Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

# Comparison of the Effect of Letrozole and Misoprostol versus Misoprostol Alone on First Trimester Abortion

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**Article Type**

**Research Paper**

**Received:**
**Oct 30th 2022**
**Revised:**
**May 24th 2023**
**Accepted:**
**Jun 7th 2023**

## ABSTRACT

**Background and Objective:** The need to perform an abortion in the first three months of pregnancy with an effective and safe drug therapy is more important than other methods. The purpose of this study is to compare the effects of letrozole and misoprostol versus misoprostol alone on abortion.

**Methods:** In this clinical trial, 114 candidates for legal abortion in the first trimester of pregnancy were randomly assigned to three groups of 38 people receiving sublingual misoprostol alone with placebo (same amount of letrozole), misoprostol with letrozole 10 mg daily for 3 days and the third group was given misoprostol along with letrozole with a daily dose of 5 mg for 3 days. In addition to the demographic and obstetrical information of the patients, the primary outcome including complete and incomplete abortion, misoprostol dosage and side effects were compared in patients of three groups.

**Findings:** The mean gestational age of the patients was 73.1±9.2 days. A total of 84 (73.7%) patients had complete abortion, including 28 patients (73.7%) in the letrozole 5 mg group, 32 patients (84.2%) in the letrozole 10 mg group, and 24 patients (63.2%) were in the placebo group. In the letrozole 10 mg group, with a statistically significant difference, the rate of complete abortion was higher in them than in the placebo group (84.2 vs. 63.2%, p=0.037). 20 patients in the letrozole 5 mg group, 16 in the letrozole 10 mg group, and all patients in the placebo group received misoprostol, and the difference between the two groups of letrozole 10 mg and placebo was significant in terms of misoprostol intake (p=0.001). The most common side effect in patients of all three groups was nausea and vomiting, which did not have a statistically significant difference between all three groups.

**Conclusion:** The findings of the present study showed that letrozole 10 mg along with misoprostol is effective in patients who need legal abortion in the first trimester.

**Keywords:** *The First Trimester, Pregnancy, Medical Abortion, Letrozole, Misoprostol*.

**Cite this article:** Mokhtari M, Sadeghi S. Comparison of the Effect of Letrozole and Misoprostol versus Misoprostol Alone on First Trimester Abortion. *Journal of Babol University of Medical Sciences*. 2023; 25(1): 526-33.



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## Introduction

Abortion is often used to describe the failure of pregnancy in the first trimester (1). Abortion is the most common complication of pregnancy, which is seen in 15% of clinically diagnosed pregnancies (2). The trend of this pregnancy complication is increasing day by day, and according to the report of the World Health Organization, 53 million abortions occur every year (3, 4). Abortion may lead to serious complications such as infection, uterine rupture, or even death if performed in unauthorized centers and in unsanitary and illegal conditions (5).

Both methods of drug therapy and surgical evacuation of uterine contents are approved. With the introduction of the Mifepristone, the trend of using the drug for abortion increased significantly (6). Mifepristone is a relatively expensive drug that is not available in many developing countries, including Iran (7, 8). Therefore, it is necessary to try to find a cheaper drug with tolerable side effects that has acceptable efficacy.

Letrozole is a non-steroidal aromatase inhibitor used to treat estrogen-dependent breast cancer. Letrozole bonds reversibly and prevents the production of estrogen P and competition with iron in cytochrome 450 by aromatase enzyme. Aromatase inhibitors such as letrozole are widely used in the treatment of breast cancer patients. These compounds directly inhibit the biosynthesis of estrogen and lead to an increase in the secretion of FSH from the pituitary gland, but they do not have anti-estrogen side effects on the uterine and cervical mucosa. Third-generation aromatase inhibitors, including the non-steroidal inhibitor letrozole, have reversible and strong effects (9). Lack of anti-estrogenic effects is one of the other advantages of aromatase inhibitors, including letrozole, which prevents interference between the morphology of the endometrium and cervical mucus. Aromatase inhibitors do not have androgenic, progesteronic or estrogenic effects. For this reason, it seems that aromatase inhibitors, including letrozole, can open a new platform in medical science in the field of women and be a significant therapeutic choice (10).

