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# Comparative Study Between the Effect of Letrozole Prior to Misoprostol and Misoprostol Alone in Induction of Abortion

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## Abstract

**Background:** Missed abortions may be treated with a number of medicinal and surgical procedures. Surgical methods include vacuum aspiration and dilatation and curettage. Letrozole, aromatase inhibitor, binds to iron in P450 cytochrome in reversible and competitive manner, preventing aromatase from producing oestrogen.

**Aim:** To compare the impact of using letrozole before misoprostol in 1st-trimester termination of nonviable pregnancy to the use of misoprostol alone.

**Subject and techniques:** This was a prospective randomized clinical trial including 100 patients with a history of missed abortion confirmed by ultrasonography at Al-Hussein Hospital and Al-Azhar University Cairo.

**Results:** Curettage was significantly increased in group 1 compared with group 2. The interval of hospitalization and Duration of vaginal bleeding was significantly increased in group 1 compared with group 2. There was no substantial variation between the two study groups as regard Complication occurrence after operation, Postoperative Hb, Pregnancy remnants, Gestational Age and preoperative hemoglobin, and Previous medical and Surgical History.

**Conclusion:** Letrozole may boost the success percentage of misoprostol-induced complete abortions in the first trimester of pregnancy without increasing adverse effects.

**Keywords:** Abortion, Letrozole, Misoprostol

## 1. Introduction

Abortion is 1 of the most common pregnancy problems. Missed abortion, which is described as unrecognized intrauterine mortality of embryo and fetus without expulsion of results of conception for many days or weeks after fetus's death, happens in 15–20% of diagnosed pregnancies.<sup>1</sup>

Missed abortions are managed using a range of medicinal and surgical techniques. Dilatation and curettage, as well as vacuum aspiration, are surgical techniques. Even so, as these techniques are costly and require anesthesia, medical abortion techniques are typically favored over surgical techniques, which contain prostaglandins, alone and in mixture with other drugs.<sup>2</sup>

Promoting fetal removal with medication is a medical treatment mediation option with financial advantages but less favorable results, and a success rate of 60–95%. To trigger the removal of the fetus as part of a clinical treatment plan, many medications might be employed. The great majority of nations do not have access to mifepristone pills due to their expensive cost and lack of availability, thus elective pharmaceuticals are utilized to induce early termination instead.<sup>3</sup>

Some researchers have tested mix of 2 treatments, like aromatase inhibitors, to raise therapy efficacy. Aromatase converts androgens to estrogen, which is required for pregnancy to continue. Letrozole, aromatase inhibitor, binds to iron in P450 cytochrome in reversible and competitive manner, preventing aromatase from producing oestrogen.<sup>4</sup>

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Goal of the research was to assess the impact of using letrozole before misoprostol in the termination of nonviable pregnancy in 1st trimester compared with the usage of misoprostol alone.

## 2. Patients and techniques

Al-Hussein Hospital and Al-Azhar University Hospitals undertook this prospective, randomized clinical trial with 100 patients who had missed abortions in the past that were confirmed by ultrasonography.

### 2.1. Ethical consideration

Al-Hussein Hospital and Al-Azhar University Hospitals had approved the research protocol. Every participant in research had given their verbal consent after being informed. For 6 months, confidentiality and personal privacy were respected at all stages of research (from January 2022 till June 2022).

### 2.2. Inclusion criteria for study group

Women in the child bearing period (18–45 years) and first-trimester pregnancy (gestational age less than 12 weeks) with missed abortion established by ultrasonography and hemoglobin value greater than 12 mg/dl.

### 2.3. Exclusion criteria for groups

Coagulopathy in the form of abnormal. History of any cancer, intrauterine device, history of any thromboembolic impairment, cardiovascular illness that precludes the use of misoprostol or letrozole, uterine scars, or medication sensitivity in women.

### 2.4. Sample size calculation

Using sample size estimation formula to compare 2 ratios, sample size needed for research was expected to be 50 females for each group, with confidence level of ninety five percent and power of eighty percent with  $\alpha$  5% error, based on previous research Amer *et al.*,<sup>3</sup> the sample size was 45 patients. We conducted our study on 50 patients to assume drop-out ratio. Using Random-Maker Software Random Allocation, females enrolled in research were assigned to one of 2 research groups.<sup>5</sup>

## 3. Methods

### 3.1. Ethical approval

Approval of the ethical committee was obtained, as well as written consent was signed from all cases before participation in research.

