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# Letrozole & Misoprostol vs Misoprostol in Induction of 1st Trimesteric Abortion

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## Abstract:

**Background:** A medical abortion in the first trimester is a safe and effective method to terminate a pregnancy, allowing women to make informed reproductive decisions. This study examined the safety and effectiveness of a combination of misoprostol and letrozole compared to misoprostol alone for medical abortions in the first trimester. **Methods:** Eighty women who visited the Obstetrics and Gynecology Department at Benha University Hospitals were part of a randomized trial. They were divided into two groups: Group I (Misoprostol) received a placebo for three days, followed by 800 µg of Misoprostol vaginally. Group II (Letrozole + Misoprostol) received 10 mg of Letrozole orally for three days, followed by 800 µg of Misoprostol vaginally. **Results:** Group I had a significant decrease in hemoglobin levels (0.65±0.14) compared to Group II (0.48±0.24), with a p-value of <0.001. Group II showed a higher success rate (p=0.044) and a shorter induction to abortion interval (p=0.006). Group I experienced more adverse effects (p=0.007). **Conclusion:** A combination of Letrozole and Misoprostol is a safer and more effective option than Misoprostol alone for first-trimester medical abortions.

**Keywords:** Letrozole; Misoprostol; Misoprostol; Induction; 1st Trimesteric Abortion.

## Introduction

First-trimester medical abortion is a safe and effective option for ending a pregnancy. While misoprostol alone is commonly used, recent studies show that combining it with other drugs, such as the aromatase inhibitor letrozole, may improve effectiveness and reduce side effects [(1)].

The corpus luteum secretes progesterone to maintain early pregnancy. Medical abortion induces a deliberate decline in this hormone, facilitating the expulsion of the pregnancy [(2)].

Misoprostol, a key drug for medical abortion, softens the cervix and contracts the uterus. While effective, it doesn't always complete the abortion on its own, sometimes necessitating an additional procedure [(3)].

An aromatase inhibitor like letrozole blocks the enzyme aromatase, which changes androgens into estrogens. Misoprostol may work better if letrozole, which lowers estrogen levels, aids in the corpus luteum's breakdown and progesterone withdrawal [(4)].

The letrozole-misoprostol regimen could offer significant benefits over misoprostol alone, including higher complete abortion rates, fewer surgical interventions, and a faster process, improving patient satisfaction [(5)].

Based on its results, this study could inform clinical guidelines for medical abortion, potentially leading to a safer and more effective regimen. It also contributes valuable evidence to the developing field of evidence-based reproductive healthcare.

This study compared the safety and efficacy of letrozole-misoprostol versus misoprostol-alone for first-trimester medical abortion. Key outcomes included complete abortion rate (without surgical intervention), the induction-to-abortion interval, and the frequency of side effects.

## Patients and methods

This prospective, randomized, controlled trial was approved by the Research Ethics Committee of Benha University's Faculty of Medicine (approval no. MS 34-11-2022). The study enrolled 80 pregnant women at the Obstetrics and Gynecology Department between December 2023 and December 2024. All participants provided written informed consent after the study's objectives were explained, and each was assigned a confidential code number.

**Inclusion criteria were** the following conditions must be met: the gestational age must be less than 13 weeks as measured by the last menstrual period (LMP), the ultrasound must confirm that the pregnancy is not viable inside the uterus (a missed abortion), the mother must be at least 18 years old, and she must not have any serious medical conditions, such as heart disease, asthma, thromboembolism, cancer, renal failure, or liver disease.

**Exclusion criteria were** this pregnancy has been tried before, there is an intrauterine contraceptive device, the uterus is abnormal (e.g., fibroids or malformations), the patient is in immediate need of medical treatment for any reason, the patient has a history of adverse reactions to Misoprostol or Letrozole, or the patient refuses to participate.

