



# Comparison of Using Misoprostol with or without Letrozole in Abortion Induction: A Placebo-Controlled Clinical Trial

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## ABSTRACT

**Aims** The rate of induced abortion is growing worldwide. In this study, we aimed at comparing using misoprostol with or without Letrozole in abortion.

**Materials and Methods** In this placebo-controlled trial, 46 women with a gestational age of fewer than 20 weeks, who were candidates of legal abortion, were selected by simple randomization sampling method and randomly assigned into two groups. Drug group received 10mg daily Letrozole (4 tablets of 2.5mg) for 3 days prior to taking Misoprostol and the placebo group received daily placebo (4 tablets with the exact appearance of Letrozole) with the same instructions. After 3 days, Misoprostol was given to all the participants based on their gestational ages. The data were analyzed by SPSS 16 software, using independent sample t-test and Chi-square test.

**Findings** 21 women (45.7%) had a successful complete abortion, and curettage was needed for 25 women (54.3%). Successful abortion rate was significantly higher in the group receiving Letrozole (78.3%) than the group receiving placebo (13.0%;  $p=0.0001$ ). Mean induction-abortion interval was  $22.61\pm 7.721$  hours in the drug group and  $24.09\pm 8.251$  hours in the placebo group, which was not significantly different ( $p>0.05$ ). There was no significant difference between the two groups in terms of vaginal bleeding and adverse effects.

**Conclusion** Using 10mg daily Letrozole for 3 days followed by oral Misoprostol results in a significantly higher rate of complete abortion compared with placebo in women with a gestational age of less than 20 weeks.

**Keywords** Letrozole; Misoprostol; Induced Abortion

## CITATION LINKS

[1] Abortion jabberwocky: The need for better terminology [2] Abortion incidence between 1990 and 2014: Global, regional, and subregional levels and trends [3] Abortion law and policy around the world [4] Unsafe abortion: Global and regional incidence, trends, consequences, and challenges [5] The effectiveness of using misoprostol with and without letrozole for successful medical abortion: A randomized placebo-controlled clinical trial [6] Medical methods for first trimester abortion [7] Misoprostol for the termination of pregnancy with a live fetus at 13 to 26 weeks [8] Sublingual versus vaginal misoprostol for second trimester termination: A randomized clinical trial [9] Practice bulletin no, 143: Medical management of first-trimester abortion [10] Medical methods for mid-trimester termination of pregnancy [11] Approval summary: Letrozole in the treatment of postmenopausal women with advanced breast cancer [12] Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer [13] Clinical practice handbook for safe abortion [14] A pilot study on the use of a 7-day course of letrozole followed by misoprostol for the termination of early pregnancy up to 63 days [15] A pilot study on the combined use of letrozole, mifepristone and misoprostol in termination of first trimester pregnancy up to 9 weeks' gestation [16] A prospective double-blinded, randomized, placebo-controlled trial on the use of letrozole pretreatment with misoprostol for second-trimester medical abortion [17] A prospective double-blinded, randomized, placebo-controlled trial on the use of letrozole pretreatment with misoprostol for second-trimester medical abortion [18] Evaluation of effect of letrozole prior to misoprostol in comparison with misoprostol alone in success rate of induced abortion

## Introduction

Abortion, which is the termination of pregnancy before a fetus can potentially live outside the uterus, is a common complication of pregnancy occurring either spontaneously (miscarriage) or on purpose (induced abortion) [1]. Between 2010 and 2014, a worldwide estimation of 56 million induced abortions a year were reported, showing an increase from 50 million a year between 1990 and 1994 [2].

Due to legal and cultural restrictions, an estimation of the number of abortions is very difficult in developing countries [3].

Induction of abortion could have a huge financial burden for the families and healthcare system. Moreover, it can be accompanied by serious side effects for the mother, including rupture of uterus, sepsis, and death, especially in cases that abortion is not carried out in an appropriate environment under the supervision of a healthcare professional. Studies show that of 42 million abortions taking place in a year, 20 million abortions are not safe and lead to 70,000 maternal deaths and more than 5 million temporary or permanent cases of disability. Therefore, successful management of abortion is a crucial matter in gynecology [4, 5].

Abortion is induced by medical and surgical methods. Medical abortion became an alternative for surgical abortion after the availability of prostaglandin analogues in the 1970s [6].

Misoprostol, a prostaglandin E1 analogue, is extensively used all around the world for the termination of pregnancy. It has more benefits than the other prostaglandin analogues, including stability in room temperature, easy administration, and fewer side effects. Misoprostol has two common routes of administration (vaginal and oral) with different pharmacokinetics [7, 8]. In medical abortion, the procedure is considered successful if abortion is completed with no surgical intervention [9].

