetus (Donald, 1972).

Schele and Denman induced labor by rupture of membranes more than 150 years ago, in 1853 Kravese used the bougies. In 1861 Barner used the bags.

In 1913 Waston used Castor oil, quinine pituitary extract in doses of 1/2-1 ml in various combinations but complications occurred as uterine rupture, hypertonic uterine action and foetal death.

Indications for induction of labor:

There are many different situations in obstetrics where there is the need for labor induction in women with unripe cervices. This indication stems from a situation where the continuation of pregnancy may be life – threatening for the mother and /or the fetus. Such induction is frequently prolonged, exhausting and very often unsuccessful resulting in a cesarean section (de Aquino and Cecatli, 2003).
Review of Literature

I-Maternal indications:

Pregnancy induced hypertension, chronic nephritis, acute renal failure, uncontrolled diabetes mellitus, and chorioamnionitis are the main maternal indications (Calder, 1999).

II-Fetal indications:

Post-term pregnancy, premature rupture of membranes (PROM), intrauterine fetal death, congenital fetal malformation incompatible with life, intrauterine growth restriction, Rh iso-immunization, and severe hydramnios are the main fetal indications for labor induction (Reichler et al., 1995).

The following are the main maternal and fetal indications for induction of labor:

1-Post-term pregnancy:

The standard internationally recommended definition of post-term pregnancy, endorsed by the American college of obstetricians and gynecologists, (1997), is 42 completed weeks (294 days or more from the first day of the last menstrual period) (Cunningham et al., 2001b).

Fetal problems with prolongation of pregnancy:

1-Intrapartum fetal distress:

Non reassuring fetal heart rate patterns in the form of moderate to severe variable decelerations with slow recovery, and episodes of fetal bradycardia with loss of beat to beat variability, increase in prolonged pregnancies. In the majority of cases, these non-reassuring fetal heart rate patterns result from umbilical cord compression caused by oligohydramnios (Leveno et al., 1984), and in minority of cases. They are the result of placental insufficiency (Silver et al., 1988).
2-Meconium aspiration syndrome:

Meconium aspiration syndrome (MAS) is a severe complication of prolonged pregnancy, the problem occurs more frequently when Thick meconium, fetal tachycardia, and absence of fetal heart rate accelerations are present (Rossi et al., 1989).

3-Fetal trauma:

Difficult vaginal delivery with varied degrees of fetal trauma occur commonly in prolonged pregnancies, especially those complicated by fetal macrosomia (Arias, 1993a).

4-Post maturity syndrome:

Postmature features have; decreased amounts of subcutaneous fat and wrinkled skin, long hair and long finger nails, and their skin may have a greenish or yellowish staining if they have had prolonged exposure to meconium. Postmature fetuses are fragile, tolerate labor poorly and frequently are acidotic at birth (Cunningham et al., 2001b).

Management of post-term pregnancy:

Hannah and Colleagues, (1992) reported that induction of labor at 41 weeks or more resulted in significantly lower cesarean rate compared with pregnancies managed with antepartum testing in the form of non stress test three times weekly, assessment of the amniotic fluid volume two to three times each week (Pockets less than 3cm were considered abnormal) and asking pregnant women to count the number of times they felt the fetus move over a 2- hour period each day (Hannah et al., 1992, Goeree et al., 1995 and James et al., 2001).
2-Premature rupture of membranes:

Premature rupture of membranes (PROM) is defined as spontaneous rupture of amniochorionic membranes at any time prior to the onset of uterine contractions of labor (Parry and Strauss, 1998).

It occurs in about 5% to 15% with an average of 8% of all pregnancies beyond 37 weeks (Parry and Strauss, 1998, Crane and Young, 2003) and preterm rupture of membranes (rupture of membranes remote from term) occurs in approximately 1% of all gestations (Mc Gregor, 1999).

Complications of premature rupture of membranes:

The risks associated with PROM followed by a prolonged latent phase are significant to both the mother and the fetus. The most serious complications are chorioamnionitis, fetal sepsis, fetal distress and fetal skeletal deformities (Duff, 1996 and Merenstein & Weisman, 1996).

Management of premature rupture of membranes:

As the risks associated with PROM were increased with prolonging the period from the onset of rupture of membranes to the time of delivery, so early induction of labor in women with PROM near or at term is recommended (Milasinovic et al., 1998).

Induction of labor with prostaglandins in patients with premature rupture of membranes, Compared with expectant management, results in a reduced risk of chorioamnionitis, neonatal antibiotic therapy, Neonatal intensive care (NICU) admission, and increased maternal satisfaction. (Crane and Young, 2003).
Sanchez-Ramos and Delke, (1998) reported that misoprostal, a synthetic prostaglandin E1, was safe and effective for labor induction in women with PROM beyond thirty-six week’s gestation.

3-Pregnancy induced hypertension:

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection. That results in much of the maternal morbidity and mortality related to pregnancy (Berg et al., 1996 and Ventura et al., 2000).

Indications for termination of pregnancy in preeclampsia:

1-Severe preeclampsia and eclampsia:

Termination of pregnancy with severe preeclampsia or eclampsia should be done without delay when the gestational age is 36 weeks or more (Cowles et al., 1994).

When severe preeclampsia develops between 24 and 34 weeks, prolongation of pregnancy is advantageous for the fetus. These patients should be observed carefully in the intensive care unit and delivered if they exhibit one or more of the following conditions:

- Blood pressure persistently 160/100 or greater despite treatment.
- Urine output < 400ml in 24 hours.
- Platelet count < 50,000/ mm$^3$.
- Progressive increase in serum creatinine.
- Lactic dehydrogenase > 1000 1U/L.
- Repetitive late deceleration with poor variability.
- Severe intrapartum growth restriction (1UGR) with oligohydramnios.
- Decreased fetal movements.
Review of Literature

- Reversed umbilical diastolic blood flow.  
  (Many et al., 1999 and Hall et al., 2000).

2-Mild preeclampsia:

Labor is induced in patient with mild preeclampsia when the gestational age is 37 weeks or more to avoid the development of severe preeclampsia and its complications (Redman and Roberts, 1993).

Mode of termination of pregnancy:

Oxytocin induction has a good effect in patients near or at term with a favorable cervix. Patients remote from term and/or with unfavorable cervix need prostaglandin E2 vaginal suppositories or prostaglandin E1 analogue (misoprostol) for successful induction of labor (Redman & Roberts, 1993, Nassar et al., 1998 and Tenore., 2003).

However, in patients with eclampsia or other complicated forms of severe preeclampsia, delivery by cesarean section is preferred when vaginal delivery is not foreseen within 6-12 hours from the onset of induction of labor (Redman & Robert, 1993 and Nassar et al., 1998).

4-Diabetes mellitus with pregnancy:

Indications for termination of pregnancy in diabetes mellitus:

1-High risk gestational diabetes:

High risk gestational diabetes is characterized by one or more of the following:

- History of still birth or neonatal death.
- Concomitant obesity and/or hypertension.
- Development of oligohydraminos, polyhydramnios, preeclampsia, or premature rupture of membranes.
- Inadequate metabolic control with diet alone.

High risk gestational diabetic patients should be delivered at term (38 to 40 weeks). When this is apparent clinically and by ultrasound examination, labor should be as soon as fetal lung maturity is attained (Langer et al., 1994 and Clark & Lee, 1995).

2-Unstable insulin dependent diabetes:

Unstable insulin dependent diabetic patients should be managed carefully. Termination of pregnancy should be done as soon as fetal lung maturity; lecithin to sphingomyelin (L/S) ratio greater than 2, and positive phosphatidylglycerol is attained (Garner, 1995 & Szilagyi and Szabo., 2002).

Mode of delivery:

It is not necessary to deliver an insulin dependent diabetic patients by cesarean section. Although there are multiple indications for operative delivery of these patients, more than 50% of them can be safely delivered vaginally, either spontaneously or after labor induction (Garner, 1995).

5-Renal diseases with pregnancy:

Indications for termination of pregnancy with renal diseases:

1-Acute renal failure:

Acute renal failure may occur in pregnancy by different reasons including; severe preeclampsia, placental abruption, acute fatty liver of pregnancy and obstructive uropathy (Pertuist & Crunfeld, 1994 and Jungers & Chaveau, 1997).
2-Chronic renal diseases:

Induction of labor should be performed as soon as fetal ung maturity is reached in patients with chronic renal diseases if the patient is unstable or symptomatic. If the patient becomes severely ill, immediate termination of pregnancy is indicated without fetal lung maturity evaluation (Lindheimer and Katz, 1994).

Methods of induction of labor:

Induction of labor is common in obstetric practice. According to the most current studies. The rate varies from 9.5 to 33.7 percent of all pregnancies annually. In the absence of a ripe cervix, a successful vaginal Birth is less likely, so it is recommended that a cervical ripening agent be used before labor induction (Tenore., 2003).

A-Non pharmacological methods:

1-Mechanical stimulation of uterine cervix:

Mechanical methods were the first methods developed to ripen the cervix or to induce labor. Devices which were used include various types of catheters, introduced into the cervical canal or into the extra- amniotic space (Boulvain et al., 2001).

Mechanical stimulation of uterine cervix reduces the cervical stiffness by the release of prostaglandins from the uterus (Thiery, 1983) e.g., the use of a double balloon catheter (Atad’s Ripener Device) which was proved to be effective compared with PGE2 gel (Toppozada et al., 1994).
The double balloon device induces significant ripening and dilatation of the unfavourable cervix and the induction of labor is successfully achieved following its removal. The risk of uterine hyperstimulation from the use of Atad's ripener device is probably lower than that of PGE2 and may therefore be preferable in women with fetuses at high risk of fetal hypoxia (Atad et al., 1991 and Atad et al., 1997).

A simple foley’s catheter which can be passed through an undilated cervix before being inflated is as efficient as PGE2 gel. However, it is much less expensive but there is a risk of introducing infection into the uterus (Stonge and Connor, 1995).

Mechanical methods were never completely abandoned, but were substituted by pharmacological methods in recent decades (Boulvain et al., 2001).

2-Stripping of membranes:

Induction of labor by stripping of membranes is a relatively common practice, but the risk of infection, bleeding from placenta previa, and accidental rupture of membranes should be considered. Cervical ripening by stripping of membranes may be the result of PGF2α release from the deciduas and adjacent membranes or PGE2 form the cervix (McColgin et al., 1993 and Reichler et al., 1995).

It requires a cervix compliant enough to allow the introduction of one of the examiner’s fingers which is swept around the lower uterine segment attempting to strip or detach the amniotic membranes from the uterus. This maneuver causes local release of prostaglandins, and the
amount of release correlates with the area of membrane separated (Keirse et al., 1993 and Boulvain et al., 2001).

Stripping of membranes is an uncomfortable method for the patient but continues to be used frequently and there is no reported increase in maternal or neonatal morbidity (El-Torkey et al., 1992 and Allot et al., 1993).

3- Osmotic dilators:

These devices are effective in first and second trimester terminations of pregnancy. They have also been found to be safe and effective when used in viable third trimester pregnancies (Blumenthal & Ramanauskas, 1990 and Gilson et al., 1996).

There are two types of osmotic dilators:

1- Laminaria tents: are made from natural seaweed.

2- Synthetic dilators:

   - Dilapan (Gynotech, Middlesex, New Jersey, U.S.A.).
   - Hipan (Hypansky polymers, Princeton, New Jersey, USA).

Synthetic tents are designed to expand rather than to lengthen the cervix, thus decreasing the risk of cervical entrapment (Johnson et al., 1995; Blumenthal & Ramanauskas, 1990 and Krammer et al., 1995).

Krammer et al., (1995) found that induction of ripening by hygroscopic dilators and intracervical PGE2 was equivalent as measured by change in Bishop score. The change in the Bishop score, however, was not predictive of successful induction, and PGE2 was more frequently
associated with induction success. Dilators was associated with a higher incidence of postpartum maternal and neonatal infection due to a longer duration of labor *(Krammer et al., 1995 and Guinn et al., 2000)*.

4-Amniotomy:

Amniotomy (deliberate rupture of the membranes) is a simple procedure which can be used alone for induction of labor if the membranes are accessible, thus avoiding the need for pharmacological intervention *(Bricker and Luckas., 2000)*.

Manipulation of the membranes causes prostaglandin release, uterine contractions and cervical ripening. When the cervix is not ripe, the results of amniotomy are not good and these patients frequently require caesarean section because of "lack of progress". It is necessary, to have a reactive foetal heart rate monitoring tracing and to be certain that the head is well applied against the cervix. Care should be taken during amniotomy to avoid dislodging of the fetal head. An assistant applying fundal and suprapubic pressure may reduce the risk of cord prolapse. The fetal heart rate should be assessed immediately before and after this procedure *(Arias, 1993; Mercer et al., 1995 and Cunningham et al., 2001a)*.

5-Breast massage:

In postpartum lactating females, oxytocin secretion is enhanced by suckling which leads to about 100 fold rise than the basal values *(Czekanowski et al., 1987)*. This is the basis for using breast massage as a way of inducing labor *(Krasondebski et al., 1988)*.
6-Acupuncture :

Stambolov et al., (1986) studies acupuncture and electrical stimulation to initiate uterine contractions in prolonged pregnancy. They succeeded in achieving vaginal delivery in five or seven women.

B-Pharmacological methods :

1-Estradiol :

The hormone seems to have an effect on the cervix when it is given in high doses intravenously or as an intracervical gel (Gordon and Calder, 1969).