Misoprostol or Cytotec is a synthetic type of prostaglandin E1, which is used in more than 60 countries of the world for the treatment and prevention of stomach ulcers caused by the long-term use of non-steroidal anti-inflammatory drugs. Misoprostol is widely used for induction of labor in the second trimester, softening of the cervix before using the device, curettage, hysteroscopy, therapeutic abortions, endometrial biopsy, early termination of pregnancy, treatment of incomplete abortion or missed abortion, treatment of postpartum bleeding and delivery induction (7). This drug is available sublingually and vaginally. The use of misoprostol is common for several reasons, including its low price, easy storage (at room temperature), effective uterine contractions, and minimal systemic side effects. Oral administration works faster than vaginal administration. It has a higher blood level than vaginal, but in vaginal administration, the blood level of misoprostol remains longer (11, 12).

According to previous studies, Mifepristone along with misoprostol is an effective drug with an efficiency of about 95% for abortion with drug therapy (13, 14), which unfortunately is not available in developing countries like our country, and its use has a heavy cost for patients. Therefore, it is necessary to find an alternative method that is cheap and available and has acceptable efficiency. The combination of using letrozole and misoprostol together in different ways to induce abortion has been investigated in different studies and has been associated with diverse results (15-17). Therefore, the purpose of this clinical trial is to investigate the effectiveness of the combination of misoprostol and letrozole with different doses and misoprostol alone in patients who are candidates for legal abortion in the first trimester.

## Methods

After being approved by the Ethics Committee of Iran University of Medical Sciences with the code IR.IUMS.FMD.REC.1399.766 and registration in the Iran Clinical Trial Database (IRCT) with the code IRCT20160523028008N13, this clinical trial was performed on 114 patients with a diagnosis of legal abortion during less than 14 weeks of pregnancy in Shahid Akbar Abadi Hospital in 2020-2021. Written informed consent was obtained from the participants. Patients with age greater than or equal to 18 years, gestational age based on ultrasound findings less than 12 weeks, no systemic disease such as hypertension, kidney disease, hemoglobin greater than or equal to 10 g/dL, diastolic blood pressure less than 95 mm Hg and normal liver function were included. Patients were excluded if they had an IUD, breastfeeding, any allergy to letrozole or misoprostol, asthma and seizures.

Demographic, body mass index (BMI) and obstetric data such as pregnancy grade, gestational age, type of pregnancy, history of previous abortion and type of previous delivery were collected. If the tests were not available, liver function, blood group and Complete Blood Count (CBC) were performed for the patients. The patients who were included in the letrozole group took the first and second dose of letrozole at home every 3 hours and went to the hospital for the third dose and took the first dose of misoprostol in the hospital. Patients were randomly divided into three groups of 38 people who received sublingual misoprostol alone with placebo (same amount of letrozole), misoprostol with letrozole 10 mg daily for 3 days, and the third group of misoprostol with letrozole at a daily dose of 5 mg for 3 days. Letrozole tablets manufactured by Aburaihan Biruni pharmaceutical company are 2.5 mg per tablet. After three days of letrozole administration, according to the International Federation of Gynecology and Obstetrics (FIGO) protocol, the amount of misoprostol was given according to the gestational age (18). In this study, 800 micrograms were administered in 3 doses every 4 hours. The time of induction till abortion (the time of the first dose of misoprostol until the onset of abortion), side effects, complete abortion and the duration of vaginal bleeding and its severity (mild, moderate and severe) were collected in patients. If there were pregnancy remnants, curettage was performed for the patients. The primary outcome included the occurrence of complete or incomplete abortion requiring curettage in patients, which was determined by ultrasound of complete or incomplete abortion in patients. Investigation of side effects was considered as a secondary outcome.

**Randomization and blinding method:** For this purpose, six-block randomization method was used. For this purpose, the names of the intervention groups were written on four sheets (two sheets of letrozole 5 mg group, two sheets of letrozole 10 mg group) and the name of the placebo group was written on the other two sheets. Sheets were stacked and placed in a container, and one sheet was pulled out for each patient. Then, six sheets were returned to the container and this process was repeated until the sample size was reached. The patients were not aware of the type of intervention; so, the study was conducted in a single-blind manner.