Studies suggest that success rate of Misoprostol in abortion varies from 37% to 86%, depending mostly on the route of administration. Evidence show that Misoprostol is most effective when used in combination with Mifepristone (RU-486), which is an anti-progesterone that causes uterus contractions by blocking progesterone. This combination raises the success rate of abortion to 95% in the first 50 days of pregnancy [10]. Since Mifepristone is expensive and still not widely available in developing countries, we need to find an alternative that is more accessible and has a lower cost [7].

Letrozole is an aromatase inhibitor that is used in the treatment of hormonally-responsive breast cancer. It reversibly and competitively bonds with iron in cytochrome P450 and prevents the production of estrogen by aromatase enzyme. Letrozole functioning as a reversible anti-estrogen agent increases Follicle-Stimulating Hormone (FSH)

secretion from the pituitary gland without having the anti-estrogen adverse effects on endometrium and cervix, which is considered an advantage for this agent [11, 12]. Therefore, Letrozole, which is more accessible than Mifepristone, might be a good alternative to be used in combination with Misoprostol.

In this study, we aimed at assessing the efficacy of using Letrozole prior to using Misoprostol in successful abortion induction.

## Materials and Methods

This single-blind randomized controlled trial was performed at Akbarabadi and Firoozgar Hospitals, Tehran, Iran in 2016.

Forty-six pregnant women, who were candidates of legal abortion induction, were selected by simple random sampling method. Inclusion criteria were age more than 18 years old, gestational age less than 20 weeks (confirmed by ultrasound scanning on the first day of admittance), hemoglobin levels higher than 10g/l, diastolic pressure lower than 95mmHg, not having any history of conditions such as adrenal diseases, steroid hormone-dependent cancer, porphyria, thromboembolism, severe or recurrent liver disease. Exclusion criteria were evidence of bronchial asthma, arterial hypertension, having intra uterine device (IUD), breastfeeding, onset of any kind of illnesses, starting to take medicines other than the ones given to them in the trial, and any abnormal laboratory findings in blood or liver tests.

Patients were assigned into two groups of 23 women, using random allocation method. One group (Drug group) received 10mg daily Letrozole (4 tablets of 2.5mg) for 3 days prior to taking Misoprostol and another group (Placebo group) received daily oral placebo (4 tablets with the exact appearance of Letrozole) with the same instructions. After 3 days, according to International Federation of Gynecology and Obstetrics (FIGO) protocol [13], Misoprostol was prescribed for all the participants based on their gestational ages (for less than 13 weeks' gestation, 800µg of sublingual Misoprostol every 3 hours to a maximum of 3 doses in 12 hours, for the second trimester and for 13-20 weeks' gestation, 400µg of sublingual Misoprostol every 3 hours to a maximum of 5 doses).

The data consisted of the number of cases with successful abortion (defined as not needing any surgical intervention or elective curettage), the interval between induction and abortion (the time between taking the first dose of Misoprostol and initiation of abortion), the number of cases with incomplete abortion, duration of vaginal bleeding, severity of vaginal bleeding (classified as spotting [mild], urgent curettage [severe], and moderate), and the severity of adverse effects (including nausea, vomiting, diarrhea, fatigue, vertigo, headache, fever,

skin rash, and abdominal pain). Curettage was done in cases with incomplete abortion.

This study was approved by the Ethics Committee of Iran University of Medical Sciences and regional authorities (Ethic code: 1395.9211290017). Written informed consent was gained before each subject's participation in the study.

The data were collected and analyzed, using SPSS 16 software. Descriptive data were reported as frequency percentage and qualitative data were reported as mean values with standard deviation. Independent sample t-test and Chi-square test were used for data analysis.

## Findings

Forty-six pregnant women meeting the inclusion criteria were enrolled in the trial. There was no withdrawal from the study.

The mean age of drug group and placebo group was  $25.91 \pm 5.52$  and  $25.17 \pm 3.98$  years old, respectively. Also, the mean of gestational age was  $11.22 \pm 3.97$  weeks in drug group and  $13.22 \pm 2.90$  weeks in placebo group. There was no significant difference between the two groups in terms of age, gestational age, frequency distribution of gravid, and history of diseases (Table 1).

In 26.1% of the drug group and 13.0% of the placebo group, fetal heart rate (FHR) was positive ( $p > 0.05$ ). Mean induction-abortion interval was  $22.61 \pm 7.72$  hours in the drug group and  $24.09 \pm 8.25$  hours in the placebo group, which was not significantly different ( $p > 0.05$ ).

Of all the participants, 21 women (45.7%) had a successful abortion, and curettage was needed for 25 women (54.3%). Successful abortion rate was significantly higher in the group receiving Letrozole than the group receiving placebo (Table 2).

Severity of vaginal bleeding was not significantly different in the drug group than the placebo group; none of the cases in the two groups complained of severe vaginal bleeding (Table 2).

There was no significant difference between the two groups in terms of adverse effects ( $p > 0.05$ ; Table 3).

