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Improved effectiveness of medical management of missed abortion in second trimester with letrozole-misoprostol combination: A prospective cohort study

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ABSTRACT

Background: Second-trimester medical abortion is a crucial healthcare service, but the standard treatment, misoprostol, has limitations in terms of efficacy and safety.

Objective: The aim of this study was to compare the efficacy and safety of using letrozole as a pretreatment for second-trimester medical complete abortion with misoprostol alone.

Method: A prospective cohort study was conducted from February 2022 to October 2023. Eligible participants were women aged 18 years or older with gestational ages between 16 and 20 weeks. The patients were divided into two groups: 35 patients in the misoprostol-only group and 35 patients in the letrozole/misoprostol group. The primary outcome was the expulsion of the fetus in the first 72 hours, and secondary outcomes included time to complete and incomplete expulsions, the need for interference after 72 hours, the severity of bleeding, and the severity of pain.

Results: The letrozole/misoprostol group had a significantly higher rate of complete expulsion within 72 hours compared to the misoprostol-only group (74.29% vs. 40.00%). The mean time to complete expulsion was significantly shorter in the letrozole/misoprostol group than in the misoprostol-only group (23.61 hours vs. 47.28 hours). The need for interference after 72 hours was significantly lower in the letrozole/misoprostol group than in the misoprostol-only group (5.71% vs. 22.86%). The study found no significant difference between the two groups in terms of the severity of bleeding or pain. The adjusted odds ratio for spontaneous complete expulsion in association with the use of letrozole was 4.16 (95% CI, 1.43 - 12.08; P=0.009), and the adjusted odds ratio for the need for interference after 72 hours in association with the use of letrozole was 0.16 (95% CI, 0.03 - 0.99; P=0.049).

Conclusion: The study findings suggest that the use of letrozole as a pretreatment for second-trimester medical abortion is safe and effective.

Keywords: Medical abortion, Letrozole, Misoprostol.

INTRODUCTION

Abortion is a multifaceted and sensitive issue that has a profound impact on women globally. Unsafe abortions are a leading cause of maternal morbidity, mortality, and long-term disability, particularly in low-income countries where access to safe abortion services is limited [(1)].

Second-trimester abortions are particularly challenging and carry a higher risk of complications compared to first-trimester abortions. Approximately 10% of all induced abortions globally occur during the second trimester[(2-3)].

Missed abortion, which occurs when the fetus dies but is not expelled from the uterus, can be especially challenging in the second trimester, requiring extensive medical management and posing risks like bleeding and infection. As such, timely and appropriate medical care is vital in minimizing the risk of complications and promoting women's health[(4-6)].

Medical abortion, which refers to the use of drugs to induce abortion, is increasingly being used in second-trimester abortions. While Misoprostol is the most commonly used drug for medical abortion, its success rate decreases with increasing gestational age, and multiple doses of the drug may be necessary, leading to significant side effects[(5)].

Recently, Letrozole, an aromatase inhibitor used for breast cancer treatment, has been proposed as a potential pretreatment for second-trimester medical abortion. The expression of estrogen receptor-α (ERα) and progesterone receptor (PR) transcripts, as well as ERα protein, in placentae is suppressed by letrozole pretreatment in second trimester termination of pregnancy.

Letrozole softens the cervix and increases the uterus's responsiveness to Misoprostol, leading to higher success rates and fewer side effects, as reported in small-scale studies[(7-8)].

The present study aims to investigate the safety and efficacy of Letrozole pretreatment in second-trimester medical complete abortion, compared to Misoprostol alone. The study's findings could have significant implications for enhancing the safety and accessibility of second-trimester medical abortion**.**

MATERIAL AND METHODS

Study design

This prospective cohort study was conducted from. The study included 70 women with missed abortion at gestational age between 16 and 20 weeks. Recruitment was conducted through the outpatient clinic in Aswan University Hospital. The study was explained to all eligible women who visited the clinic, and those who agreed to participate were enrolled in the study after providing written informed consent. The recruitment process was conducted over a period of three years from February 2022 to October 2023.

