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Induction of abortion in the first trimester of pregnancy using letrozole and misoprostol combination versus misoprostol alone - A comparative observational study

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ABSTRACT

Background: Medical abortion is safer than surgical abortion. Several studies have shown that combination of antiprogesterone drug mifepristone and prostaglandin misoprostol can increase complete abortion rate in medical management of first-trimester miscarriage compared to misoprostol alone. Letrozole, an aromatase inhibitor, has emerged as an alternative to mifepristone for induction of medical abortion as mifepristone is expensive and not registered in many countries. **Aims and Objectives:** The aim of the present study was to evaluate the safety and efficacy of combined regimen of letrozole and misoprostol in first-trimester medical abortion compared to misoprostol alone. **Materials and Methods:** It was a comparative observational study conducted at R. G. Kar Medical College, a tertiary care hospital in West Bengal, India. The study population was the antenatal mothers booked at antenatal clinic willing for termination of pregnancy at <12 weeks of gestational age. Participants were allocated, 39 in each group in a non-randomized manner. Patients in one group (Group A) were posted for medical abortion with combination regimen of tablet letrozole (10 mg) once daily for 3 days followed by application of tablet misoprostol 800 mcg sublingually on day 4. In other group (Group B), patients were on misoprostol-only regimen with the application of tablet misoprostol 800 mcg sublingually. **Results:** Induction-abortion time was significantly less in the letrozole group (11 ± 0.79 h) than the misoprostol group (13.23 ± 0.81 h), P = 0.0001. Complete abortion rate was significantly higher in the letrozole group compared to misoprostol group (84.62% and 64.10%, respectively, P = 0.03). 15.38% patients in the letrozole group and 35.90% patients in the misoprostol group had excessive vaginal bleeding and the difference was statistically significant, P = 0.03. The duration of vaginal bleeding was also significantly less in the letrozole group (2.45 ± 0.29 days) than the misoprostol group (2.82 ± 0.37 days), P < 0.0001. Incidence of side-effects was comparable and the severity of side-effects was not significantly different between the groups. **Conclusion:** Letrozole and misoprostol combination regimen leads to significant increase in complete abortion rate and also significant reduction of the duration of vaginal bleeding, induction-abortion time, and need for surgical intervention when compared to misoprostol regimen.

Key words: Induction of abortion; Letrozole and misoprostol; Gestational age; Mifepristone; Antenatal mothers

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INTRODUCTION

The World Health Organization (WHO) reported that annually about 79 million unintended pregnancies excluding miscarriages occur worldwide[1] and annually about 46 million induced abortions occur in the world.[2,3] The worldwide unintended pregnancy rate has declined over the past 30 years, while the abortion rate has returned to levels last seen in the 1990s, e.g., about 39/1000 women aged 15–49 years.[4]

Induction of abortion could have a huge financial burden for the families and health-care system with its inherent chances of serious side effects for the mother, including rupture of uterus, sepsis, and death, especially in cases where abortion is not carried out in an appropriate environment under the supervision of a health-care professional. This global scenario demands continuous planning, research, and implementation of high-quality sexual and reproductive health services including contraception and safe abortion care for all.

Abortion can be induced by medical and surgical methods. Medical abortion became an alternative to surgical abortion after the availability of prostaglandin analogs in the 1970s. In medical abortion, the procedure is considered successful if abortion is completed without the need for surgical intervention. Medical abortion plays a crucial role in providing access to safe, effective, and acceptable abortion care. Mifepristone and misoprostol in combination or misoprostol alone are the medications generally used to induce abortion and they are on the WHO list of essential medicines.[5] Combination regimens are recommended for induced abortion than misoprostol alone as it is more effective in achieving complete abortion.[6] Progesterone is pivotal in the maintenance of pregnancy and the use of progesterone receptor (PR) antagonist, mifepristone, during pregnancy, facilitates the abortion process. In the second trimester of pregnancy, the combined regimen of mifepristone followed by misoprostol produces a high abortion rate of 97–100% within 24 h, with an induction-to-abortion interval of ~5–10 h.[7,8] The abortion rate of a misoprostol-alone regimen is only 37–86% in 15–24 h depending on the regimen, route of administration, and dosage used.[9,10] However, mifepristone is expensive and not registered in many countries, so exploration of new regimens to achieve a safe abortion is important, especially in developing countries.