**Randomization:**

Eighty women who had an abortion during the first trimester but did not complete it were divided into two equal groups: Group I (Misoprostol): A placebo of letrozole was taken orally twice a day for three days, followed by 800 µg of Misoprostol (Misotac, Tab. 200 µg Sigma ®, Egypt) given vaginally as a single dose. Group II (Letrozole + Misoprostol): Oral administration of 10 mg of Letrozole (Femara Tab. 2.5 mg, Novartis ®, Egypt) twice a day for three days, followed by a vaginal administration of 800 µg of Misoprostol.

The demographic, maternal characteristics were extracted during their antenatal health care visit.

**All cases studied were subjected to the following:**

**History, including** Extensive medical background, including personal details

(age, marital status, occupation, smoking), obstetric details (previous pregnancies, abortions, ectopic pregnancies, outcomes), and current pregnancy details (LMP, estimated gestational age), as well as previous medical and family conditions.

**Clinical examination including** [vital signs blood pressure, pulse, temperature, weight, height, and body mass index (BMI)].

**Laboratory investigations including** [full blood count, blood group and Rh type and coagulation profile (prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen)].

**Ultrasound** among other things, a transvaginal ultrasound can confirm a missed abortion and find out how far along in the pregnancy the baby is. Other criteria for a missed abortion diagnosis usually include a fetal pole with a crown-rump length of at least 7 mm and no signs of heart activity, as well as a mean gestational sac diameter of at least 25 mm without a visible yolk sac.

Patients were instructed to record: the start date of vaginal bleeding and tissue passage, the severity and frequency of pain and bleeding (mild/moderate/severe), and the duration of any side effects (e.g., nausea, vomiting, fever, shivering, colic). They were also advised to return to the clinic on days 3 and 7 after taking misoprostol, or earlier if severe side effects, acute pain, or heavy bleeding occurred [(6)].

An ultrasound was performed on day 3 to assess abortion completeness. If the abortion was missed or incomplete, a second misoprostol dose was given. A follow-up ultrasound and evacuation were performed on day 7 if needed. A uterine remnant ≥2 cm was classified as an incomplete abortion.

**Outcomes:**

The success rate of full-term abortions is one of the main outcomes. Among the unintended consequences include the length of time the patient is bleeding, the frequency with which adverse symptoms occur, and the need for emergency medical evacuation.

**Approval code:** MS 34-11-2022

**Statistical analysis**

Statistical analysis was performed using SPSS version 23.0. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data are presented as mean ± SD or median (IQR) for quantitative variables, and as numbers (percentages) for categorical variables. Comparisons were made using the independent t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. A p-value $< 0.05$ was considered statistically significant.

## Results

**Table 1** there was no statistically significant difference between the groups when it came to the following variables: age, parity, body mass index (BMI), gestational age (GA) as measured by live birth weight (LMP), method of delivery (MOD), anemia ($p>0.05$), and surgical history. In group 1, the delta hemoglobin (Hb) decrease value was 0.65±0.14, which was significantly different from group 2's 0.48±0.24, as shown by the p-value ($p<0.001$).

**Table 2** demonstrates a statistically significant increase in the frequency of the successful result from 37.5% in group 1 to 60.0% in group 2, with a p-value of just 0.044.

**Table 3** provides a statistically significant difference between the two groups, with a median value of 14 (ranging from 0 to 24 hours) for group 1 and 9 (ranging from 0 to 11 hours) for group 2 ($p=0.006$).

**Table 4** reveals a significantly greater incidence of adverse effects in group 1 (39 patients, or 97.5% of the total) compared to group 2 (31 patients, or 77.5% of the total), with a p-value of around 0.007.

