Vaginal PGE_1 analogue (misoprostol) versus PGE_2 (dinoprostone) for Induction of labor; A randomized controlled trial

Thesis

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Presented by

Mohammed Saeed El-Labany

(M.B.B.Ch.2009)

Faculty of Medicine, Al-Azhar University

Resident in Kafr El-Zyat General hospital

Under the supervision of

Prof. Amr Hassan El-Shalakany

Professor of Obstetrics and Gynecology

Faculty of Medicine – Ain Shams University

Dr. Walied El-Basuony Mohammed

Lecturer in Obstetrics and Gynecology

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain-Shams University

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Mohamed Saeed Al Labany

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LIST OF ABBREVIATIONS

ACOG	American College Of Obstetricians & Gynecologists
ATP	Adenosine Triphosphate
COX	Cyclooxygenase enzyme
CRH	Corticotropin Releasing Hormone
Cx43	Connexin 43
GR	Glucocorticoid Receptor
HETEs	Hydroxyeicosatetraenoic acid
HPA	Hypothalamic Pituitary Axis
HPETES	Hydro Peroxyeicosatetraenoic acid
IMN	Isosorbid Mono Nitrite
LT	Leukotrienes
MLCK	Myosine Light Chain Kinase
MMP	Matrix Metalloproteinases
NST	Non Stress Test
PAF	Platelet Activating Factor
PGDH	Prostaglandin Dehydrogenase Enzyme
PO	Per Oris
PR	Per Rectum
PV	Per Vagina
RCT	Randomized Controlled Trial
TVU-CL	Trans Vaginal U/S- Cervical Length
TXA2	Thromboxane A2
11b-HSD1	11b-Hydroxy Steroid Type 1

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Introduction

Induction of labor is defined as using artificial means to assist the mother in delivering her baby.Another definition is an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. This includes both women with intact membranes and women with spontaneous rupture of the membranes but who are not in labor. The term is usually restricted to pregnancies at gestations greater than the legal definition of fetal viability (24 weeks in UK) **(Dutta.2009).**

Cervical ripening is a component of induction of labor employed when the cervix is unfavorable in order to facilitate dilatation when labor is established**. (Rozenberg,et al. 2001).**

For majority of women labor starts spontaneously and results in vaginal delivery. Many medical and obstetrical complication of pregnancy overweighs the risk of spontaneous delivery.Labor induction in presence of unfavorable cervix is oftenprolonged and may lead to induction failure. Hence ,cervicalripening is required before induction of labor to achieve
more successful outcome **(Joy, et al. 2003).**

Induction should only be considered when vaginal delivery is felt to be the most appropriate mode of delivery.

Many clinical circumstances such as pregnancy-induced hypertension, prelabor rupture of membranes, suspected fetal jeopardy or death, or maternal morbidity (e.g. diabetes) lead to the use of labor induction.(**Wasim ,et al. 2008).**

The most common reasons for inducing labor are: **(Dutta.2009)**.

- Prolonged pregnancy - 70% of such cases are induced after 41 weeks, often at the mother's request. The obstetrician will usually agree if the cervix is ripe.
- Suspected fetal growth retardation.
- Hypertension and pre-eclampsia; approximately 50% of women with this problem are induced.
- Planned time of delivery in best interests of baby, e.g. cardiac abnormalities which may need immediate surgery after birth.

Prostaglandins act on the cervix to enable ripening by a number of different mechanisms. They alter the extracellular ground substance of the cervix, and PGE_2 increases the activity of collagenase in the cervix. They cause an increase in elastase, glycosaminoglycan, dermatan sulfate, and hyaluronic acid levels in the cervix. A relaxation of cervical smooth muscle facilitates dilation. Finally, prostaglandins allow for an increase in intracellular calcium levels, causing contraction of myometrial muscle. Risks associated with the use of prostaglandins include uterine hyperstimulation and maternal side effects such as nausea, vomiting, diarrhea, and fever (**Smiti,et al. 2007).**

Misoprostol- a prostaglandin E_1 analogue - is a hormone given by insertion through the vagina or rectum, or by mouth to ripen the cervix and bring on labor. Vaginal misoprostol in doses above(25 mcg) four-hourly was more effective than conventional methods of labour induction, but with more uterine hyperstimulation. Lower doses were similar to conventional methods in effectiveness and risks **(Szczesny,et al.2006)**.

