Sublingual Versus Vaginal Misoprostol In Medical Treatment of First Trimestric Missed Miscarriage: A Randomized Controlled Trial.

Thesis

Submitted for partial fulfillment of the master degree in obstetrics and gynecology

By

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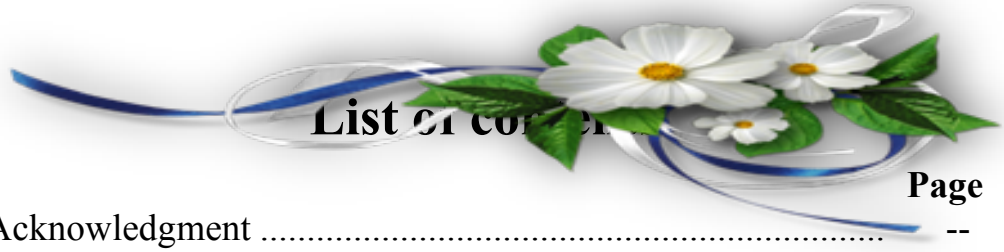

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List of Abbreviations

ACR	:	American College of Radiology
AUC	:	Area under the curve
CDC	:	Center for Disease Control and Prevention
CMV	:	Cytomegalovirus
CRL	:	Crown rump length
D&C	:	Dilatation and curettage
D&E	:	Dilatation and evacuation
DES	:	Diethylstilbestrol
DNA	:	Deoxyribonucleic acid
EM	:	Expectant management
ET	:	Endometrial thickness
FDA	:	Food and Drug Administration
HbA1C	:	Haemoglobin A1C
IDDM	:	Insulin-dependent diabetes mellitus
IUCD	:	Intrauterine device
MSD	:	Mean sac diameter
NICE	:	National institute for Health and Care Excellence
NSAIDs	:	Non-steroidal anti-inflammatory drugs
PBLAC	:	Pictorial Blood Loss Assessment Chart
PGE1	:	Prostaglandin E_1
PGE_2	:	Prostaglandin E_2
$PGF_{2\alpha}$	:	Prostaglandin $F_{2\alpha}$
POC	:	Products of conception
POC	:	Products of conception
RCOG	:	Royal College of Obstetricians and Gynecologists
RS	:	Retained sac
SLE	:	Systemic lupus erythromatosus
SRU	:	Society of Radiologists in Ultrasound
WHO	:	World Health Organization

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Abstract

Objective: To compare the effectiveness of sublingual and vaginal misoprostol in the medical treatment of first trimester missed miscarriage.

Methods: Two hundred women diagnosed as having missed miscarriage of gestational age less than 12 weeks were assigned randomly into two groups to receive 800µg of either sublingual or vaginal misoprostol every four hours for three doses. The primary outcome was visual inspection of product of conception. The secondary outcomes were measurement of endometrial thickness on day7, day14, and day 30 from first dose of misoprostol administration, administration-expulsion interval, duration of bleeding, and occurrence of adverse effects.

Results: During the follow up of our cases we found that sublingual route is more effective than vaginal route in the management of first trimester missed miscarriage. The difference between the sublingual and vaginal groups was statistically significant being increased with increase follow up duration (70% Vs. 50% at day 7, 83% Vs. 69% at day 14, and 87% Vs. 78% at day 30). The mean induction to delivery time was statistically shorter among sublingual group compared to vaginal group (Mean= 12 hours ±3.1 vs. 16.4 hours ±4.2, P<0.001). Duration of bleeding was significantly shorter among sublingual group than among vaginal group (Mean= 14.6 days ±2.5 Vs. 15.2±2.9). Side effects were more common in the sublingual group compared to vaginal group. The most common side effects were unpleasant taste which present in 62% in sublingual group and in 5% in vaginal group (P<0.001). Then low-grade fever presents in 34% in sublingual group and in 16% in vaginal group (P=0.003) and diarrhea presents in 34% in sublingual group and in 16% in vaginal group (P=0.003). Then shivering presents in 32% in sublingual group and in 14% in vaginal group (P=0.002). Then nausea presents in 32% in sublingual group and in 17% in vaginal group (P<0.001). Then vomiting presents in 15% in sublingual group and 6% in vaginal group (P=0.038).

Conclusion: Sublingual administration of misoprostol is more effective than its vaginal administration in missed abortion management. While side effects were more common in sublingual group compared with the vaginal group.

Keywords: Miscarriage. Abortion. Missed Miscarriage. First Trimester. Misoprostol. Sublingual. Vaginal.

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Introduction

Miscarriage is the termination of pregnancy before the fetus has attained viability, i.e. becomes capable of independent extra-uterine life ***(kailash and Parbati, 2015)***.

Approximately 11-15% of pregnancies end in spontaneous first trimester miscarriage ***(Shokry et al., 2014).*** Therefore, safe and legal abortion is considered a key intervention for improving women's health and quality of life ***(Pandey et al., 2015).***

For decades, the traditional management of incomplete miscarriage has always been surgical evacuation; the reason for many is determined by tradition, custom and habit rather than evidence-based. Risk of anesthesia with added risk of uterine perforation, intrauterine adhesions, cervical trauma and infections leading to: infertility, pelvic pain, dyspareunia and increased risks of ectopic pregnancy. Hence, a safer and effective alternative like medical treatment was sought for to reduce these risks ***(Hooker et al., 2014)***. In addition, surgical evacuation requires in patient care, which increases the healthcare cost even for a short duration ***(Harris et al., 2007).***

Conservative management although would reduce the need of hospital stay but it requires frequent and prolonged follow up, which is time consuming and taking manpower ***(Geyman et al., 1999).***

Available Cochrane systemic review evidence suggests that expectant care as well as medical treatment with misoprostol is acceptable alternative to routine vaginal evacuation ***(Neilson et al., 2010)***.