**Table 1:** Comparison between Group 1and Group 2 according to Baseline characteristics, mode of delivery, medical history, surgical history, and Hb

| | | Group 1 (n=40) | Group 2 (n=40) | Test value | p-value | Sig. |
|---|---|---|---|---|---|---|
| Baseline characteristics | **Age (years)** | | | | | |
| | **Mean±SD** | 29.33±6.38 | 28.13±6.85 | 0.811 | 0.420 | NS |
| | **Range** | 20-41 | 19-40 | | | |
| | **Parity** | | | | | |
| | **Multipara** | 32 (80.0%) | 30 (75.0%) | 0.287 | 0.592 | NS |
| | **Nullipara** | 8 (20.0%) | 10 (25.0%) | | | |
| | **BMI** | | | | | |
| | **Mean±SD** | 24.44±2.49 | 24.49±2.74 | -0.090 | 0.929 | NS |
| | **Range** | 20-28 | 19.5-29 | | | |
| | **GA by LMP** | | | | | |
| | **Mean±SD** | 7.06±0.50 | 6.88±0.33 | 1.056 | 0.582 | NS |
| | **Range** | 7-8 | 6-7 | | | |
| Mode of delivery | **CS** | 15 (37.5%) | 7 (17.5%) | 5.881 | 0.118 | NS |
| | **VD** | 17 (42.5%) | 17 (42.5%) | | | |
| | **VD and CS** | 4 (10.0%) | 6 (15.0%) | | | |
| Medical History | **Anaemia** | 3 (7.5%) | 2 (5.0%) | 0.213 | 0.644 | NS |
| | **Free** | 37 (92.5%) | 38 (95.0%) | | | |
| Surgical History | **Appendectomy** | 1 (2.5%) | 2 (5.0%) | 0.342 | 0.558 | NS |
| | **Breast lobectomy** | 0 (0.0% | 1 (2.5%) | 1.000 | 0.317 | NS |
| | **Cholecystectomy** | 1 (2.5%) | 0 (0.0%) | 1.000 | 0.317 | NS |
| | **CS** | 17 (42.5%) | 12 (30.0%) | 1.335 | 0.248 | NS |
| | **D&C** | 3 (7.5%) | 2 (5.0%) | 0.211 | 0.646 | NS |
| | **Haemorrhoidectomy** | 1 (2.5%) | 0 (0.0%) | 1.000 | 0.317 | NS |
| Hb g/dL | **Hb before** | | | | | |
| | **Mean±SD** | 10.94±1.29 | 11.39±0.99 | -1.753 | 0.084 | NS |
| | **Range** | 8-13 | 9.8-13.2 | -- | -- | -- |
| | **Hb after** | | | | | |
| | **Mean±SD** | 10.29±1.30 | 10.92±1.00 | -2.402 | **0.019** | **S** |
| | **Range** | 7.5-12.7 | 9-12.8 | -- | -- | -- |
| | **Delta** | | | | | |
| | **Mean±SD** | 0.65±0.14 | 0.48±0.24 | 3.911 | **0.000** | **HS** |

Data presents as mean ± SD or range or numbers. Hb: haemoglobin, CS: caesarean section, VD: vaginal delivery, using: t-Independent Sample t-test for Mean ± SD; Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate, NS: Non-significant; S: Significant; HS: Highly significant, Group I: 40 cases receiving misoprostol alone, Group II: 40 women receiving Letrozole + misoprostol.

**Table 2:** Comparison between group 1and group 2 according to result (Outcome)

| Result (Outcome) | Group 1 (n=40) | Group 2 (n=40) | OR (95% C.I.) | p-value | Sig. |
|---|---|---|---|---|---|
| Failed | 25 (62.5%) | 16 (40.0%) | 2.5 | **0.046** | **S** |
| Succeeded | 15 (37.5%) | 24 (60.0%) | (1.02-6.15) | | |

Data presents as frequency (%). Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate NS: Non-significant; S: Significant; HS: Highly significant

**Table 3:** Comparison between group 1and group 2 according to induction-to-abortion interval (hour)

| Induction-to-abortion interval (hour) | Group 1 (n=40) | Group 2 (n=40) | Test value | p-value | Sig. |
|---|---|---|---|---|---|
| Median (IQR) | 14 (0-24) | 9 (0-11) | 2.835 | **0.006** | **S** |
| Range | 0-46 | 0-22 | | | |

Data presents as Median (IQR) or range. IQR: Interquartile range, Using: U=Mann-Whitney test for non-parametric data "Median (IQR)", S: Significant; p value <0.05.

