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Comparing the Effects of Misoprostol/Letrozole and Misoprostol/Placebo on Medical Abortion Success Rate: A Randomized Clinical Trial

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Abstract

Background: Abortion is the medical or surgical termination of pregnancy before the 20th week. However, dilation and curettage have been associated with hazards such as uterine rupture, heavy bleeding, and infection. Therefore, in recent decades, pharmacological therapies have become more widely accepted.
Objectives: This research compared the medical abortion success rates of misoprostol/letrozole versus misoprostol/placebo.
Methods: This randomized clinical study was conducted at Mashhad University of Medical Sciences hospitals between 2018 and 2019, involving pregnant women who were candidates for medical abortion. The study population was divided into two groups based on whether they had undergone cesarean section (CS). Each group was randomly assigned to either a control or an intervention group. In the CS group, there were 52 patients in the intervention group and 52 in the control group. The control group received a regimen of misoprostol and placebo, while the intervention group received a combination of misoprostol and letrozole.
Results: There was no statistically significant difference in age (31.59 ± 5.6 vs. 31.06 ± 4.6, P value = 0.605), gestational age by ultrasound (11.20 ± 3.3 vs. 10.29 ± 2.6, P value = 0.135), or blood pressure between the control and intervention groups. However, the analysis showed a statistically significant difference in the rate of complete abortion (12 (23.5%) vs. 28 (54.9%), P value = 0.001) between the two groups. In the non-CS group, there was a significant difference in age between the control and intervention groups. The study analyses also revealed a significant difference in the rate of complete abortion between the two groups (24 (46.2%) vs. 36 (72.0%), P value = 0.008).
Conclusions: Letrozole is recommended in combination with misoprostol for medical abortions because it increases the likelihood of complete abortion and reduces the duration of the abortion process.

Keywords: Abortion, Misoprostol, Letrozole

1. Background

Abortion means terminating a pregnancy before the twentieth week through medical or surgical means (1). It may be utilized as a treatment when the mother's or fetus's health is at risk (therapeutic abortion) or when a woman desires pregnancy termination due to an unexpected pregnancy (elective abortion). Globally, there are around 205 million pregnancies yearly, and more than a third of them are unplanned, with one-fifth of mothers desiring an induced abortion (2, 3). Most abortions are performed to avoid unwanted pregnancies, while most therapeutic abortions aim to prevent the birth of a child with physical, metabolic, or cognitive abnormalities (4). The choice of procedure depends on the gestational age and the patient's preferences. The success rate for surgical abortions during the first trimester is approximately 98 percent, with a complication rate of about 7.8 percent (5). The success rate of medical abortions is not as high as that of surgical abortions, and approximately 4 to 10 percent of patients require curettage due to an incomplete abortion. One advantage of medical abortion is that it does not require surgery or anesthesia. However, a disadvantage is the time needed to complete the process and the likelihood of

an incomplete abortion (6, 7).

Dilation and curettage used to be a primary therapy for first-trimester abortion, but it came with risks such as uterine rupture, excessive bleeding, and infection (8). Therefore, non-invasive medicinal therapies have been advocated as an acceptable treatment in recent decades. Among them, the most common approach is mifepristone with misoprostol or misoprostol alone, and hygroscopic dilators may be used in conjunction with this approach (9, 10). In addition to treating gastric ulcers, misoprostol improves cervical effusion and induces uterus contractions (11). Letrozole, a third-generation non-steroidal aromatase inhibitor, has a half-life of approximately 45 hours and is eliminated from the body through the liver. Its antiestrogenic properties treat breast cancer (12). Recent trials have used letrozole in conjunction with misoprostol to induce abortion. By reducing estrogen production from the corpus luteum, this medication can assist in inducing abortion.

2. Objectives

This study aimed to compare the success rate of medical abortions between misoprostol/letrozole and misoprostol/placebo.

3. Methods

This double-blind, randomized clinical trial was conducted on pregnant women who were candidates for medical abortion at the teaching hospitals of Mashhad University of Medical Sciences between 2018 and 2019. The inclusion criteria were: Age over 18 years, gestational age under twenty weeks as determined by ultrasound, hemoglobin level above 10 dl/mg, lower diastolic pressure less than 95 mmHg, no history of thromboembolism, malignancy, or liver disease, no history of asthma or porphyria, and no intrauterine device (IUD) in place. The exclusion criteria included drug sensitivity and patient refusal to participate.