The inclusion criteria were women aged 18 years or older with gestational ages between 16 and 20 weeks, while women with previous cesarean delivery or hysterotomy, and women with contraindications to misoprostol or letrozole use were excluded from the study.

Method

Participants were divided into two equal groups. Misoprostol group consisted of 35 women who were hospitalized and received 800 mg of Misoprostol vaginally at the time of diagnosis. Letrozole/Misoprostol group included 35 women who received 5 mg of Letrozole once a day for three days as pretreatment before hospitalization, followed by 800 mg of vaginal Misoprostol for induction of abortion. The primary outcome was the rate of successful abortion, defined as complete abortion without the need for surgical intervention. The secondary outcomes included the time of abortion, the need for surgical intervention, and the incidence of side effects (e.g., pain, bleeding). Bleeding was assessed as follows: Light bleeding was defined as less than 20ml/24h, mild bleeding was defined as 20-120ml/24h, and moderate bleeding was defined as more than 150ml/24h. A numeric pain scale was used to evaluate pain; each woman rated her pain on a scale of 0 to 10. Zero meant no pain, 1-3 indicated mild pain, 4-6 indicated moderate pain, and 7-10 indicated severe pain.

Follow-up

Follow-up procedures were conducted on all participants at two and four weeks after induction of abortion to assess for any complications or need for further intervention. The participants were followed up through phone calls and in-person visits to the outpatient clinic. In case of loss to follow-up, attempts were made to contact the participant through phone calls and home visits. If the participant could not be reached, her data was considered missing for the follow-up assessment.

Sample size calculations

We calculated the sample size based on a randomized controlled trial [9]. The study results showed that the use of letrozole in addition to misoprostol resulted in an improvement in the rate of complete abortion from 42.6% in the control group to 76.7% in the letrozole group. With 80% power and a two-sided significance level of 0.05, we calculated the sample size. We considered 64 patients (32 patients in each group) adequate to detect a 34.1% difference in the rate of complete abortion between the two groups. We enrolled 70 patients (35 patients in each group) to adjust for dropout.

Ethical consideration

The ethics committee at Faculty of Medicine, Aswan University has given its approval for the study . Prior to their registration in the trial, each participant gave their informed permission.

Statistical analysis

Software STATA version 17 was used to evaluate the data gathered for this investigation. The presentation of continuous variables included mean ± standard deviation and median with interquartile ranges. We used the Shapiro-Wilk W test to check for data normality. The frequencies and percentages of the categorical variables were displayed. To compare means, we utilized independent samples t-tests, and to analyze medians, we used the Mann-Whitney test, also known as the Wilcoxon rank sum test. Fisher's exact test or the chi-square test for proportions and independent samples t-tests for mean were employed in the result analysis.

The study employed multiple logistic regression analysis to evaluate the correlation between letrozole usage and spontaneous complete expulsion, taking into account any confounding variables. The ordinal outcome was fitted with an ordered logistic regression model, and the time to expulsion was compared between the two groups using a Cox proportional hazards model. When the p-value was equal to or less than 0.05, it was deemed significant.

RESULTS

The study enrolled a total of 70 patients, with 35 patients (50%) in the misoprostol-only group and 35 patients (50%) in the Letrozole/Misoprostol group. The basic characteristics of the two groups are presented in Table 1. The analysis showed that there was no significant difference between the two groups in terms of basic characteristics such as age, body mass index (BMI), gestational age, and history of previous abortion. This suggests that the groups were well-matched, and any differences in outcomes between the two groups are more likely to be due to the intervention (i.e., the use of letrozole) rather than other factors.

Table (1): Comparison between Letrozole/ Misoprostol and Misoprostol groups regarding patients' basic characteristics.