The human cervix contains receptors for both estrogen (Sanborn et al., 1975) and progesterone (Sanborn et al., 1976) and it is probable that the changing steroid environment during late pregnancy and at term has a direct action on the cervix. Estradiol appears to soften the bovine cervix without producing uterine activity (Mumo et al., 1978).

Gordon & Colder, 1977 have demonstrated a similar ripening effect in women with 150mg estradiol valerate instilled into the extra-amniotic space, suspended in Tylose gel.

MacIennan et al., (1981) found that estradiol was equally effective to prostaglandin F2α and relaxin for pre-induction cervical ripening (MacIennan et al., 1981).

Magann et al., (1995) used 4mg estradiol as a vaginal cream in comparison with intracervical prostaglandin E2 gel (0.5mg) and oxytocin for cervical ripening and reported that there were no difference among estradiol cream, prostaglandin E2 gel and oxytocin for cervical ripening.
in patients with unfavorable cervix who require induction of labor \textit{(Magann et al., 1995)}.

\section*{2-Oxytocin :}

Endogenous oxytocin is an anapepitide (nine amino acids) synthesized in the magnocellular neurones of the supranoctic and paraventricular nuclei of the hypothalamus. It is transported by carrier proteins from the hypothalamus to the posterior pituitary where it is eventually released in a pulsatile manner. Oxytocin has a half life of 3 to 4 minutes and duration of action approximately 20 minutes. Its main virtue is to cause contraction of the gravid uterus \textit{(Leake, 1990 and Cunningham et al., 1993)}.

\textit{Mechanism of action :}

\textbf{On the gravid uterus:}

Synthetically prepared oxytocin elicits all of the pharmacological reactions produced by the endogenous hormone. The response of the uterus to oxytocin is dependent on the stage of pregnancy, it increases as the third trimester progresses. Maximal sensitivity to oxytocin is achieved by 34-36 weeks of gestation \textit{(Earn, 1982 and O'Brien & Cefalo, 1996)}.

The mode of action of oxytocin is to depolarize cell membrane potential and alter its permeability to sodium. Also, it is possible that oxytocin acts by increasing the gap junctions in the myometrial cells and facilitating optimal increase in the myometrial cell calcium \textit{(Earn, 1982)}.

In late pregnancy, oxytocin increases the frequency and amplitude of uterine contractions, thus potentiating an already existing contraction pattern \textit{(O'Brien & Cefalo, 1996)}. 
High concentrations of estrogen increase the response to oxytocin by inducing the formation of oxytocin receptors in the myometrial cell membranes. Another factor that affects oxytocin receptor concentrations is distension, which acts synergistically with estrogen to increase oxytocin receptor density especially during the last days of pregnancy (O’Brien and Cefalo, 1996).

**On the breast:**
Oxytocin also causes contraction of the myoepithelial cells surrounding the alveolar ducts of the breast, stimulating milk ejection, milk is forced from the alveolar channels into the large sinuses from where it is readily available, if oxytocin is absent, the milk ejection reflex in the breast fails (O’Brien and Cefalo, 1996).

**Pharmacokinetics:**
Oxytocin is metabolized by chemotrypsin in the gastro-intestinal tract and therefore is not administered orally. Administration by any parenteral route is effective (O’Brien and Cefalo, 1996).

The uterine response to oxytocin administration is almost instantaneous following IV injection and occurs within 3-5 minutes following IM injection. Uterine response subsides within 1hr following IV administration and within 2-3 hours following 1M administration. The drug distributes throughout the extracellular fluid, with minimal amounts reaching the fetus (O’Brien and Cefalo, 1996).

**Mode of administration:**
Except for the administration by intravenous drip, all other parameters of oxytocin implementation are still debatable; the initial
dose, as well as the incremental time period, and the steady-state dose \cite{reichler1995}.

A typical oxytocin infusate consists of 10 units (equivalent to 10,000 mu) mixed into 1000ml of located ringer solution, resulting in an oxytocin concentration of 10mu/ml. Manual pulsatile administration of oxytocin is cumbersome. A computer controlled pulsatile system is preferred \cite{cumminskey1990, cunningham2001a}.

In the United States, the prevailing obstetrical practice was to use low dosage oxytocin regimen to induce labor or to correct ineffective labor. For example, Satin et al., \cite{Satin1992} began oxytocin at 0.5 to 1mu/min and increased the dosage by 1 or 2 mu/min increments every 40 to 60 minutes depending upon uterine response \cite{Satin1992}.

\textit{Merrill and Zlatnik, (1999)} described success with a high dose oxytocin regimen for labor stimulation in nulliparous women starting by 4.5 mu/min with incremental increase of the same magnitude every 15 minutes \cite{merrill1999}.

\textit{Disadvantages of oxytocin}:

Oxytocin has a potent antidiuretic action. If aqueous fluids especially dextrose in water, are infused in appreciable amounts along with oxytocin, water intoxication can occur which may lead to convulsions, coma and even death \cite{cunningham2001a}.

Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone above 15-20 mmHg between contractions can lead to cervical laceration, postpartum hemorrhage, pelvic hematoma,
uterine rupture, uteroplacental hyperfusion and fetal distress from hypoxia (*O'Brien and Cefalo, 1996*).

The most fearful of all adverse effects is uterine rupture, especially in the group of patients with predisposing factors that include; a previous uterine scar, grand multiparity, and overdistended uterus caused by multifetal pregnancy, macrosomia or polyhydramnios (*Reichler et al., 1995*). So the mother should never be left alone while an oxytocin infusion is running. When hyperstimulation occurs immediate discontinuation of oxytocin nearly always corrects the disturbance (the oxytocin concentration in plasma rapidly falls because of the short half-life of oxytocin which is approximately 5 minutes) (*Cunningham et al., 2001a*).

*Schwartz and Jones (1978)* had described convulsions in both the mother and her newborn baby due to the hyponatremic and hypoosmotic states affecting both the mother and her fetus (*Schwartz and Jones, 1978*).

The possibility of oxytocin-induced afibrinogenemia should be considered because there can be an increase in postpartum bleeding. Careful delivery may help to minimize the risk of hemorrhage (*O'Brien and Cefalo, 1996*).

Oxytocin-induced labor has been implicated in an increased incidence of neonatal hyperbilirubinemia, about 1-6 times more likely than after spontaneous labor. This can lead to neonatal jaundice. There is also the possibility of neonatal retinal hemorrhage. Other possible adverse effects that can develop as a result of increased uterine motility are permanent C.N.S. or neonatal brain damage, fetal bradycardia, premature
ventricular contractions (PVCs) or other fetal arrhythmias or in the extreme fetal death (*O'Brien and Cefalo, 1996*).

Some of the adverse effects reported during administration of oxytocin, including nausea, vomiting, premature ventricular contractions (PVCs) and maternal sinus bradycardia, may be associated with labor and not caused by the drug (*O'Brien and Cefalo, 1996*).

**3-Relaxin:**

Relaxin hormone, a polypeptide of low molecular weight whose major source is the corpus luteum of the sow, has been identified as a secretory product of the human corpus luteum in early and late pregnancy (*Schwabe et al., 1978*).

Relaxin, in the human, appears to be solely produced by the corpus luteum (circulating relaxin levels disappear following luteectomy in late pregnancy). It is accordingly suggested that relaxin is the only hormone in the peripheral circulation that can be used as an index of the function of the corpus luteum in pregnancy (*Schwabe et al., 1978*).

The relaxin receptors have recently been identified on human myometrial cells and in fetal membranes, but the post-receptor effects remain unclear (*Osheroff & King, 1995 and Garibay-Tupus et al., 1995*).

*Von Maillot et al.* in 1997 measured cervical tissue level of relaxin during pregnancy and parturition in women they found that the concentration increased to maximum level at term, but that during the parturition the concentration decreased to normal.
Relaxin causes myometrial relaxation, but the exact mechanisms involved are uncertain, so relaxin may play a role in the maintenance of early human pregnancy, although this is speculative at present and the true function of this hormone has yet to be clarified (Ginslauung et al., 1988 and Anwer et al., 1989).

Procine relaxin affects connective tissue remodeling and clinical trials demonstrated equivalent efficacy of procine relaxin to PGF2α regarding cervical ripening, without an increase in uterine contractility (Evans et al., 1983 and Maclennan et al., 1986).

However, relaxin hormone has similar effect as PGs on the cervical ripening, but unlike PGs, relaxin has selective effect on the cervix and devoid of any stimulatory effect on uterine contractility. Such a selective effect would be of value in induction of labor, avoiding the stimulation of uterine activity prior to adequate cervical ripening (Von Maillot et al., 1977 and Maclennan et al., 1981).

4-Mifepristone:

Mifepristone (RU 486; Roussel-Uclaf, Paris, France) which is an anti-progesterone, has emerged as an oral alternative for cervical ripening and induction of labor in early pregnancy termination (Durlot et al., 1988).

Mifepristone is also effective in term pregnancies concerning cervical ripening when compared with placebo (Frydman et al., 1992; Su H et al., 1996 and Wing et al., 2000a).
Mifepristone is also a successful drug for induction of labor in patients with a previous cesarean section (*Lelaider et al., 1994*).

5-Prostaglandins ad induction of labor:

Induction of labor with prostaglandins offers the advantage of promoting both cervical ripening and myometrial contractility (*Sanchez-Ramos et al., 1993 and Birlain, 2001*).

Prostaglandins administered orally or locally were found to be more effective than oxytocin for induction of abortion and labor in patients with unripe cervix (*Sanchez-Ramos et al., 1993 and Birlain, 2001*).

Prostaglandin analogues:

Misoprostol, a synthetic prostaglandin E1 analogue is a gastric cytoprotective agent currently marketed in the United states for the prevention of peptic ulcer (*Hofmeyr and Gulmezoglu., 2001 & de Aquino and Cecath., 2003*).

Studies performed and shown that the use of misoprostol intravaginal as well as oral producing saftening as well as ripening of the human cervix (*Rabe et al., 1997 and Norman et al., 2000*).

Misoprostol is a potent cervical ripening agent in doses of 600 µg throughout its collagenolytic effect on the human cervix. There is possibility that the higher doses of misoprostol may be potent than other cervical ripening agents (*El-Refaey et al., 2000*).
PROSTAGLANDINS

Prostaglandins are highly active organic chemical compounds. They are produced by almost every tissue in the body and play fundamental roles in the regulation of reproductive events. They are the most recent addition to the uterine stimulants (Jing Song, 2000).

Prostaglandins have been prominent in obstetrics and gynecology for the last few decades because of our increasing knowledge of their role in reproduction as well as its therapeutic effect on a large scale. They were first used clinically for induction of labor in the early 1970s and since then, obstetricians in many European countries have become familiar with their benefits. They are now widely used for cervical ripening, induction of labor, induction of second trimester abortions and increasingly so for first trimester abortions (Elder, 1992).

Prostaglandins are long-chain 20 carbon derivatives of arachidonic acid that are produced in the human tissues from phospholipids. They bear a common chemical structure of the C20 prostanoic acid that contains acyclopentane ring between C8 and C12, they are given the name prostaglandins because of the erroneous belief they were the secretory products of only the prostate gland.

Prostaglandin structure and nomenclature:

Prostaglandins have been found so far nine groups (A, B, C, D, E, F, G, H, I) and three types (PG1, PG2 and PG3).

Nomenclature of the complex prostaglandin is governed by three conventions. First, the capital letter after "PG" refers to the chemical
structure of the five membered ring. Originally E stood for ether and F for phosphate buffer, indicating the substance in which the prostaglandin was more readily dissolved. Second, the subscript numeral tells how many double bonds, or unsaturated functions, are present in the two side chains of the molecule. Third, the Greek letter-subscript $\alpha$ or $\beta$ describes take relative to the plan of the ring (Jing Song, 2000).

**Prostaglandin biosynthesis:**

The family prostaglandins with the greatest biologic activity is due to having two double bonds derived from arachidonic acid.

Arachidonic acid can be obtained from two-sources, directly from the deit (from meats) or by formation from its precursor linoleic acid which is found in vegetables (Ramwell et al., 1980).

![Figure (1) Arachidonic Acid](image)

"Eicosanoids" refer to all the 20- carbon derivatives while "prostanoids" indicate only those containing a structural ring (Speroff et al., 1998).

For eicosanoid synthesis to occur, arachidonate must first be released or mobilized from membrane phospholipids by one or more lipases of the phospholipase A2 (PLA2) type. Following mobilization, arachidonic acid is oxygenated by 4 separate routes. The cyclooxygenase, lipoxygenase, P450 epoxygenase and isoprostane pathways according to
the species, the type of the cell, the manner in which the cell is stimulated, and the nature of the precursor polyunsaturated fatty acid that has been esterified in specific manner phospholipids (Marie et al., 1998).

Through the cyclooxygenase route the two cyclooxygenase isoenzymes PGH synthase-1 (Cox-I) and PGH synthase-2 (Cox-II). Promote the uptake of the 2 molecules of oxygen by the cyclization of arachidonic acid to yield a C9-C11 endoperoxide C15 hydroxyperoxide PGG2. PGG2 is rapidly modified by the peroxidase moiety of the cyclooxygenase enzyme to PGH2. PGH2 then yields prostaglandin, thromboxane and prostacycline. The prostaglandins differ from each other by the substitutent of the pentane ring (indicated by E and F) and the number of double bonds in the side chain) (Marie et al., 1998).
Prostaglandin metabolism:

The metabolism of prostaglandins occurs primarily in the lungs, and liver. The lungs are important in metabolism of PGE and PGF, there is an active transport mechanism which specifically carries E & F prostaglandins from the circulation into the lungs. Any active prostaglandins in the circulation are metabolized during one passage through the lung. Therefore, members of the prostaglandins family have a short half-life and in most instances exert actions at the site of their synthesis (Speroff et al., 1999).
Prostaglandin inhibition:

Corticosteroids were previously thought to inhibit the prostaglandin family by stabilizing membranes and preventing the release of phospholipase. It is now recognized that corticosteroids induce the synthesis of proteins called lipocortins (or armexins) which block the action of phospholipase. Thus far, steroids and some local anaesthetic agents are the only substances known to work at this step (Olson and Zakart, 1993).

