Assessment of Efficacy and Safety of Vaginal Acidity Enhancement with 3% Acetic Acid on Response to Vaginal Misoprostol Induction of Abortion in Missed Mid-Trimesteric Abortion

Protocol of Thesis

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By:

Islam Mostafa Gamal El-Din
M.B.B.Ch - Ain Shams University 2006
Resident in Obstetrics and Gynecology
Ain Shams University Maternity Hospital

Under supervision of

Dr. Karim H. I. Abd El Maeboud
Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Ahmed Mohamed Ibrahim
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Nashwa EL Said Hassan
Lecturer in Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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Introduction

In practice, mid-trimester termination of pregnancy (TOP) is a problematic procedure. Currently, though the use of laminaria tents **(Jain and Mishell, 1996)** and cervical Foley's catheter **(Khadem and Khadivzadeh, 2003)** have been investigated, Termination of second trimester pregnancy is frequently performed by administration of prostaglandins or their analogues by various routes. Patients usually receive misoprostol therapy alone and this may result in protracted induction-to-abortion interval and failure of medical therapy. Side effects of misoprostol therapy include fever, nausea, vomiting, diarrhea, dizziness, fatigue, headache, and breast tenderness. This is distressing to both patients and health care staff and further prejudices the implementation of safe obstetric service. Optimal regimens for mid-trimester TOP are essential if the morbidity and mortality of unsafe abortion are to be reduced. Many studies have been performed aiming at minimizing the dose required, and hence side effects and expense **(Jain and Mishell, 1994; Nuutila et al., 1997; Wong et al., 2000)**.

Other studies addressed the use of adjuvant therapies: such as mifepristone (**Webster et al, 1996; Ngai et al., 2000)** and trilostane **(le Roux et al, 2000)**. It is known that termination of pregnancy by medical or surgical methods, especially in the presence of unfavorable cervix may lead to additional difficulties and complications. Cervical ripening, before induction of abortion, is needed to increase the success of induction, to reduce complications and to diminish the rate of operative interventions and duration of abortion.

The human cervix, in contrast to the uterine corpus, is essentially a fibrous connective tissue organ, mainly composed of collagen and

proteoglycans. The connective tissue content is ~90-95% in the lower part of the human cervix and ~75% in the isthmic region of the uterus **(Granström L. et al., 1989)**. In obstetric practice, it is well known that an extensive remodeling of the connective tissue prior to parturition, i.e., cervical ripening, is necessary for a harmless and successful delivery of the fetus. The idea of the cervix as a passive, inert, connective tissue structure is no longer tenable. The cervix is in fact a dynamic structure, the control of which we still do not fully understand.

During ripening, marked biochemical changes take place in the cervix, causing it to become soft and dilatable at the time of parturition **(Uldbjerg N. et al., 1983; Leppert PC 1995)**. The most striking changes are the decrease in concentrations of collagen and glycosaminoglycans, estimated to be about 50-70%, concomitantly with an increase in collagen synthesis. This higher proteolytic activity coincides with an increase in the solubility of collagen. This change in turnover of matrix components results in a reorganization of the collagen fibrillar network **(Uldbjerg N. et al., 1983; Granström L. et al., 1989)**. Also, there is a marked increase in hyaluronic acid concentrations **(von Maillot K. et al., 1979; El Maradny E. et al., 1997)**. The final ripening is characterized by an influx of neutrophils capable of secreting collagenase and elastase **(Junqueria, L.C.U. et al., 1980)**.

Major events in the female reproductive tract, including ovulation, menstruation, implantation, and parturition, require extensive remodeling of extracellular matrix (ECM). Matrix metalloproteinases (MMPs) are known to play a central role in breakdown of ECM components and are important in reorganization of ECM. The MMP family consists of 20 members with broad substrate specificities, which can be partly explained by the presence of specific structural domains. Main substrates for

