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Original Article

# Evaluation of effect of letrozole prior to misoprostol in comparison with misoprostol alone in success rate of induced abortion

T. Behroozi-Lak [a,*], S. Derakhshan-Aydenloo [b], F. Broomand [a]

[a] Reproductive Health Research Center, Department of Infertility, Urmia University of Medical Sciences, Urmia, Iran
[b] Urmia University of Medical Sciences, Urmia, Iran

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ABSTRACT

*Background.* – Abortion, spontaneous or induced, is a common complication of pregnancy and exploration of available and safe regimens for medical abortion in developing countries seems crucial.
*Aims.* – The present study was aimed to assess the effect of letrozole in combination with misoprostol in women eligible for legal therapeutic abortion with gestational age ≤ 14weeks.
*Materials and methods.* – This clinical randomized trial was conducted on 78 women who were candidate of medical abortion and eligible for legal abortion with gestational age ≤ 14 weeks that were randomly divided into two groups of case and controls. Case group received daily oral dose of 10 mg letrozole for three days followed by vaginal misoprostol. In control group the patients received only vaginal misoprostol. The rate of complete abortion, induction-of-abortion time, and side-effects were assessed.
*Results.* – Complete abortion was observed in 30 patients (76.9%) in case group and 9 (23.1%) cases were failed. In control group there was 16 (41.03%) complete abortions and 23 (58.97%) cases were failed to abort. Patients with gestational age of between 6 and 10 weeks did not show significant difference in both groups ($P = 0.134$). Regarding pregnancy remnants there were significant differences between two groups ($P = 0.034$). The time form admission to discharge in case groups were significantly shorter than those in control group ($P = 0.001$). The indication for curettage in case group was significantly less than control group ($P = 0.001$).
*Conclusion.* – A 3-day course of letrozole (10 mg/daily) followed by misoprostol was associated with a higher complete abortion and lower curettage rates and reduction in time from admission to discharge in women with gestational age ≤ 14 weeks compared to misoprostol alone.


## Introduction

Abortion, spontaneous or induced, is a common complication of pregnancy. The World Health Organization reported that annually about 79 million unintended pregnancies excluding miscarriages are occurring worldwide [1]. And annually, about 46 million induced abortions occur in the world [2,3]. The estimation of the total number of abortions is quite difficult, especially in developing countries, and it is usually underreported due to the legal restrictions a huge number of the inducted abortions are performed in non-hygienic situations. The abortion might load an undesirable cost to the families and health care system. Serious complications such as maternal death, uterine rupture, and sepsis may occur after abortions that are not taken place under medical observation [4]. The safety of the procedure has a dramatic importance in order to achieve a non-life threatening result.

Induced abortion can be performed by medical and surgical methods. Medical abortion is the induction of early abortion by consumption of special of medications and is named successful if it is completed without the need of any surgical intervention. Also, the medical approach is a safe and effective alternative to surgical methods with a high level of patient satisfaction [5,6].

Prostaglandins and their analogs are widely used for medical induced abortion. Misoprostol, a prostaglandin E1 analog, is used widely for early abortion and has been shown to be a better alternative to other prostaglandin substances due to feasibility, simple and easy administration, low price, stability at room temperature, and fewer systemic side-effects [7,8]. Sublingual and vaginal are two common routes of misoprostol administration with different pharmacokinetics and effectiveness. Sublingual misoprostol reaches its peak concentration in a short time and vaginal route has less adverse effects after administration [9]. The

* Corresponding author.
*E-mail address:* t.behrooz2@yahoo.com (T. Behroozi-Lak).

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range of reported successes rate of abortion induction with misoprostol is quite different in several studies (between 37% and 86%) depending on the regimen, route of administration, and dosage used. However, in combination with other drugs was more effective [10–12]. Letrozole, aromatase inhibitors, in combined with vaginal misoprostol shown that was more effective than misoprostol alone with lower, but not significant induction-of-abortion time in termination of pregnancy [13]. Letrozole is a third generation aromatase inhibitor and its action is suppressing estrogen production [14,15].

Misoprostol is a synthetic prostaglandin E1 analogue, manufactured as an oral preparation available as 200 μg tablets used to prevent and treat gastroduodenal damage induced by nonsteroidal anti-inflammatory drugs [16]. The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever, all of which are dose-dependent [17]. Misoprostol taken by pregnant women increases uterine tone and contractions.

The success rate of abortion of mifepristone in combination with misoprostol is significant, however, this medication is not available in our country. Therefore, we decided to study effect of letrozole prior to misoprostol in success rate of induced abortion. In this study patients with missed abortion were included and patients with failure pregnancy and incomplete abortion were not included.

The aim of this study was to evaluate effect of letrozole prior to misoprostol in comparison with misoprostol alone in success rate of induced abortion in women with gestational age of $\leq$ 14 weeks.