**Statistical analysis and sample size:** Based on the study of Abbasalizadeh et al. (17) who stated that the complete abortion rate in the intervention group was 93% and in the control group was 68% using Gpower statistical software, the sample size equal to 38 people in each group and a total of 114 patients were included in the study. In this study, SPSS version 20 software was used for data analysis, and $p<0.05$ was considered significant. Data description was done using descriptive statistics by expressing mean and standard deviation for quantitative variables and ratio and percentage for qualitative variables. Chi-square test or Fisher's exact test was used to compare qualitative variables, analysis of variance was used to examine quantitative variables between groups, and Bonferroni's post hoc test was used to compare two groups together.

## Results

The findings showed that all three study groups had no statistically significant differences in terms of maternal age, gestational age, number of pregnancies, body mass index, and number of abortions (Table 1). A total of 84 (73.7%) patients had complete abortion; 28 patients (73.7%) in group A or letrozole 10 mg, 32 patients (84.2%) in group B (5 mg letrozole), and 24 people (63.2%) belonged to the P group (placebo group) and all three groups had no statistically significant difference. However, in comparing the two groups, the rate of complete abortion was higher in group B than in the placebo group with a statistically significant difference (Table 2).

18 (47.4%) patients in group A and 22 (57.9%) patients in group B had abortions without receiving misoprostol, and the two groups had no statistically significant difference. 20 patients in group A, 16 people in group B and all people in group P received misoprostol, and in terms of the dose of misoprostol received by all three groups, there was a statistically significant difference. When comparing the two groups together, Bonferroni's post hoc test showed that only the two groups of P and B had a statistically significant difference (Table 3).

The mean induction time in patients with complete abortion after receiving the first dose of misoprostol was 7.7±1.5 hours in group A, 7.02±1.4 hours in group B, and 8.6±1.9 hours in group P. There was no statistically significant difference between the three groups. The most common side effect in the patients of letrozole 10 mg, 5 mg and control group was nausea and vomiting, which were 34.2%, 26.3% and 28.9%, respectively, and there was no statistically significant difference between the three groups (p=0.726).

**Table 1. Comparison of basic and midwifery variables in three study groups**

| Group<br>Variable | Group A<br>Mean±SD or<br>Number(%) | Group B<br>Mean±SD or<br>Number(%) | Group P<br>Mean±SD or<br>Number(%) | p-value |
|---|---|---|---|---|
| Age (years) | 33.0±6.1 | 32.5±4.6 | 31.1±4.0 | 0.219† |
| Gestational age (days) | 73.6±10.0 | 72.5±8.6 | 73.1±9.2 | 0.896† |
| BMI (kg/m$^2$) | 26.8±3.2 | 26.4±2.1 | 27.6±4.4 | 0.279† |
| **Pregnancy** | | | | |
| First pregnancy | 8(21.1) | 7(18.4) | 8(21.0) | 0.947* |
| Second and more | 30(78.9) | 31(81.6) | 30(78.9) | |
| **History of abortion** | | | | |
| Yes | 13(34.2) | 12(31.6) | 11(29.7) | 0.916* |
| No | 25(65.8) | 26(68.4) | 27(71.1) | |

†ANOVA, *Chi$^2$, A: letrozole 5 mg, B: letrozole 10 mg, P: placebo

**Table 2. The frequency of the number of complete abortions in the three study groups and comparing the groups together**

| Group<br>Variable | Group A<br>Number(%) | Group B<br>Number(%) | Group P<br>Number(%) | p-value<br>(B, A) | p-value<br>(P, A) | p-value<br>(P, B) |
|---|---|---|---|---|---|---|
| **Complete abortion** | | | | | | |
| Yes | 28(73.7) | 32(84.2) | 24(63.2) | 0.260 | 0.324 | 0.037 |
| No | 10(26.3) | 6(84.2) | 14(36.8) | | | |

A: letrozole 5 mg, B: letrozole 10 mg, P: placebo

**Table 3. Comparison of misoprostol dose received in patients of three study groups**

| Variable | Group A (n=18) Mean±SD | Group B (n=16) Mean±SD | Group P (n=38) Mean±SD | p-value* |
|---|---|---|---|---|
| Misoprostol (micrograms) | 2200.0±510.9[ab] | 1850.0±634.6[a] | 2526.3±543.1[b] | F=8.7 p=0.001 |

