ORIGINAL ARTICLE

The Comparison of the Rate of Complete Abortion between Letrozole Plus Misoprostol versus Misoprostol Alone in First-Trimester Spontaneous Pregnancy Loss: A Randomized Controlled Trials

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Background: Prior studies have indicated that using letrozole together with misoprostol is more effective than misoprostol alone for medical termination. At present, there are no studies about letrozole for termination of pregnancy in the Thai population.

Objective: To compare the rate of complete abortion between the regimen of letrozole followed by misoprostol and misoprostol alone in women diagnosed with early pregnancy loss at a gestational age of 14 weeks or less, and to evaluate the adverse effects of both regimens.

Materials and Methods: A clinical randomized control trial was conducted with 70 women diagnosed with early pregnancy loss. The intervention group, with 35 patients, received 10 mg of letrozole daily for three days followed by three doses of 800 mcg sublingual misoprostol. The control group, with 35 patients, received sublingual misoprostol alone. The primary outcome was to compare the rate of complete abortion between letrozole administered three days prior to misoprostol versus misoprostol alone. The secondary outcomes were to evaluate the adverse effects of both regimens.

Results: There were no significant differences in demographic data between the two groups, including age, underlying disease, body weight, height, body mass index and gestational age. In the intervention group, complete abortion occurred in 65.7% of cases compared to 62.9% in the control group. This showed no significant differences between the two groups (p-value of 0.803). Additionally, there were no significant differences in clinical adverse effects, including nausea and vomiting, diarrhea, dizziness, headache, abdominal pain, fever, and chills.

Conclusion: The combination of letrozole and misoprostol does not enhance the rate of complete abortion for termination of first trimester pregnancy. In addition, the adverse effects are not significantly decreased.

Keywords: Early pregnancy loss; First trimester pregnancy; Letrozole; Misoprostol

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Currently, there are several methods for termination of a first-trimester pregnancy. Medical termination is easier and has fewer complications than surgical methods such as dilation and curettage or vacuum aspiration. There are two common methods for medical termination, first, use of misoprostol, as prostaglandin E1 analog, alone[1,2] and second, combine misoprostol with mifepristone as progesterone antagonist[1,2], which is more effective[3]. However, mifepristone is not widely available in many areas of Thailand and is expensive. Other studies have shown that the use of letrozole together with misoprostol is more effective for medical termination than misoprostol alone[4-6].

Letrozole is a third-generation aromatase inhibitor that can inhibit estrogen production. One study showed that real-time polymerase chain reaction indicated a significant decrease in median progesterone and estrogen-alpha receptors in the placenta of pregnancies between 12- and 20-weeks' gestation after termination with letrozole prior to misoprostol[7]. According to a regimen of three days of letrozole followed by misoprostol, the rate of complete abortion is 76.9% compared with 41.3% in the misoprostol-alone group (p=0.001)[4].

Currently, there are no studies investigating the use of letrozole for medical termination in the Thai

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population. Therefore, the aim of the present study was to compare the efficacy of letrozole followed by misoprostol and misoprostol alone for termination of pregnancy in the Thai population. If the efficacy of the letrozole group is significantly better, it would be used as an alternative regimen for areas where mifepristone is not available.

Materials and Methods

The present study was a single-center, randomized trial. The study was approved by the Institutional Review Board (IRB) of Queen Savang Vadhana Memorial Hospital, Thailand IRB No. 014/2566, and registered in the ClinicalTrials.gov, No. NCT05940233. Participants were recruited from the outpatient and emergency departments of Queen Savang Vadhana Memorial Hospital between May 2023 and February 2024. The trial was unblinded, and randomization was generated using a computer-generated block of four with a one-to-one ratio.

The primary outcome was to compare the rate of complete abortion between letrozole administered three days prior to misoprostol versus misoprostol alone among patients diagnosed with early pregnancy loss. The secondary outcome was to evaluate the adverse effects of both regimens.