collagenases (MMP-1, -8, and -13) are fibrillar and nonfibrillar collagens. In particular, MMP-1, MMP-3, MMP-8, and MMP-9 and TIMP-1 all are increased during cervical ripening and are critically important to ECM remodeling at this time **(Curry TE JR. et al., 2003)**. The mechanism of cervical ripening or maturation remains an enigma. The mediators of the cervical ripening process are still largely unknown. Many mediators are suggested to be involved in the ripening process, including estrogen **(Rajabi MR et al., 1991; Stjernholm, Y. et al., 1996)**, progesterone **(Wallis RM et al. 1981; Râdestad A et al, 1990; Sato T et al., 1991)** , dehydroepiandrosterone **(Mochizuki M et al., 1978; Belayet HM et al., 1999)**, and prostaglandins **(Calder, A., and Embrey, M.P, 1973; Ulmsten, U. et al., 1982; Kelly RW, 1994)**, cytokines such as IL-I **(EL-Maradney E et al., 1995)**, IL-8 **(Barclay CG et al., 1993; Chwalisz K et al., 1994; El-Maradney E et al. 1994; Osmers R et al., 1995; Winkler M et al., 1998)**, IL-6, and granulocyte colony-stimulating factor (G-CSF) **(Sennström M.B. et al., 2000)**, and nitric oxide (NO) **(Thomson AJ et al., 1997; Calder, 1998; Chwalisz, K. and Garfield, R., 1998; Norman L. et al., 1998; Romero, R., 1998; Tschuggguel W et al., 1999)**.

It is suggested that decreased expression of type I collagen, the main macromolecular component of the ECM of the cervix, might be a key event in cervical dilatation at parturition. The reduced cervical levels of type I collagen in the process of cervical softening suggest at least two possible mechanisms for regulation of the turnover of this collagen. First, the synthesis of type I collagen by cervical stromal cells might be reduced at the gene level in the process of cervical softening. Second, the degradation of cervical type I collagen might be intensified in the process of cervical softening **(Iwahashi M et al, 2003)**. A more comprehensive

knowledge of this control mechanism may help us to manage preterm labour and mid-trimester pregnancy loss, and conversely it may help us to manipulate the cervical state at term and prior to induction of labour or mid-trimester abortion.

Misoprostol, a cheap synthetic prostaglandin analogue with few gastro-intestinal side-effects, has been shown to be effective in cervical dilatation prior to suction evacuation in first trimester pregnancy **(El-Rafaey H. et al., 1994; Ngai SW et al., 1995; Ngai SW et al., 1999)** and also in third trimester pregnancy **(Ngia SW** et al., 1996)**.** Moreover, a previous study showed that it was also effective in non-pregnant patients **(Ngai, SW et al., 1997, Preutthipan S and Herabutya Y, 1999 Preutthipan S and Herabutya Y, 2000; Thomas JA et al., 2002)**, yet others claim no effect overall **(Perrone JF et al., 2002; Bunnasathiansri S et al., 2004; Fernandez H et al., 2004)** or in postmenopausal **(Ngai, SW et al., 2001; Fung TM et al., 2002)** or hypo-oestrogenic women **(Bisharah M et al., 2003)**. On the other hand, others demonstrated effectiveness in all patients **(Thomas JA et al., 2002)**. The discrepancy in these findings can be partially explained by the fact that endogenous oestrogen may be essential for the cervical priming induced by prostaglandin, and therefore women in hypo-oestrogenic state would show no response to prostaglandins **(Ngai SW et al., 2001)**.

Reviewing studies on the efficacy of intravaginally administered misoprostol for cervical ripening and labor induction, another explanation seems plausible, that is the difference in vaginal pH. The presence of a vaginal pH <5 was suggested to affect the pharmacokinetics of vaginally administered misoprostol, and increase the efficacy of the drug marked by shortening of induction to delivery interval in one study entailing 103

women **(Gunalp S and Bildirici I, 2000)**, yet not in another one entailing a smaller number (37) of women **(Ramsey PS et al., 2000)**.