**Table 1)** Frequency distribution of gravid and history of diseases in studied groups (n=23 in each group; the numbers in the parentheses are percentages)

Variables	Drug Group	Placebo Group
<b>Past Medical History (PMH)</b>		
Negative	12 (52.2)	7 (30.4)
GDM	2 (8.7)	8 (34.8)
Hypothyroidism	6 (26.1)	5 (21.7)
Both	3 (13.0)	3 (13.0)
<b>Gravid</b>		
1	10 (43.5)	5 (21.7)
2	8 (34.8)	9 (39.1)
3	4 (17.4)	7 (30.4)
4	1 (4.3)	2 (8.7)

GDM: Gestational Diabetes Mellitus

**Table 2)** Frequency distribution of outcomes of the treatment in the drug and placebo groups (n=23 in each group; the numbers in the parentheses are percentages)

Variables	Drug	Placebo	p-value
<b>Successful abortion</b>	18 (78.3)	3 (13.0)	0.0001
<b>Severity of vaginal bleeding</b>			
Mild	13 (56.5)	11 (47.8)	>0.05
Moderate	10 (43.5)	12 (52.2)	>0.05

**Table 3)** Frequency distribution of adverse effects in the drug and placebo groups (n=23 in each group; the numbers in the parentheses are percentages)

Adverse Effects	Drug group	Placebo group
<b>Negative</b>	1 (4.3)	1 (4.3)
<b>Diarrhea</b>	3 (13.0)	3 (13.0)
<b>Pain+ Diarrhea</b>	6 (26.1)	4 (17.4)
<b>Pain+ Diarrhea+</b>	0	2 (8.7)
<b>Vomiting</b>		
<b>Headache+ Pain+</b>	1 (4.3)	1 (4.3)
<b>Vomiting</b>		
<b>Headache+ Pain</b>	1 (4.3)	3 (13.0)
<b>Pain+ Vomiting</b>	0	2 (8.7)
<b>Pain</b>	4 (17.4)	1 (4.3)
<b>Headache+ Vomiting</b>	1 (4.3)	2 (8.7)
<b>Diarrhea+ Vomiting</b>	4 (17.4)	3 (13.0)
<b>Vomiting</b>	2 (8.7)	1 (4.3)

## Discussion

The present study showed that using Letrozole before Misoprostol for induction of abortion results in a considerable increase in success rate without imposing any serious side effects. According to the findings, Letrozole did not have a significant impact on induction-abortion interval compared to placebo. In a placebo-controlled trial in 2015 performed on 130 women by Naghshineh *et al.*, the efficacy of Letrozole in abortion induction was evaluated. In this trial, the rate of complete abortion was higher in the Letrozole group, which was in accordance with the results of the present study. Unlike the present study that the dosage of Misoprostol was not different in the two groups, in the mentioned study, the placebo group received more dosage of Misoprostol [5].

Yeung *et al.* conducted a trial in 2012 on 20 women that were candidates of abortion induction. The subjects were given Letrozole 7 days prior to receiving vaginal Misoprostol, which was different than the present study since our patients started receiving Letrozole 3 days prior to taking oral Misoprostol. The mentioned study reported an overall complete abortion rate of 95% with no major adverse effects. These findings were similar to the findings of the present study [14].

Likewise, Chai *et al.* in 2013 performed a trial on 50 women and gave them a single dose of 200mg Mifepristone and 10mg Letrozole daily 3 days prior to giving them 800µg vaginal Misoprostol. They concluded that Letrozole increases the rate of complete abortion to 98% without having any

considerable side effects [15].

A placebo-controlled trial carried out by Lee *et al.* in 2011 on 130 women evaluating the effectiveness of using Letrozole with Misoprostol reported that when using Letrozole pre-treatment with Misoprostol in the second trimester, the rate of complete abortion is not significantly different than using Misoprostol alone [16]. This difference might be due to difference in ethnicity. These findings were in contrast with our findings of the rate of complete abortion.

However, Lee *et al.* in another similar trial with 168 participants concluded that using Letrozole 3 days prior to using Misoprostol results in a higher rate of complete abortion in women with an early pregnancy [17].

Also, another trial conducted by Behroozi-Lak *et al.* showed that using Letrozole prior to vaginal Misoprostol increases the rate of complete abortion and decreases the induction-abortion interval in women with a gestational age of less than 14 weeks [18].

The most important limitation of this study was low sample size and we suggest longer time and larger sample size for future studies for better results.

## Conclusion

Using 10mg daily Letrozole for 3 days followed by oral Misoprostol results in a significantly higher rate of complete abortion compared with placebo in women with a gestational age of less than 20 weeks.

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**Ethical Permissions:** The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (1395.9211290017 ethical code), and the privacy of the patients was assured.

**Conflict of Interests:** There is no conflict of interest.

**Authors' Contribution:** Forough Javanmanesh (First author), Introduction author/ Methodologist/ Original researcher (40%); Maryam Kashanian (Second author), Assistant/ Statistical analyst (30%); Sara Mirpangi (Third author), Assistant/ Discussion author (30%).

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