Characteristics	Misoprostol group	Letrozole/misoprostol group	Significance P value	Test
Maternal age, mean (SD), (years)	29.74 (± 4.78)	29.8 (± 5.19)	0.962	t = -0.0479
Gestational age, mean (SD), (weeks)	17.86 (± 1.61)	17.74 (± 1.56)	0.764	t = 0.3015
Parity, mean (SD)	2.11 (± 1.34)	2 (± 1.41)	0.730	t = 0.3464
Previous abortion, median	0 (0-1)	0 (0-1)	0.631	z = 0.479
BMI, median	30 (28-33)	29 (25-31)	0.145	z= 1.456

The primary outcome of the study was the expulsion of the fetus within the first 72 hours, while the secondary outcomes included the time to complete and incomplete expulsions, the need for intervention after 72 hours, the severity of bleeding, and the severity of pain. According to Table 2, the Letrozole/Misoprostol group had a significantly higher rate of complete expulsion within 72 hours compared to the Misoprostol-only group (74.29% vs. 40.00%, p=0.004). The mean time to complete expulsion was 23.61 hours (± 11.18) in the Letrozole/Misoprostol group and 47.28 hours (± 15.89) in the Misoprostol group; the p-value was 0.001. The need for intervention after 72 hours was significantly lower in the Letrozole/Misoprostol group compared to the Misoprostol group (5.71% vs. 22.86%, p=0.040). There was no significant difference between the two groups in terms of the severity of bleeding or pain.

Table (2): Comparison between Letrozole/ Misoprostol and Misoprostol groups regarding patients' outcomes.

Characteristics	Misoprostol group	Letrozole/ misoprostol group	Significance P value	Test
Expulsion during 72 hour				
Complete expulsion	14 (40.00%)	26 (74.29%)	0.004	
Incomplete expulsion	13 (37.14%)	7 (20%)	0.112	z = -2.978
No expulsion	8 (22.86%)	2 (5.71%)	0.040	
Wilcoxon test (Rank-sum)	1017.5	1467.5	0.004	
Time to complete expulsion, mean (SD) (hours)	47.28 (± 15.89)	23.61 (± 11.18)	0.001	t = 5.4974
Mean difference	23.67, 95% CI (14.95 - 32.39)			
Time to incomplete expulsion, mean (SD) (hours)	41.23 (±16.82)	24.57 (±11.17)	0.031	t = 2.3414
Mean difference	16.66, 95% CI (1.71 - 31.61)			
Interference after 72 hours of misoprostol	8 (22.86%)	2 (5.71%)	0.040	$x^2 = 4.2$
Severity of bleeding From misoprostol to expulsion				
Light	6 (17.14%)	3 (8.57 %)	0.284	
Mild	4 (11.43%)	9 (25.71%)	0.124	
Moderate	21 (60.00%)	20 (57.14%)	0.808	z = 0.297
Severe	4 (11.43%)	3 (8.57%)	0.690	
Wilcoxon test (Rank-sum)	1265	1220	0.761	
Pain severity				
Mild	3 (8.57%)	3 (8.57%)	1.000	
Moderate	26 (74.29%)	27 (77.14%)	0.780	z = 0.251
Severe	6 (17.14%)	5 (14.29%)	0.743	
Wilcoxon test (rank-sum)	1258.5	1226.5	0.802	

The study used a multiple regression model to analyze the association between the use of letrozole and the achievement of spontaneous complete expulsion in the two groups (Table 3). The model included several confounding variables, such as age, BMI, gestational age, history of previous abortion, and parity, to adjust for their effect on the outcome. After adjusting for these confounders, the adjusted odds ratio for spontaneous complete expulsion in association with the use of letrozole was 4.16 (95% CI, 1.43 - 12.08; P=0.009). The adjusted odds ratio for the need for interference after 72 hours in association with the use of letrozole was 0.16 (95% CI, 0.03 - 0.99; P=0.049). The results for other outcomes, such as time to complete or incomplete expulsion, were also significant, while the severity of bleeding and pain severity were not statistically significant.

Table (3): A multivariable analysis of predictors of primary and secondary outcomes regarding the studied groups.

