Letrozole Pretreatment with Misoprostol Versus Misoprostol Alone For Induction of First Trimesteric Missed Miscarriage A Randomized Controlled Trial

Thesis

Submitted for Partial Fulfillment of
Master degree in Obstetrics & Gynecology

By

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Thesis Protocol

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Peter Samir Garas

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List of Abbreviations

Abb.	Full term
ACOG	American College of Obstetricians and Gynecologists
ACR	American College of Radiology
AIs	Aromatase inhibitors
APS	Anti-phospholipid syndrome
ASRM	American Society for Reproductive Medicine
AUC	Area under the curve
CC	Clomiphene citrate
ERs	Estrogen receptors
FIGO	International Federation of Gynecology and Obstetrics
FSH	Follicular stimulating hormone
HbA1c	Glycosylated hemoglobin
HCG	Human chorionic gonadotropin
IGF-1	Insulin like growth factor 1
IUCD	Intrauterine contraceptive device
IVF	In Vitro Fertilization
LPD	Luteal phase defect
NICE	National Institute for Health and Clinical Excellence
NKC	Natural killer cells
NSAIDs	Non-steroidal Anti-inflammatory drugs
OGTT	Oral glucose tolerance test
OHSS	Ovarian Hyperstimulation Syndrome

List of Abbreviations Cont..

Abb.	Full term
PCOS	Polycystic ovary syndrome
PGE1	Prostaglandin E1
PR	Progesterone receptors
PTL	Preterm labor
PTT	Partial thromboplastin time
RCOG	Royal College of Obstetricians and Gynecologists
RPL	Recurrent pregnancy loss
RU-486	Mifepristone
SGPT	Serum glutamic pyruvic transaminase
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
WHO	World Health Organization

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INTRODUCTION

Missed miscarriage is defined as retention of dead products of conception inside the uterus. ***(Cunningham et al., 2001).*** It occurs in up to 15% of all clinically recognized pregnancies. ***(Torre et al., 2012).***

Each year, more than forty million abortions are occurred all over the world. ***(Sedgh et al., 2007).***

Missed miscarriages in the first trimester are characterized by the arrest of embryonic or fetal development with ultrasound findings of an empty gestational sac or an embryo/fetus without cardiac activity. ***(Danielson et al., 2007).*** The cervix is closed and there is no or only slight bleeding. ***(Silver 2010).***

Expectance, surgery or medication is usually referred. Surgical interventions are effective and may lead to a complete abortion, but such procedures may be risky. ***(Kapp et al., 2010).***

Over the past decade, medical termination of pregnancy in the first trimester gained popularity with the highly effective regimen combining mifepristone and misoprostol. ***(Lee et al., 2011)c.***

Misoprostol is a synthetic analogue of prostaglandin E1, it has an uterotonic action and it can stimulate myometrial contraction and cause cervical ripening and dilatation. ***(Chai and Ho 2013).***

So misoprostol is a medication that is used to start labor, induce abortion, treat postpartum bleeding due to insufficient uterine contractions and prevent and treat stomach ulcers. ***(Tang et al., 2007).***

Misoprostol alone is used for medical abortion as an alternative to surgical abortion with range of efficacy is 65-93% being more effective in earlier gestation. A synthetic prostaglandin E1 (PGE1) is most effective when it is used with methotrexate or mifepristone (RU-486). Misoprostol can also be used to dilate cervix in preparation for surgical abortion, particularly in second trimester either alone or in combination with laminaria tents. Medical abortion has the advantage of being cheaper, simple, less invasive, not requiring anesthesia, and not having the risk of scarring and adhesions associated with surgical abortion. ***(Ferring 2013).***

The frequency of side effects of misoprostol is mainly related to the used dose and the route of administration. ***(Dodd & Crowther 2006).***

These side effects include fever, diarrhea and abdominal pain. It is pregnancy category X known to result in negative fetal outcome and uterine rupture may occur. It is recommended due to its cost effectiveness, stability and low rate of side effects. It is on the World Health Organization's List of Essential Medicines, most important medications needed in a basic health system. It was invented and marketed by Pfizer under trade name Cytotec. ***(WHO Model List, 2014).***

Estrogen is important in the maintenance of pregnancy. Aromatase inhibitors, such as Letrozole, suppress the peripheral conversion of androgens to estrogens. ***(Yeung et al., 2012).***

Letrozole is a selective and reversible aromatase inhibitor used to treat estrogen-dependent breast cancer. ***(Gibson et al., 2009).***

One study shown that Letrozole 7.5 mg given daily for two days and then followed by 800 mcg of vaginal misoprostol induces complete abortion in 80% of patients. ***(Kallner 2012).***

The most common side effects of letrozole are sweating, hot flushes, arthralgia (joint pain) and fatigue. There is concern that long term use may lead to osteoporosis, which is in certain patients such as post-menopausal women or osteoporotics, bisphosphonates may also be prescribed. ***(Chen et al., 2009).***

Aim of the Work

This study aims to compare between the safety and efficacy of two treatment modalities in medical termination of first trimesteric missed miscarriage.

Research question:

In women undergoing termination of first trimester missed abortion, does pretreatment with letrozole followed by misoprostol increase the rate of medical evacuation than misoprostol alone?

Hypothesis:

In women undergoing termination of first trimesteric missed abortion, pretreatment with letrozole followed by misoprostol may be more effective than misoprostol alone.

Patients and Methods

Type of the study:

A randomized controlled clinical trial.

Ethical consideration:

The study will be carried out on pregnant outpatients with first trimester missed miscarriage after having their informed written consent about the manipulation they subjected to.

Place of the study:

Conducted at outpatient Obstetric clinic of Ain Shams maternity hospital.

Sample Size Calculation:

The required sample size has been calculated using the Power Analysis and Sample Size software (PASS©) version 11.0.10 (NCSS©, LLC, Kaysville, Utah).

The primary outcome measure is the complete abortion rate.

It is estimated that a sample size of 44 patients in either study group (total, 88 patients) would achieve a power of 80% (type II error, 0.2) to detect a statistically significant difference between the two groups as regards the complete abortion rate for a medium effect size corresponding to a w coefficient of 0.3 using a two-sided chi-squared test with 1 degree of freedom and the targeted test confidence set at a level of 95% (type I error, 0.05). The effect size (w) is calculated as follows:

$w = \sqrt{\chi^2/N}$, Where $\chi 2$ is the chi-squared statistic and N is the total sample size (Chow et al., 2003).

The targeted effect size of w = 0.3 has been selected as it could be regarded as a clinically relevant difference to seek in this exploratory study.

Inclusion criteria:

- Maternal age more than 18 years old.

- Gestational age less than 13 weeks gestation.

- Hemoglobin ≥ 10 g/dl.

- Missed abortion.

Exclusion criteria:

- Maternal age less than 18 years old.

- Gestational age more than 13 weeks gestation.

- Hemoglobin < 10 g/dl.

-Previous attempts for termination of pregnancy in the current pregnancy.

- Fibroid uterus.

- IUCD in utero.

- Molar pregnancy.

- Allergy to misoprostol or letrozole.

- Chronic medical disorders

Study methods:

Consent is obtained.

Each patient will be subjected to full history taking with special emphasis on first day of her last menstrual period and the gestational age is calculated. Detailed examination including vaginal examination will be done. Investigations including ABO, Rh and ultra-sound will be done.

Patients will be randomly allocated into two groups:

1. First group (44) women will receive 800 mcg misoprostol vaginally the first day of enrollment in the study.