The included women were separated into 2 groups: Group 1: use Misoprostol (Misotac, SIGMA) alone (50 women). Group 2: use Letrozole (Femara, NOVARTS)+Misoprostol (Misotac, SIGMA) (50 women).

Using random allocation technique, studied cases were split into 2 groups of fifty females.

Group 2 (Drug group) got 10 mg daily Letrozole (four tablets of 2.5 mg) for three days before taking Misoprostol, while Group 1 (Placebo group) got daily oral placebo (four tablets that looked exactly like Letrozole) with same instructions.

After three days, studied cases in both groups received single dose of 600  $\mu$ g misoprostol.

Studied cases in groups who had abortion prior to actually taking misoprostol in 1st 3 days of research were excluded.

Trans abdominal and transvaginal Ultrasound examination after three to seven days of used treatment to determine the occurrence of complete or incomplete abortion.

Hemoglobin levels were measured in both groups of studied cases at start and end of research.

Studied cases were subjected to:

### 3.2. Complete history taking

Personal history containing: Name, birth date, marital state, address, consanguinity, pregnancy history: gravida, parity, previous delivery's mood, prior abortions' frequency in the past, and a history of sibling deaths, medical history: Diabetes, high blood pressure, anemia, preeclampsia, past surgical procedures, history of IUCD (intrauterine contraceptive device) usage and pregnancy age based on last menstrual period (weeks).

### 3.3. Examination

General examination: Vital signs, weight and height and chest and cardiac examination. Chest test: Inspection, palpation, Percussion and auscultation. Cardiovascular test: Inspection, taking the pulse, Palpation, auscultation and test of blood pressure.

### 3.4. Lab investigation

Hemoglobin before and after received treatment. Ultrasound examination after 3–7 days of used treatment to determine complete or incomplete abortion: The curvilinear probe is used to achieve transabdominal view while studied case is supine. Probe is attached to studied case's head above pubis symphysis in midline, with marker. During a

transvaginal examination following bladder evacuation, vaginal probe was inserted under direct visualization. The midline sagittal plane of the cervix was located, and the probe was withdrawn until the lightest touch produced a clear picture of the cervical canal with the internal os fixed in the proximal third of the image. The optimal longitudinal axis of the cervix was then obtained by shifting the probe (Fig. 1).

### 3.5. Primary outcome measures

Success rate was confirmed by transvaginal ultrasound to have complete abortion or if the remnant inside the uterus less than 2 cm, Failure rate was considered if the remnant inside the uterus 2 cm or more and so evacuation was done, and Induction period started from the first day of Miso-prostol and ended at the 7th day either by occurrence of complete abortion or incomplete and evacuation.

### 3.6. Secondary result measurements

Number of people that undergo uterine evacuation surgery due to retained product of conception (POC), number of people that need ongoing medical treatment for persistent POC, the quantity of misoprostol dosages (one or two doses) given for POC expulsion, the period of time between the first misoprostol dosage and POC ejection, patients who need blood transfusions, the proportion of patients that need analgesia based on the analgesic ladder, how many people suffer from mild side effects including pain, bleeding, fever, vomiting, and diarrhea, number of patients who need an unplanned trip to the emergency room or hospital admission, and how many people get life-threatening allergic reactions Day 1 through 28 of the study process.

### 3.7. Data management and statistical analysis

Microsoft Excel software was used to code, input, and analyze data from the history, basic clinical tests, laboratory investigations, and outcome measurements. Data were then entered into the SPSS version 20.0 program for analysis. The following tests were used to check for significance: connection by Pearson's relationship and Spearman's correlation. Depending on the type of data, qualitative data is displayed as number and percentage, quantitative



Fig. 1. (a) Ultrasonographic image prior to medical abortion. (b) Ultrasonographic image following a medical abortion.

data is displayed as mean SD, and following evaluations were utilized to check for significance. *P* values were established at <0.05 for results that were significant and <0.001 for results that were very important.

#### 4. Results

There was no variation among study groups regarding patient's demographic data (Table 1) (Fig. 2).

There was no variation among study groups regarding obstetrics history (Table 2).

There was no variation among study groups regarding Previous medical and Surgical History (Table 3).

There was no variation among study groups concerning Gestational Age and preoperative hemoglobin (Table 4).

Curettage was enlarged in group 1 compared with group 2. Pregnancy remnants of both study groups showed no significance difference (Table 5).

Interval of hospitalization and Duration of vaginal bleeding were significantly increased in group 1 compared with group 2.