Letrozole is an aromatase inhibitor that is used in the treatment of hormone-responsive breast cancer. It reversibly and competitively binds with iron in cytochrome P450 and prevents the production of estrogen by aromatase enzyme. Letrozole functioning as a reversible antiestrogen agent increases follicle-stimulating hormone secretion from the pituitary gland without having the anti-estrogen adverse effects on the endometrium and cervix, which is considered an advantage for this agent.[11,12] However, the role of estradiol in supporting pregnancy had not yet been as clearly elucidated as the role of progesterone in supporting pregnancy. Thus, the exact mechanism of action of letrozole in inducing abortion is not known. Some hypothesize that letrozole suppresses endothelial growth factors involved in remodeling of spiral arteries thus altering the blood flow there.[13-16] Some hypothesize that letrozole suppresses PR transcripts, estrogen receptor alpha, and estrogen receptor alpha protein in the placenta thus inducing abortion.[17] The use of letrozole pre-treatment followed by vaginal misoprostol in the first-trimester abortion is more effective than misoprostol alone.[13] The use of letrozole in the second trimester abortions seems to be promising with an abortion rate of 100% within 24 h, with a median induction-to-abortion interval of 11 h (range 6.1–19.3 h).[17] Studies suggest that the success rate of misoprostol in abortion varies from 37% to 86%, depending mostly on the route of administration. Evidence shows that misoprostol is most effective when used in combination with mifepristone (RU-486), which is an antiprogesterone that causes uterine contractions by blocking progesterone. This combination raises the success rate of abortion to 95% in the first 50 days of pregnancy.[18] Since mifepristone is expensive and still not widely available in developing countries, we need to find an alternative that is more accessible and has a lower cost.[19] Letrozole, which is more available than mifepristone, might be a good alternative to be used in combination with misoprostol.

Aims and objectives

The objectives of the present study were to compare the safety and efficacy of two regimens such as letrozole and misoprostol combination and misoprostol alone used for induction of medical abortion in the first trimester of pregnancy.

MATERIALS AND METHODS

It was a comparative observational study conducted at R.G. Kar Medical College and Hospital, Kolkata, for a period of 1 year. The study population was the antenatal mothers booked at antenatal clinic wanting termination of pregnancy at the first trimester of pregnancy.

Inclusion criteria

The criteria during the inclusion of study participants were as follows: Maternal age more than 18 years old (age of legal consent), gestational age <12 weeks, having hemoglobin level in blood >10 g/dL, and history of missed abortion.

Exclusion criteria

Whereas some of the mothers were excluded from the study depending on their age having <18 years, gestational age >12 weeks, hemoglobin level <10 g/dL, presence of fibroid uterus, presence of an intrauterine device, history of breastfeeding, any abnormal laboratory findings in blood or liver function tests, presence of an acute illness of any nature, history or evidence of coagulopathy or thromboembolism, history or evidence of adrenal diseases or steroid hormone-dependent cancer, previous attempts for induction of abortion in the current pregnancy, history of allergy to misoprostol or letrozole, any medical disorder like severe or recurrent liver disease, history or evidence of bronchial asthma, porphyria, hypertension (diastolic blood pressure [DBP]>95 mmHg), and heart diseases. Age, parity, gravidity, educational status, body mass index, socioeconomic status, and gestational age were the independent variables in the study in consideration of the primary outcome variable as time (h) between medication and incidence of complete abortion and secondary outcome variables as the total length of hospital stay in days, post-abortion fall in hemoglobin level, need for surgical intervention, and patient-reported side effects. History of excessive vaginal bleeding, severe pain abdomen, nausea, vomiting, dizziness, bronchospasm, constipation, fever, and rigor were also taken into account as patient-reported side effects during the assessment of outcome as well.

