Original Article

Misoprostol Alone Versus Misoprostol Preceded by Letrozole for Time Needed for Induction of Miscarriage in Cases of Missed Miscarriage

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ABSTRACT

Objective: The aim is to assess the effect of use of letrozole prior to misoprostol versus use of misoprostol only on termination time during induction of medical evacuation in cases of missed abortion.

Methods: This is a randomized controlled trial including a total of 70 pregnant women diagnosed with first trimesteric missed miscarriage , divided into two groups. First group was given letrozole before start of induction with Misoprostol, second group was given misoprostol only.

The rate of successful medical abortion without the need for surgical intervention was calculated as a primary outcome, with secondary outcomes including need of surgical intervention, and time needed for complete medical abortion.

Results: The induction to complete abortion interval was significantly different between the two groups (6.77±2.21 in letrozole group vs. 11.72±3.18 in misoprostol group, $P<0.05$). Complete abortion was significantly higher in the letrozole group (71.4%) than in the misoprostol group (48.5%), *P value* 0.031.

Conclusion: Letrozole when added to misoprostol can increase the rate of successful medical abortion.

Key Words: Induction of miscarriage, letrozole, misoprostol, missed miscarriage.

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INTRODUCTION

Abortion, spontaneous or induced, is a common complication of pregnancy. According to CDC and WHO, it is defined as spontaneous or induced termination of pregnancy before fetal viability; prior to the 20th week of gestation or with a fetus weighing <500gm. Spontaneous abortion rate was estimated to be 31%[1].

The WHO reported that about 8% of maternal mortality can be attributed to abortion. And thus, induced abortion is commonly investigated in order to decrease its burden on maternal morbidity and mortality[2].

Spontaneous abortion in the absence of serious bleeding or infection can be managed by either expectant, medical, or surgical management. Each has its own risks and benefits. For example, even though surgical management is definitive, predictable& sometimes inevitable, it's invasive and might not be needed in all cases of spontaneous miscarriage[3].

Misoprostol; a synthetic PGE1 analogue, is widely used. It causes abortion by cervical softening and stimulation of uterine contractions. Misoprostol, according to NICE guidance, has a wide variation in efficacy rates, ranging from 13% up to 96%, with higher success rates in incomplete miscarriage and high dosage (1200-1400mcg)[4].

Estrogen and progesterone, produced by the corpus luteum in early pregnancy and the placenta later on, are important in maintaining pregnancy. Even though, progesterone has the upper hand but estrogen was proved to be important as well. Aromatase enzyme is essential for estrogen production through aromatization of androgens[5].

And so, drugs that can reduce or block estrogen and progesterone may have a role in medical induction of abortion. As proved by Mifeprostone, a progesterone antagonist, that has high success rate (reaching to more than 90%) when accompanied with Misoprostol in countries where it's available. Its wide use, however, is hindered by its expenses and unavailability in some countries. And so a cheaper, more available alternative had to be thought of and investigated[6].

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Letrozole, an aromatase enzyme inhibitor, is most commonly used in hormone dependent breast cancer after surgery. It acts via reversible competitive inhibition of aromatase enzyme, inhibiting estrogen production[7].

Since estrogen is essential for early pregnancy maintenance, we hypothesize that Letrozole, by decreasing the serum estradiol level, can facilitate pregnancy termination.

PATIENTS AND METHODS

Study design:

Prospective Randomized Clinical Trial.

Study location:

Kasr Al Ainy Hospital , Cairo University, in the period between September 2022 and February 2023.

Study Population:

We enrolled all women that presented to Kasr Al Ainy Hospital with missed miscarriage during the first trimester of pregnancy. They were divided into two groups, First group was offered 10 mg of Letrozole daily for three days prior to the proper Misoprostol dosage according to the RCOG guidelines (Group A) and was compared to the other group who was offered Misoprostol only according to the RCOG guidelines (Group B).

Inclusion criteria:

All women presenting with singleton missed miscarriage & gestational age equal to or less than 13 weeks confirmed by ultrasound scan , were included in the study.

Exclusion criteria:

Patients who were managed by surgical evacuation from the start , with known allergy to Letrozole and/ or Misoprostol , severe impairment of liver functions , bronchial asthma & maternal morbidity due to non-surgical management (i.e. sepsis, severe vaginal bleeding) , were excluded.

Informed consent:

Patients who seemed fulfilling the criteria of the study were recruited, an informed consent was taken and they were included in the study.

Intervention:

A) History taking including:

Personal history (age, gravidity, parity), Menstrual history (1st day of the last menstrual period and the estimated gestational age by dates), Medical history and Surgical history.