Medical methods for induced abortion have emerged over the past two decades as safe, effective, and feasible alternatives to surgery. Nonsurgical alternatives expand a

woman's treatment options and, in turn, the quality of care (***Borgatta et al., 2004).***

Women can avoid the risk of surgery and anesthesia. Mifepristone in combination with misoprostol is highly effective for first trimester medical abortion ***(Norman et al., 1991).*** It is the pharmacological agent of choice for medical abortion ***(Shail and Harleen, 2015).***

Alternative regimens had been explored because mifepristone was not readily available in many countries. Misoprostol as it is cheap and stable at room temperature; it has been shown to be effective for first trimester termination of pregnancy ***(Chaudhari et al., 2006).***

Misoprostol is a synthetic prostaglandin E1 analogue. It has several advantages over other forms of prostaglandin that made it the focus in obstetrics and gynecology research over the past two and half decades. Misoprostol is rapidly absorbed orally, sublingual, rectally and vaginally. It is substantially less expensive than other preparations of prostaglandins and dose not require refrigeration, simple to store and transport. These characteristics make it particularly suitable to be used in developing countries ***(Khan et al., 2003).***

In this, regards repeated doses of misoprostol have been in used widely. Initially, misoprostol was used orally for medical abortion. However, the use of vaginal misoprostol is becoming a common practice for both medical abortion and cervical priming for other indications. Many clinical trials have found that vaginal administration is more effective than oral administration. This was supported by pharmacokinetic study showing that systemic bioavailability after vagnial administration of misoprostol was three times higher than that after oral administration ***(Tang et al., 2007).***

However, there has been suggestive evidence showing that absorption through vaginal route is inconsistent and it is not uncommon to find that undissolved misoprostol tablets several hours after vaginal administration. Subsequently a new route of giving misoprostol by sublingual administration has been developed ***(ACOG 2009).***

The sublingual mucosa, being vascular, serves the purpose of better absorption. Sublingual application also avoids the first pass effect through the liver. The misoprostol tablets, when placed under the tongue, dissolved within 10-15 minutes. A pharmacokinetic study has demonstrated that sublingual administration could achieve the peak concentration in the shortest time and has the highest bioavailability ***(Tang et al., 2002).***

Aim of the work

The aim of this work is to compare the effectiveness of vaginal to sublingual misoprostol for medical treatment of first trimester missed miscarriage.

Study Question:

In women with first trimester missed miscarriage, is sublingual misoprostol effective as vaginal misoprostol to achieve a successful miscarriage?

Research Hypothesis:

In women with first trimetric-missed miscarriage, sublingual misoprostol may be as vaginal misoprostol in achievement of successful miscarriage.

Patients and methods

Study Design:

A Randomized controlled Trial.

Setting:

This study will be conducted in Ain Shams University Maternity Hospital.

Population of the study:

The patients will be recruited from those attending the OPC or ER of Ain Shams university Hospital with missed miscarriage less than 12 weeks of pregnancy.

A written informed consent will be obtained from each patient before participation in the study.

Inclusion criteria:

- All women above 18 years of age
- Less than 12 weeks of gestation.
- Pregnancy is confirmed by pregnancy test or ultrasound scan.
- Normal general and gynecological examination.
- The size of the uterus on pelvic examination was compatible with the estimated duration of pregnancy

Exclusion criteria:

- Hemodynamically unstable.
- Suspected sepsis with temperature 38 °C.
- Concurrent medical illness e.g. hematological, cardiovascular, thromboembolism, respiratory illnesses, recent liver disease or pruritus of pregnancy.
- Presence of intrauterine contraceptive device (IUCD).
- Suspect or proven ectopic pregnancy.
- Failed medical or surgical evacuation before presentation.
- Known allergy to misoprostol.

Intervention

The study protocol and patient informed consent will be reviewed and approved by the Ethics Committee of the Obstetrics and Gynecology Department Ain-Shams University.

All women who met the inclusion criteria will be assessed:

Detailed history:

- Demographic factors like age and parity were recorded, detailed history of any cardiovascular or thromboembolic disease, or use of IUCD.
- Gestational age will be determined from last menstrual period or previous ultrasound scanning report.

Physical examination:

- General examination including: pulse, blood pressure, temperature, body weight, auscultation of lungs and heart.
- Abdominal examination: for previous scar and fundal level.
- Pelvic examination: for evaluation of uterine size, cervical motion tenderness for possibility of ectopic pregnancy.

Investigation:

- Baseline Hemoglobin, hematocrit level, and blood grouping were reported for every patient.
- Ultrasonography to confirm gestational age and exclude ectopic or other pelvic pathology.

Sample Size

Sample size will be 100 patients with 1st trimesteric missed miscarriage that will administrate intravaginal Misoprostol and another 100 patients that will administer