Aspirin is an irreversible inhibitor, selectively acetylation of the cyclo-oxygenase involved in prostaglandin synthesis. The other inhibiting agents, non-steroidal anti-inflammatory agents such as indomethacin and naproxen, are reversible agents, forming a reversible bond with the active site of the enzyme. Acetaminaopphen, accounting for its analgesic and anti-pyretic properties, but has no anti-inflammatory properties nor does it affect platelets. However, acetaminophen does reduce prostacyclin synthesis, the reason for this effect is unknown (Green et al., 1998).

The role of prostaglandins in labor:

Afoetal source of prostaglandin has been suggested. The foetal membranes can synthesize and metabolize prostaglandin. The chorion more than amnion. So foetal membranes may play a role in initiation of labor (Mitchel et al., 1997).

Secretory products of the fetal membranes are active stimulators of membrane prostaglandin production including rennin derived from chorion prorenin (Lundin Schiller and Mitchell, 1991).
Phospholipase M. has been demonstrated in both human chorioamnion and uterine deciduas. Although the precise mechanism for initiating prostaglandin synthesis by activation of the enzyme phospholipase A2 remains unknown (Okazaki et al., 1991 and Direnzo et al., 1991).

Oestrogens stimulate the release of arachidonic acid by affecting the activity of lipase enzymes. The activity of these phospholipase is increased by increasing concentration of calcium, and therefore the regulation of intra cellular calcium is important in prostaglandin synthesis. Oestrogen stimulate the synthesis and inhibit the metabolism of prostaglandin. While progesterone inhibit their synthesis (Mitchel et al., 1997).

The human foetal membranes and deciduas are incredibly active. Human chorion and decidua produce estrogen utilizing a variety of substrates, especially estrone sulfate and dehydro-epiandrosterone (DHAS), and this activity is increased around the time of parturition (Romano et al., 1986 and Chibbar et al., 1986).

In addition, the human fetal membranes synthesize and metabolize progesterone (Mitchell et al., 1997). The membranes contain a 17, 20 hydroxysteroid dehydrogenase system. One active site converts a dihydroprogesterone to progesterone, while another active site on this enzyme converts estrone to estradiol. Thus this enzyme can play an important role in altering the estrogen/progesterone ratio (Challis and Vaughan, 1997).

The membranes and decidua contain distinct cell population with different biochemical activities. Steroidogenic and prostaglandin
interactions among these cells could produce the changes necessary for parturition without affecting the concentration of circulating hormones. With labor, the arachidenic acid pathway in the fetal membranes shift in the cyclo-oxygenase direction with a large increase in the production of PGE2, specific protein inhibitors of prostaglandin synthetase have been demonstrated in placenta, amnion and chorion and these proteins can be found in tissue from patients who have established labor (Martiner et al., 1995).

The link between infection and the onset of labor (especially preterm labor) may be due to conversion by bacterial medium (with factors such as the interleukins) of a rachidonic metabolism in the membranes and decidua to a condition associated with labor marked by the production of PGE2 (Bennett et al., 1987 and Romero et al., 1991).

Prostaglandin production by amnion, chorion and decidual cells is stimulated by corticotrophin releasing hormone and modulated by progesterone (Jones et al., 1989).

Activin and inhibin are involved here as well, amnion and chorion produce activin and inhibin subunits, and activin stimulates prostaglandin PGE2 release from amnion cells (Petraglia et al., 1993).

During labor the maternal circulating level of PGE2, PGf2α and PGF2α metabolite are increased, a change which can be directly attributed to uterine production in that the gradient across the uterus for these substance is also increased. This increase in production of prostaglandin within the uterus must be the key factor, because the concentration and affinity of prostaglandin in receptors don’t change at parturition (Giannopoulis et al., 1995).
There is evidence for the transfer of prostaglandin E2 across the membranes to the decidua and possibly the myometrium (Nakla et al., 1986).

Prostaglandins produced on one side of the membranes don’t contribute to the prostaglandins on the other side; arguing that uterine contraction must be primarily influenced by the decidual or myometrial prostaglandins (Milchell et al., 1997).

Animal studies have implicated the formation of low resistance pathway in they myometrium, called gap junction, as an important action of steroids and prostaglandins during labor (Burghardt et al., 1993).

In the gap-junction, a pore forms which allows communication from cytoplasm to cytoplasm between two cells. The pore is a cylinder-shaped channel formed of 6 special proteins called connexins. Either substances or electrical current (ions) can follow this pathway without leakage into extracellular space. Thus, gap junctions provide a means of communication between myometrial cells, allowing enhancement of electrical conductivity and synchronization of activity. Gap junction formation is related to the estrogen progesterone ratio (estrogen stimulatory and progesterone is inhibitory) and to the presence of the stimulating prostaglandins. Therefore, it is not surprising that the number of gap junctions increases in the final weeks of pregnancy, especially just before labor. The modulation of the number and permeability of gap junctions is another contributing factor in the control of uterine contractility (Mitchel et al., 1997).

The final contraction of uterine muscle results from increased free calcium concentration in the myofibril, the result of prostaglandin action.
an action opposed to that of progesterone which promotes calcium binding in the sarcoplasmic reticulum (Garsten and Miller, 1987). Thus, prostaglandins and oxytocin increase while progesterone decreases intracellular calcium levels. The intracellular calcium concentration is affected by cellular entry and exit of calcium as well as binding in the sacroplasmic reticulum.

Tocolytic therapy (the use of beta-adrenergic agents) stimulates adenylate cyclase activity which increases the level of cellular cyclic AMP, which in turn decreases intracellular calcium concentration as well as inhibiting actin-myosin interaction by modulating kinase phosphorylation.

**The role of prostaglandins in cervical ripening:**

Pharmacologically and physiologically, prostaglandins have two direct actions associated with labor: ripening of the cervix and a direct oxytocic action. Successful parturition requires organized changes in the cervix. The cervical changes are in response to the estrogen ratio and the local release of prostaglandins (Hofmeyr and Gulmezoglu 2001 and Birlain., 2001).

A major clinical application for the induction of labor in the United States in the use of intravaginal prostaglandins in case of fetal demise and anencephalic fetuses. Based on our experience, certain precautions have been developed. The patient should be well hydrated with an electrolyte solution to counteract the induced vasodilatation and decreased peripheral resistance, if satisfactory uterine activity is established. The next application should be withheld. and finally, because there is synergistic effect when oxytocin is used shortly after prostaglandin, there should be a
minimum of 3 hours between the last prostaglandin dose and beginning oxytocin augmentation (Wing et al., 1997).

Prostaglandins are used to induce term labor. Intravenous prostaglandins are not an acceptable method due to the side effects achieved by the high dosage necessary to reach the uterus. The intravaginal and oral administration of prostaglandin is as effective as intravenous oxytocin. These methods in addition to intracervical administration are in routine use in many parts of the world (Ray & Garite, 1992, Sanchez-Ramos et al., 1995 and Maclennan et al., 1994).

Evidence for the role of prostaglandins in parturition includes the following:

- Prostaglandin levels in maternal blood and amniotic fluid increase in association with labor (Dudley et al., 1994 and Keirse., 1990).
- Arachidonic acid levels in the amniotic fluid also rise in labor and arachidenic acid injected into the amniotic sac initiates parturition (Mitchel et al., 1997).
- Patients taking high doses of aspirin have a highly significant increase in the average length of gestation, incidence of postmaturity and duration of labor (Green et al., 1998).
- Indomethacin prevents the normal onset of labor and stops premature labor (Green et al., 1998).
- Stimuli known to cause the release of prostaglandins (cervical manipulation, stripping of membranes and rupture of membranes) augment or induce uterine contraction (Mc Clogin et al., 1993, Reichler et al., 1995 and Boulvain et al., 2001).

Non obstetrical actions of prostaglandins:

Prostaglandins regulate the capacity of the RBCS to undergo deformation in passing capillaries, decrease gastric secretion, decrease renin secretions, decrease effects of T.S.H and ACTH, antilipolytic; play a role in glucagon, catecholamines and in free fatty acid release and alter or affect of neurotransmitters (Ganong, 1991).
PROSTAGLANDIN ANALOGUES

The main disadvantages of prostaglandins are a short half life and the occurrence of gastrointestinal side effects. These drawbacks are partly overcome by using intrauterine administration. Another alternative has been development of prostaglandin analogues which are not substrates for the initial steps of enzymatic degradation by 15-dehydrogenase and have a more specific effect towards uterine rather than gastro-intestinal muscle (Drug Facts and Comparisons, 1998).

A number of such analogues have been developed. Some of which are in routine clinical use such as carboprost- PGF2α analogue, sulprostone PGE2 analogue and Gemeprost and misoprostol as PGE1 analogue.

In contrast to the primary prostaglandins, these compounds can be administered by non-invasive routes. Gemeprost vaginally, sulprostone and carboprost intramuscularly. Misoprostol orally and vaginally carboprost also available for intravenous and intrauterine administration.

Among the known prostaglandin analogues are:

1-Gemeprost:
16, 16 dimethyl trans PGE1 methyl ester vaginal pessaries. It is useful in cervical priming before early abortion as well as in 2nd trimester abortion. However, it is an expensive drug (Drug Facts and Comparisons, 1998).

2-Sulprostone:
A parenterally administered PGE2 analogue that has been withdrawn from the market after cases of myocardial infarction and cases
of severe hypotension during medical induction of abortion were reported. Its exact mechanism is unknown but may have been idiosyncrasy (Drug Facts & Comparisons, 1998).

3-Misoprostol:

Misoprostol is a synthetic PGE1 analogue that was approved by the FDA in 1988 for use in the treatment of gastro duodenal ulcer and peptic ulcer (Hofmeyr and Gulmezoglu, 2001).

![Figure (3): Misoprostol](image-url)
MISOPROSTOL FOR INDUCTION OF LABOR

Misoprostol is a methyl ester of PGE1 additionally methylated at C-16 it acts by selectively binding to EP-2 / EP-3 prostanoid receptors (Senior et al., 1993).

Misoprostol (cytotec; G.D. Searle and Co., Chicago, IL), a synthetic PGE1 analogue, is gastric cytoprotective agent currently marketed in the united states for the prevention of peptic ulcer. Recent studies performed and shown that the use of misoprostol intravaginal as well as oral producing softening and ripening of the human cervix (Rabe et al., 1997, Norman et al., 2000 & de Aquino and Cecatti., 2003).

Misoprostol produces uterine contractions that may endanger pregnancy, causing partial or complete expulsion of uterine contents and increased uterine bleeding. But at term misoprostol can be used for cervical ripening (Srisomboon et al., 1996). Intravaginal as well as oral administration of misoprostol have been shown to affect cervical ripening and induction of labor (Margulies, 1992, Wing et al., 1995 & de Aquino and Cecatti., 2003). In Brazil were the first to report the use of misoprostol for labor induction.

Misoprostol has also both antisecretory (inhibit gastric acid secretion) mucosal proective properties and produces a moderate decrease in pepsin concentration during basal histamine release.
Pharmacokinetics of misoprostol:

Misoprostol is extensively absorbed and undergoes rapid de-esterification to its free acid which is responsible for its clinical activity, and unlike the parent compound, it is detectable in plasma.

Its effect occurs within 30 minutes, the plasma elimination half life of misoprostol in 20-30 minutes. No accumulation of misoprostol acid in plasma occurs after repeated dosage of 400 mg twice daily.

It is rapidly metabolized by the fatty acid oxidizing system in the organs throughout the body. Its metabolism and plasma levels unlikely to be affected markedly in patients with hepatic impairment.

When misoprostol is given by intravaginal route, the systemic bioavailability is three times higher than that of orally administered misoprostol.

With vaginal administration, peak plasma levels are reached more slowly and are slightly lower but are sustained for up to 4 hours than oral administration.

(Zieman et al., 1997).

These differences in the bioavailability between oral and vaginal routes are likely the result of presystemic gastrointestinal or hepatic metabolism that occurs with oral but not vaginal administration. The greater bioavailability of vaginal misoprostol may explain why intravaginal misoprostol has been reported to be more effective than oral misoprostol for medical induction (El-Refaey et al., 1995).

Assuming a relationship between plasma levels of misoprostol and its therapeutic effect, it is desirable to administer the drug in a dosage form that results in a relatively consistent plasma level profile for different patients.
Although a high degree of consistency may be impossible for a drug with a large extent of first pass metabolism, it may be possible to improve consistency of dosing by the vaginal route by developing preparations that dissolve more completely, such as a suppository or gel.

The serum protein binding of misoprostol acid is $< 90\%$ and is concentration independent in the therapeutic range.

\cite{Ziemanetal2017}.

**Preparation and dosage:**

Misoprostol is a PGE1 analogue inactive ingredients are hydrogenated castor oil, hydroxy propy methyl cellulose, microcrystalline cellulose and sodium starch glycolate. It doesn’t require special storage conditions and has a shelf-life of several years \cite{Fletcheretall1993}.