3.1. Study Design

After obtaining written informed consent, eligible women were separated into two groups based on their history of cesarean section. The groups were randomly assigned to either the intervention or control group within each subgroup. A computer software-generated list of 104 numbers was used for each subgroup. Each number corresponded to a patient and was written on a prepared envelope containing either four pieces of letrozole or four pieces of placebo. The patients were instructed on taking the medication, and both the patient and the nurse who provided the envelope were unaware of the group to which the patient was assigned. In the cesarean section group, 52 patients were included in each group. The intervention group was given letrozole 2.5 mg every 6 hours (manufactured by Iran Hormone Company) two days before admission. The third dose of letrozole was taken at the time of admission. Misoprostol was administered vaginally to both groups after admission, and the dosing was adjusted based on gestational age and national norms. Adverse symptoms such as fever and chills, nausea and vomiting, headache, and rash were monitored by a midwife unaware of the group assignment. Patients who underwent abortion were evaluated with ultrasound 12 hours after the abortion to ensure complete abortion. An endometrial thickness of less than 15 mm was defined as complete abortion, while a thickness greater than 15 mm was considered incomplete and required curettage. The consort diagram is shown in Figure 1.

3.2. Outcomes

The primary outcome of this study was the rate of complete abortion in each group. The secondary outcomes were the total dose of misoprostol used for complete abortion and the time interval between the first misoprostol dose and abortion.

3.3. Statistical Analysis

The collected data were analyzed using SPSS version 16 software. Descriptive statistical methods, including central indicators, dispersion, and frequency distribution, were used to overview the data in tables and graphs. An independent *t*-test was used to compare quantitative variables between the two groups when the data were normally distributed, while the Mann-Whitney test was used otherwise. The chi-square test and Fisher's exact test were used to analyze qualitative factors between the two groups. The significance level for all analyses was set at 0.05. The sample size was determined based on the similar study (13), which provided the necessary variables for computing the sample size. With a significance level of $\alpha = 0.05$, power of $\beta = 0.1$, P1 = 76.7%, and P2 = 42.6%, a sample size of 41 participants was calculated for each group using the PASS program. Fifty-two participants were included in each group, comprising 208 participants, to account for a hypothetical 20% dropout rate.

3.4. Ethics

The ethics committee approved the study protocol recorded on the clinical trial site. All patients completed the informed consent form and were removed from the trial if unsatisfied. Patients were also assured that all