**Table 4:** Comparison between group 1and group 2 according to side effects

| | Group 1 (n=40) | Group 2 (n=40) | Test value | p-value | Sig. |
|---|---|---|---|---|---|
| Side Effects | 39 (97.5%) | 31 (77.5%) | 7.223 | **0.007** | **S** |
| Lower abdominal pain | 25 (62.5%) | 17 (42.5%) | 3.168 | **0.075** | **S** |
| Mild bleeding | 1 (2.5%) | 20 (50.0%) | 23.018 | **0.001** | **S** |
| Mild to moderate vaginal bleeding | 16 (40.0%) | 0 (0.0%) | 19.750 | **0.001** | **S** |
| Nausea | 0 (0.0%) | 12 (30.0%) | 13.941 | **0.001** | **S** |
| Minimal bleeding | 5 (12.5%) | 4 (10.0%) | 0.124 | 0.725 | NS |
| Mild vaginal bleeding | 8 (20.0%) | 0 (0.0%) | 8.778 | **0.003** | **S** |
| Minimal to Mild vaginal bleeding | 8 (20.0% | 0 (0.0%) | 8.778 | **0.003** | **S** |
| Back pain | 0 (0.0%) | 2 (5.0%) | 2.026 | 0.155 | NS |
| Dizziness | 0 (0.0%) | 1 (2.5%)) | 1.000 | 0.317 | NS |
| Headache | 0 (0.0%) | 1 (2.5%) | 1.000 | 0.317 | NS |
| Moderate vaginal bleeding | 1 (2.5%) | 0 (0.0%) | 1.000 | 0.317 | NS |

Data presents as frequency (%). Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate
NS: Non-significant; S: Significant; HS: Highly significant.

## Discussion

Medical abortion in the first trimester is a safe and effective procedure [(7)]. While the combined regimen of mifepristone and misoprostol is standard, misoprostol-alone is used when mifepristone is unavailable, though it may be less effective and require higher doses [(8,9)].

Letrozole, an aromatase inhibitor used in breast cancer, is being studied for its role in medical abortion. The current study found significantly lower hemoglobin reduction (delta Hb) in the letrozole-plus-misoprostol group compared to misoprostol-alone, suggesting letrozole may mitigate bleeding [(10)]. This aligns with prior research indicating misoprostol can increase post-abortion bleeding [(11)], an effect which varies by dosage and administration route [(12)].

Letrozole may protect hemoglobin levels by modulating the hormonal environment to reduce excessive bleeding. This is supported by studies showing hormonal manipulations, including aromatase inhibitors, can decrease blood loss during abortion [(13,14)].

Studies show misoprostol alone is effective for early pregnancy termination without significant concern for hemoglobin drop [(15)]. However, its use can be associated with clinically relevant decreases in hemoglobin, increasing risks like anemia and the need for intervention; thus, blood loss remains a critical management consideration [(16)].

The combination of letrozole and misoprostol may offer a safer profile, particularly for patients prone to heavy bleeding [(17)]. The difference in hemoglobin levels between regimens may also be influenced by patient-specific factors like comorbidities and dosage. Future research

should control for these variables to better understand the outcomes, as personalized treatment approaches are essential for safe and effective care [18].

In this study, the letrozole and misoprostol regimen was 2.5 times more effective than misoprostol alone.

Combining Letrozole with Misoprostol may improve medical abortion efficacy, though evidence is conflicting. Allameh et al. [14] and a meta-analysis by Yazdani et al. [19] found the combination significantly more successful than Misoprostol alone, potentially by enhancing uterine readiness. However, a randomized trial by Chai et al. [20] showed no significant difference in success rates. These discrepancies may be due to variations in dosage, timing, or sample size. Therefore, while promising, the combination therapy requires further large-scale studies for validation [20, 21].