Outcome	**Misoprostol group**	**Letrozole/misoprostol group**	**Adjusted Odds ratio**	**Confidence interval**	**P value**
Spontaneous complete expulsion	14 (40.00%)	26 (74.29%)	4.16	1.43 - 12.08	0.009
Interference after 72 hours of misoprostol	8 (22.86%)	2 (5.71%)	0.16	0.03 - 0.99	0.049
Ordered logistic regression model					
Expulsion during 72 hours -Complete expulsion -Incomplete expulsion -No expulsion	 14 (40.00%) 13 (37.14%) 8 (22.86%)	 26 (74.29%) 7 (20%) 2 (5.71%)	4.26	1.51 – 12.00	0.006
Severity of bleeding From misoprostol to expulsion Light Mild Moderate Severe	 6 (17.14%) 4 (11.43%) 21 (60.00%) 4 (11.43%)	 3 (8.57 %) 9 (25.71%) 20 (57.14%) 3 (8.57%)	0.88	0.35 - 2.23	0.787
Pain severity Mild	 3 (8.57%)	 3 (8.57%)			

Moderate Severe	26 (74.29%) 6 (17.14%)	27 (77.14%) 5 (14.29%)	0.89	0.29 - 2.68	0.832

The Kaplan-Meier curve clearly shows a difference in time to expulsion between the two groups, with the letrozole/misoprostol group achieving complete expulsion significantly faster than the misoprostol-only group and the number of cases with complete expulsion was higher in the letrozole group, as shown in Figure 1. In The Cox proportional hazards model, which adjusts for potential confounders, supports this finding. The adjusted hazard ratio for complete expulsion associated with the use of letrozole was 5.35 (95% CI, 2.17 - 13.19, P=0.001), indicating that the letrozole/misoprostol group achieved complete expulsion more than five times faster than the misoprostol-only group. The adjusted hazard ratio for incomplete expulsion associated with the use of letrozole was 7.77 (95% CI, 1.82 - 33.22, P=0.006), indicating that the letrozole/misoprostol group also achieved incomplete expulsion almost eight times faster than the misoprostol-only group (Table 4).

Table (4): Multivariable survival analysis regarding time to expulsion in the two groups

Outcome	Misoprostol group	Letrozole/misoprostol group	Adjusted hazard ratio	Confidence interval	P value
Time to complete expulsion (hours)	47.28 (± 15.89)	23.61 (± 11.18)	5.35	2.17 - 13.19	0.001
Time to incomplete expulsion (hours)	41.23 (±16.82)	24.57 (±11.17)	7.77	1.82 - 33.22	0.006

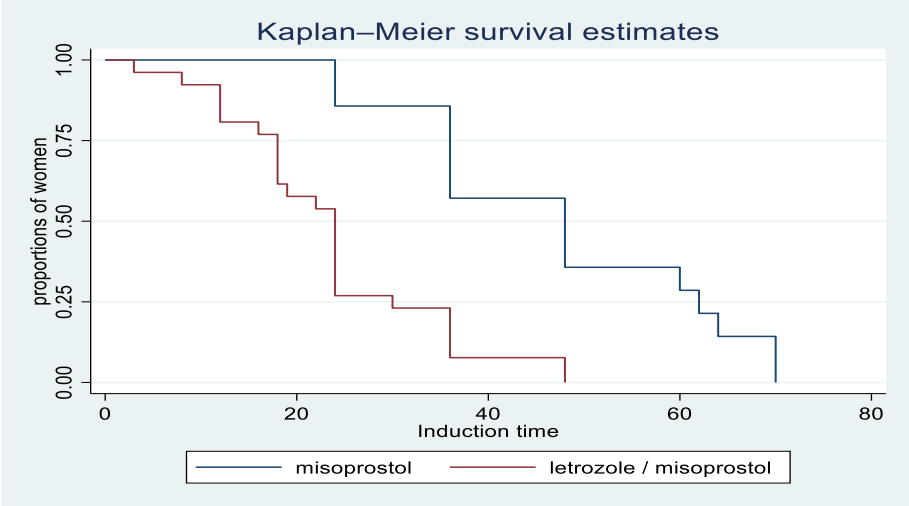

Figure (1): Kaplan Meier survival by time to expulsion: Kaplan Meier Curves shows the proportion of patients with complete expulsion versus time, in the two groups.