The participants were women diagnosed with early pregnancy loss at a gestational age of 14 weeks or less[1]. Physical examination, including pelvic examination and transvaginal ultrasound, was performed in all participants to confirm the diagnosis and gestational age. Laboratory testing, including hematocrit, aspartate aminotransferase (AST) or alanine aminotransferase (ALT), and serum creatinine, were conducted to assess the patient's status. The inclusion criteria were women with intrauterine pregnancy diagnosed with early pregnancy loss according to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin of 2018[1], gestational age of 14 weeks or less calculated by crown-rump length (CRL) or gestational sac (GS) measurements on ultrasound, cervical os open at 1 cm or less with no passing conceptus, systolic blood pressure of 95 mmHg or more, agreement to participate and affirmation of informed consent. The exclusion criteria included allergy to letrozole or misoprostol, use of an intrauterine device, breastfeeding, suspected pregnancy of unknown location or undiagnosed adnexal mass, severe or recurrent liver disease including AST or ALT elevation more than three times the upper limit, multiple pregnancy, submucous myoma uteri or myoma uteri invading the uterine cavity, current or history of thromboembolism, and abnormal creatinine clearance with serum creatinine of 2 or greater. Patients who met the inclusion criteria were enrolled in the experiment. Informed consent was obtained before the experiment began.

In the intervention group, letrozole 2.5 mg taking four tabs orally (10 mg/day) was administered from day one to day three, followed by misoprostol at 200 mcg with four tabs sublingually (800 mcg), every six hours for three doses on the fourth day[4-6]. In the control group, only sublingual misoprostol, three doses, was administered, using the same dosage as in the intervention group. All medications were initiated at home. A 7-day follow-up was established to confirm the diagnosis of complete abortion. In the case of life-threatening conditions, all participants were instructed to visit the hospital earlier if there were any unstable clinical manifestations. The criteria for diagnosing complete abortion included endometrial thickness of 10 mm or less by transvaginal ultrasound on the follow-up day or an earlier visit if the patient returned sooner[8], no active vaginal bleeding, relief of abdominal pain, and stable vital signs. Dilatation and curettage were offered to all participants not meeting the criteria or those who found it inconvenient to continue the experiment. To assess the clinical adverse effects, the questionnaire was administered. Each clinical adverse effect was categorized as mild, moderate, or severe.

Statistical analysis

Based on prior study[4], the estimated sample size was calculated using a two-sample proportions test: Pearson's chi-squared test, with an alpha of 0.05, power of 0.80, and a delta (difference) of –0.36. The estimated sample size was 58 participants. To account for potential missing data, an additional 20% was added to the estimated sample size, resulting in a total of 70 participants enrolled in the study. The intervention group consisted of 35 participants, while the remaining 35 were in the control group. Category data were presented as frequency and percentage while continuous data were described as mean ± standard deviation (SD) or median with interquartile range (IQR). Unpaired t-tests and chi-square tests with Fisher's exact test were used to compare continuous and categorical data between the two groups, respectively. A p-value of less than 0.05 was considered statistically significant. IBM SPSS Statistics, version 29.0.2 (IBM Corp., Armonk, NY, USA) was used for data analysis.

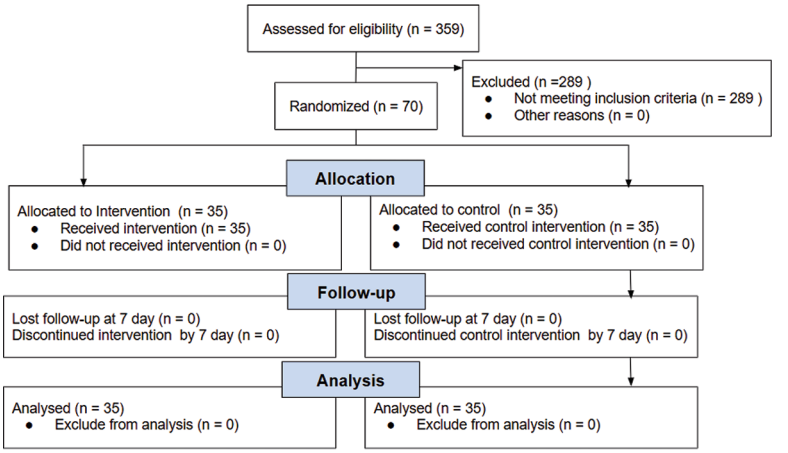

Figure 1. CONSORT flow diagram.

