Prospective randomized comparative study between vaginal and sublingual misoprostol in relation to preoperative priming of the cervix in first trimesteric missed abortion.

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Abstract

Aim: to compare the effect and complications of sublingual versus vaginal administration of misoprostol for pre-operative cervical priming before surgical evacuation of pregnancy in first trimesteric missed abortions.

Material and Methods: 80 women diagnosed with first trimesteric missed abortion were randomized into either sublingual or vaginal groups of 40 each. They were given 400 µg misoprostol via sublingual or vaginal route for cervical priming 4 hours before the procedure. The outcome measures assessed were cervical dilatation (1ry) before surgery, duration of procedure, intraoperative blood loss, post abortive Et by U/S, post abortive bleeding and preoperative side effects.

Results: Subjects in the sublingual group achieved significantly higher mean cervical dilatation compared to vaginal group (8.63 ± 1.58 mm vs. 7.62 ± 2.22 mm, $p = 0.03$). The mean duration of procedure for sublingual group was significantly lower compared to the vaginal group (4.7 ± 1.87 minutes vs. 5.65 ± 2.48 minutes, $p = 0.01$). The intraoperative blood loss in both groups was found to be of no statistically significant difference same for post abortive bleeding. There was no statistically significant difference between both groups as regard ET by U/S. The sublingual group experienced more nausea and vomiting as compared to vaginal group. The vaginal group experienced more tachycardia and abdominal pain, which were statistically insignificant differences.

Conclusions: Sublingual misoprostol is more effective and convenient route than vaginal misoprostol for preoperative cervical priming in first trimester abortion.

Key words: Sublingual, Vaginal, Misoprostol, 1st trimesteric, missed abortion, surgical evacuation, cervical priming.

List of Abbreviations

ACA	:	Anticardiolipin antibody
ACOG	:	American college of obstetrics and gynecology
ANA	:	Antinuclear antibody
aPL	:	Antiphospholipid antibody
BMA	:	British Medical Association
BMI	:	Body mass index
BPD	:	Biparietal diameter
CI	:	Confidence interval
CRL	:	Crown rump length
D and C	:	Dilatation and curettage
DBP	:	Diastolic blood pressure
DIC	:	Disseminated intravascular coagulopathy
DM	:	Diabetes mellitus
ET	:	Endometrial thickness
FDA	:	Food and drug administration
FL	:	Femur length
GA	:	Gestational age
Hb	:	Hemoglobin
hCG	:	Human chorionic gonadotropin
HIV	:	Human immunodeficiency virus
HLA	:	Human leucocytic antigen
IAI	:	Induction abortion interval
ICI	:	Induction contraction interval
IDI	:	Induction dilatation interval
IP3	:	Inositol triphosphate
IUFD	:	Intrauterine fetal death
IUGR	:	Intrauterine growth retardation
IVF	:	In-vitro fertilization
LAC	:	Lupus anticoagulant
LH	:	Luteinizing hormone
LMP	:	Last menstrual period
MVA	:	Manual vacuum aspiration
NS	:	Non significant
NSAID	:	Non steroidal anti inflammatory drugs

List of Abbreviations (cont.)

OR	:	Odds ratio
P/V	:	Per vagina
PCO	:	Polycystic ovarian syndrome
PG	:	Primigravida
PGE1	:	Prostaglandin E1
S	:	Significant
SBP	:	Systolic blood pressure
TLX	:	Trophoblast/lymphocyte cross reactive
TVS	:	Transvaginal sonography
U/S	:	Ultrasound
β hCG	:	Beta subunit human chorionic gonadotropin

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Introduction

Spontaneous abortion is the most common complication of pregnancy occurring in 10 – 20 % of clinically recognized pregnancies **(Alberman.; 1992)**. Each year there are about 40 – 50 million abortions performed worldwide, (World Health Organization.; 2003) and many of these abortions are done in areas where facilities and expertise are lacking **(Tang.; 2004)**.

Missed abortion is defined as retention of the products of conception after death of the embryo or the fetus. It is characterized by regression of earlier signs and symptoms of pregnancy, the uterus is small for dates, and the cervix is closed and ultrasonic examination shows either a collapsed gestational sac or fails to detect the fetal heart or movement. **(Gordon.; 1991)**.

