

Moistening of Misoprostol Tablets with Acetic Acid Prior to Vaginal Administration for Mid-Trimester Termination of Pregnancy

Thesis

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By

Fatma E Zahraa Mohammed Bassary

M.B.B.,Ch., Assuit University,
Resident in Luxor General Hospital

Under Supervision of

Prof. Essam El-Dien Mohammed Amaar

Professor of Gynecology and Obstetrics
Faculty of Medicine - Ain Shams University

Dr. Mohammed Abd El-Hameed Abd El-Hafeez

Lecturer of Gynecology and Obstetrics
Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain shams University**

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List of Abbreviations

Acl	: Anticardiolipin antibodies
ACTH	: Adrenocorticotrophic hormone
AMH	: Anti-müllerian hormone
APL	: Antiphospholipid antibodies
BMI	: Body mass index
BP	: Blood pressure
C	: Corrosive
CARS	: Childhood autism rating scale
COX	: cyclooxygenase
COX	: Cyclooxygenase
DIC	: Disseminated Intravascular Coagulopathy
EEA	: Ethylene glycol monoethyl ether acetate
EPSTS	: False positive serological test for syphilis
ER	: Estrogen receptor
ERPC	: Evacuation of retained products of conception
F	: Flammable
FHR	: Fetal heart rate
GAG	: glycosaminoglycans
GR	: Glucocorticoid receptor
HA	: Hyaluronic acid
HCG	: Human chorionic gonadotrophin
HETES	: Hydroxytetraenoic acid
HPETES	: Hydroperoxytetraenoic acid
IL	: Interleukin
LPDs	: Luteal phase defects
LTS	: leukotrienes
MCA	: Monochloroacetic acid
MPA	: Misoprostol acid
Mt/a	: Million tonnes per year
mU	: Milliunits

List of Abbreviations (*Cont...*)

NF	: Nuclear factor
NSAID	: Non steroidal anti-inflammatory drugs
OT	: Oxytocin
PBLs	: Periphral blood leukocytes
PET	: Polyethylene Terephthalate
PGs	: Prostaglandins
SD	: Standard deviation
SLE	: Systemic lupus erythematosis
SPSS	: Statistical Package for the Social Sciences
SQ	: Squamous epithelium
TPA	: Terephthalic Acid
VAM	: Vinyl acetate monomer
WHO	: World Health Organization

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا

عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة آية (٣٢)



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*I would like to dedicate this thesis to the soul of my
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To My brother and my Kids

Introduction

Mid trimester abortion represents 10-15% of all induced abortions but is responsible for two-thirds of all major complications. Over the last 20 years there have been continuing efforts to improve abortion. Technology in terms of effectiveness, ease of performance, acceptability and reduction of side effects and complications (*Lalitkumars et al., 2007*).

The role of the cervix shifts between two opposing functions during pregnancy. In order to hold the products of conception inside the uterus, the cervix has to resist tension and remain closed and rigid throughout most of gestation. At term, however, a drastic change in cervical function is required in order to accommodate stretch and delivery (*Leppert, 1997*).

Misoprostol, a PGE₁ analogue, has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus, selectively binds to EP-2/EP-3 prostanoid receptors (*Senior et al., 1997*).

Because misoprostol is a prostaglandin E₁ analogue it acts on the myometrium by increasing the frequency of uterine contraction and acts on the cervix causing cervical ripening which is responsible for its abortifacient capability (*El-Refaey and Templeton, 1994*).

Over the past decade, misoprostol has been extensively assessed and has been widely incorporated into the field of obstetrics and gynecology. It has been shown to be an effective agent for the induction of abortion whether administered orally or vaginally (*El-Refaey and Templeton, 1994*).

Recent studies have compared various dosages (from 100 to 800 mg), intervals between doses (from 3 to 12 h), and routes of administration. Efficacy improved when higher doses (400–800 mg) were given at shorter intervals (3–6 h).

Vaginal administration was attended with better results compared to oral route either due to better absorption or direct local effect in induction of abortion (*Nuutila et al., 1997*).

Recent pharmacokinetic study suggested that the bioavailability of misoprostol after sublingual administration was higher than those after oral or vaginal administration (*Ho et al., 1997 and Bebbington et al., 2007*).

In spite of the large body of literature detailing the efficacy of transvaginal misoprostol for cervical ripening and labor induction, few studies have addressed factors that influence the efficacy of misoprostol. One potentially important factor is the vaginal pH. Studies of orally administered misoprostol, used for the prevention of gastric ulceration, have demonstrated only modest effects of stomach pH on drug absorption, with little effect on the clinical cytoprotective effect of misoprostol on gastric mucosa. Anecdotal reports of limited

efficacy and undissolved tablets in some patients have raised concern that the pH of the vaginal environment may be an important factor in the dissolution and absorption of misoprostol. In light of the water-soluble nature of misoprostol, dissolution of the tablet matrix should result in misoprostol available for absorption. No pharmacokinetic data are available evaluating the effect of vaginal pH on absorption of misoprostol (*Ramsey et al.*, 2000).

Absorption of misoprostol from the vagina may vary according to the medium in which the tablet is placed. Misoprostol tablets disintegrate better in an acidic medium (*American Hospital Formulary Service Drug Information*, 1994). Various studies have shown that moistening of misoprostol tablets with acetic acid is associated with greater efficacy than moistening with saline (*Yilmaz et al.*, 2002).

Aim of the Work

To evaluate the efficacy and safety of vaginal misoprostol moistening with acetoacetic acid in termination of mid trimester pregnancy (14-24 week) in comparison with the use of vaginal misoprostol moistening with placebo (*normal saline*).

Induction of Abortion

Definition of abortion:

The World Health Organization (WHO) defined abortion as: the expulsion or extraction from its mother of a fetus or an embryo weighing 500 grams or less, or any otherwise product of gestation of any weight irrespective of gestational age and whether or not there is evidence of life and whether or not the abortion was spontaneous or induced (*Hook and Porter, 1980*).

Spontaneous abortion is a pregnancy loss before 20 to 21 weeks after the last menstrual period, as detected by β -subunit of human chorionic gonadotrophin (HCG) assays performed 28 to 30 days after the previous menses (*Martha and Thomas, 2007*). First trimesteric abortion is through completed 13 weeks of pregnancy.

Incidence:

Of clinically recognized pregnancies, 12% are lost in the first trimester, studies with ultrasound demonstrate that fetal viability ceases weeks before maternal symptoms occur; thus fetuses aborting clinically at 10 to 12 weeks gestation usually died weeks before (*Simpson, 2007*). A recent study of 232 pregnancies observed with ultrasound, demonstrated that embryonic losses occurred by 8.5 weeks gestation, no losses occurred between 8.5 and 14 weeks gestation, and 2% were lost after 14 weeks. This suggests that early pregnancy loss is complete by the end of the embryonic period (50 days after woman's LMP).