The effects of prostaglandins on the uterus cannot be solely explained by contractility. Treatment with PGE_1 significantly increased myometrial contractions decreased both total collagen content and the area covered by connective tissue. Such findings may explain the higher rates of vaginal delivery, tachysystole and uterine rupture associated with PGE_1 use **(Urban,et al.2003)**.

The search for an effective, easily stored, affordable labour inducing agent has led to the use of misoprostol. Unlike dinoprostone, it is very stable at room temperature and is extremely inexpensive. The general concern in the use of intravaginal misoprostol for induction of labour was significant incidence of uterine tachysystole, hyperstimulation and potential of foetal threat. At lower doses of 25 μg, misoprostol was found to be effective with less frequent incidence of hyperstimulation and meconium passage **(Kudagi , et al 2013).**

Aim of the work

Rational:
In women undergoing induction of labor, Misoprostol appeared more effective compared with dinoprostone **(Neelu,et al 2004) (Kulshreshtha,et al 2007) (Kudagi , et al 2013).**

Research question:
In women undergoing induction of labor, Does misoprostol is more effective and safe than dinoprostone.

Aim:

The aim of the current trial is to compare between vaginal PGE_1 analogue and vaginal PGE_2 in the induction of labor regarding both efficacy and safety.

Patients and Methods

Methods setting:The labor ward at Ain Shams University Maternity hospital.
Duration: To be started in February 2014.
Design: Randomized control trial**.**

Study Population:
Pregnant women planned for induction of labor with the following inclusion/exclusion criteria:
Inclusioncriteria*:*
1) Singleton pregnancy.
2) Gestational age≥36 weeks (calculated from reliable menstrual dates and/or late first-trimester or early second- trimester ultrasound scan).
3) Modified Bishop score ≤6.
4) Intact fetal membranes.
5) Valid Indication for induction of labor.
6) Normal fetal non stress test.
Exclusioncriteria*:*
1) Any contraindication for vaginal delivery (e.g. placenta previa).
2) Any contraindication for induction of labor (e.g. previously uterus or fetal malpresentation).
3) Any contraindication for use of prostaglandins or their analogues (e.g. bronchial asthma or drug allergy).

Randomization:
The eligible women are to be randomized into one of the following two groups:
1. **Group 1**: including 50 women who will receive vaginal misoprostol tablet (50 μg) at 4-hour intervals for up 3 doses per day.
2. **Group 2**: including 50 women who will receive vaginal dinoprostone tablet (2 mg) at 6-hour intervals for up to 2 doses per day.
Randomization is performed using a computer-generated randomization system. The tablets are contained in sealed envelopes numbered according to the randomization table to be opened just before starting induction.

Drugs:

- Women of the first group will receive 50 μg of misoprostol vaginally(a quarter of tablet of scored cytotec® tablet [PfIzer Inc., New York, NY, USA].
- Women of the second group will receive 2 mg of dinoprostone vaginally (a Dinoglandin® tablet [Egypharma, Nasr City, Cairo, Egypt].

Procedures:

- All women planned for induction of labor at the labor ward in Ain Shams University Maternity Hospital will be approached. Routine assessment is performed [including history revision, general and abdominal examination as well as vaginal examination].
- Modified Bishop score is calculated for all approached women.
- All approached women undergo a non-stress test on admission, as well as obstetric ultrasound scan for assessment of liquor volume, placental location and fetal biometry and anatomy.
- Eligible women are counseled about precipitating in the trial. Women who consent for precipitation are recruited and allocated to one of two study groups according to the randomization table:

1. Women of group 1 will receive vaginal misoprostol [50 μg] at 4-hour interval for up to 3 doses per day.
2. Women of group 2 will receive vaginal dinoprostone [2 mg] at 6 hour interval for up to 2 doses per day.

- Women are assessed for uterine contractions every 1 hour. Fetal heart rate is monitored with intermittent auscultation every 30 minutes.
- Women are examined by investigator at the time of the next dose, when regular uterine contractions are palpable, or fetal membranes spontaneously rupture.
- Modified Bishop score is recalculated with examination at the time of the next dose. Women are then assessed every 2-4 hours [according to the frequency of uterine contractions].