Surgical evacuation is currently the standard management for termination of pregnancies in the first trimester in many parts of the world. It is considered to be safe and effective with a success rate of >95% **(Child *et al*.; 2001)**. However, it is associated with major morbidity in ≤1% of women and minor morbidity in 10% **(Royal College of General Practitioners and the Royal College of Obstetricians and Gynecologists, 1985)**.

A more recent study of 170 000 first trimester abortions carried out in New York City, USA reported that <0.1% of the women experienced serious complication requiring hospitalization **(Hakim-Elahi *et al*.; 1990)**. It might appear that the incidence of severe morbidity has decreased recently in some of the countries in the developed world. Another more recent study, however, showed that the incidences of uterine perforation, blood transfusion and pelvic infection

were 0.24, 0.97 and 1.69% respectively. The seniority of the surgeon was found to affect the outcome of the surgical evacuation **(Child *et al* 2001)**.

Prostaglandin analogues are the cervical priming agents of choice and misoprostol has been studied for this purpose **(El-Refaey *et al*.; 1994)**. Both vaginal and oral administrations were found to be useful **(Ngai *et al*.; 1999)**. It was found that 400 µg misoprostol given 3 h before the procedure was the optimal dose for vaginal application **(Fong *et al*.; 1998)**.

However, oral administration is more convenient. It can avoid a vaginal examination in a busy day-patient surgery admission clinic and is more acceptable to women **(Ho *et al*.; 1997)**. Recently, it has been shown that oral administration of 400 µg misoprostol 3 hours before the vacuum aspiration is as effective as a similar regimen of vaginal misoprostol **(Ngai *et al*.; 1999)**. However, administration of oral drug with water 3 hours before operation may cause problems if the patient undergoes the operation under general anesthesia.

We have studied a new route of sublingual administration of misoprostol in medical abortion recently. Misoprostol is absorbed through the vaginal mucosa in vaginal administration. The buccal mucosa, being very vascular, should be able to serve the same purpose. The misoprostol tablet is very soluble in water and dissolves within 10–15 min when administered under the tongue. Sublingual administration of misoprostol avoids the first-pass effect via the liver as in oral administration. A pharmacokinetic study showed that sublingual misoprostol was absorbed as rapidly as oral misoprostol and more rapidly than vaginal misoprostol. **(Tang *et al*.; 2002)**. The peak serum concentration after sublingual misoprostol and the area under the curve was also significantly higher than those after oral or vaginal misoprostol. We have shown that sublingual misoprostol is effective in medical abortion and the management of miscarriage **(Tang *et al*.; 2003)**. Sublingual misoprostol is convenient to use, avoids vaginal administration and avoids the ingestion of water before anesthesia.

Aim of the Work

It is the aim of this randomized study to compare the efficacy of sublingual with vaginal misoprostol for pre-operative cervical priming before surgical termination of missed abortion in the first trimester.

Abortion

Loss of pregnancy occurs with decreasing frequency as gestation increases. In the first trimester at least 25 % of pregnancies basis will end in spontaneous miscarriage. This number may be as high as 43 % of pregnancies diagnosed purely on the raised serum B-HCG (**Miller et al.; 1980).**

Current recommendation is that in early pregnancy loss the term abortion should be avoided and more sensitive terminology substituted. Spontaneous abortion should be replaced by miscarriage. Blighted ovum, missed abortion or anembryonic pregnancy should be replaced by early embryonic or fetal demise. Incomplete abortion should be replaced by incomplete miscarriage. Recurrent or habitual abortion should be replaced by recurrent miscarriage **(Slemons et al.; 2004).**

Terminology:

Abortion is the spontaneous or induced termination of pregnancy before fetal viability. Because popular use of the word abortion implies a deliberate pregnancy termination, some prefer the word miscarriage to refer to spontaneous fetal loss before viability **(Schorge et al., 2008)**.

Abortion is termination of a pregnancy either spontaneously or intentionally, before the fetus develops sufficiently to survive independently. **(Saxeena et al.; 2003)**

Abortion is the termination of pregnancy by any means before the fetus is sufficiently developed to survive. In the United States this definition is confined to the termination of pregnancy before 20 weeks gestation **(Cunningham et al.; 2005)**.