**Adverse reactions:**

Preclinical toxological studies indicate the safety margin of misoprostol to be at least 500 to 1000 fold the lethal doses in animals and therapeutic doses in humans \cite{Collins1990}.

Any of these adverse reactions may occur with prolonged use of misoprostol:

**I=Gastrointestinal:**

Diarrhea (13\% - 40\%):

Diarrhea is the major adverse reaction that has been consistently with misoprostol. It is dose dependent and occurs in 10\% of patients receiving 200\,\mu{g} four times a day. It is usually mild and doesn’t require any therapeutic intervention in the majority of cases \cite{Inman1991andWingetal1995b}. 
Abdominal pain (7% - 20%) 

Nauseas and vomiting:  
They are two of the more commonly reported adverse effects. The rate of nausea and vomiting with misoprostol is 4% during the 1st month of treatment. The ratio of this rate for the subsequent 5 months of treatment is 6 : 1 reflecting that nausea and vomiting are more frequent during the initial stages of treatment (*Inman, 1991 and Raudall Bond, 1994*).

Flatulence (2.9%).  
Dyspepsia (2%).  
Constipation (1.1%).

**II- Genitourinary:**  
- Spotting (0.7%).  
- Cramps (0.6%).  
- Hypermenorrhea (0.5%).  
- Menstrual disorders (0.3%).  
- Dysmenorrhea (0.1%).

**III- Miscellaneous:**  
- Headache (2.4%).  

(*Drug Facts and Comparison, 1998*).

**High risk patients to misoprostol:**  
Patients with contraindications to use of prostaglandins:
- Bronchial asthma, cardiovascular disease, allergy to prostaglandins, epilepsy, and history of glaucoma.
- Renal function impairment.
- Due to its uterotonic effect, misoprostol is contraindicated in pregnant women and women planning for pregnancy.

Pharmacokinetic studies in patients with varying degree of renal function impairment showed an approximate doubling of half life, maximum concentration. Although no routine dosage adjustment is required still dosage may be reduced if useful dose is not tolerated.

*(Drug Facts and Comparisons, 1998)*

**Maternal and neonatal effects of misoprostol:**

**Maternal effect:**

High doses of oral or intravaginal misoprostol were associated with tachysystole (at least 6 contractions/10 minutes for 2 consecutive 10-minute periods), hypersystole (single contraction with duration > 2 minutes) or hyperstimulation syndrome (presence of tachysystole or hypersystole associated with abnormal fetal heart rate patterns), meconium staining and postpartum hemorrhage *(Crane et al., 2000 and Carlan et al., 2001)*.

*Akhan et al., (2001)* reported a case of intrapartum rupture of an intact uterus after using intravaginal misoprostol for cervical ripening and labor induction in a term pregnancy.

**Teratogenicity of misoprostol:**
Malformations of the fronto-temporal region of the skull were reported in a study on malformations in children whose mothers had taken misoprostol early in pregnancy in unsuccessful abortion attempts. These mothers were found to have taken misoprostol tablets (400-600μg) orally and/or intravaginally in the first trimester of pregnancy (The Lancet, 1999 and Fonseca et al., 1999).

In a study by Genest et al., (1999), they reported limb defects in a fetus from elective termination at 17 weeks gestation following maternal ingestion of 1200 μg misoprostol at 7 weeks gestation.

In another study in Brazil over 29 pregnant women who were seeking counseling after unsuccessful use of misoprostol as an abortifacient during the first trimester of gestation. Three of these 29 pregnancies ended in second trimesteric spontaneous abortion. Among the others no major malformations were found in these babies. One of them had a preauricular tag (The Lancet, 1992).

Over dosage:

Although the toxic dose in human has not been reported, cumulative total dose of 1600μg has been tolerated with only symptoms of gastrointestinal discomfort.

Clinical signs of overdosage are sedation, tremors convulsion, dyspnea, abdominal pain, diarrhea, fever, palpitation and hypotension.

If overdose occurs, treatment is usually supportive, it is not known if misoprostol acid is dialyzable but because it is metabolized as a
fatty acid it is unlikely that dialysis would be of any use in overdosage treatment.

*(Drug Facts and Comparisons., 1998)*

**Actions of misoprostol:**

**On gastrointestinal tract:**

Misoprostol reduces. The incidence of non-steroidal anti-inflammatory drugs (NSALD) related ulcers, both gastric and duodenal *(Davis et al., 1995)*.

Misoprostol promotes peptic and duodenal ulcer healing and produces symptomatic relief. It protects the gastro-duodenal mucosa by inhibiting basal stimulated and nocturnal acid secretions. Also, it reduces the volume of gastric secretions, the proteolytic activity of gastric fluid, and increases bicarbonate and mucus secretion *(Davis et al., 1995)*.

**On the liver:**

PGE1 is a promising agent against ischaemic liver damage. The benefit could be attributed solely to direct action on hepatocytes *(Shinohara et al., 1997)*. *(Yagi et al., 1997)* reported a protective effect of PGE1 on sinusoidal endothelial cells in xenogenic pig liver perfusion *(Yagi et al., 1997)*.

**On immunological system:**

Misoprostol potentially inhibit cytokine release from activated human monocytes. Also, a potential immunomodulatory role for the misoprostol in the therapeutic treatment of inflammatory diseases such as, ulcerative colitis, chron’s disease, and auto-immune diseases of the nervous system was suggested *(Widomski et al., 1997)*.
**Review of Literature**

**On endocrine glands:**

Multiple prostaglandins, including PGE1, PGE2 and PGF2α were largely equipotent in stimulating adrenocorticotrophic hormone (ACTH) release when administered intravenously in rats. These PGS may play a role in regulating the hypothalamo-pituitary adrenal axis (Nasushita et al., 1997).

**On spermatozoa:**

PGE1 acts as a capacitating factor in vitro for mouse spermatozoa and enhances acrosome-reaction induction with calcium ionophore in human spermatozoa (Herrero et al., 1997).

**On connective tissue:**

Prostaglandin E1 significantly, enhances collagenase activity and raises the collagenase type I collagen ratio in the hypertrophic scar fibroblasts (HSF) supernatants. It also increases production of transforming growth factor (TGF)- beta 1, interleukin type 8 (IL-8), IL-6, and levels of adenosine 3.5- cyclic mono-phosphate (CAMP) in normal human dermal fibroblasts (NDF) and HSF. This offers a potential role of PGE1 in preventing scar formation (Zhou et al., 1997).

**On cardiovascular system:**

PGE1 is quite an important therapeutic drug for keeping the arterial duct open in patients with congenital heart disease whose pulmonary blood flow depends on patency of the arterial duct (Silove, 1986).

PGE1 is also administered to patients with severe peripheral vascular disease and was used to induce hypotension for reduction of blood loss during surgery (Clifford et al., 1980 and Goto et al., 1982).
PGE1 is used worldwide for self-injection therapy in erectile failure and was officially approved for this purpose in the United States and most European countries. The drug has a direct relaxing effect on smooth muscle cells of vessels and cavernous bodies (Porst, 1996).

**On uterine, umbilical and placental bed vaculature:**

In vitro, study demonstrated that PGE2 and PGF2α cause vasoconstriction in human uterine arteries in non-pregnant women (Withelmsson et al., 1981).

Vaginal application of PGE1 analogue (Gemeprost), in early pregnancy, increases the vascular resistance of uterine arteries, this may be caused by a direct vasoconstrictor effect or be secondary to uterine contractions (Jouppila and Kony, 1994).

The reaction of uterine arteries to vaginal application of PGs seems to be different in early pregnancy from that found in late pregnancy. Contrary of the findings in early pregnancy from that found in late pregnancy. No effect on blood flow velocity wave forms of the uterine and umbilical arteries has been observed after vaginal application of PGE2 for the induction of labor in late pregnancy (Fairlie et al., 1990 and Rayburn et al., 1997).

The relative lack of physiological compensatory mechanisms and the specific anatomic properties existing in early pregnancy could explain the sensitivity of the uterine vasculature to the vasoconstrictor effects of focal gemeprost application (Jouppila and Kony, 1994).
It could be speculated that the utroplacental vascular bed is anatomically so wide in late pregnancy, and the increase in maternal blood volume is so great that the blood concentrations of locally applied prostaglandin are unable to produce any vasoactive changes in the uterus. On the other hand, the uterine vascular bed is refractory to physiological vasoconstrictor agents, such as angiotensin II in late pregnancy (Rayburn et al., 1997).

This refractoriness of the uterine vascular bed, in late pregnancy, could be attributed to the marked increase in endogenous vasodilator agents such as PGI₂ and estrogens during pregnancy, it is possible that these also protect against vasoconstrictor effect of exogenous local prostaglandin in late pregnancy (Fairlie et al., 1990 and Rayburn et al., 1997).

Role of misoprostol in labor induction:

1-Through vaginal route:

Several studies evaluated the vaginal route of misoprostol for induction of labor and showed that misoprostol was very effective in cervical ripening and labor induction (Gemund et al., 2004 and Shetty et al., 2003).

Other studies evaluated intravaginal misoprostol versus oxytocin infusion and found that vaginal misoprostol is as effective as oxytocin infusion, but vaginal misoprostol is better in cases with unripe cervix (Krammer et al., 1997, Escudero and Contreras, 1997, de Aquino and Cecatti., 2003, Mozurkewich et al., 2003 & Mulchev et al., 2003).
Several studies compared intravaginal misoprostol and prostaglandin E2 gel for cervical ripening and labor induction and found that the average interval from the start of induction to vaginal delivery was shorter in the misoprostol group and the need for oxytocin augmentation of labor was more with prostaglandin E2 gel group (Wing et al., 1995a; Gottschall et al., 1997, Katz et al., 2000, Gemund et al., 2004, Raio et al., 2001, Majoko et al., 2002 & de Aquino and Cecatti., 2003).

Dose finding studies reported that intravaginal misoprostol in doses higher than 50 g were associated with unacceptable higher uterine contraction abnormalities and meconium passage (Wing et al., 1995a and Wing et al., 1995b).

**Bique et al., (1999)** used 50 g vaginal misoprostol in the grand multiparous women, with five or more previous deliveries, and they reported that misoprostol at this dose was safe and effective for labor induction without any adverse neonatal or maternal outcomes.

**2-Through cervical route:**

**Liue et al., (1999)** found that intracervical misoprostol at a single dose of 50 g was an effective method for labor induction at term, but they reported that caution should be taken in cases with unfavourable cervix as tachysystole, hypersystole and hyperstimulation syndrome were more common with unfavorable cervix.

In a comparison between the intravaginal and intra cervical route for cervical ripening, both routes were found to be almost equally effective in term of bishop score changes, interval to delivery, route of
delivery and delivery outcome, yet uterine tachysystole occur in 24% of intra cervical route versus 32% in intravaginal route with no fetal distress. Spillage of gel outside the cervix was observed in 70% of intra cervical route making intravaginal route more convenient (Srisomboon et al., 1997).

3-Through oral route :

Mariani-Neto et al., (1987), in Brazil, were the first to report the use of misoprostol for labor induction. They studies 20 patients with gestational ages 18-41 weeks who presented with fetal death. Misoprostol was administered orally at 400 μg every 4 hours until delivery occurred. Pregnancy was successfully terminated in all cases (Mariani-Neto et al., 1987).

Other studies demonstrated that oral misoprostol is an effective agent for cervical ripening and labor induction in patients with prelabor rupture of membranes at term (Sanchez-Ramos & Delke, 1998; Hallak & Bottoms, 1999 and Hoffmann et al., 2001).

4-Through buccal route:

Blust and Carlan, (2001) compared the buccal administration of the misoprostol, for cervical ripening and labor induction, with vaginal route and reported that both routes were similar in efficacy and safety.
Patients and Methods

PATIENTS AND METHODS

I- Patients

The study was carried out on a randomized sample consisting of fifty pregnant females, each one had at least one obstetrical or medical indication for labor induction. Cases were admitted to the emergency unit of the Obstetrics and Gynaecology Department, Benha Faculty Hospital, in the period starting from February 2003, after fulfillment of inclusion criteria and obtaining an informed consent after explanation of the procedure.

All enrolled females fulfilled the following criteria:

Single intrauterine pregnancy.
Vertex presentation.
Gravity from 1-5 and parity from 0-4.
Gestational age ≥ 37 wk.
Bishop score ≤ 5 (Bishop, 1964). (Table 1)
Medical or obstetrical indication for labor induction.
Intact or ruptured membranes.
Age ≥ 18 years.
Adequate pelvis.

Exclusion criteria:
cases of intrauterine death.
Maternal age > 35 years.
Multiple pregnancy.
Abnormal presentation.
Placenta previa or unexplained vaginal bleeding.
Previous major uterine surgery.
Patients and Methods

Non-reactive non stress test.
Cephalo pelvic disproportion or any contraindication to vaginal delivery.
Evidence of chorioamnionitis as determined by maternal temperature $\geq 37.8$ and two or more of the following conditions; maternal Tachycaria, uterine tenderness, foul adour of amniotic fluid, maternal leukocytosis, or positive C-reactive protein (*Arias, 1993b*).
Three or more uterine contractions in 10 minutes or a Bishop score $> 5$.
Any contraindication to the use of PGs such as bronchial asthma, epilepsy, glaucoma and mitral stenosis.
Known or suspected fetal anomalies.

Table (1): Bishop score (pelvic scoring) (*Bishop, 1964*).