There was no variation among study groups regarding Postoperative Hb (Table 6).

There was no variation among 2 study groups regarding Complication occurrence after operation.

#### 5. Discussion

One of the most frequent problems with pregnancy is abortion. One form of abortion, known as a missed abortion, is described as the undiagnosed intrauterine deaths of the embryo or fetus without expulsion of the products of conception (POC) for many days or weeks following death of the fetus. Missed abortions account for 15–20% of clinically diagnosed pregnancies.<sup>6</sup>

Goal of research was to assess impact of using letrozole before misoprostol in termination of nonviable pregnancy in 1st trimester compared with usage of misoprostol alone.

There was no difference among study groups concerning patient's demographic data.

Abbasalizadeh *et al.*<sup>7</sup> study aimed to compare effectiveness of letrozole plus misoprostol in terminating nonviable pregnancies in 1st trimester to misoprostol alone. Mean years old of the intervention group was  $29.21 \pm 4.08$  years, while the control group was  $28.53 \pm 5.24$  years ( $P = 0.402$ ). The intervention group had mean pregnancy years old of  $7.74 \pm 0.95$  weeks and the control group had mean pregnancy years old of  $8.52 \pm 1.29$  weeks depending on LMP. In addition, the average pregnancy years old depend on ultrasound was  $8.09 \pm 0.90$  weeks in the intervention group and  $8.80 \pm 1.17$  weeks in the control group. In terms of pregnancy years old, there was no variation between the 2 understudied groups ( $P = 0.103$ ). This result was in agreement with our results.

Affi *et al.*<sup>8</sup> meant to match security and efficiency of two treatment modalities in medical treatment of 1st trimesteric missed miscarriages. Their findings demonstrated that there were no ages-related differences between groups ( $P$  value = 0.48). This result was in agreement with our results.

There was no variation among study groups concerning obstetrics history. There was no variation between study groups concerning Previous medical and Surgical History.

Abbasalizadeh *et al.*<sup>7</sup> showed that in drug group, 17.2% of mothers were mentioned for blighted ovum and 82.8% were referred for missed abortion, whereas in control group, these ratios were 14.1% and 85.9%.

Like Abbasalizadeh *et al.*<sup>7</sup> study, in a clinical trial by Lee *et al.*<sup>9</sup> Letrozole treatment prior to misoprostol was studied in 168 females under sixty three years old days pregnant. Rate of complete abortion success in letrozole-treated group was greater than in misoprostol-only group. Vomiting was more common in letrozole group than in control group.

There was no variation among study groups concerning Gestational Age and preoperative hemoglobin.

Amer *et al.*<sup>3</sup> showed that there were no differences in hemoglobin levels between groups prior to the sampling.

Behroozi *et al.*<sup>10</sup> showed that despite random selection, there were differences in the mean values for gestational age based on ultrasound between the two groups ( $P < 0.05$ ).

Curettage was substantially increased in group 1 compared with group 2. Pregnancy remnants of both study groups showed no significance difference.

Table 1. Patients demographic data in both research groups.

	Group 1 (N = fifty)	Group 2 (N = fifty)	P value
Years old	29.22 ± 3.59	28.22 ± 3.66	0.17117 <sup>[t]</sup>
BMI (kg/M <sup>2</sup> )	22.92 ± 1.06	22.69 ± 1.1	0.29579 <sup>[t]</sup>
Residence			
Rural	24 (48%)	21 (42%)	0.5465 <sup>[X]</sup>
Urban	26 (52%)	29 (58%)	
Consanguinity	27 (54%)	21 (42%)	0.2298 <sup>[X]</sup>

t, T. Test; X, Chi Square test.

\* $P < 0.05$  |  $P < 0.05$  significant |  $P > 0.05$  Not Significant.