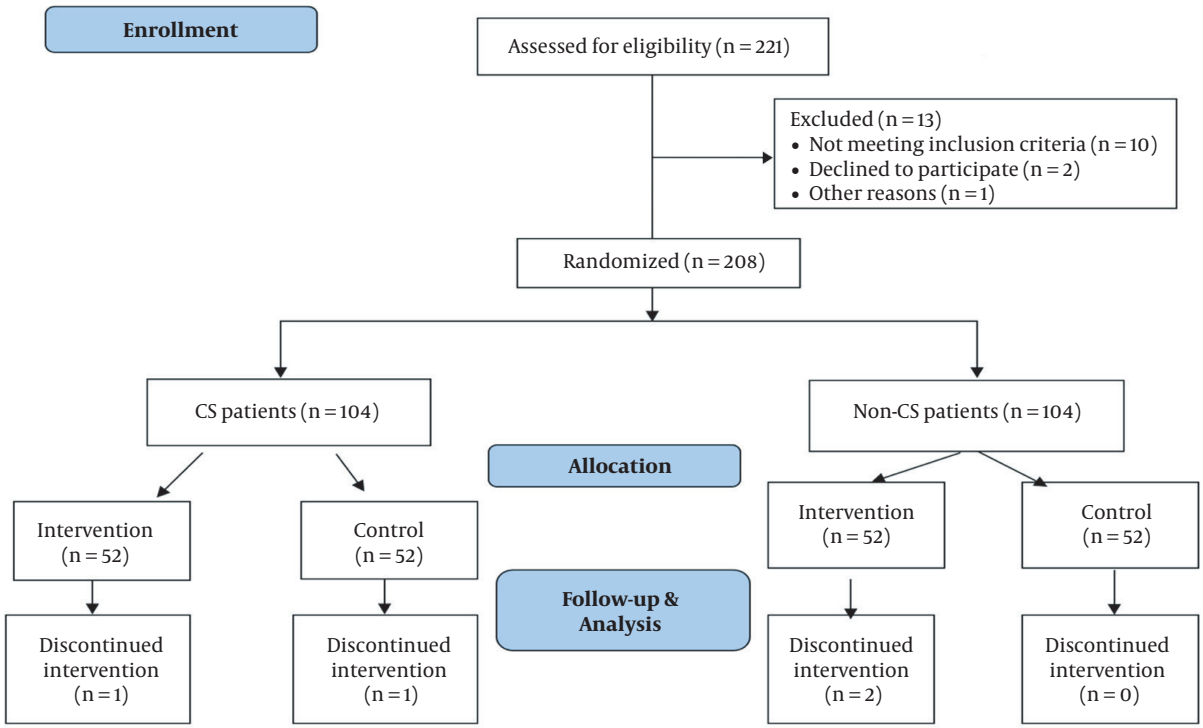

Figure 1. Consort diagram of the study

their information would be evaluated anonymously, and their identities would not be disclosed in the research. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the code IR.MUMS.fm. REC.1395.569. The study protocol was registered in IRCT with IRCTID: IRCT2017042933680N1 (Link: https://fa.irct.ir/trial/25916).

4. Results

The study results are presented in two sections: The group with a previous history of cesarean section (CS group) and the group with no history of cesarean section (non-CS group).

As presented in Table 1, the CS group consisted of 52 patients in the intervention group and 52 in the control group. The mean age in the control and intervention groups was 31.59 ± 5.6 and 31.06 ± 4.6, respectively, and no statistically significant difference was found between the two groups (P = 0.605). Similarly, the mean gestational age, determined by sonography, in the control and intervention groups was 11.20 ± 3.3 and 10.29 ± 2.6 weeks, respectively, which did not show a statistically significant difference between the two groups (P = 0.135). Additionally, the two groups had no significant difference in systolic blood pressure (P = 0.66).

Furthermore, the study compared the rate of complete abortion between the two groups. The results showed that the rate of complete abortion in the intervention group was significantly higher than in the control group (P = 0.001). There was no significant difference between the misoprostol dose in the control group and the intervention group in the CS group (P = 0.111). However, there was a significant difference in the time interval between the first misoprostol dose and abortion between the two groups (P < 0.001) (Table 2).

In the non-CS group, the study included 52 patients in the control group and 50 in the intervention group. The mean age in the control and intervention groups was 29.50 ± 7.4 and 27.8 ± 6.16, respectively. There was no statistically significant difference between the two groups (P = 0.078). The mean gestational age by ultrasound in the control and intervention groups was 9.88 ± 3.9 and 9.46 ± 2.09 weeks, respectively, showing no statistically significant difference (P = 0.500). However, a significant difference was found between the systolic blood pressure of the two groups (P = 0.356) (Table 3).

As shown in Table 4, the rate of complete fetal excretion

Table 1. Characteristics of the Control and Intervention Groups in the Cesarean Section Patients [a]

Characteristics	Control Group (N = 51)	Intervention Group (N = 51)	P-Value
Age (y)	31.59 ± 5.6	31.06 ± 4.6	0.605
Gestational age by ultrasound (weeks)	11.20 ± 3.3	10.29 ± 2.6	0.135
Blood pressure (mmHg)	107.06 ± 4.6	107.45 ± 4.4	0.66

[a] Values are expressed as Mean ± SD.

Table 2. Comparison of Complete Abortion, Misoprostol Dose, and Time Interval Between First Misoprostol Dose and Abortion in the Control and Intervention Groups Among Cesarean Section Patients [a]

	Control Group (N = 51)	Intervention Group (N = 51)	P-Value
Complete abortion			0.001
Yes	12 (23.5)	28 (54.9)	
No	39 (76.5)	23 (45.1)	
Misoprostol dose (mg)	1039.22 ± 583.8	1223.53±573.6	0.111
The time interval between the first misoprostol dose and abortion	10.71 ± 2.5	6.65 ± 2.1	< 0.001

[a] Values are expressed as No. (%) or Mean ± SD.