<table>
<thead>
<tr>
<th>Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dilatation (cm)</td>
<td>Closed</td>
<td>1-2</td>
<td>3-4</td>
<td>5+</td>
</tr>
<tr>
<td>Cervical effacement (%)</td>
<td>0-30</td>
<td>40-50</td>
<td>60-70</td>
<td>80+</td>
</tr>
<tr>
<td>Fetal station</td>
<td>-3</td>
<td>-2</td>
<td>-1,0</td>
<td>+1,+2</td>
</tr>
<tr>
<td>Cervical consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td></td>
</tr>
<tr>
<td>Cervical position</td>
<td>Posterior</td>
<td>Mid.</td>
<td>Anterior</td>
<td></td>
</tr>
</tbody>
</table>
II-Methods

All pregnant females included in this study were recruited from the outpatient clinic and admitted to the Emergency Unit of the Obstetrics and Gynaecology Department where careful history, accurate medical and obstetric examination and different modalities of investigation were performed before induction of labor.

1-History: including :
Personal history: including name, residence, age.
Past history:
Obstetric history:
Present history:
2-Thorough clinical examination including :
Complete general examination :
Obstetric examination :
Vaginal examination :
Investigations :
Laboratory :
   a. CBC to evaluate haemoglobin level.
   b. Blood glucose level.
   c. Complete urine analysis.
   o Abdominal ultrasonography : was performed to assess gestational age, presentation, fetal welfare and to exclude severe oligohydramnios.
Ultrasonography was done by NEW SONICS, INTERNATIONAL ELECTRONICS, 3.5 MHZ curvi-linear transabdominal probe.
Patients and Methods

- Cardiotocography: was performed at the time of admission to assess fetal wellbeing, and to confirm the absence of uterine contractions and was repeated after starting induction and during active phase of labor, cardiotocography was done by SEWARD, FETATRACK condiotocograph

Women were randomly enrolled into two equal groups (women taking single numbers at the time of admission entered the misoprostol group and those taking double numbers entered the non-misoprostol group). After fulfilling all the inclusion criteria, induction of labor was done in the misoprostol group by misoprostol, a synthetic PGE1 analogue, (cytotec®). Cytotec (Searle, Chicago) is available in the form of tablets, each tablet contains 200μg of misoprostol and was divided by a pharmacist into 4 equal quadrants (each 50μg).

1-Misoprostol group:

In this group, induction of labor was done by using misoprostol vaginally and the initial dose was 50mg, applied in the posterior fornix.

The initial dose was repeated every 4 hours after reevaluation of the condition. This repetition was done till demonstration of adequate uterine contraction frequency (> 3 contractions in a 10- minute period of observation) or for elapse 24 hours.

2-The non-misoprostol group:

In this group, induction of labor was done by using physician-chosen combinations of stripping of membranes and artificial rupture of membranes in cases with intact membranes, castor oil, enemas and
Patients and Methods

Oxytocin infusion (with an oxytocin concentration of 5 mu/ml of 5% dextrose). Oxytocin infusion was begun at an initial flow rate of 2mu/min and doubled half hourly to a maximum rate of 32 mu/min or regularly occurring uterine contraction at a frequency of 3 times in every 10-min.

The flow rate at which 3 contractions in every 10-min was achieved, was maintained until delivery. This approach was adopted in order to avoid hyperstimulation.

In both groups, no other uterotonic agents were used when a positive response was achieved. On the other hand, cases with failure to achieve a positive response underwent cesarean section if there was any risk for continuation of pregnancy, or a second induction after 3 days when there was no risk for continuation of pregnancy.

All cases were strictly observed for changes in bishop score, start and progress of labor and any fetal, maternal or early neonatal side effects.

Tachysystole was defined as at least 6 contractions in 10 minutes for 2 consecutive 10-minute periods. Hypersystole was defined as a single contraction with a duration > 2 minutes (Crane et al., 2001 and Carlan et al., 2001).

Hyperstimulation syndrome was defined as, either tachysystole or hypersystole associated with abnormal fetal heart rate patterns. (Crane et al., 2001 and Carlan et al., 2001).

Statistical analysis:

Statistics of the results were carried out according to the following formulae:

1- Arithmetic mean (X):
Patients and Methods

Was calculated as follows:

\[ x = \frac{\sum x}{n} \]

Where:

\( X \) = arithmetic mean.

\( \Sigma x \) = Sum of observations.

\( N \) = number of observations.

2- Standard deviation (SD):

Was calculated as follows:

\[ SD = \sqrt{\frac{\sum x^2 - (\sum x)^2}{n - 1}} \]

Where:

\( \Sigma x^2 \) = sum of squared observations.

\( (\sum x)^2 \) = square of the sum of observations.

\( n \) = number of observations.

3- Student “t” test:

\[ t = \frac{X_1 - X_2}{\sqrt{S^2_p \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}} \]

\[ S^2_p = \frac{S^2_1(n_1 - 1) + S^2_2(n_2 - 1)}{n_1 + n_2 - 2} \]

Where:

\( S^2_p \) = Pooled variance.

\( S^2_1 \) = Variance of sample (1).

\( S^2_2 \) = Variance of sample (2).

\( n_1 \) = Size of sample (1).

\( n_2 \) = Size of sample (1).
Patients and Methods

$X_1 =$ Mean of sample (1).

$X_2 =$ Mean of sample (2).

$S_1 =$ Standard deviation of sample (1).

$S_2 =$ Standard deviation of sample (2).

Specificity: The ability of a test to indicate non-disease when no disease is present.

Sensitivity: The ability of a test to detect a disease when it is present.

4- Chi-square ($X^2$):

For comparison between distribution of patients according to different items of study, and use this formula for calculation:

$$X^2 = \sum \frac{(O - E)^2}{E}$$

$O =$ Observed results.

$E =$ Expected results.

$(O-E)^2 =$ difference squared.

Where $E = \frac{\text{Total row} \times \text{Total column}}{\text{grand total}}$
RESULTS

In this study fifty pregnant women with an indication for induction of labor were included. They were divided into two group each of 25 women.

- One group received misoprostol 50mg (quarter of cytotec 200μg) every 4 hours.
- The other group underwent physician-chosen combinations of stripping of membranes, artificial rupture of membranes, enemas, castor oil and oxytocin infusion.
Results

Demographic characteristics of the study groups including age, height, weight, gestational age, and initial Bishop score are shown in (table 2).

The mean age among the misoprostol group was (26.04 ± 4.97) while in the non-misoprostol group it was (25.4 ± 4.42). The mean height among the misoprostol group was (166.4 ± 4.38) while it was (165.9 ± 4.11) in the non-misoprostol group. The mean weight among the misoprostol group was (81.68 ± 4.79) while it was (80.28 ± 4.1) in the non-misoprostol group. The mean gestational age among the misoprostol group was (39.97 ± 1.72) while it was (40.2 ± 1.8) in the non-misoprostol group. The mean initial Bishop score among the misoprostol group was (3.92 ± 0.74) while it was (4 ± 0.75) in the non-misoprostol group.

Table (2): Demographic characteristics of the study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group</th>
<th>Non-misoprostol group</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 25</td>
<td>N = 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>26.04 ± 4.97</td>
<td>25.4 ± 4.42</td>
<td>t = 0.48</td>
</tr>
<tr>
<td>Height (Cm)</td>
<td>166.4 ± 4.38</td>
<td>165.9 ± 4.11</td>
<td>t =</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>81.68 ± 4.79</td>
<td>80.28 ± 4.1</td>
<td>t = 1.11</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.97 ± 1.72</td>
<td>40.2 ± 1.8</td>
<td>t = 0.52</td>
</tr>
<tr>
<td>Initial Bishop score</td>
<td>3.92 ± 0.74</td>
<td>4 ± 0.75</td>
<td>t = 0.38</td>
</tr>
</tbody>
</table>

NS = non significant difference, P≤ 0.05
Results

* Distribution of parity:

Both groups had comparable parity, with a mean of (1.62 ± 0.69) in the misoprostol group versus (1.75 ± 0.8) in the non-misoprostol group. The number of primi-para was (n = 8, 32%) in the misoprostol group comparable to (n = 9, 36%) in the non-misoprostol group. There was only three women in the either group that was Para 3 making 12% in each group. The rest of patients had parity ranging between 1-2. The data are reported in table (3).

Table (3): Distribution of parity in the study groups.

<table>
<thead>
<tr>
<th>Parity</th>
<th>Misoprostol group (n = 25)</th>
<th>Non-misoprostol group (n = 25)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>1.62 ± 0.69</td>
<td>1.75 ± 0.8</td>
<td>t = 0.62 NS</td>
</tr>
<tr>
<td>P0 : no (%)</td>
<td>8 (32%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>P1 : no (%)</td>
<td>6 (24%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>P2 : no (%)</td>
<td>8 (32%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>P3 : no (%)</td>
<td>3 (12%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>P4 : no (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as number (percentage).

NS : Non significant difference P ≤ 0.05.
Results

Indications for induction of labor:

In the misoprostol group, 11 cases were induced for labor because of post-term pregnancy, 9 cases because of premature rupture of membranes and 5 cases for other different reasons. In the non-misoprostol group, 14 cases were induced for labor because of post-term pregnancy, 5 cases because of premature rupture of membranes and 6 cases for other different reasons. Thus, post-term pregnancy constituted 50% and premature rupture of membranes constituted 28% of the indications for labor induction in the study groups (table 4).

Table 4: Indications for induction of labor in the study groups.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Misoprostol group</th>
<th>Non-misoprostol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 25</td>
<td>No (%)</td>
<td>N = 25</td>
</tr>
<tr>
<td>Post term pregnancy</td>
<td>11 (44%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Pre-labor rupture of membranes</td>
<td>9 (36%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>2 (8%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are given as number (percentage).
**Results**

The initial Bishop score in both groups was ≤ 5 as shown in (table 5) patients with Bishop score 5 constituted (24%) in the misoprostol group versus 28% in the non-misoprostol group while in both group, there was no any patient with Bishop score zero. The rest of patients had Bishop score ranging from (1-4)

**Table (5) Distribution of the initial Bishop score in the study groups**

<table>
<thead>
<tr>
<th>Initial Bishop score</th>
<th>Misoprostol group N = 25</th>
<th>Non-misoprostol group N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (24%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>4</td>
<td>11 (44%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>5</td>
<td>6 (24%)</td>
<td>7 (28%)</td>
</tr>
</tbody>
</table>

Values are given as number (Percentage).

**Labor characteristics in the study groups:**

**Induction – activation time:**

The mean induction-activation time was (126.84 ± 26.8) minutes in the misoprostol group versus (285.4 ± 116.1) minutes in the non-misoprostol group. This difference was statistically highly significant. (table 6), (Fig 4).

**Table (6): Induction- activation time.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group N = 25</th>
<th>Non-misoprostol group N = 25</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction-activation time</td>
<td>126.84 ± 26.8</td>
<td>285.4 ± 116.1</td>
<td>t = 6.65 ++</td>
</tr>
</tbody>
</table>

++ = Highly significant  P ≤ 0.05
Fig (4): Induction – Activation Time (min)

![Bar Chart]

The bar chart compares the induction–activation time (in minutes) between the Misoprostol group and the Non-misoprostol group. The chart shows:

- **Misoprostol group**: 126.84 minutes
- **Non-misoprostol group**: 285.4 minutes
Results

Success and failure rates:

Labor was successfully induced in 22 cases (88%) in the misoprostol group versus 20 cases (80%) in the non-misoprostol group.

However, the failure to achieve vaginal delivery in the misoprostol group was due to operative interference for hyperstimulation syndrome while, the failure to achieve vaginal delivery in the non-misoprostol group was due to operative interference due to failure to progress in labor.

Three cases (12%) in the misoprostol group showed failed induction of labor versus 5 cases (20%) in the non-misoprostol group. The causes of induction failure were arrested progress of cervical condition (1 versus 4), failure of head descent (1 versus 1) and fetal distress (2 versus 1) in the misoprostol and non-misoprostol groups, respectively (table 7).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group</th>
<th>Non-Misoprostol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful induction: no (%)</td>
<td>22 (88%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Failed induction: no (%)</td>
<td>3 (12%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Causes of induction failure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Arrested progress: no (%)</td>
<td>1 (4%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>1-Failure of head descent: no (%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>1-Fetal distress: no (%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Values are given as number (Percentage).
Results

Uterine overactivity:

Uterine overactivity was recorded in 4 cases (16%) in misoprostol group versus 3 cases (12%) in non-misoprostol group (table 8).

Passage of meconium:

Passage of thin meconium was noticed in 2 cases (8%) in both misoprostol and non-misoprostol groups.

Maternal side effects:

Maternal side effects in the form of vomiting (one case in misoprostol group versus 3 cases in the non-misoprostol group) and diarrhea 2 cases (8%) in the misoprostol group versus 17 cases (68%) in the non-misoprostol group (table 8).

Fetal distress:

Intrapartum fetal distress was noticed in 2 cases (8%) in the misoprostol group versus one case (4%) in the non-misoprostol group (table 8).