Examination:

General examination including (BMI,Vital data, Presence of pallor or jaundice), Abdominal examination including (Size of the uterus and scars of previous laparotomies) and Per-vaginal examination including (Cervical dilatation, effacement, position and consistency).

Investigations: including blood group typing (Rh status), full blood count & coagulation profile. Pelvic Ultrasound scan to confirm missed miscarriage and gestational age. Gestational age was based on: Gestation sac diameter or Crown Rump length. Missed miscarriage was diagnosed by presence of anembryonic sac (MSD 25 mm with no fetal pole), or absence of fetal pulsations with CRL of 12mm.

Patients not fulfilling the inclusion criteria were dropped from the study and were not considered as part of the calculated sample size.

Randomization was done using computer generated program (MedCalc®) and Patients were equally allocated to one of the two study groups:

Group (A) (Letrozole & Misoprostol): received 10 mg of Letrozole (Femara ®) for 3 days and then were given misoprostol according to the RCOG guidelines.

Group (B) (Misoprostol only): Induction of abortion was given according to the RCOG guidelines for induction of abortion.

For all gestations, misoprostol (Misotac ®) 800 micrograms was given by the sublingual route, followed by misoprostol 400 micrograms every 3 hours until miscarriage occurred.

Patients were either admitted (those with previous uterine scars) or followed up on out-patient basis and were told to come for follow up at the beginning of bleeding after misoprostol tablets intake or after 3 days of commencement of misoprostol.

Data were collected then regarding Transvaginal ultrasound scan was done to confirm complete abortion and to assess if there's any retained products of conception. Surgical evacuation of retained products of conception was done in cases of considerable bleeding, retained products of conception that weren't evacuated medically or upon patients' demand.

Primary outcome: The successful rate of complete medical induction of miscarriage, defined as complete expulsion of products of conception without need of surgical evacuation, and without any complication.

Secondary outcome:

1. The time from start of induction of miscarriage till successful medical miscarriage with no need for surgical evacuation within one week of misoprostol intake.

2. Need for surgical evacuation of remnants of conception due to either:
   - Considerable vaginal bleeding leading to hemodynamic instability necessitating immediate surgical evacuation.
   - Incomplete expulsion of products of conception confirmed by ultrasound scan.

3. Side effects of drugs: nausea, vomiting, fever, diarrhea.

Statistical Analysis:

Patient information was collected using patient sheet forms, coded, and entered onto an Excel sheet. SPSS (statistical program for social science version 23) was then used for statistical analysis. Quantitative data was represented using mean and standard deviation (SD), whilst categorical data was shown using number and percentage. Quantitative data was compared using the independent Mann Whitney U test, and categorical data was compared using the appropriate Chi squared test or Fisher exact test. Different variables were ranked against one another using the correlation coefficient test, where a probability value (*p value*) of greater than 0.05 was deemed statistically non-significant, a probability value (*p value*) of less than 0.05 was deemed statistically significant, and a probability value (*p value*) of less than 0.001 was deemed statistically highly significant.

RESULTS

This study is a prospective randomized controlled trial, performed at the Kasr Al-Ainy obstetrics and gynecology hospital, during the period from September 2022 to March 2023, including 70 pregnant women diagnosed with missed miscarriage.

All selected patients met the inclusion criteria and were further subdivided into two groups:

Group A (Study group) (n=35) : included patients who received induction of abortion by daily 10 mg Letrozole prior to Misoprostol.

Group B (Control group) (n=35) : included patients who received induction of abortion via Misoprostol only.

Results of the study are summarized in the following (Tables 1,2):

Table 1: General Patient characteristics

	Group (A) (n=35) Letrozole & Misoprostol	Control (n=35) Misoprostol only	*p-value*
Age	32.06±5.703	31.66±5.74	0.797
Gravidity	3.91±1.915	4.11±2	0.117
Parity	2.51±1.869	2.8±1.779	0.392
BMI	29 ± 4.16	29.89 ± 3.58	0.973
Gestational age	9.23±1.42	9.13±2.11	0.212

Table 2: comparison between the study groups regarding treatment outcomes

	Group (A) (n=35) Letrozole & Misoprostol	Control (n=35) Misoprostol only	*P-value*
Dose of misoprostol (in terms of 200 cg)	1462.85 ± 335.26	2182.85 ± 437.56	0.004
Time from induction to complete bortion	6.77±2.21	11.72±3.18	0.024
Percentage of complete abortion	(25) 71.4%	(17) 48.5%	0.031
Need for surgical evacuation	(10) 28.6%	(18) 51.5%	
Side effects of drugs	(5) 14.3%	(6) 17.1%	0.32

DISCUSSION

Medical abortion has evolved globally over the past three decades and is now a common way to provide abortion services. For women who opt for terminating a pregnancy before 24 weeks, medical abortion, which involves using medications instead of a surgical approach to induce the abortion, is an option[1].

