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

## Thesis

Submitted for Partial Fulfillment of the Master Degree
in *Obstetrics and Gynecology*

## By

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# List of Abbreviations

| | |
|---|---|
| **Acl** | : Anticardiolipin antibodies |
| **ACTH** | : Adrenocorticotropic 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** | : Cycloxygenase |
| **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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**بسم الله الرحمن الرحيم**

قَالُوا سُبْحَانكَ لاَ علِمَ لَنَا إلاّ مَا

عَلَّمْتَنَا إنَّكَ أنتَ الْعَلِيمُ الْحَكِيمُ

**صدق الله العظيم**

**سورة البقرة آية (٣٢)**

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*To My brother and my Kids*

# Introduction

Mid trimester abortion represents ١٠-١٥٪ of all induced abortions but is responsible for two-thirds of all major complications. Over the last ٢٠ 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., ٢٠٠٧)***.

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, ١٩٩٢).***

Misoprostol, a PGE١ analogue, has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus, selectively binds to EP-٢/EP-٣ prostanoid receptors ***(Senior et al., ١٩٩٣).***

Because misoprostol is a prostaglandin E١ 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 abortificient capability ***(El-Refaey and Templeton, ١٩٩٤).***

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, ١٩٩٤).***

Recent studies have compared various dosages (from ١٠٠ to ٨٠٠ mg), intervals between doses (from ٣ to ١٢ h), and routes of administration. Efficacy improved when higher doses (٤٠٠–٨٠٠ mg) were given at shorter intervals (٣–٤ 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., ١٩٩٦).***

Recent pharmacokinetic study suggested that the bioavailability of misoprostol after sublingual administration was higher than those after oral or vaginal administration ***(Ho et al., ١٩٩٧ and Bebbington et al., ٢٠٠٢).***

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 administrated 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., ٢٠٠٠).***

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 Hosptial Formularly Service Drug Information, ١٩٩٨).*** Various studies have shown that moistening of misoprostol tablets with acetic acid is associated with greater efficacy than moistening with saline ***(Yilmaz et al., ٢٠٠٥)***.

# Aim of the Work

To evaluate the efficacy and safety of vaginal misoprostol moistening with acetoacetic acid in termination of mid trimester pregnancy (١٤-٢٤ 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 ٥٠٠ 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, ١٩٨٠).***

Spontaneous abortion is a pregnancy loss before ٥ to ٦ weeks after the last menstrual period, as detected by β-subunit of human chorionic gonadotrophin (HCG) assays performed ٢٨ to ٣٥ days after the previous menses ***(Martha and Thomas, ٢٠٠٢).*** First trimesteric abortion is through completed ١٣ weeks of pregnancy.

## Incidence:

Of clinically recognized pregnancies, ١٢% are lost in the first trimester, studies with ultrasound demonstrate that fetal viability ceases weeks before maternal symptoms occur; thus fetuses aborting clinically at ١٠ to ١٢ weeks gestation usually died weeks before ***(Simpson, ٢٠٠٢).*** A recent study of ٢٣٢ pregnancies observed with ultrasound, demonstrated that embryonic losses occurred by ٨,٥ weeks gestation, no losses occurred between ٨,٥ and ١٤ weeks gestation, and ٢٪ were lost after ١٤ weeks. This suggests that early pregnancy loss is complete by the end of the embryonic period (٧٠ days after woman's LMP٠.