Table 3. Characteristics of the Control and Intervention Groups in Non-cesarean Section Patients [a]

Characteristics	Control Group (N = 52)	Intervention Group (N = 50)	P-Value
Age (y)	29.50 ± 7.4	27.8 ± 6.16	0.078
Gestational age by ultrasound (weeks)	9.88 ± 3.9	9.46 ± 2.09	0.500
Blood pressure (mmHg)	107 ± 4.6	107.80 ± 4.98	0.356

[a] Values are expressed as Mean ± SD.

in the intervention group was significantly higher than that of the control group in the non-CS patients. The complete abortion rate was higher in the intervention group (P = 0.008). There was no significant difference between the misoprostol dose in the control group and the intervention group in the non-CS group (P = 0.172). However, there was a significant difference in the time interval between the first misoprostol dose and abortion between the two groups (P = 0.003).

The study did not observe any side effects in any of the groups, including nausea, vomiting, fever, or rash.

5. Discussion

Compared to surgery, abortion has fewer adverse effects, such as bleeding and infection, and it puts less stress on patients (13). Inducing abortion is feasible using various medication regimens. Misoprostol is a relatively safe and affordable choice, a prostaglandin analog used to induce abortion. Letrozole, on the other hand, is a non-steroidal third-generation aromatase inhibitor with an average half-life of about 45 hours, eliminated in the urine. Possible adverse effects include edema, headache, and dizziness. Letrozole is contraindicated during pregnancy and breastfeeding (14, 15). This medication can aid in the induction of abortion by decreasing estrogen production in the corpus luteum (16).

Previous studies have reported similar findings to the present study. In 2018, Abbasalizadeh et al. examined the effect of letrozole combined with misoprostol against misoprostol alone on the incidence of miscarriage in the first trimester. Their findings indicated that complete abortion occurred in 93.7 percent of the intervention group and 68.7 percent of the control group. They concluded that letrozole medication during the first trimester, combined with misoprostol, can raise the rate of complete abortion without raising adverse effects (17). Their study findings were in line with the present study. In a pilot randomized double-blind trial by Jain et al., researchers compared abortion using mifepristone in combination with misoprostol and a misoprostol-alone regimen. They concluded that complete abortion success rates were considerably greater with mifepristone and misoprostol than with the misoprostol-alone regimen (18). In a 2011 study, Lee et al. examined the use of letrozole in combination with misoprostol or mifepristone for second-trimester abortion

Table 4. Comparison of Misoprostol Dose, Time Interval to Abortion, and Complete Abortion Between the Control and Intervention Groups in Non-cesarean Section Patients [a]

	Control Group (N = 52)	Intervention Group (N = 50)	P-Value
Misoprostol dose (mg)	1026.92 ± 453.36	1168.00 ± 573.36	0.172
The time interval between the first misoprostol dose and abortion	8.12 ± 2.25	6.78 ± 2.25	0.003
Complete abortion	24 (46.2)	36 (72.0)	0.008

[a] Values are expressed as Mean ± SD or No. (%).

(16). The results indicated that both groups had a similar rate of abortion at 24 and 48 hours, which is in contrast to our findings. Yeung et al. (19) and Naghshineh et al. (20) conducted research that revealed supporting results. Additionally, Lee et al. conducted a pilot trial to explore the use of letrozole in combination with misoprostol or mifepristone for the termination of pregnancy for up to 63 days. According to their findings, letrozole with misoprostol may be advantageous in abortion, but its combination with mifepristone is less effective and takes longer (21), which completely matched our findings.

One limitation of the study was that some patients did not comply with taking four tablets concurrently, and others were excluded due to a history of certain disorders such as asthma, thromboembolism, malignancy, liver disease, or porphyria.

5.1. Conclusions

Combining letrozole with misoprostol is recommended for medical abortions due to its positive impact on achieving complete abortion and reducing the time required for abortion.

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Footnotes

Authors' Contribution: SP designed the study, collected data, and collaborated on drafting the manuscript. AA and MM supervised the implementation of the study protocol, designed the study, and collaborated on drafting the manuscript. FA and NT participated in designing the study protocol, supervised its implementation, and collaborated on drafting the manuscript. SN conducted data analysis, interpreted the results, and revised the manuscript according to the editor's comments. ND designed the study, collected data and partcipated in drafting the manuscript.

Clinical Trial Registration Code: IRCTID: IRCT2017042933680N1.

Conflict of Interests: The authors declare no conflicts of interest regarding the materials, methods, or findings presented in this study.

Data Reproducibility: Data are available from the authors upon reasonable request, with the permission of Mashhad University of Medical Sciences.

Ethical Approval: This study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the code IR.MUMS.fm.REC.1395.569.

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Informed Consent: Written informed consent was obtained from all participants.

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