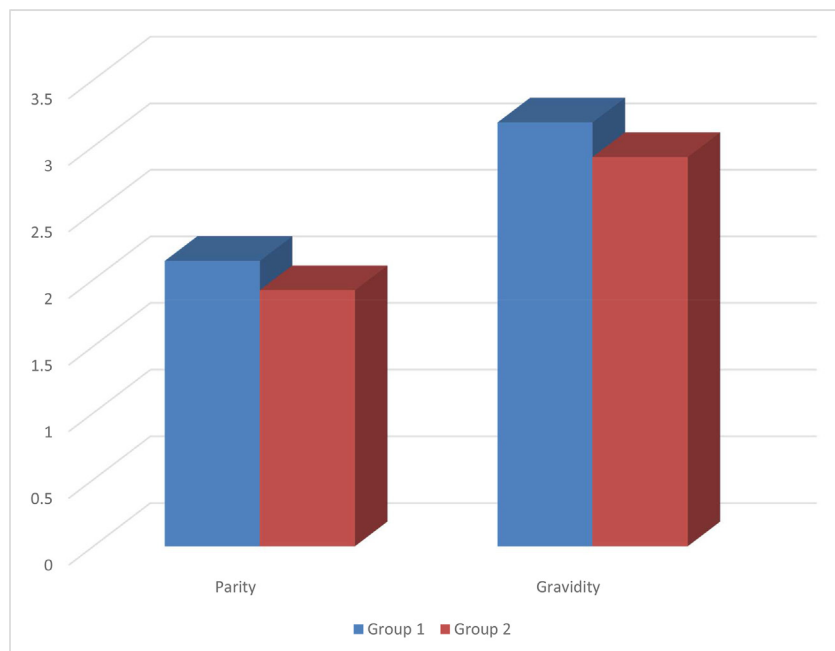


Fig. 2. Patients obstetrics history in study groups.

Table 2. Previous medical and Surgical History in study Groups.

	Group 1 (N = 50)	Group 2 (N = 50)	P value
Medical History			
Anemia	4 (8%)	2 (4%)	0.3998 <sup>[X]</sup>
DM	3 (6%)	5 (10%)	0.461 <sup>[X]</sup>
HTN	7 (14%)	6 (12%)	0.1824 <sup>[X]</sup>
Previous Abdominal Surgery	17 (34%)	17 (34%)	1 <sup>[X]</sup>
History of IUCD	21 (42%)	15 (30%)	0.2113 <sup>[X]</sup>

IUCD, Intrauterine contraceptive device; t, T. Test; X, Chi Square test.

Behroozi *et al.*<sup>10</sup> showed that concerning pregnancy, remnants there were variations among 2 groups ( $P = 0.034$ ).

Amer *et al.*<sup>3</sup> showed that Both groups of individuals saw a statistically substantial decline in Hb levels, although the misoprostol group experienced a greater decline and statistically substantial variance.

Also, Afifi *et al.*<sup>8</sup> showed that group-I had a significantly higher duration of vaginal bleeding after the 1st misoprostol dose and time passed after 1st misoprostol dose till the 1st passage of POC in comparison with group-II.

Table 3. Gestational age and preoperative hemoglobin.

	Group 1 (N = 50)	Group 2 (N = 50)	P value
GA	8.26 ± 1.85	8.28 ± 1.69	0.9551 <sup>[t]</sup>
Pre-Hb	11.82 ± 0.89	11.86 ± 0.69	0.78768 <sup>[t]</sup>

GA, Gestational Age; Pre-Hb, Preoperative hemoglobin; t, T. Test; X, Chi Square test.

Table 4. Curettage and Pregnancy remnants in both study groups.

	Group 1 (N = 50)	Group 2 (N = 50)	P value
Curettage	34 (68%)	9 (18%)	<0.00001* <sup>[X]</sup>
Pregnancy remnants (CC)	15.39 ± 4.72	14.82 ± 5.23	0.66302 <sup>[t]</sup>

There was no significant variation among 2 study groups concerning problem occurrence after operation.

Drugs side effects in 2 study groups throughout research are presented in Abbasalizadeh *et al.*<sup>7</sup> The intervention group's abdominal pain was lower than control group's ( $P = 0.013$ ). When comparing period of bleeding between two groups, drug group had lower period of bleeding than control group ( $P = 0.006$ ).

Afifi *et al.*<sup>8</sup> showed that nonsignificant change was found among groups in regard to the occurrence of side effects (37 studied cases in group-I versus 32 studied cases in group-II, ( $P$  value = 0.46), but nausea and vomiting were prevalent in group-II.

Table 5. Postoperative evaluations in both study groups.

	Group 1 (N = 50)	Group 2 (N = 50)	P value
The interval of hospitalization	4.4 ± 1.7	2.18 ± 1.1	<0.00001* <sup>[t]</sup>
Duration of vaginal bleeding	3.78 ± 1.18	1.8 ± 0.81	<0.00001* <sup>[t]</sup>
Post Hb	10.94 ± 0.73	11.15 ± 0.59	0.11728 <sup>[t]</sup>

Hb, Hemoglobin; t, T. Test; X, Chi Square test.

Table 6. Complication occurrence in groups after operation.