It is known that glycogen, which is deposited in large amounts in the vaginal epithelium during times of high oestrogen availability could be metabolized to lactic acid by vaginal bacteria and/or the epithelium itself, with the former being the primary source of lactic acid in the vagina **(Boskey ER et al., 2001)**. In a recent study on termination of pregnancy using misoprostol, entailing 110 women with a missed abortion by gestational age of 14–26 weeks, all patients aborted within 48 hrs with a significant positive correlation between vaginal pH and the misoprostol application-abortion interval. The mean induction-abortion interval was significantly shorter in those with initial vaginal pH < 5 compared to those with pH ≥5 (12.1 hrs vs 23.6 hrs, $P < 0.001$), with abortion rates at 24 hrs being 100% and 63.8%, respectively. Moreover, a significantly lower dose of misoprostol was used in the former group with a lower incidence of fever and abdominal pain. In this study, all of the women received intravaginal misoprostol tablets moistened with 3 ml of 5% acetic acid, 200 mg every 4 hrs for a maximum of 5 doses within 24 h. If the patient did not have adequate uterine contractions, the same regimen was repeated over the following 24 h and if no response was achieved, this was considered a failure of therapy. Hence, it was concluded that vaginal pH influences the efficacy of misoprostol administered vaginally for the induction of midtrimester abortion. However, the presence of this relationship, despite premoistening misoprostol with an acidifying agent, suggests that the effect of vaginal pH might extend beyond affecting the pharmacokinetics of the drug **(Abd-El_maeboud et al, 2008)**. One may hypothesize that acidity is important in the modulation of ripening process, and may be active in the connective tissue remodelling.

1. Protocol Outline

1.1 Title

Assessment of efficacy and safety of vaginal acidity enhancement with 3% acetic acid on response to vaginal misoprostol induction of abortion in missed mid-trimester abortion.

1.2 Study Site

Ain Shams University Maternity Hospital.

1.3 Study Phase

III.

2. Study Objectives

2.1 Primary Objective

To document the efficacy of vaginal acidity enhancement on cervical softening in women with missed abortion undergoing misoprostol induction of abortion in the second trimester, as demonstrated by success rate of termination within 12, 24, 36 and 48 hours.

2.2 Secondary Objectives

- To correlate the effectiveness of the medication with clinical parameters, including analgesia requirements.
- To find out the women's acceptability of the priming agent.
- To document safety and evaluate adverse events recorded during the study.

3. Study Design

It is a prospective double–blind placebo-controlled randomized clinical trial (RCT), comparing the effects of vaginal acidity enhancement in women pregnant with missed mid-trimesteric abortion and planned for induction of abortion.

3.1 Population

The population of this study comprises pregnant women with missed mid-trimesteric abortion attending outpatient clinic and casualty of Ain Shams University Maternity Hospital being admitted and planned for induction of abortion. Forty eight women will be selected according to inclusion and exclusion criteria. Subjects included in the study will be randomized into 2 groups:

- **Group I:** Subjects (n=24) who will be treated with acidifying vaginal gel applied every 12 hours, starting 2 days ahead of the planned procedure.

- **Group II:** Subjects (n=24) who will be treated with neutral (placebo) vaginal gel applied every 12 hours, starting 2 days ahead of the planned procedure.

3.2. Study Treatment And Dosages

3.2.1. Test Drug (Manufactured by Wyth Co., Cairo)

Code No: A

Presentation: Acidifying vaginal medicament (3% Acetic acid gel). Administration frequency: two times/day, i.e. four doses over 2 days.

3.2.2. Placebo Drug (Manufactured by Wyth Co., Cairo)

Code No: P

Presentation: Neutral vaginal medicament (the base of the gel without active agent).

Administration frequency: two times/day, i.e. four doses over 2 days.

3.2.3. Supplies and Accountability

The investigator will deliver the study treatment only to patients included according to inclusion criteria described in the protocol. The treatment will be provided by main investigators and stored in independent premises far from usual medicine held by authorized people. The study medications will be applied by the patient under supervision (dose by dose). The unused treatment –for any reason- will be given back to the investigator. The investigator will have to acknowledge receipt of all received treatments for the study.