Bishop score (points assigned):

Factors	Rating			
	0	1	2	3
Dilatation	Closed	1 – 2 cm	3 – 4 cm	5 cm
Effacement	0 – 1 cm	1 – 2 cm	2 – 3 cm	3 – 4 cm
Station	-3	-1, -2	-1, 0	+1, +2
Consistency	Firm	Medium	Soft	-
Position	Posterior	Middle	anterior	-

Unfavorable cervix Bishop score < 6**(Szczesny,et al. 2006).**

- Women who show slow progressof labor (cervical dilatation is lower than 1 ml./1 h.) receive oxytocin infusion for augmentation of labor .

Oxytocin use:

Adding 5 units of oxytocin (Syntocinon®) to a 500 mL flask of ringer lactate solution or normal saline. Commencing the oxytocin (Syntocinon®) infusion at 2 milliunits/min (12 mL/hr) via volumetric infusion pump. Increasing the rate every 30 minutes (per increment schedule below) aiming for4 contractions in 10 minutes lasting 40 – 90 seconds each.

- Women who receive maximum allowed doses of the allocated drug for 24 hours are subjected to an overnight rest and have a repeat trial next day if the fetal and maternal condition allow.
- Women who fail induction after second trial will assigned as (failed induction of labor) and undergo c.s. according to the protocol of Ain Shams University Maternity Hospital.

<u>Definitions</u>: (Dutta.2009)

***First stage of labor*:**

Begins with regular uterine contractions and ends with complete cervical dilatation at 10 cm. It divided into a latent phase and an active phase. The latent phase begins with mild, irregular uterine contractions that soften and shorten the cervix. The active phase usually begins at about 3-4 cm of cervical dilation and is characterized by rapid cervical dilation and descent of the presenting fetal part.

Second stage of labor:

Begins with complete cervical dilatation and ends with the delivery of the

fetus.

Third stage of labor:

The period between the delivery of the fetus and the delivery of the placenta and fetal membranes**.**

Primary outcome measure:

The induction- to- delivery interval.

Secondary outcome measures:

1) Duration of the first and second stage of labor.
2) Proportion of women who had successful induction of labor(those who deliver vaginally).
3) Proportion of women who need oxytocin for augmentation of labor..
4) Uterine hyperstimulation.
5) Intrapartum fetal compromise.
6) Side effects: nausea, vomiting, shivering or diarrhea.
7) Labor pain intensity assessment: a visual analogue scale (VAS) and the number of doses of analgesia needed during labor.
8) Women who satisfied using the 5-point likert scale(very satisfied – satisfied – indifferent – unsatisfied - very unsatisfied).
9) Prenatal outcome: 1- and 5-min Apgar scores – need for admission to NICU
and its reason.

Ethical aspects:

- The study protocol is designed in agreement to the declaration of Helsinki for ethical medical research. The protocol is to be approved by ethical committee of the Obstetric and Gynecology Department, Ain Shams University.
- The study purpose and procedures are to be explained to all approached and eligible women. Women have to sign an informed written consent before participate in the trial.
- Any participating woman is informed that she has the right to withdraw from the study at any phase without any adverse impact on the medical service she receive.

Statistical methods:

Sample size justification:

Data from a previous similar study (**Ozkan et al., 2009**) showed that the induction-to-delivery interval was 680±329 min (in misoprostol group) in contrast to 1070±435 min (in dinoprostone group).
Calculation according to these values setting the type-1 error (α) at 0.05 and the power (1-β) at 80% produces a minimal sample size of 48 women in each group. Assuming a drop-out rate of 5%, a minimum of 50 women are needed in each group. Therefore 100 women are needed to be recruited in the current trial.

Statistical analysis:

Demographic data of included women will be presented as descriptive statistics (using range, mean and standard deviation of metric data) (using range, mean and interquartil rang of discrete data)
Demographic data and primary and secondary outcomes of both groups will be compared using t-test (for quantitative measures) and chi-square test (for categorical measures).
Microsoft, Excel (version 2010) and SPSS for windows (version 16.0) will be used for data presentation and statistical analysis.

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