Table 1. Comparison of demographic data

Demographic data	Intervention group (n=35)	Control group (n=35)	p-value
Age (years); mean±SD	30.97±6.09	31.40±6.16	0.771
Underlying disease; n (%)			1
No	32 (91.4)	32 (91.4)	
Yes	3 (8.6)	3 (8.6)	
Body weight (kg); mean±SD	61.62±13.80	57.38±10.29	0.15
Height (cm); mean±SD	160.34±6.69	158.54±5.48	0.222
Body mass index (BMI) (kg/m^2); mean±SD	23.84±5.02	22.86±4.22	0.377
Baseline obstetric data			
Gestational age (day); mean±SD	54.54±8.14	53.31±8.45	0.538

SD=standard deviation

Results

In the present 70 patients were randomized into two groups of each 35, as shown in Figure 1. All participants were analyzed. No participant dropped out. Demographic data of the two groups are shown in Table 1. There were no significant differences in demographic data between the two groups, including age, underlying disease, body weight, height, and body mass index (p>0.05). The gestational age was not statistically different between the two groups at 54.54±8.14 days in the intervention group and 53.31±8.45 days in the control group, with a p-value of 0.538.

Table 2 presents the rate of complete abortion between the intervention and the control groups, which was the primary outcome of the study. There were no significant differences between the two groups. In the intervention group, complete abortion occurred in 23 participants (65.7%). In the control group, the rate of complete abortion was 62.9%, with a p-value of 0.803.

All participants diagnosed with incomplete abortion underwent dilatation and curettage, which was 34.3% in the intervention group and 37.1% in the control group. The clinical adverse effects are shown in Table 3. There were no significant differences in clinical adverse effects, including nausea and vomiting, diarrhea, dizziness, headache, abdominal pain, fever, and chills. The three most common severe clinical adverse effects were abdominal pain, chill, and diarrhea. Severe abdominal pain occurred in 19 patients (54%) in the intervention group and 16 patients (45.7%) in the control group. Severe chills occurred in 11 patients (31.4%) in the intervention group and 15 patients (42.9%) in the control group. Severe diarrhea occurred in 13 patients (37.1%) in the intervention group and 10 patients (28.6%) in the control group. However, these differences were not statistically significant between the two groups (p>0.05).

Table 2. Comparison of the rate of complete abortion

Group	Intervention group (n=35); n (%)	Control group (n=35); n (%)	p-value
Complete abortion	23 (65.7)	22 (62.9)	0.803
Incomplete abortion	12 (34.3)	13 (37.1)	

Table 3. Comparison of clinical adverse effects

Adverse effects	Intervention group (n=35); n (%)	Control group (n=35); n (%)	p-value
Nausea and vomiting			0.64
No	21 (60.0)	21 (60.0)	
Mild	10 (28.6)	7 (20.0)	
Moderate	3 (8.6)	4 (11.4)	
Severe	1 (2.9)	3 (8.6)	
Diarrhea			0.20
No	8 (22.9)	4 (11.4)	
Mild	9 (25.7)	9 (25.7)	
Moderate	5 (14.3)	12 (34.3)	
Severe	13 (37.1)	10 (28.6)	
Dizziness			0.66
No	19 (54.3)	23 (65.7)	
Mild	10 (28.6)	8 (22.9)	
Moderate	3 (8.6)	3 (8.6)	
Severe	3 (8.6)	1 (2.9)	
Headache			0.67
No	22 (62.9)	25 (71.4)	
Mild	9 (25.7)	5 (14.3)	
Moderate	2 (5.7)	3 (8.6)	
Severe	2 (5.7)	2 (5.7)	
Abdominal pain			0.50
No	3 (8.6)	4 (11.4)	
Mild	3 (8.6)	7 (20.0)	
Moderate	10 (28.6)	7 (20.0)	
Severe	19 (54.3)	17 (48.6)	
Fever			0.32
No	10 (28.6)	16 (45.7)	
Mild	11 (31.4)	8 (22.9)	
Moderate	7 (20.0)	8 (22.9)	
Severe	7 (20.0)	3 (8.6)	
Chill			0.25
No	11 (31.4)	5 (14.3)	
Mild	6 (17.1)	4 (11.4)	
Moderate	7 (20.0)	11 (31.4)	
Severe	11 (31.4)	15 (42.9)	

Discussion

According to the present study, the result has not shown the benefit of using letrozole combined with misoprostol for enhancing the rate of complete abortion. From previous studies, the regimen of letrozole for three days followed by misoprostol is superior to misoprostol alone in both vaginal and sublingual route[1,2,9].