3.3. Study Entry And Duration

3.3.1. Recruitment and Randomization

During the pre-selection visit, exclusion and inclusion criteria will be applied. When the patient's consent is obtained, the investigator will receive the medication package with a label carrying the corresponding number. Baseline investigations-ABO and Rhesus Blood Group, Complete Blood Count (C.B.C.), Random Blood sugar, Serum Glutamate Oxalate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), S. Creatinine, and coagulation profile will be done. The investigator will supervise application of the medication (dose by dose) from the package carrying the number matching with the patient's entry number. The biometrician will keep the sealed envelopes with the

numbers of order till the end of the study. The medication will be strictly allocated in the numbers order, according to the randomization plan. The randomization schedule will be constructed so that the number in each group would be balanced for every 10 women recruited. Subjects withdrawn from the study before the onset of uterine pains will not be substituted. The next patient included in the study will receive the next number.

3.3.2. Sample Size Justification

The estimation of sample size was based on the following assumptions: (i) the primary outcome indicator was abortion rate within 24 h; (ii) from a previous study on missed mid-trimesteric abortion **(Abd-El-Maeboud et *al.*, 2008)**, the successful abortion rate in 24 hrs of women using misoprostol was 100% when baseline vaginal pH was <5 compared to 63.8% in those with vaginal pH ≥5. Considering this and to avoid the possibility of recruiting a small sample size, we opted to set criterion for significance (alpha) has been set at 0.05 (2-tailed, an effect in either direction will be interpreted) and type II error (beta) at 0.80. Applying these assumptions, the sample size was calculated to be 40 patients. Assuming a drop-out rate of 20% (e.g. spontaneous onset of abortion during vaginal acidity enhancement), the total study population is adjusted to 48 subjects.

3.3.3. Study Duration

The duration of the study is 6 months.

3.4. Selection of Patients

3.4.1. Subjects' recruitment:

Pregnant women with missed mid-trimesteric abortion, planned for termination of pregnancy within our trust will be approached to

participate in this study. The patients will be approached on admission. The study will be discussed with the patient and consent will be taken by the investigator involved with the patient.

3.4.2. Inclusion Criteria

1. Age 18-40 years of age.
2. Missed Abortion.
3. Singleton pregnancy.
4. Gestational age ranging between 14 and 26 weeks of pregnancy (by calculation, examination and/or ultrasound).
5. Uterus and cervix apparently normal on clinical examination.
6. Cervix not dilated with absence of effacement.
7. Absence of uterine activity.
8. Written and signed informed consent by the patient to participate in the study.

3.4.3. Exclusion Criteria

1. A contraindication to medical termination of pregnancy e.g. placenta praevia.
2. Evidences suggesting onset of spontaneous abortion (uterine contractions with or without cervical changes).
3. Presence of vaginal bleeding.
4. Presence of IUCD in situ.
5. Presence of ruptured membranes and/or suspicion of septic abortion as evidenced by maternal temperature of 38 C or more, uterine tenderness or foul-smelling vaginal discharge.
6. Previous trial to induce abortion or the use of pre-induction agent during the current pregnancy.

7. Any contraindication to receiving prostaglandins, including known hypersensitivity to misoprostol or other prostaglandins (PGs), history of asthma, glaucoma, cardiac or cardiovascular disease.
8. Parity six or more.
9. Multifetal pregnancy.
10. Polyhydramnios.
11. Uterine anomaly, previous uterine surgery e.g. Caesarean section or trauma e.g. uterine perforation.
12. History of any cervical surgery or manipulation: Cervical cerclage during current pregnancy or during a previous pregnancy, previous cauterization of cervical erosion, previous cervical dilatation or operation with resultant apparent cervical tears or lacerations
13. Associated collagen or autoimmune medical disorder.
14. Metabolic acidosis as a result of a medical disorder.
15. History of adverse effects to vaginally administered medications.
16. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol which include all vaginal forms of medications.
17. Mental condition rendering the patients unable to understand the nature, scope and possible consequences of the study.