Table (8): Intrapartum complications and side effects in the study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group N = 25</th>
<th>Non-misoprostol group N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine overactivity : no (%)</td>
<td>4 (16%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>- Hyperstimulation syndrome</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>- Tachysystole</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Passage of thin meconium: no (%)</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Vomiting : no (%)</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Diarrhea : no (%)</td>
<td>2 (8%)</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Intrapartum fetal Distress : no (%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Values are given as number (Percentage).
**Results**

**Induction-delivery interval:**

The mean induction delivery interval was \((572 \pm 109.6)\) minutes in the misoprostol group versus \((805 \pm 201.5)\) minutes in the non-misoprostol group and this difference was statistically highly significant (table 9), (Fig 5).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group No = 22</th>
<th>Non-misoprostol group N= 20</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction-delivery Interval (min.) Mean ± SD.</td>
<td>572 ± 109.6</td>
<td>805 ± 201.5</td>
<td>(t = 4.72) ++</td>
</tr>
</tbody>
</table>

++ = highly significant difference \(P < 0.05\)
Fig (5): Induction – Delivery Interval (min)

![Bar graph showing induction delivery interval in two groups. The Misoprostol group has an interval of 572 minutes, and the Non-misoprostol group has an interval of 805 minutes.]
Results

-Mode of delivery and its indications:

Vaginal delivery occurred in 22 cases (88%) in the misoprostol group versus 20 cases (80%) in the non-misoprostol group.

Vacuum extraction was done for one case (4%) in the misoprostol group versus 3 cases (12%) in the non-misoprostol group.

Casarean section was performed for 3 cases (12%) in the misoprostol group versus 5 cases (20%) in the non-misoprostol group (table 10).

Table (10): Mode of delivery and its indications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group</th>
<th>Non-misoprostol group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No = 25</td>
<td>N = 25</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery: no (%)</td>
<td>21 (84%)</td>
<td>17 (68%)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vaginal delivery after retrial: no (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccum extraction due to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Prolonged 2\textsuperscript{nd} stage: no (%)</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>-Fetal distress: no (%)</td>
<td>0 (0)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Cesarean section due to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Arrested progress: no (%)</td>
<td>1 (4%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>-Failure of head descent: no (%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>-Fetal distress: no (%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Values are given as number (Percentage).
NEONATAL OUTCOME

The mean birth weight was $(3495.4 \pm 219.9)$gm. In the misoprostol group versus $(3413.2 \pm 165)$gm in the non misoprostol group without significant difference between both groups.

Three newborns (12%) in the misoprostol group versus 4 newborns (16%) in the non misoprostol group needed admission to the neonatal intensive care unit (NICU) (table 11, Fig 6).

Table (11): Birth weight and admission to neonatal intensive care units in the study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group N = 25</th>
<th>Non-Misoprostol group N = 25</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (gm)</td>
<td>3495.4 ± 219.9</td>
<td>3413.2 ± 165</td>
<td>t = 1.49</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to NICU#</td>
<td>3 (12%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

NS: Non significant difference $P \leq 0.05$

# NICU : Neonatal Intensive Care Unit.
Fig (6): Neonatal outcome in the study group (admittion to NICU)
Results

Apgar score in the study groups:

Apgar score at 1 min < 7 was observed in 4 cases (16%) in the misoprostol group versus 3 cases (12%) in the non-misoprostol group. While Apgar score at 5 min. <7 was observed in one case (4%) in both groups.

The mean Apgar score 1 min was (6.56 ± 0.9) in the misoprostol group versus (6.4 ± 1.06) in the non-misoprostol group without significant difference between both groups.

The mean Apgar score 5 min was (8.24 ± 0.95) in the misoprostol group versus (7.8 ± 1.02) in the non-misoprostol group without significant difference (table 12).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group</th>
<th>Non-misoprostol group</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 25</td>
<td>N = 25</td>
<td></td>
</tr>
<tr>
<td>Apgar score 1 min &lt; 7</td>
<td>4 (16%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Apgar score 5 min &lt; 7</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Apgar score 1 min (Mean ± SD)</td>
<td>6.66 ± 0.9</td>
<td>6.7 ± 1.06</td>
<td>t = 0.58 NS</td>
</tr>
<tr>
<td>Apgar score 5 min. (Mean ± SD)</td>
<td>8.24 ± 0.95</td>
<td>8.8 ± 1.02</td>
<td>t = 1.57 NS</td>
</tr>
</tbody>
</table>

NS = Non Significant difference. P ≤ 0.05.
Results

-Umbilical cord blood gases in the study groups:

The mean umbilical cord pH was (7.29 ± 0.09) in the misoprostol group versus (7.285 ± 0.033) in the non-misoprostol group without significant difference between both groups.

The mean PO2 was (37.31 ± 5.26) in the misoprostol group versus (35.75 ± 4.74) in the non-misoprostol group without significant difference.

The mean PCO2 was (42.42 ± 3.42) in the misoprostol group versus (41.9 ± 5.43) in the non-misoprostol group without significant difference.

Neonatal outcomes here were similar in both groups, no newborn developed respiratory distress syndrome, meconium aspiration, seizures or other neurologic signs indicating intrapartum asphyxia. Cord-blood acid-base analysis did not differ between both groups, no neonate met the ACOG criteria for Birth asphyxia (table 13).

Table (13): Umbilical cord blood gases in the study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group</th>
<th>Non-misoprostol group</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord pH (mean ± SD)</td>
<td>7.29 ± 0.09</td>
<td>7.285 ± 0.033</td>
<td>t = 0.26 NS</td>
</tr>
<tr>
<td>PO2 (mean ± SD)</td>
<td>37.31 ± 5.26</td>
<td>35.75 ± 4.74</td>
<td>t = 1.1 NS</td>
</tr>
<tr>
<td>PCO2 (mean ± SD)</td>
<td>42.42 ± 3.42</td>
<td>41.9 ± 5.43</td>
<td>t = 0.41 NS</td>
</tr>
<tr>
<td>ACOG criteria for Birth asphyxia.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar score ≤ 3 at 5 min : no (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cord pH &lt; 7.0 : no (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

NS : Non-significant difference. P < 0.05
**Results**

**The third stage of labor:**

The mean duration of the third stage of labor for the misoprostol group was $(9.42 \pm 2.1 \text{ min})$ versus $(10.23 \pm 1.7 \text{ min})$ in the non-misoprostol group without significant difference between both groups (table 14).

**Post-partum hemorrhage:**

One case in each group presented with postpartum hemorrhage with no statistical significance between both groups (table 14).

**Table (14): The third stage of labor and postpartum hemorrhage in the study groups.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group N = 25</th>
<th>Non-misoprostol group N = 25</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd stage of labor (mm)</td>
<td></td>
<td></td>
<td>t = 1.637  NS</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.42 ± 2.1</td>
<td>10.23 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Postpartum hemorrhage : no (%)</td>
<td>1 (4.5%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

NS: Non-significant difference. P < 0.05.
**Results**

**Perineal trauma in the study groups:**

Episiotomy was done in 6 cases (27.2%) in the misoprostol group versus 5 cases (25%) in the non-misoprostol group.

Lacerations occurred in 5 cases (22.7%) in the misoprostol group versus 5 cases (25%) in the non-misoprostol group.

There was no ay case in both groups with 3rd or 4th degree perineal lacerations.

In about 14 cases (63.6%) in the misoprostol group versus 15 cases (75%) in the non-misoprostol group. There was intact perineum (table 15).

**Table (15): Perineal trauma in the study groups.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Misoprostol group N = 25</th>
<th>Non-misoprostol group N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal trauma :</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Episiotomy : no (%)</td>
<td>6 (27%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>-Laceration : no (%)</td>
<td>5 (22.7%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>3rd or 4th degree perineal lacerations: no (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intact perineum : no (%)</td>
<td>14 (63.6%)</td>
<td>15 (75%)</td>
</tr>
</tbody>
</table>

Values are given as number (Percentage).
Induction of labor is one of the most important means for therapeutic intervention in modern obstetrics.

The aim of labor induction is to achieve a better perinatal result for the mother and the baby as compared to expectative management (Surbek et al., 2002).

Cervical ripening or preparation for induction should be assessed before a regimen is selected. Assessment is accomplished by calculating a Bishop score. When the Bishop score is less than 6, it is recommended that a cervical ripening agent should be used before labor induction (Tenore, 2003).

The optimal ripening agent should be easily administered, inexpensive, non-invasive, without maternal or fetal side effects and effective within a reasonable time (Mosa et al., 2002).

The optimal regimen for pre-induction cervical ripening and labor induction is not established. The method of administration that has been explored most thoroughly in controlled studies is endo cervical prostaglandin E2 gel. (Dino Prostone®). This preparation was therefore selected for comparison (Fuchs et al., 1983 and Keirse, 1993).

The widespread use of prostaglandine E2 in its currently approved form is limited because of its high cost and thermal instability, which leads to difficult storage, plus the occasional need to use oxytocin to augment labor (de Aquino and Cecatli., 2003).
Oxytocin is the commonest induction agent used worldwide. It has been used alone or in combination with amniotomy but, it was associated with prolonged induction periods, a high failure rate and a considerable degree of patient discomfort (Thiery, 1983 and Kelly & Tan, 2001).

Misoprostol (Cytotec ®), a synthetic E1 methyl analog prostaglandin, is at present receiving more attention as a cervical modifying agent and labor inductor, as it has the advantages of low cost, stability in relation to temperature, easy handling and storage, easy administration (vaginal or endocervical) and has few systemic side effects. Also, is rapidly absorbed orally and vaginally (Hofmeyr and Gulmezoglu, 2001 and de Aquino & Cecatti, 2003).

In many studies, vaginal misoprostal was evaluated and proved to be superior to both PGE2 gel and oxytocin for cervical ripening and labor induction (Raio et al., 2001; MajoKo et al., 2002; de Aquino & Cecatti, 2003 and Gemund et al., 2004).

Dose finding studies reported that intravaginal misoprostal in doses higher than 50 μg were associated with higher incidence of uterine contraction abnormalities (Wing et al., 1995a; Wing et al., 1995b; Ozan et al., 2001 and Rokhead et al., 2003). Additional indirect evidence supporting the efficacy and safety of repeated intravaginal misoprostal doses of 50 μg can be found in a meta-analysis of 44 RCTs (randomized controlled trials) by Sanchez-Ramos and Kaunitz, 2000 for this reason we used 50 μg misoprostol for induction of labor in the misoprostol group of our study.
The study of Zieeman et al., 1997 on the pharmacokinetics of misoprostol showed that its serum levels, after vaginal administration, remain stable for at least 4 hours, suggesting that the ideal time interval between doses should be at least 4 hours.

In this study fifty pregnancy women with an obstetric or medical indication for induction of labor were included. Cases with post-term pregnancy, prelabor rupture of membranes, diabetes mellitus and preeclampsia were included. They were divided into two groups each of 25 women.

One group received misoprostal 50 μg (quarter of cytotec 200 μg tablet) every 4 hours and the other group underwent physician-chosen combinations of stripping of membranes, artificial rupture of membranes, enemas, castor oil and IV infusion of oxytocin.

In the study of Gemund et al., (2004). They used misoprostol vaginally (25 μg) every 4 hours for induction of labor in 341 patients and achieved vaginal delivery in 83.9%. lower segment cesarean section was done for 16.1% of patients.

Shetty et al., (2003) used vaginal misoprostal (25 μg) every 4 hours for induction of labor and achieved vaginal delivery in 72% of their patients while lower segment cesarean section was done for 28% of patients.

Milchev et al., (2003) used misoprostol intravaginal (25 g) versus oxytocin for induction of labor and reported that 79.3% of patients in the misoprostol group versus 72% in the oxytocin group achieved vaginal
delivery while lower segment cesarean section was done for 20.7% in the misoprostol group versus 28% in the oxytocin group.

_Ferguson et al., (2002)_ compared vaginal misoprostol (25 g) repeated every 4 hours and intravenous infusion of oxytocin for induction of labor and showed that vaginal delivery occurred in 61% in misoprostol group versus 66% in oxytocin group. Indications for cesarean delivery in the misoprostol group was fetal intolerance to labor in 27% compared with 8% in the oxytocin group.

_Pajak et al., (2001)_ compared vaginal misoprostol (50 g) repeated every 12 hours and intravenous oxytocin for induction of labor and vaginal delivery occurred in 88% in the misoprostol group versus 68% in the oxytocin group while lower segment cesarean section was done for 12% of patients in the misoprostol group versus 32% in the oxytocin group.

_Boulvain et al., (2001)_ used oxytocin for induction of labor and vaginal delivery occurred in 68% while cesarean section was done for 32% of their patients.

_Mozurkewich et al., (2003)_ used intravenous oxytocin in nuliparous women with premature rupture of membranes at term for induction of labor and showed that 80.1% of patients delivered vaginally while 19.9% of patients underwent cesarean delivery.

In the study of _Fletcher and Hutchinson (2001)_ , they used intravaginal misoprostol 50-100 g once daily for induction of labor and reported that the cesarean section rate was (9.3%) and vaginal delivery was achieved for (90.7%) of their patients.
**Discussion**

*Escudevo and Contreras (1997)* used misoprostol vaginally (50 μg for induction of labor in 57 patients and achieved vaginal delivery in 45 patients (78.9%). Lower segment cesarean section was done for 12 patients (21.1%).

In the study of *Ozan et al., (2001)*, they used misoprostol vaginally (50mg) every 3 hours for induction of labor and achieved vaginal delivery in (94.8%), and lower segment cesarean section was done for (5.2%) of their patients.

In the study of *Kelly and Tan (2001)*, they used oxytocin for induction of labor and achieved vaginal delivery in (81%) of patients. While lower segment cesarean section was done in 19% of patients.

*de Aquino and Cecatti (2003)* compared vaginal misoprostol (25mg) every 4 hours versus oxytocin for induction of labor and vaginal delivery was achieved in 81% of patients in the misoprostol group versus 64% in oxytocin group. Lower segment cesarean section was done for 19% of patients in the misoprostol group versus 36% in the oxytocin group.