Sixty four percent of abortions, according to the Centers for Disease Control and Prevention, were carried out prior to 63 days of gestation. In the United States, medical abortions presently account for 16.5% of all abortions and 25.2% of abortions that occur at or before 9 weeks of conception. The most popular medical abortion protocol in the USA and Western Europe comprises mifepristone and misoprostol. Mifepristone, however, is still unavailable in several regions of the world[8].

The success rates for misoprostol-assisted induction of abortion are extremely variable across studies (ranging from 37% to 86%) and rely on the protocol, route of administration, and dosage applied. Misoprostol, however, may be more efficient when taken in conjunction with other medications[9]. Third-generation aromatase inhibitor letrozole works by reducing the production of estrogen, which can aid in the induction of an abortion[10].

Our study aims at finding a cheaper, more available substitute to mifepristone, which when combined with misoprostol can reduce the time and doses of misoprostol needed for completion of abortion and can decrease the rate of needed surgical evacuation in cases of medically induced abortion.

In our study there was no statistically significant differences between study groups in the age, gravidity or parity ($p > 0.05$).

In 2017, a study done by Behroozi and colleagues showed also no significant differences, in age, gravidity and parity ($p > 0.05$)[10]. As such , there were no significant differences in age, parity, history of miscarriages, height, weight, and gestational age between the letrozole group and the placebo group in a similar study done by Ramy H. and colleagues in 2023[9].

In our study, the mean induction to abortion interval was significantly different between the two study groups with the mean interval in the letrozole group was 6.77 (SD±2.21), while the mean interval in the misoprostol only group was 11.72 (SD±3.18) ($P<0.05$). This was supported by the results found in Fathy's study in 2023 as the mean interval induction to abortion was 7.5 h (SD±1.7) in letrozole group & 8.3 h (SD±2) in control group (*P value* 0.003)[11].

A meta-analysis of randomized controlled trials done by zhuo and colleagues show no remarkable effect on induction to abortion time ($P= 0.3$)[12].

A systematic review done by Nash and colleagues in 2018 show that for abortions over 9 weeks' gestation, one trial supported and one trial refuted a decrease in time to abortion interval with letrozole and misoprostol, but Time to abortion interval for abortions up to 9 weeks' gestation was not improved with the addition of letrozole to misoprostol[13].

The doses needed for completion of abortion in the letrozole group were significantly less than those needed in the misoprostol only group , as the mean in the case group is 1462 mcg (SD ±335.26) compared to the mean in the control group which is 2182 mcg (SD ±437.56) ($P<0.001$). A study done by Hanaa and colleagues in 2021 on total 90 pregnant women with range of 11–22 weeks gestational age obtained a complete abortion rate of 75.6%, with total doses varying from 600 to 1000 mcg of misoprostol[14].

In our study, in the Letrozole group, complete abortion was achieved in 25(71.4%) patients with no need for surgical intervention. In 10 cases (28.6%) induction of abortion resulted in incomplete miscarriage and surgical intervention (whether curettage or suction evacuation) was done.

In the Misoprostol only group, complete abortion was achieved in 17 (48.5%) patients with no need for surgical evacuation. Eighteen (51.5%) cases necessitated surgical intervention whether curettage or suction evacuation.

In our study, the rate of complete abortion, the primary outcome, was significantly higher in the Letrozole group (71.4%) compared to the misoprostol only group (48.5%). ($P= 0.031$)

In a study done in 2019 by Aisha and colleagues, the complete abortion rate in the Letrozole group was also significantly higher than that in the misoprostol group (80 % compared with 51.8 %)[15]. While in the study done by Javanmanesh and colleagues in 2018, the complete abortion rate in the Letrozole group was 78.9 % vs. 45.7% in the Misoprostol only group. The success rate of abortion was completely different in the Letrozole group compared to the Misoprostol only group ($P= 0.001$)[16].

CONCLUSION AND RECOMMENDATIONS

The study showed that Letrozole, can in fact, decrease induction to abortion time and increase the rate of complete abortion achieved solely by medical induction of abortion, thus decreasing the need for surgical intervention. Health education regarding safe options of termination

of pregnancy in indicated cases should be offered to all mothers in the pre- and antenatal care physician visits.

CONFLICT OF INTERESTS

There are no conflict of interest.

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