Despite promising results, the long-term safety, and ethical considerations of using letrozole—a drug for fertility treatments—for abortion remain unclear [22]. Although the letrozole-misoprostol combination significantly shortened the induction-to-abortion time compared to misoprostol alone, reflecting possible synergistic effects [24, 26], findings are inconsistent across studies [25]. Further research is essential to confirm the safety, efficacy, and ethical implications of this off-label protocol [22, 23].

The Letrozole-Misoprostol regimen demonstrated a shorter induction-to-abortion interval, which improves patient comfort, reduces complication risks, and may optimize healthcare resources [17]. This combination also resulted in fewer and less severe adverse effects, such as abdominal pain and bleeding, compared to misoprostol alone [30].

However, Soon et al. [27] suggest individual variation in hormone receptors may limit efficacy for some, necessitating more stratified research. Furthermore, Grossman et al. [28] raise ethical and cost concerns, noting letrozole may be inaccessible in resource-limited settings.

While promising, these findings require validation in larger, multicentric studies across diverse populations to account for confounding variables and ensure generalizability [29]. Further investigation into the long-term safety of this combination is also warranted.

The difference in adverse effects may be attributed to the pharmacodynamics of the drugs. Misoprostol, a prostaglandin analog, induces uterine contractions—leading to abortion—but also causes gastrointestinal discomfort and heavy bleeding. Letrozole, an aromatase inhibitor, reduces estrogen levels and may sensitize the uterus to misoprostol, potentially improving efficacy and moderating side effects. This is supported by Mohammed et al. [31], who found the combination improved abortion success and reduced adverse effects.

The more frequent and severe side effects in the misoprostol-only group may result from unmodulated prostaglandin activity. However, conflicting evidence exists, such as Javanmanesh et al. [32], who reported no significant reduction in side effects with letrozole, suggesting context-specific outcomes.

No significant differences in baseline characteristics (age, parity, BMI, gestational age) were observed between groups, indicating well-matched cohorts and supporting the methodological rigor of the trial, consistent with other studies [33].

Despite the theoretical benefit of letrozole increasing uterine sensitivity to misoprostol, this study found no statistically significant differences in outcomes between the combination therapy and misoprostol-alone groups [34]. This aligns with previous research questioning letrozole's additive efficacy.

Both regimens demonstrated comparable safety profiles, reinforcing the established safety of misoprostol for first-trimester abortion [35]. However, further investigation is needed to determine if letrozole could benefit specific subgroups

(e.g., prior uterine surgery) or reduce misoprostol-related side effects.

Although letrozole may improve efficacy by reducing gestational sac retention, our data showed no significant difference in abortion success or delivery outcomes. This consistent finding across studies [(36)] suggests that the clinical impact of letrozole on key outcomes remains unclear, warranting caution in standardizing its use in existing protocols.

This study found no statistically significant differences in the prevalence of anemia or prior surgical history between the two groups.

Letrozole is used in medical abortion for its anti-estrogenic effect, which primes the endometrium for prostaglandin-induced expulsion. While our results show no significant differences in these baseline characteristics, they contribute to the growing research on the letrozole-misoprostol regimen. Few studies have examined its effect on clinical variables like surgical history and anemia, despite its potential to improve outcomes [(37)].

Our data underscores the importance of considering patient factors like baseline hemoglobin and surgical history. Future studies should compare the efficacy and safety of letrozole-misoprostol to misoprostol alone in groups with similar rates of these characteristics, which may help identify subgroups that respond better to specific regimens [(38)].

From a safety perspective, all regimens appear equally feasible regarding these parameters. However, larger randomized controlled trials are needed to validate these findings and investigate critical outcomes such as success rates, patient satisfaction, and cost-effectiveness. A deeper understanding of these features will help refine medical abortion guidelines for diverse patient groups [(39)].

## Conclusion

The letrozole-misoprostol regimen shows promise as a superior treatment for first trimester missed abortion compared to misoprostol alone. Further research should focus on larger trials, long-term outcomes, and measuring patient experiences to solidify its role in improving care.

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**Conflicts of interest**

No conflicts of interest

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