*Butt et al., (1999)*, used oxytocin for induction of labor in 53 pregnant women with prelabor rupture of membranes and vaginal delivery occurred in 46 patients (86.8%) while lower segment cesarean section was done for 7 patients (13.2%).

*Sahin et al., (2001)* used intravaginal misoprostol 50 g given at 4 hours intervals. In 59 women without toxemia of pregnancy and vaginal delivery was achieved in 84.6% of patients lower segment cesarean section was done for 15.4% of their patients.
**Krusteva et al., (2000)** used oxytocin alone for induction of labor in post-term pregnancy and vaginal delivery was achieved in 87.1% while lower segment cesarean section was done for 12.8% of their patients.

In the study of **Sanchez-Ramos et al., (2002)**, a formal meta-analysis was performed using five RCTs (Randomized controlled trials) which directly compared two dosing regimens (25 μg every 3 hours, versus 50 μg every 3 hours) of vaginal misoprostol for labor induction and vaginal delivery was achieved in (80.9%) of patients versus (81.1%) of patients in the 25 μg group versus 50 μg group. Lower segment cesarean section was done for (18.9%) versus (19.1%) of patients.

This study showed that vaginal delivery was successfully established in 88% of patients in the misoprostol group versus 80% of patients in the non-misoprostol group.

Lower segment cesarean section was done for 12% of patients in the misoprostol group versus 20% in the non-misoprostol group showing a reduction in the rate of cesarean delivery in the misoprostol group.

In the misoprostol group of our study, vaginal delivery was achieved in 22 patients (88%). This result was similar to the result in the misoprostol group of **Pajak et al., (2001)** and nearly similar to the result of **Fletcher and Hutchinson, (2001)**. And this narrow difference may be attributed to higher doses in the study of **Fletcher and Hutchinson, (2001)** which were (50-100 μg). But lower than the result of **Ozan et al., (2001)**, and this difference may be explained by the repetition of doses at shorter intervals (3 hours instead of 4 hours in our study). However, our result was higher than the result of **Gemund et al., 2004; Shetty et al., 2003;**
Escudero & Contreras 1997; Sahin et al., 2001 and Sanchez-Ramos et al., 2002). This difference may be attributed to small dose of misoprostol (25 μg) used in the study of (Gemund et al., 2004; Shetty et al., 2003) and the 25 g group in Sanchez-Ramos et al., (2002). But may be attributed to the development of uterine hyperstimulation in higher rates of patients which underwent cesarean sections in the studies of (Escudero & Contreras, 1997 and Sahin et al., 2001) and the 50 g group in the study of (Sanchez Ramos et al., 2002).

In the non-misoprostol group of our study, vaginal delivery was achieved in 20 patients (80%). This result was similar to the result of Mozurkewich et al., (2003) and nearly similar to the result of Kelly and Tan (2001) in which vaginal delivery was achieved in (81%) of patients, and this narrow difference may be attributed to the small number of patients in our study (25) patients which can’t detect this small percent while in the study of Kelly and Tan (2001) very large number of patients (11,129) women were included in 58 trials.

This result was lower than the result of (Butt et al., 1999 and Krusteva et al., 2000). This difference may attributed to the inclusion of cases of preedampsia and diabetes mellitus in our study while in Butt et al.,(1999). They included cases with prelabor rupture of membranes only and in the study of Krusteva et al., (2000). They included cases with post-term pregnancy only.

On the other hand, this result was higher than the result of (Milchev et al., 2003; Furguson et al., 2002; Pajak et al., 2001; Bouvlain et al., 2001 and de Aquino and Cecatti, 2003). This difference was attributed to the use of other mechanical methods for cervical
ripening and induction of labor such as stripping of membranes. Artificial rupture of membranes, rather than Castro oil and enemas in our study. While in the other studies, they used oxytocin alone.

Lower segment cesarean section was done for 3 patients (12%) in the misoprostol group of our study. This result was similar to the result of Pajak \textit{et al.}, (2001) which was (12%) and higher than the result of Fletcher and Hutchinson (2001). Which was (9.3%) and higher than the result of Ozan \textit{et al.}, (2001) which was 5.2%. The lower rate of cesarean delivery in the study of Fletcher and Hutchinson (2001) may be attributed to lower incidence of hyperstimulation syndrome because the dose (50-100 μg) was given once daily.

This result was lower than the result of (Gemnd \textit{et al.}, 2004; Shetty \textit{et al.}, 2003; Milchev \textit{et al.}, 2003; Furguson \textit{et al.}, 2002; Escudero & Contreras, 1997; de Aquino and Cecatti, 2003; Sahin \textit{et al.}, 2001 and Sanchez-Ramos \textit{et al.}, 2002). The lower rate of cesarean delivery may be explained by the lower incidence of uterine hyperstimulation with less need for operative interference.

In the non misoprostol group of our study, the lower segment cesarean section was done for 5 cases (20%). This result was similar to the result of Mozurkewich \textit{et al.}, (2003) and nearly similar to the result of Kelly and Tan (2001) which was (19.9%).

This result was higher than the result of (Butt \textit{et al.}, 1999) which was (13.2%) and the result of Krusteva \textit{et al.}, (2000) which was (12.9%). The lower result of Butt \textit{et al.}, (1999) may be attributed to that they included only cases with pre-labor rupture of membranes.
Discussion

This result was lower than the result of Milchev et al., (2003) which was (28%), Furguson et al., (2002) which was (34%), Pajak et al., (2001) which was (32%), Bouvlain et al., (2001) which was (32%) and de Aquiro and Cecatti (2003) which was (36%). This difference may be attributed to the use of other methods for cervical ripening and labor induction such as stripping of membranes, artificial rupture of membranes, Castor oil, enemas in our study while in the other studies they used oxytocin alone for induction of labor leading higher rate of failure to progress which needs operative interference.

Butt et al., (1999) used intravenous oxytocin for induction of labor and showed that failure to progress was the main indication for cesarean delivery, Where lower segment cesarean section was done for 11.3% of patients due to failure to progress and done for 2% due to fetal distress.

Kenneth et al., (1999) used vaginal misoprostal (50 μg) every 4 hours for induction of labor and lower segment cesarean section was done for 20% of patients due to fetal distress.

Majoko et al., (2002) used vaginal misoprostol for induction of labor and found that significantly reduced risk of cesarean section for failure to progress.

Sanchez-Ramos et al., (2002) compared misoprostol (25 g) versus (50 g) intravaginal for induction of labor and reported that fetal distress was the indication for cesarean delivery in 6.5% versus 4.5% in both groups respectively.
Kramer et al., (1997) compared vaginal misoprostol (100 μg) every 4 hours versus oxytocin for induction of labor and reported that failure to progress was the indication for cesarean delivery in 8% of patients versus 21% of patients in the misoprostol and oxytocin groups respectively.

Furguson et al., (2002) compared vaginal misoprostol (25 μg) every 4 hours and intravenous oxytocin for induction of labor and reported that fetal distress was the indication for cesarean delivery in (27%) of patients versus (8%) of patients in the misoprostol and oxytocin groups respectively.

The indications for operative interference by lower segment cesarean section in our study were arrested progress of cervical condition in one case (4%) versus 4 cases (16%), and fetal distress in 2 cases (8%) versus 1 case (4%) in the misoprostol and non-misoprostol groups respectively. Indicating that fetal distress was the main cause of cesarean sections in the misoprostol group while failure to progress was the main cause of cesarean section in the oxytocin group. This result was similar to the result of (Butt et al., 1999; Kenneth et al., 1999; Kramer et al., 1997; Majoko et al., 2002 and Furguson et al., 2002).

These studies also reported that fetal distress was the main indication for cesarean delivery when vaginal misoprostol was used for induction of labor and the rate of fetal distress depends on the dose and dosing interval. These studies also reported that failure to progress was the main indication for cesarean delivery when oxytocin was used for induction of labor.
Shetly et al., (2003) used vaginal misoprostol (25 g) for induction of labor and reported induction-delivery interval (1236 +/- 960) min.


Milchev et al., (2003) compared intravaginal misoprostol (25 g) versus oxytocin for induction of labor and reported that induction-delivery interval was (1332.4 +/- 846.5 min) in the misoprostol group versus (1523 +/- 705.6) in the oxytocin group.

Meydanli et al., (2003) used vaginal misoprostol (50 g) in patients with post-term pregnancy and reported induction-delivery interval (627 +/- 177) min.

Rockhead et al., (2003) used vaginal misoprostol (50 g) for induction of labor and reported that induction-delivery interval was (560.14 +/- 269.20) min.

Morgan et al., (2002) compared intravenous oxytocin and vaginal misoprostol for induction of labor in patients with premature rupture of membranes and reported that the induction delivery interval was 537.05 min with oxytocin versus 474.54 min with misoprostol.

Pajak et al., (2001) compared vaginal misoprostol (50 g) repeated every 12 hours and intravenous oxytocin and reported that the induction-delivery interval was (1236 +/- 912) min. in the misoprostol group versus (673 +/- 444) min in the oxytocin group.
Discussion

*Raio et al., (2001)*, used vaginal misoprostol (50 g) repeated every 6 hours for induction of labor and reported that the mean induction-delivery interval was 690 min.

*de Aquino and cecatti (2003)* compared vaginal misoprostol (25mg) every 4 hours versus Intravenous oxytocin and reported that the induction-delivery interval was (636 +/- 264)min. in the misoprostol versus (888 +/- 306) min. in the oxytocin group.

In Turkey, in a study of *Kadanali et al., (1996)*, they compared misoprostol versus oxytocin for induction of labor and reported that. The mean induction-delivery interval was 540 min in the misoprostol versus 900 min in the oxytocin group.

*Bugalho et al., (1995)* used 50 g vaginal misoprostol every 12 hours for induction of labor and reported mean induction-delivery interval of 624 min.

*Kramer et al., (1997)* compared vaginal misoprostol 100 g every 4 hours versus IV oxytocin for induction of labor and reported induction-delivery interval (585 versus 885)min. in the misoprostol and oxytocin groups.

Windrim et al., (1997) used oxytocin for induction of labor in patients with prelabor rupture of membranes and reported induction-delivery interval of $(557 \pm 312)$ min.

In the meta-analysis of 5 (RCTs) Randomized Controlled Trials in the study of Sanchez-Ramos et al., (2002), vaginal misoprostol was used in a dose of $25\text{mg}$ for induction of labor and reported induction-delivery interval of $(1323 \pm 844)$ min.

As regard the induction-delivery interval in the misoprostol group of our study, it was $(572 \pm 109.6)$ min. This result was nearly similar to the result of Meydanli et al., (2003), Rockhead et al., (2003), Kadanali et al., (1996), Kramer et al., (1997) and Bugalho et al., (1995), But was longer than the result of Morgan et al., (2002), This difference could be explained by that in the study of Morgan et al., they used misoprostol in patients with prelabor rupture of membrane only. While our study included only (36%) with prelabor rupture of membranes and the other (64%) of patients included patients with post-term pregnancy, diabetes mellitus and preeclampsia.

On the other hand, the induction-delivery interval in the misoprostol group of our study was shorter than that recorded in the study of Shetty et al., (2003), Milchev et al., (2003), Pajak et al., (2001), Raio et al., (2001), de Aquino and Cecatti (2003) and Sanchez-Ramos et al.,(2002). This difference may be due to the lower dose of misoprostol used in the other studies and/or the longer dosing interval in these studies. Also the presence of 36% of patients with premature rupture of membranes in our study, with absence of patients with premature rupture of membranes in some of the other studies may lead to lowering of the induction-delivery interval in our study.
Discussion

In the non-misoprostol group of our study. The induction-delivery interval was \((805 \pm 201.5)\) min. This result was nearly similar to the result of Milchev et al., (2003). But was shorter than the result of de Aquino and Cecatti (2003) & Kadanali et al., (1996). This difference may be due to that in our study we not only, used intravenous oxytocin but also we used other physician-chosen combinations stripping of membranes or artificial rupture of membranes. Castor oil, or enemas. While in their studies, they used intravenous oxytocin only for induction. Also our study includes 36% of patients with premature rupture of membranes.

On the other hand, the induction-delivery interval in the non-misoprostol group of our study was longer than that recorded in the study of Morgan et al., (2002), Pajak et al., (2001), Butt et al., (1999) and Windrim et al., (1997). This difference may be attributed to the fact that these studies included only patients with premature rupture of membranes while our study included patients with post-term pregnancy, preeclampsia and diabetes mellitus.

Morgan et al., (2002) compared misoprostol and intravenous oxytocin for induction of labor in patients with premature rupture of membranes and reported that the mean time from induction to beginning of labor was 95.94 minutes with misoprostol versus 107.5 minutes with oxytocin.

Raio et al., (2001) used vaginal misoprostol (50 g) every 6 hours for induction of labor and reported induction-initiation time of 443 minutes.
Discussion

*de Aquino and Cecatti* (2003) compared vaginal misoprostol (25mg) every 4 hours versus oxytocin for induction of labor and reported that the mean induction-activation time was (253 ± 149.1) min. in the misoprostol group versus (352.3 ± 151.9) min. in the oxytocin group.

As regard the induction-activation time in the misoprostol group of our study, it was (126.84 ± 26.8) min. This result was longer than that recorded in the study of *Morgan et al.,* (2002) and this difference may be explained by the fact that their study were included only patients with premature rupture of membranes while our study included patients with post-term pregnancy, diabetes mellitus and preclampsia.