Sensitivity analysis:

Regarding the efficacy of letrozole, we conducted a sensitivity analysis by excluding women with a history of previous abortion. After exclusion, the adjusted odds ratio for spontaneous complete expulsion in association with letrozole use was 24.47, 95% CI, 3.34-178.99, P 0.002, indicating a significant difference between the two groups in spontaneous complete expulsion.

DISCUSSION

The results suggest that the addition of letrozole significantly improved the rate of complete expulsion within 72 hours, the time to complete expulsion, and reduced the need for interference after 72 hours. The study also found that the severity of bleeding and pain were similar in both groups. The addition of letrozole appears to increase the rate of complete expulsion, possibly by improving the response of the cervix to misoprostol or by enhancing the contractile activity of the uterus. The shorter time to complete expulsion in the Letrozole/Misoprostol group may be beneficial for women who seek a quicker resolution of their missed abortion.

In comparison to the present study, which showed that letrozole improved the rate of complete expulsion and shortened the time to expulsion in women with missed abortion, **Lee et al.**[10] found no significant difference in the abortion rate between letrozole and placebo groups in women with gestational age between 12 and 20 weeks. However, another study with a smaller sample size reported similar results to our study, showing that letrozole improved the rate of complete abortion and shortened the induction-to-abortion time in women with gestational age less than 17 weeks[11].

Another study by **Yung et al.** [8] did not detect any difference in the expression of progesterone receptor and apoptotic markers in placental and decidual tissues after letrozole pretreatment for 7 days in first-trimester abortion.

A meta-analysis by **Zhuo et al.** [13] confirmed that letrozole supplementation is beneficial for medical abortion in pregnant women, as it increased the rate of complete abortion significantly. However, it did not affect the induction-abortion time remarkably.

Overall, these studies support our findings that the use of letrozole/misoprostol for medical management of missed abortion is associated with a higher rate of complete abortion and shorter time to abortion compared to misoprostol alone. However, it is important to note that the gestational ages, sample sizes and study designs of these studies vary, which may affect the generalizability of their findings. Additionally, further studies may be needed to investigate the long-term outcomes and safety of letrozole/misoprostol for medical management of missed abortion.

Based on the information provided, there are several potential limitations and biases in this study that may affect its validity and generalizability.

Firstly, the study design is a prospective cohort study, which may be prone to selection bias, as the participants were selected from a single outpatient clinic. This may limit the

generalizability of the findings to other settings or populations. Secondly, the sample size was relatively small, which may limit the statistical power of the study and reduce the precision of the estimates. Additionally, the study did not perform a formal sample size calculation for the sensitivity analysis, which may further limit the validity of the findings. Thirdly, the study did not use blinding or randomization, which may increase the risk of performance and detection bias. Finally, the study did not report any information on the cost-effectiveness or acceptability of the interventions, which may be important factors for decision-making and implementation.

In terms of external validity, the results of this study may not be generalizable to all populations or settings. For example, the study excluded women with previous cesarean delivery or hysterotomy, which may limit the generalizability to this population. Additionally, the study was conducted in a single center, which may limit the generalizability to other centers or countries with different healthcare systems or cultural norms.

Overall, while this study provides valuable insights into the efficacy and safety of letrozole and misoprostol for the induction of abortion, there are several potential limitations and biases that may affect the validity and generalizability of the findings. Future studies with larger sample sizes, randomized designs, and more comprehensive follow-up procedures are needed to further explore the efficacy, safety, and cost-effectiveness of these interventions.

CONCLUSION

The use of letrozole in combination with misoprostol was associated with a significantly higher rate of spontaneous complete expulsion and a lower rate of the need for interference after 72 hours compared to the use of misoprostol alone in the medical management of missed abortion. The results of this study suggest that adding letrozole to misoprostol may be a promising approach to improving the effectiveness of medical management of missed abortion and reducing the need for surgical intervention. However, further larger randomized controlled trials are needed to confirm these findings and evaluate the safety and cost-effectiveness of this approach.

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