*ANOVA, A: letrozole 5 mg, B: letrozole 10 mg, P: placebo

## Discussion

The findings of the present study showed that adding 5 and 10 mg of letrozole for three days before the administration of misoprostol increases the rate of complete abortion in patients who need a legal abortion in the first three months of pregnancy. In this study, there was no statistically significant difference between the two groups receiving letrozole 5 and 10 mg in terms of complete abortion rate (84.2% vs. 73.7%), which may be due to the sample size. However, the observed difference could have clinical significance. Comparing the groups together, it was observed that the patients who received 10 mg of letrozole had a higher abortion rate with a statistically significant difference than the group receiving misoprostol alone. However, the amount of misoprostol received and their induction time were lower; thus, in this study we observed a synergistic effect between two drugs for complete abortion.

Medical abortion reduces complications such as bleeding, infection and stress caused by surgery in patients. In medical abortion, different drugs can be used to induce abortion. In line with the findings of the present study, other studies, including the clinical trial study by Javanmanesh et al. (16), Abbasalizadeh et al. (17), Behroozi-Lak et al. (19), Naghshineh et al. (20), and Yeung et al. (21) showed that adding letrozole to misoprostol can be more effective for complete abortion in the first trimester of pregnancy. In another study by Torky et al. (15), they also reported that the rate of complete abortion after three days of administration of letrozole in the amount of 10 mg and 800 mg of misoprostol was 78% and it was 39% in the misoprostol group. In line with the findings of the present study, it was shown in the study conducted in Iraq by Mohammed Al-Taie et al. (22) that adding letrozole to misoprostol significantly increases the abortion rate compared to misoprostol (68.7% vs. 93.2%). Therefore, it seems that adding letrozole to misoprostol can reduce the need for surgical abortion in patients who are candidates for abortion in the first trimester of pregnancy.

Misoprostol is a cheap prostaglandin analog that is used to induce medical abortion, the success rate of which is different in the conducted studies and ranges from 37 to 86% (16, 23, 24). The reason for this range is due to the method of administration, gestational age and drug dose. However, its combination with other drugs is more effective (6, 16). In a clinical trial by Abbasalizadeh et al. (17) on 128 patients, the rate of abortion in patients who referred for a legal abortion in the first trimester and received only misoprostol was 68.7%, which is in line with the findings of the present study. In a study by Javanmanesh et al. (16), the rate of complete abortion in patients who only received misoprostol for legal abortion was 13%, which is not consistent with the results of the present study. One of the reasons for the difference in the results of the studies is that the decision to perform curettage depends on the amount of bleeding, the patient's condition and the surgeon's decision. Prostaglandins and their analogs are widely used to induce abortion. Misoprostol is a prostaglandin E1 analog that is widely used for abortions in early pregnancy and has been shown to be preferred over other prostaglandins due to its availability, ease of use, low cost, convenient storage, and few side effects. Sublingual and vaginal pills are two common ways to use this pill, which have different pharmacokinetics and effectiveness. In the sublingual method, the peak amount of serum gallate occurs in a short time, while the vaginal method has fewer side effects (24, 25).

In terms of side effects, it was observed that the most common complication of patients in all three groups was nausea and vomiting, which did not have a statistically significant difference. Some therapists recommend that patients use nonsteroidal anti-inflammatory drugs such as ibuprofen and antiemetics before or immediately after misoprostol. However, there is concern that the use of non-steroidal anti-inflammatory drugs may reduce the effectiveness of misoprostol (26). Contraindication for medical abortion is sensitivity to misoprostol or other prostaglandins. Other cases that should be considered in these patients are ectopic pregnancy and anemia (27).

The findings of the present study show that the administration of letrozole before misoprostol, especially with a dose of 10 mg, is more effective in the first three months of pregnancy in patients who need a legal abortion, which is not accompanied by significant side effects.

**Financial sources:** The financial sponsor of this study is Iran University of Medical Sciences.

**Conflict of interest:** This study has no conflict of interest for the authors.

## Acknowledgment

We hereby acknowledge the material and spiritual support of the Vice-Chancellor of Research and Technology of Iran University of Medical Sciences and the honorable patients who cooperated in this research.

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