	Group 1 (N = 50)	Group 2 (N = 50)	P value
Nausea	24 (48%)	29 (58%)	0.3164 <sup>[X]</sup>
Vomiting	21 (42%)	26 (52%)	0.316 <sup>[X]</sup>
Diarrhea	18 (36%)	21 (42%)	0.5385 <sup>[X]</sup>
Abdominal pain	33 (66%)	37 (74%)	0.3827 <sup>[X]</sup>
Dizziness	23 (46%)	26 (52%)	0.5484 <sup>[X]</sup>
Fever	14 (28%)	17 (34%)	0.5166 <sup>[X]</sup>

‡, T. Test; X, Chi Square test.

\* $P < 0.05$  |  $P < 0.05$  significant |  $P > 0.05$  Not Significant.

On the other hand, Abbasalizadeh *et al.*<sup>7</sup> found that side effects of Letrozole + Misoprostol were significantly low in comparison to that of Misoprostol only ( $P$ -value = 0.013).

Also, Naghshineh *et al.*<sup>11</sup> reported that letrozole + Misoprostol achieved a complete abortion rate of 76.7% in comparison to 42.6% using Misoprostol alone ( $P < 0.001$ ).

Furthermore, Lee *et al.*<sup>9</sup> reported that the administration of Letrozole for 3 days followed by misoprostol achieved greater rate of success of complete abortions versus Misoprostol alone (86.9% vs. 72.6%).

### 5.1. Strengths points and limitations

The comparatively large number of subjects included is one of the study's strengths, but it also has certain drawbacks. Regarding the restrictions, we were unable to compare the effectiveness of various misoprostol dosages with regard to reducing side effects, as well as the various administration methods.

### 5.2. Conclusion

Letrozole was prescribed before misoprostol to increase the drug's effectiveness in causing a complete abortion of a nonviable fetus in the first trimester of pregnancy. Letrozole was not harmful to patients' health, and the amount of time that they experienced abdominal pain and bleeding was also significantly reduced.

Letrozole may boost the success percentage of misoprostol-induced complete abortions in the first trimester of pregnancy without enhancing adverse effects.

## Disclosure

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## Conflicts of interest

No.

## References

- Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. *Cochrane Database Syst Rev.* 2017;1:CD007223.
- Wu HL, Marwah S, Wang P, Wang QM, Chen XW. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. *Sci Rep.* 2017;7:1664.
- Amer W, Abdel-Hai M, Osman I. Letrozole and misoprostol vs. misoprostol alone in management of first trimester missed abortion, a randomized controlled trial. *Benha J Appl Sci.* 2021; 6:149–153.
- Rezai Z, Heydari Bazardehi SS, Ghasemi Nezhad A, Sadeghi AS, Ghorbani YB. Letrozole and misoprostol versus misoprostol alone for termination of pregnancy: a randomized clinical trial. *Tehran Univ Med J.* 2014;71:700–706.
- Saghaei M. Random allocation software for parallel group randomized trials. *BMC Med Res Methodol.* 2004;4:26.
- Bankole A, Adewole IF, Hussain R, Awolude O, Singh S, Akinyemi JO. The incidence of abortion in Nigeria. *Int Perspect Sex Reprod Health.* 2015;41:170.
- Abbasalizadeh F, Sahhaf F, Sadeghi-Shabestari P, Mirza-Aghazadeh-Attari M, Naghavi-Behzad M. Comparison between effect of letrozole plus misoprostol and misoprostol alone in terminating non-viable first trimester pregnancies: a single blind randomized trial. *J Family Reprod Health.* 2018;12: 27–33. PMID: 30647756; PMCID: PMC6329994.
- Affi AE, Hassan F, Mohammed M. Misoprostol versus Letrozol with Misoprostol in management of first trimester missed miscarriage. *Al-Azhar Int Med J.* 2021;2(10):59–65. <https://doi.org/10.21608/aimj.2021.89692.1545>.
- Lee VC, Ng EH, Yeung WS. Misoprostol with or without letrozole pretreatment for termination of pregnancy: a randomized controlled trial. *Obstet Gynecol.* 2011;117:317–323.
- 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 Human Reprod.* 2018;47:113–117. <https://doi.org/10.1016/j.jogoh.2017.11.002>.
- Naghshineh E, Allame Z, Farhat F. The effectiveness of using misoprostol with and without Letrozole for successful medical abortion: a randomized placebocontrolled clinical trial. *J Res Med Sci.* 2015;20:585–589.