Intravenous Dexamethasone Versus Vaginal Misoprostol in Enhancing Cervical Ripening and Labor Induction; Randomized Controlled Clinical Trial

Thesis

Submitted For Partial Fulfillment of Master Degree in Obstetrics and Gynaecology

By

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List of Abbreviations

Abbr.	Full term
ACTH	Adrenocorticotropic Hormone
AP	Activating Protein
AROM	Artificial Rupture Of Membranes
BMI	Body Mass Index
CBP	CREB-Binding Protein
CRH	Corticotropin Releasing Hormone
CSF	Colony Stimulating Factor
DHEAS	Dehydroepiandrosterone Sulphate
fFN	Fetal Fibronectin
GA	Gestational Age
GRE	Glucocorticoid Responsive Elements
HFA	Human Fetal Adrenal
IOL	Induction of Labor
IU	International Units
IUFD	Intra-Uterine Fetal Death
MCSF	Macrophage Stimulating Factor
MMP	Metallo Proteinase
mPR	Membrane Progesterone Receptor
NO	Nitric Oxide
P450c17	Cytochrome (steroid17 alpha-hydroxylase/17,20 lyase)
PGE2	Prostaglandin E2
PPROM	Prelabor Premature Rupture of Membranes
PR	Progesterone Receptor
ROM	Rupture of Membranes
TNF	Tumor Necrosis Factor

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PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS & GYNAECOLOGY

Title of the Protocol: Intravenous Dexamethasone Versus Vaginal Misoprostol in Enhancing Cervical Ripening and Labor Induction; Randomized Controlled Clinical Trial

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What is already known on this subject? AND What does this study add?

One of the problems in midwifery is induction of cases in which it is necessary to terminate pregnancy. One of the methods proposed for the strengthening and speeding up of the labor process (labor induction) is the use of corticosteroids (Dexamethasone) and Vaginal Misoprostol. According to recent studies, it was found that the average interval between labor induction and the start of active stage of labor in the group injected with dexamethasone (2.87+/- 0.93 hours) was significantly shorter than those receiving Vaginal Misoprostol (9.8 +/- 5.8 hours).

1.INTRODUCTION/ REVIEW

Labor induction is any procedure that stimulates uterine contraction before labor begins naturally. The process of childbirth starts from the axis of the hypothalamus, the pituitary gland, and the adrenal glands. Steroid substances produced in the adrenal glands of the human fetus affect the placenta and the membranes and transform the myometrium from the static to the contractile state.The placenta may play a role in this process because it produces a lot of CRH(Corticotropin releasing hormone). The adrenal glands of the fetus do not produce a considerable amount of cortisol until the third trimester. During the last weeks of pregnancy, the cortisol and DHEAS-S (Dehydroepiandrosterone Sulfate)contents of the fetus rise and this leads to an increase in maternal estrogens, a particularly esterol ***(Hoffman et al., 2012)***.

The concentration of CRH in the fetus rises during the last 12 weeks of pregnancy.This results in modification of the contractility of the uterus, stimulation of the membranes to produce more prostaglandins, stimulation to produce C19 steroids from placental adrenaline and increase in the estrogen content ***(Racowsky et al., 2013)***.

The onset of spontaneous labor pains is a physiological sign of termination of pregnancy. However, in many pregnant women, due to medical and obstetric complications, cervical ripening and induction of labor are required prior to the onset of labor pains. This procedure has many benefits for both the mother and the fetus ***(Kenneth et al., 2014)***.

Induction of labor consists of stimulation of uterine contractions using various artificial methods before the onset of spontaneous labor, with or without rupture of membranes, which leads to progressive cervical dilatation and fetal delivery. The main mechanical methods are the following: artificial rupture of membranes (amniotomy), breast stimulation, cervical dilators, and digital sweeping in the lower segment. Pharmacological methods include the use of oxytocin and synthetic prostaglandins ***(Sanchez-Ramos et al., 2005)***.

Induction of labor is the most common obstetrics technique and the fastest growing medical method in the United States of America ***(Murphy 2013)***.

Misoprostol is a synthetic prostaglandin E1 (PGE1) analogue that acts as an inducer of the ripening process, thus favoring dilation and causing uterine contractions. It is indicated for labor induction in cases of unfavorable uterine cervix (Bishop score < 6). Misoprostol can be administered via the vaginal, oral, and sublingual routes, with the vaginal route being the preferred one ***(Stephenson et al., 2015)***.