Abortion is also defined as the expulsion or extraction of a fetus (embryo) weighing less than 500 grams equivalent to the approximately 20-22 weeks gestation **(World Health Organization 1977)**, or as termination before 24 weeks of gestation with no evidence of life (United Kingdom legal definition) **(Keith et al.; 1999).**

The term abortion is often interpreted by patients to mean induced termination of pregnancy, and this lead some to use the better term miscarriage in cases of spontaneous loss of pregnancy (**Beard, 1985**). However, this view has not yet gained wide spread acceptance.

This has led many groups to reviewing the law and in 1985 the department of Health and Social Security in combination with the Colleges of Obstetricians, General Practitioners, and Midwives, the British Pediatric Association and the British Medical Association published a report on fetal viability in clinical practice which may be summarized as follows:

1) The lower limit of fetal viability should be changed to 24 completed weeks of gestation.

2) All fetuses born alive or dead after 22 weeks gestation or weighting 500gm or more should be recorded**.**

3) If a decision is made to terminate pregnancy thought to be greater than 20 weeks gestation, all reasonable methods to confirm gestation should be used including carefully assessment and ultrasound. **(David et al.; 1984).**

Etiology:

The exact mechanisms responsible for abortion are not always apparent, but in the first 3 months of pregnancy, death of the embryo or fetus nearly always precedes spontaneous expulsion of the ovum. For this reason, finding the cause of early abortion involves ascertaining the cause of fetal death. In subsequent months, the fetus frequently dose not die before expulsion; therefore, other explanations for its expulsion should be sought **(Cunningham et al.; 2005).**

More than 80 percent of abortions occur in the first 12-week and the rate decreases rapidly thereafter (**Harlap and Shiono, 1980**).

The risk of spontaneous abortion increases with parity as well as with maternal and paternal age (**Warburton and Fraiser, 1964; Wilson and associates 1986**).

The frequency of clinically recognized abortion increases from 12 percent in women less than 20 years old to 26 percent in those over the age of 40 (**Cunningham et al.; 2001**)

Table 1: Causes of spontaneous abortion **(Keith et al.; 1999).**

▪ Fetal abnormality :40% or more (Genetic, chromosomal (30-60%) or structural)
▪ Abnormalities of implantation.
▪ Multiple pregnancy.
▪ Intrauterine adhesions.
▪ Endocrine abnormalities.
▪ Uterine abnormalities.
▪ Maternal disease.
▪ Infections
▪ Poisons
▪ Immunological disease.
▪ Cervical incompetence / weakness.
▪ Trauma (Amniocentesis or pelvic surgery)

1. Genetic Causes:

Miscarriage is a heterogeneous condition but the single largest cause is chromosomal abnormalities, accounting for about 50 percent of all cases **(Katy et al.; 2001).**

Evidence from pre implantation genetic diagnosis studies of embryos created as results of in vitro fertilization suggests that at lest 65 percent of all embryos are chromosomally abnormal **(Gianroli et al.; 2000).**

Approximately one fourth of chromosomal abnormalities were due to maternal gametogenesis errors and 5 percent to paternal errors (**Jacobs and Hassold 1980**).

The most commonly found chromosomal abnormality is autosomal trisomies which account for over 50 percent of cytogenetically abnormal miscarriages, apart from chromosome1 trisomies for every chromosome have been reported and the most frequently found is trisomy for chromosome 16. Trisomy 16 gives rise to the most rudimentary embryonic growth with an empty sac (**Katy et al.; 2001**).

Trisomies can be the result of an isolated non disjunction, maternal or paternal balanced translocation, or balanced chromosomal inversions (**Cunningham et al.; 2001**). Structural chromosomal rearrangements are present in 2 to 3 percent of couples with history of recurrent abortions (**American collage of Obstetricians and Gynecologists, 1995**).

In a study of fetuses and newborn with trisomy 13 it is reported that in 21 of 23 cases the extra chromosome was of maternal origin (**Robinson and Colleagues 1996**).

Monosomy X (45X0) is thought to result from paternal sexchromosome loss. It is usually associated with the presence of fetus focal abnormalities such as encephalocele or hygromata (**Katy et al.; 2001**).

Triploidy is often associated with hydropic placental degeneration. Incomplete hydatiform moles may have fetal development that is triploid or trisomic for chromosome number 16.