3.5. Clinical Management:

3.5.1. Assessment of vaginal pH:

Before digital vaginal examination, a speculum examination will be performed and vaginal pH value will be measured by using indicator paper **(pH-indicator strips pH 0-14 Universal indicator paper, Merck KGbA, Darmstadt, Germany)**. The indicator will be held with an artery forceps against the vaginal wall –in the midvagina- until it becomes wet. Then, another indicator paper will be held with an artery forceps against

the vaginal wall –high up in the vagina- until it becomes wet. Colour change of the strip will be immediately compared with the colorimetric scale and the measurement of vaginal pH at the two positions, mid and high vagina, will be recorded.

3.5.2. Digital (clinical) assessment of the cervix:

Digital vaginal examination will be then performed assessing four criteria only. These are dilatation, length, position (posterior, midway, anterior or central), and consistency (firm or soft).

3.5.3. Induction of abortion with misoprostol

After pretreatment with the vaginal gel for two days, induction of abortion will be performed, starting at 8 am. Peri-abortion prophylaxis will entail metronidazole 1 g rectally at the time of abortion plus doxycycline 100 mg orally twice daily for 7 days, commencing on the day of abortion. All women will receive misoprostol 800 μg vaginally, then misoprostol 400 μg vaginal, 4-hourly, to a maximum of five doses in the first 24 hours. Before inserting the tablet in the posterior fornix, it will be wetted with acetic acid (7%) to assure its complete dissolution. If a woman does not have adequate uterine contractions within 8 hours following the last dose, the same regimen will be repeated over the following 24 hrs and if no response was achieved, this will be considered a failure of therapy, and alternative interventions (treatment with high-dose oxytocin, administration of extra-amniotic prostaglandin $F_2\alpha$, mechanical cervical dilatation with a 16-French Foley balloon catheter or performing a hysterotomy) are to be carried out on the basis of judgment of the clinicians.

Vital signs of the patients including temperature, pulse rate, blood pressure and the frequency of uterine contractions will be monitored

every 3 hrs, with a recording of the time of the onset of regular uterine contractions, and the time of the expulsion of conceptus. Pethidine hydrochloride 50 mg will be given for pain relief if women requested. After abortion, the products of conception (fetus and placenta) will be examined to see whether the abortion was complete. Evacuation of the uterus will be performed under general anaesthesia only if the placenta is found to be incomplete. The amount of blood loss during abortion will be assessed clinically. After abortion, oxytocin 50 U/ 1000 ml normal saline will be administered intravenously at the rate of 100 ml/h. The side-effects of misoprsotol therapy, including nausea, vomiting, diarrhea, fever and marked abdominal pain, will be recorded. Anti-D immunoglobulin G (120 vs. 300 mg) will be given, by injection into the deltoid muscle, to all non-sensitized RhD negative women within 72 hours following termination. The abortus will be handled to the pathologist for further study.

3.5.4. Post-termination information and follow up

Following termination of pregnancy, women will be given a written account of the symptoms they may experience and a list of those that would make an urgent medical consultation necessary. They will be given a 24-hour telephone helpline number to use if they feel worried about pain, bleeding or high temperature. Urgent clinical assessment and emergency gynaecology admission will be available when necessary. Also, each woman will be offered a follow-up appointment within 2 weeks of the termination. On discharge, each woman will be given a letter that includes sufficient information about the procedure, with referral for further genetic counseling if necessary.

3.5.5. Contraception following termination

Future contraception will be discussed before discharge following termination.

3.6. Data Collection And Schedule

3.6.1. Enrollment (recruitment) Data [Case Record Form (CRF) No. 2]

Following admission, all patients will undergo complete clinical examination and detailed medical history will be obtained. Each patient will have a Case Record Form (CRF) in which the following data will be recorded.

- Patient initials.
- Patient number (according to the randomization schedule).
- Age, height, weight.
- Known allergies.
- Past medical and surgical history (no longer present).
- Medications taken within the last 4 weeks and discontinued.
- Concomitant illnesses.
- Concomitant medications which will not be discontinued.
- Clinical examination: including full gynaecological examination including vaginal and speculum examination with recording of vaginal pH and cervical condition.
- Investigations done on admission into the study.

3.6.2. Efficacy and Safety Data: [CRF No.3]

3.6.2.1. Efficacy data

Efficacy will be assessed on the basis of improved cervical softening as evidenced by success of induction and its duration.