However, misoprostol has contraindications, such as previous cesarean delivery, previous uterine surgery, placenta previa, asthma, coronary disease, and cephalopelvic disproportion. The risks associated with labor induction using misoprostol are uterine hyperstimulation with hypertonia, tachysystole, and uterine rupture, also maternal complications such as nausea,vomiting,diarrhea and fever. Additionally induction failure can have physical and psychological complications for the mother ***(Batista et al., 2015)***.

It was found that the interval from initial dose of vaginal misoprostol to the active phase of labor was (9.8 +/- 5.8 hours) and the interval time from initial dose to delivery was(15.3 +/- 9.8 hours) ***(Hofmeyr et al., 2010)***.

The conventional method for induction is using oxytocin, which may involve postpartum atony and water intoxication ***(MAY et al., 2015)***.

Another medication that may help cervical ripening and delivery process is the use of Dexamethasone. Although their role in onset of labor is unknown, finding corticosteroids receptors on fetal membranes at onset of delivery strengthens this role ***(Wolfe et al. 2012)***.

Studies conducted on animals indicate the importance of the secretion of cortisol by adrenal glands in sheep fetuses and in fetuses of other animals on starting labor ***(McAuliffe et al., 2014)***.

Moreover,it has been observed that infusion of glucocorticoids into sheep fetuses causes premature birth induction ***(Santana et al., 2011)***. These studies have prepared the way for bringing up the role of corticosteroids in the speeding up of labor induction in women ***(Zhao et al., 2013)***.

2.STUDY HYPOTHESIS

In pregnant women undergoing induction of labor by Intravenous Dexamethasone may accelerate labor induction similar to Vaginal Misoprostol.

3.RESEARCH QUESTION

Does Intravenous Dexamethasone accelerate labour induction if compared to that of Vaginal Misoprostol ?

4.AIM / OBJECTIVES

The aim of this study is to evaluate the efficacy of intravenous dexamethasone versus vaginal misoprostol in enhancing cervical ripening and labor induction.

5.METHODOLOGY:
Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:** Randomized Controlled Clinical Study.
- **Study Setting:** This study will be conducted at Ain Shams University Maternity Hospital.
- **Study Population:** Will include 60 primiparous pregnant women at 39-42 weeks gestation for termination of prenancy who will be recruited from the prelabor ward of Ain Shams University Maternity Hospital.
- **Sample Size:** 60 primiparous pregnant women.
- **Sample Size Justification:** Using PASS program, setting alpha error at 5% and power at 95%. Results from previous study ***(F.Laloha et al., 2014)*** showed that the mean time between induction of labor and active stage of labor was 2.87 +/- 0.93 hours for IV Dexamethasone group compared to 9.8 +/- 5.8 hours for the Vaginal Misoprostol group according to ***(Hofmeyr et al., 2010)***. Based on this, with taking in consideration 20% dropout rate, the needed sample is 30 cases per group (60 cases total).

    - ***Inclusion Criteria:***

      - Age: 18-35 years old.
      - Body Mass Index BMI : 18 - 30 kg/m^2.
      - Primiparous pregnant women at 39 – 42 weeks gestation.
      - Bishop score < 6.
      - Singleton fetus.
      - Cephalic presentation.
      - Absence of abnormalities diagnosed by second

trimesteric ultrasound.
- Normal Amniotic fluid.
- Reassuring CTG (Normal FHR 120-160 bpm, beat to beat variability, variable accelerations, no decelerations)

- ***Exclusion Criteria:***
  - Diabetes.
  - Preeclampsia.
  - Fetal macrosomia.
  - Twin pregnancy.
  - Breech presentation.
  - Rupture of membranes (ROM).
  - Placenta previa or placental abruption.
  - Small for Gestational Age.
  - History of surgery on uterus

- **Sampling Method:** Random Sample
- **Randomization:** Randomization will be done using genuine computer-based software such as MedCalc.
- **Ethical Considerations:** An informed consent will be taken from all participants, it will be in Arabic language & confirmed by date and time.
  Confidentiality will be preserved by assigning a number to patient's initials and only the investigator will know it.
- **Allocation and Concealment:** Will be done using opaque envelopes that contains the corresponding letter that had been predefined and sorted serially containing the group to which the patient will be assigned. When the patient arrives, the first envelope will be opened and the patient will be allocated according to the serial letter inside.
- **Study Procedures:**
  After approval of the ethical committee, recruitment of the participants, explaining the procedure to all of them and

obtaining a written informed consent to participate in the study, all participants will be subjected to:

- Thorough history taking, to rule out exclusion criteria.
- Calculation of gestational age (GA) from the date of the last menstrual period and/or the 1st trimesteric Ultrasound examination.
- General examination: Vital data, vital colors, Blood pressure, pulse, temperature, body weight, height and BMI in kg/m^2.
- Abdominal examination: Fundal height, fetal lie and presentation, estimated fetal weight and fetal heart sounds for fetal viability.
- Vaginal Examination:
  Bishop Score will be calculated according to the following criteria:

The original Bishop score table

Component	Subscore			
	0	1	2	3
Dilatation (cm)	0	1-2	3-4	5-6
Station	-3	-2	-1 or 0	+1 or +2
Effacement (%)	0-30	40-50	60-70	80
Consistency	Firm	Medium	Soft	--
Position	Posterior	Mid	Anterior	--

- **Study Interventions:**

Group A (Vaginal Misoprostol Group):

- Induction of labour will be done using misoprostol (1 tab of Vagiprost® 25mcg) will be inserted in the posterior vaginal fornix and the cervix will be reassessed after 4 hours.
- If no cervical ripening was achieved (Bishop Score <6), second dose of 25 mcg of misoprostol will be used and will

be repeated after 4 hours of total four doses if needed.

- If no cervical ripening was achieved (Bishop Score <6) after the previous four doses of misoprostol, the outcome was considered to be failed induction of labor and the infant will be delivered by cesarean delivery (in accordance with the hospital's policy for induction of labor).
- Women with a soft cervix and those who progressed after misoprostol administration (Bishop Score >6), will receive an intravenous infusion of oxytocin (Syntocinon®, Novartis, Basel, Switzerland).
- The starting dose is 5 units (in 500 mL Ringer Solution) at a rate 12 drops/minute the dose is doubled every 30 minute until efficient contractions achieved.
- Artificial rupture of membranes (AROM) will be done when cervix is 6 cm dilated with accessible membranes.
- The partogram will be commenced at the beginning of the induction process the alert and action lines will be drawn when the woman is in the active phase of labor.
- External cardiotocography will be done regularly performed to monitor the condition of the fetus; continuous cardiotocography will be used in all cases.

Group B (Dexamethasone Group):

- Induction of labor will be done using Dexamethasone (Dexonium® 8mg, Alex Pharma, Alexandria, Egypt) which will be administrated as a single dose Intravenously.
- Cervix will then be reassessed after 4 hours and will start augmentation of labor by intravenous infusion of oxytocin (Syntocinon®, Novartis, Basel, Switzerland).
- The starting dose is 5 units (in 500 mL Ringer Solution) at a rate 12 drops/minute the dose is doubled every 30 minute until efficient contractions achieved
- Artificial rupture of membranes (AROM) will be done when cervix is 6 cm dilated with accessible membranes.
- If latent phase continues for 24 hours, the outcome was

considered to be failed induction of labor and the infant will be delivered by cesarean delivery

- The partogram will be commenced at the beginning of the induction process the alert and action lines will be drawn when the woman is in the active phase of labor.
- External cardiotocography will be regularly performed to monitor the condition of the fetus; continuous cardiotocography will be used in all cases.

- **Outcomes:**

  Primary Outcome Variables:

  - Successful vaginal delivery.

  Secondary Outcome Variables:

  - Time interval between induction of labor and delivery time.
  - Duration of Latent phase (From start of induction of labor till Cervix is dilated from 0 to 4 cm with mild to moderate contractions every 5 to 20 minutes).
  - Time interval from beginning of Active phase (Cervix is 4 cm dilated with mild to moderate contraction) till delivery.
  - Failure of labor induction.
  - Maternal side effects as uterine hyperstimulation.
  - Fetal distress.

- **Statistical Analysis:** Analysis is to be performed using SPSS for Windows v20.0, Data to be presented in terms of range, mean and standard deviation (for numeric parametric variables); range, median and inter-quartile range (for numeric non-parametric variables); or number and percentage (for categorical variables).Difference between two independent groups is to be analyzed using independent student's t-test as well as the mean difference and its 95% CI (for numeric parametric variables);