On the other hand, the induction-activation time in the misoprostol group of our study was shorter than that recorded in the study of *Raio et al.,* (2001) and *de Aquino and Cecatti* (2003) and this difference may be attributed to the smaller dose of misoprostol used in their studies or the longer dosing interval.

In the non-misoprostol group of our study, the induction-activation time was (285.4 ± 116.1) min. This result was longer than that recorded in *Morgan et al.,* (2002) and this difference may be explained by the fact that their study included only cases with premature rupture of membranes. While our study included only 36% of patients with premature rupture of membranes.

On other hand, the induction-activation time in the non-misoprostol group of our study was shorter than that recorded in the study of *de Aquino and Cecatti* (2003) and this difference may attributed to that in our study we used physician chosen combinations of stripping or artificial
rapture of membranes, castor oil and enemas plus oxytocin for induction while in their study they used oxytocin only. Also our study included 20% of patients with prelabor rupture of membranes.

_Pajak et al., (2001)_ compared vaginal misoprostol (50 g) repeated every 12 hours and intravenous oxytocin for induction of labor and reported that there were no episodes of uterine hyperstimulation in both groups.

_Bouvlain et al., (2001)_ used misoprostol for induction of labor and reported hyper stimulation with fetal heart rate changes in 9% of cases.

_Crane et al., (2001)_ used vaginal misoprostol for induction of labor and reported that uterine hyperstimulation occurred in 7.6% of cases.

_Wing et al., (1997)_ used vaginal misoprostol (25 g) every 4 hours for induction of labor and reported that uterine hyperstimulation occurred in 1% of patients.

In the study of _Kenneth et al., (1999)_ they used intravaginal misoprostol (50 g) every 4 hours for induction of labor and reported that 6% of patients developed uterine hyperstimulation.

_Blust and Carlan (2001)_ used misoprostol vaginally (50 g/4 hours) for induction of labor. They recorded the development of uterine hyperstimulation in (18.5%) of their patients.

In the study of _El-Sherbiny et al., (2001)_ they compared vaginal misoprostol (25 g) versus (50 g) every 3 hours for induction of labor and
reported that hyperstimulation occurred in 4.4% versus 9.3% of patients in the (25 g) and (50 g) groups.

In our study, hyperstimulation occurred in 2 cases (8%) in the misoprostol group versus 1 case (4%) in the non-misoprostol group.

In the misoprostol group of our study, the rate of hyperstimulation was nearly similar to that recorded in the study of Bouvlain et al., (2001), Crane et al., (2001) and El-Sherbiny et al., (2001), but was higher than that recorded in Pajak et al., (2001), Wing et al., (1997) and Keneth et al., (1999).

On the other hand, the rate of uterine hyperstimulation in our study was lower than that recorded by Blust and Carlan (2001).

The divergent incidences of uterine hyperstimulation recorded in these studies may reflect differences in the doses used, different intervals for dose repetition, different definitions of hyperstimulation, differences in sample size, or differences in the population response to the given dose.

Vomiting was observed in (3.5%) in the vaginal misoprostol group of Ozan et al., (2001). This result was nearly similar to our results, where vomiting was observed in (4%) of our patients.

In the study of Kelly et al., (2003) they used castor oil and/or enema for induction of labor and reported that all women who ingested castor oil felt nauseous. This result was nearly similar to our result where nausea occurred almost in all cases in the non-misoprostol group who ingested castor oil while vomiting occurs only in 12% of patients.
In the study of *Fletcher et al., (1993)*, they used (50 g/ 4 hours) vaginal misoprostol and reported passage of meconium-stained liquor in (8.5%) of their patients. This result was nearly similar to our result in the misoprostol group which was (8%).

In the oxytocin group of the study of *Furguson et al., (2002)*, the rate of passage of meconium stained liquor was (8%). This result was similar to our result in the non-misoprostol group which was also (8%).

In the study of *Fletcher and Hutchinson (2001)*, they used intravaginal misoprostol 50-100 g once daily for induction of labor and reported that Apgar score less than 7 at one minute was observed in (10.2%) and at 5 minutes was observed in (2.9%) of their patients.  

*Mundle and Young (1996)* they compared vaginal misoprostol (50 g) versus physician-chosen combinations for induction of labor and reported that Apgar score < 7 at 1 minute was observed in (16.3%) versus (11.8%) of their patients in the misoprostol and non-misoprostol groups respectively. While Apgar score < 7 at 5 minutes was observed in (1.8%) of patients versus (0.9%) in the misoprostol versus oxytocin group.

In the study of *Sanchez-Ramos et al., (2002)*, a formal meta-analysis was performed using five RCTs. (Randomized Controlled Trials) which directly compared two dosing regimens (25 g versus 50 g) of vaginal misoprostol for labor induction and reported that Apgar score < 7 at 5 minutes was observed in (1.8%) of patients in the 25 g group versus (3.3%) in the 50 g group.
Butt et al., (1999) used oxytocin for induction of labor and reported that Apgar score <7 at 1 minute was observed in (11.4%) of their patients and Apgar score < 7 at 5 minutes was observed in (3.8%) of their patients.

In the study of Adair et al., (1998), they used vaginal misoprostol 50 μg every 6 hours for induction of labor and reported that, the Apgar score < 7 after 1 minute was observed in (11.8%).

In our study, the Apgar score < 7 at 1 minute was observed in (16%) in the misoprostol group versus (12%) in the non-misoprostol group.

Our result in the misoprostol group was nearly similar to that recorded in the study of Mundle and Young (1996). But was higher than that recorded in the study of Fletcher and Hutchinson (2001) and Adair et al., (1998). This difference may be attributed to the shorter the interval of dose repetition in our study.

On the other hand, Apgar score < 7 at 5 minutes was observed in one case (4%) of patients in the misoprostol group and this result was nearly similar to that recorded in the (50 g) group of Sanchez-Ramos et al., (2002) while it was higher than that observed in the study of Fletcher and Hutchinson (2001) & Mundle and Young, (1996). This difference may be attributed to the shorter the period of dose repetition in our study.

As regard the Apgar score < 7 at 1 minute in the non-misoprostol group of our study, it was observed in 3 cases (12%). This result was nearly similar to that recorded in the study of Butt et al., (1999) and Mundle & Young (1996).
On the other hand, Apgar score < 7 at 5 minutes in the non-misoprostol group of our study was observed in one case (4%). This result was nearly similar to that recorded in the study of Butt et al., (1999).

*Mundle and Young (1996)*, compared vaginal misoprostol (50 g) versus physician-chosen combinations for induction of labor and reported that the mean umbilical cord pH was (7.28 ± 0.9) versus (7.28 ± 0.10) in the misoprostol and non-misoprostol groups.

In our study, the mean cord pH was (7.29 ± 0.09) in the misoprostol group versus (7.285 ± 0.033) in the non-misoprostol group. This result was nearly similar to that recorded in the study of Mundle and Young (1996).

*Butt et al., (1999)* used oxytocin for induction of labor in patients with prelabor rupture of membranes and reported that about (15.2%) of neonates needed admission of NICU (Neonatal Intensive Care Unit).

In the study of Kenneth et al., (1999) they used vaginal misoprostol (50 g) every 4 hours for induction of labor and recorded that about 13% of neonates needed admission to NICU.

In the study of Sanchez-Ramos et al., (2002), a comparison between 25 g vaginal misoprostol versus 50 g every 3 hours for induction of labor reported that about (12.3%) of neonates in the 25mg group versus (19.1%) in the 50 g group needed admission to NICU.

In our study, (12%) of neonates in the misoprostol group needed admission to NICU. This result was nearly similar to that recorded in the
Discussion

study of *Kenneth et al., (1999)* and the 25 g group of *Sanchez-Ramos et al., (2002)*, but was lower than that recorded in the 50 g group of *Sanchez-Ramos et al., (2002)*. This difference may be explained by the shorter the period of dose repetition in the study of *Sanchez-Ramos.*

In the non-misoprostol group of our study, (16%) of neonates needed admission to NICU. This result was nearly similar to that of *Butt et al., (1999).*
CONCLUSION

From our results, we may conclude the following:

Misoprostol is an apparently safe and low-cost agent for labor induction.

At the administered doses, vaginal misoprostol was more effective than IV infusion of oxytocin.

The rate of occurrence of uterine hyperstimulation was more with misoprostol than oxytocin.

Fetal side effects (bradycardia, late decelerations and lower Apgar score at one minute) were more common with misoprostol than oxytocin.

In cases of uterine hyperstimulation, the use of misoprostol in conjunction with tocolytic agent could be tried.

Fetal side effects and uterine hyperstimulation were more common with 50 μg vaginal dose of misoprostol, so, studies using smaller dose are warranted for labor induction.
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Pharmacologically and physiologically, prostaglandins have two direct actions associated with labor: ripening of the cervix and a direct oxytocic action and therefore have been widely used for induction of labor in late pregnancy and as abortifacient agents in early pregnancy (Hofmeyr and Gulmezoglu., 2001 and Calder., 1999).

The use of natural prostaglandins has been limited by their instability, high cost, rapid metabolism and high incidence of gastrointestinal side effects (Egarter et al., 1990 & Calder 1999).

Misoprostol (cytotec ®), asynthetic PGE1 analogue, is as effective as dinoprostone for pre induction cervical ripening and induction of labor in patients with low bishop score misoprostol is inexpensive, safe and simple to administer. (de Aquino and Ceatti., 2003, Gherman et al., 2001, Birlain et., 2001 and Ozan et al., 2001).

The aim of this study is to find out if the use of misoprostol for labor induction has any undesirable effects on the mother and the neonate.

The study included 50 pregnant females with different indications for labor induction women were enrolled into two groups, each containing 25 women. In the misoprostol group, induction of labor was by 50 g intravaginal misoprostol and in the non-misoprostol group, induction of labor was by physician chosen combinations of stripping or artificial rupture of membranes, enemas, castor oil and IV infusion oxytocin.
Summary

The Bishop score were used to evaluate the cervical ripening, cardiotocographic monitoring was used to evaluate the effects on uterine contraction and fetal heart rate.

All cases were followed up till delivery. Induction-activation interval, induction-delivery interval, mode of delivery, uterine contraction abnormalities, fetal heart rate changes, fetal outcome: A pgar score, umbilical card blood gases and maternal side effects were recorded and evaluated.

Our results showed that; misoprostol was accompanied by significantly shorter induction-activation and induction – delivery intervals, but also accompanied by a higher incidence of hyperstimulation syndrome.

Successful outcome was achieved in 22 cases (88%) in the misoprostol group and in 20 cases (80%) in the non – misoprostol group.

Failure to achieve vaginal delivery in the misoprostol group was due to operative interference for hyperstimulation syndrome while, the failure to achieve vaginal delivery in the non-misoprostol group was due to operative interference due to failure to progress in labor.

Neonatal outcomes were similar in both groups, no neonate met the ACOG criteria for birth asphyxia.
تأثير استخدام الميزوبروستول في تحفيز الولادة على الأم والمولود

الملخص العربي

يتمتع عقار البروستاجلاندين في الكثير من أنواعه المختلفة بالقدرة على تحسين خصائص عنق الرحم والحث على الولادة ولذلك تم استخدامه على نطاق واسع للتحريض على الولادة في الشهور الأخيرة من الحمل وفي التحريض على الإجهاض في الشهر الأول من الحمل. ولكن يعد استخدام عقار البروستاجلاندين الطبيعي مفهومًا كثيرة تشتمل عدم ذئبه في درجات حرارة الجو المعتدلة، ارتفاع سعره، سرعة تمثيله وكذلك كثرة حدوث أعراض جانبية في الجهاز الهضمي عند استخدامه.

كذلك يحذر استخدامه في بعض الحالات المرضية كحساسية الصدر، أمراض القلب والأوعية الدموية، والمياز الزرقاء.

يعتبر عقار الميزوبروستول (سيتودوك) من مشتقات البروستاجلاندين الرخيمة الثمن والسحيلة الحفظ في درجات الحرارة المختلفة وقد أثبت هذا العقار مقدرته المساهمة في تعزيز البروستاجلاندين H2 (دينورستون) في تحسين خصائص عنق الرحم وكذلك في الحث على الولادة. إن الهدف من هذه الدراسة هو معرفة ما إذا كان استخدام الميزوبروستول في تحريض الولادة له أي أعراض غير مرغوبة على أي من الأم والمولود.

وقد اشتملت الدراسة على 50 سيدة من الحوامل ذوات أسباب مختلفة لإحداث الولادة على أن تكون فترة حملهن أكثر من 37 أسبوع وعنق الرحم أقل من أو يساوي 5 نقاط حسب قياس بيشوب.

وقد تم تقسيم الحالات إلى مجموعتين كلاً منهما تحتوي على 25 حالة. في المجموعة الأولى تم استخدام عقار الميزوبروستول عن طريق المهبل بجرعة 50 ميكروجرام.

وفي المجموعة الثانية تم استخدام عقار الأكسيبت�ين بالإضافة إلى وسائل أخرى مساعدة مثل نزع الأغشية الأمينوزة تفعيل الأغشية الأمينوزة، زيت الخروع والحقن الشرجية.
 penetrate the uterus during childbirth in different stages.

1- A study found that Pethidine is effective in promoting the characteristics of uterine contractions in the cervix, as it is more effective than meperidine.

2- The study found that the use of meperidine is more effective than Pethidine in promoting the characteristics of uterine contractions.

3- The side effects of meperidine were more severe than those of Pethidine.

4- Increased incidence of hemorrhage after childbirth in women who used meperidine.

5- The study recommended that meperidine, when used during childbirth, should be used at low doses and not exceed the recommended dosage.