## Patients and methods

This clinical randomized trial study was conducted on 78 women who were candidate of medical abortion and eligible for legal abortion with gestational age $\leq$ 14 weeks, attending Motahari Hospital in Urmia, Iran.

The inclusion criteria were: good general health; older than the age of legal consent (ie, older than 18 years); the gestational age $\leq$ 14 weeks as confirmed by ultrasound scanning on day 1 of the study, hemoglobin $\geq$ 10 g/L and diastolic pressure $<$ 95 mmHg. The exclusion criteria were: history or evidence of adrenal pathology, steroid-dependent, cancer, porphyria, diastolic pressure over 95 mmHg, bronchial asthma, arterial hypertension, history or evidence of thromboembolism, severe or recurrent liver disease, breast feeding, anomaly of fetus, regular use of prescription drugs before admission to the study, any abnormal values in pretreatment blood tests, namely complete blood picture, renal and liver function tests. Individuals who fulfilled the selection criteria and death of the fetus was confirmed by two separate ultra-sonographies and were willing to participate gave their informed written consent.

The study was approved by the Institutional Ethical Committee of the Urmia University of Medical Sciences, Urmia, Iran. The study was registered with the trial number IR.UMSU.REC.1395.436

The participants were randomized into the two groups of 39 patients each by the hospital pharmacists according to computer-generated random numbers. Until the completion of the study, both patients and the clinicians were blinded to the group assigned.

Ultrasound examination was performed on eligible women to confirm intrauterine pregnancy and the gestational age. After a detailed history and a full body examination, complete blood count, renal, and liver function were checked.

Women in case group were given 10 mg letrozole orally on days 1–3 followed by vaginal misoprostol each 12 hrs for 3 times. In control group, the patients were received only vaginal misoprostol with the same method. The initial dose of misoprostol was 800 mg per 12 h and transvaginally.

Until abortion was occurred within 3-dose misoprostol administration, the regimen was continued. Where abortion was not occurred 48 hours after termination of regimen or pregnancy remnant after abortion was more than 15 mL, or hemorrhage was a lot, the patient was undergone curettage. In cases with pregnancy remnant less than 15 mL, the patients with the same remnants were discharged and then these patients were followed by ultrasonography after 1 week. If pregnancy remnant persisted in control ultrasonography, the curettage was performed. Indications for hospitalization of the patients were severe hemorrhage, pain, anxiety of abortion within 3-day letrozole therapy and no abortion with only letrozole (for vaginal misoprostol use).

In both group frequency of complete abortion, interval form induction to complete exit of pregnancy products, frequency of need for curettage, consumed misoprostol and side effects (nausea, vomiting, diarrhea, fatigue, dizziness, headache, lower abdominal pain, fever, rash, and chills or shivering) were assessed.

In case group patients, in each step of letrozole or misoprostol administration, the administration of the medicine was stopped if the abortion was achieved. In other patients the administration was continued until achievement of abortion based on the study design. Therefore, the total administration of letrozole and misoprostol was not the same in patients.

The clinical criteria of successful abortion included lack of severe hemorrhage and hemodynamic stability of patients after abortion that avoided curettage. The sonographic criteria of successful abortion included no pregnancy remnant or remnants less than 15 mL in transvaginal ultrasonography, provided that the remnants were cleared in one week follow up.

## Statistical analysis

The sample size was calculated as 78 subjects using the comparison of proportion formula with two-sided log-rank test, $\alpha$ = 0.05, and 84% of power. All statistical analyses were done using SPSS version 20 (SPSS Inc, Chicago, IL, USA). Descriptive data are reported as mean $\pm$ standard deviation, or number (percent) as appropriate. Independent sample t-test, Chi-square test, and Kaplan-Meier were used for data analysis. The level of significance is considered to be $P < 0.05$.

## Results

In the present study 78 patients were randomized into two groups of 39 patients each. In control group only vaginal misoprostol and in case group letrozole and vaginal misoprostol were assessed. The demographic data are shown in Table 1. There were no significant differences in age, gravidity, parity, history of miscarriages, natural delivery and C-section and history of abortion ($P > 0.05$). Despite randomized sampling, mean values for gestational age based on ultrasonography was significantly different between two groups ($P < 0.05$).

Complete abortion was observed in 30 patients (76.9%) in case group and 9 (23.1%) cases were failed. In control group there was 16 (41.03%) complete abortions and 23 (58.97%) cases were failed to abort. The successful rate of abortion was completely different in case group compared to control group ($P = 0.001$). In case group 58.97% of the patients received only letrozole and 41.03% of the patients received letrozole and misoprostol. In case group 1 (2.6%), 2 (5.1%), 2 (5.1%), 1 (2.6%) and 33 (84/6%) patients received 15, 20, 22.5, 25 and 30 mg letrozole, respectively.

Regarding the administered misoprostol doses, in case group 8 (50%), 1 (6.2%) and 7 (43.8%) patients received 800, 1600 and

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