However, the present study showed a different result. In the intervention group, complete abortion occurred in 65.7% compared with 76.9% in prior study[1]. The rate of complete abortion in the letrozole group in the present study was slightly lower than the reference. In the misoprostol alone group, the rate of complete abortion was 62.9%, which is more efficient compared to 41.3% in prior study[1]. The present study chose sublingual misoprostol because it is easier and more convenient to use than the vaginal route, although it differs from the reference that uses the vaginal route[1].

According to a prior study by Naghshineh et al., the rate of complete abortion with sublingual misoprostol was 42.6%[6]. In contrast, Abdelshafy et al. found that the rate of complete abortion with sublingual misoprostol was 71.4%[10]. In the present study, the authors found a different rate of complete abortion with sublingual misoprostol, resulting in minimal differences in the rate of complete abortion between the letrozole and control groups. This may explain why the outcome is not significant. Consequently, further studies with larger populations and experiments with the sublingual route may be required for more accurate outcomes.

The clinical adverse effects, which is the secondary outcome, were not significantly different in both groups including nausea and vomiting, diarrhea, dizziness, headache, abdominal pain, fever, and chills. This is similar to prior studies. The three most common severe clinical adverse effects were abdominal pain, chill, and diarrhea. Based on the side effects mentioned above, the healthcare provider may prepare medication for the patient to alleviate symptoms during the termination of pregnancy.

Strength

The present study is the first trial investigating the efficacy of letrozole prior to misoprostol for medical termination in early pregnancy loss in Thailand. The strength of this research lies in its design as a Randomized Controlled Trial, which can be applied to Thai patients.

Limitation

First, the trial was an unblinded study. This may increase the bias during the experiment. Second, misoprostol was given in the sublingual route in the present study, which is different from the reference

using the vaginal route[1]. The rate of complete abortion of sublingual misoprostol varies from 42.6% to 71.4%[3]. This may result in slightly different rate of complete abortion and no significant difference in outcome. Further studies with larger populations and experiments with the sublingual route may be required for more accurate outcomes.

Conclusion

The combination of letrozole and misoprostol does not enhance the rate of complete abortion for termination of first trimester pregnancy. However, the adverse effects are not significantly increased.

What is already known about this topic?

From previous studies, the regimen of letrozole for three days followed by misoprostol is superior to misoprostol alone in both vaginal and sublingual route[4,5,8].

What does this study add?

The regimen of letrozole for three days followed by sublingual misoprostol does not enhance the rate of complete abortion for termination of first trimester pregnancy in Thai population. The adverse effects are not significantly increased.

Conflicts of interest

The authors declare no conflict of interest.

References

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early pregnancy loss. Obstet Gynecol 2018;132:e197-207.
2. World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee. Abortion care guideline. Geneva: WHO; 2022.
3. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 2018;378:2161-70.
4. Behroozi-Lak T, Derakhshan-Aydenloo S, Broomand F. Evaluation of effect of letrozole prior to misoprostol in comparison with misoprostol alone in success rate of induced abortion. J Gynecol Obstet Hum Reprod 2018;47:113-7.
5. Torky HA, Marie H, ElDesouky E, Gebreel S, Raslan O, Moussa AA, et al. Correction: Letrozole vs. Placebo pretreatment in the medical management of first trimester missed miscarriage: A randomized controlled trial. Geburtshilfe Frauenheilkd 2018;78:e2-3.
6. Naghshineh E, Allame Z, Farhat F. The effectiveness of using misoprostol with and without letrozole for successful medical abortion: A randomized placebo-controlled clinical trial. J Res Med Sci 2015;20:585-9.
7. Lee VC, Gao J, Lee KF, Ng EH, Yeung WS, Ho PC. The effect of letrozole with misoprostol for medical termination of pregnancy on the expression of steroid receptors in the placenta. Hum Reprod 2013;28:2912-9.
8. Tzeng CR, Hwang JL, Au HK, Chien LW. Sonographic patterns of the endometrium in assessment of medical abortion outcomes. Contraception 2013;88:153-9.
9. Lee VCY, Ng EHY, Yeung WSB, Ho PC. Misoprostol with or without letrozole pretreatment for termination of pregnancy: a randomized controlled trial. Obstet Gynecol 2011;117:317-23.
10. Abdelshafy A, Awwad H, Abo-Gamra A, Alanwar A, Elkotb AM, Shahin M, et al. Sublingual vs vaginal misoprostol for completion of first trimester missed abortion: a randomised controlled trial. Eur J Contracept Reprod Health Care 2019;24:134-9.