Sample size was calculated taking the result of the study Naghshineh et al.,[20] as guidance data and power of the study as 80% and level of significance as 5%, using the formula $(Z_{\alpha/2}+Z_{\beta})^2\times[p1(1-p1)+p2\ (1-p2)]/(p1-p2)^2$ (where $Z_{\alpha/2}=1.96$, $Z_{\beta}=0.84$, p1=0.76, p2=0.42). A total of 78 patients were needed (39 in each group) as study participants for this study. Participants were allocated in each group in a non-randomized manner. Patients in one group (Group A) were posted for medical abortion with combination regime of tablet letrozole (10 mg) once daily for 3 days followed by application of tablet misoprostol 800 mcg sublingually on day 4. In other group (Group B), patients were on misoprostol-only regimen that was application of tablet misoprostol 800 mcg sublingually. Safety, efficacy, acceptability, and feasibility were considered in every points of study.

A well-designed pre-tested proforma containing various parameters under study was used for data collection. Patients were recruited as per inclusion and exclusion criteria. Informed written consent was taken from each study subject. Those who did not wish to give consent were also excluded. Ethical clearance for the study was obtained from the institutional ethics committee (IEC Reference No: RKC/327, dated February 18th, 2021). A detailed medical, surgical, and obstetrical history and complete medical and obstetrical examination were done. Some laboratory investigations were done as and when necessary such as hemoglobin estimation, ABO grouping and Rh typing, human immunodeficiency virus testing, liver function test, renal function test, ultrasonography of lower abdomen, and histopathological examination of expelled product of conception.

The results were analyzed as per protocol analysis basis. Chi-square test was used for categorical data, and two-tailed unpaired student t-test was used for continuous data considering P≤0.05 as statistically significant. MS Excel 2021 and IBM Statistical Package for the Social Sciences version 16 were used as statistical software for analysis.

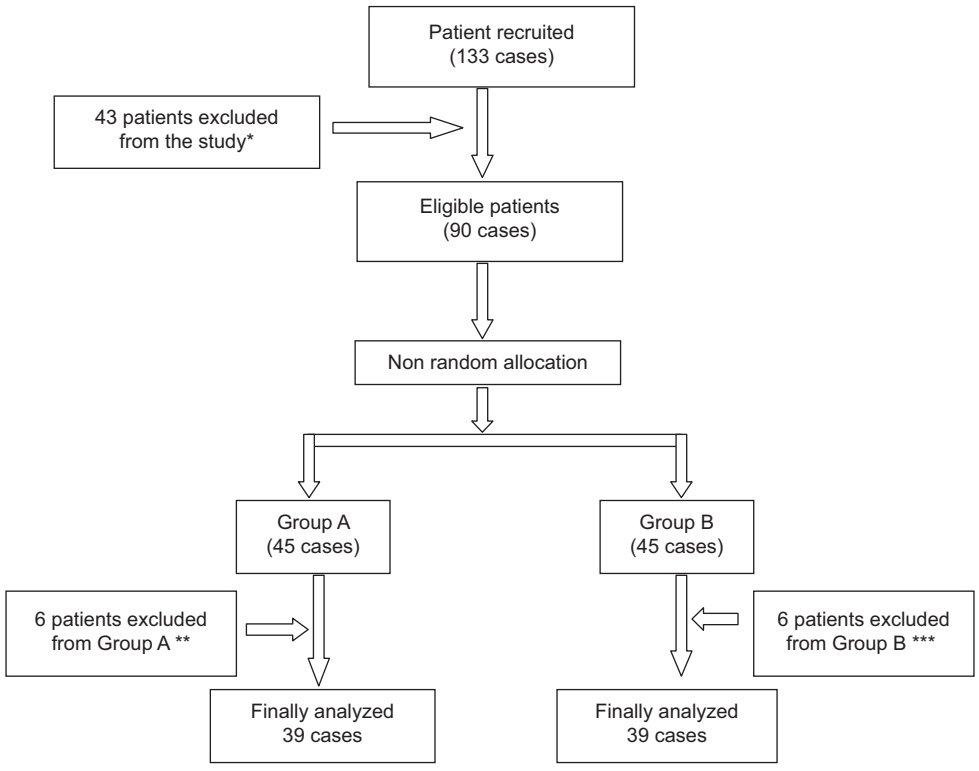
RESULTS

Demographic characteristics show that there was no statistically significant difference between the two groups regarding the distribution of maternal age, body mass index (BMI), and gestational age. The mean maternal age and mean gestational age between the two groups were almost similar. For letrozole group and misoprostol group, maternal age was 30 years (±6.68) and 29.5 years (±6.01), respectively, with a P=0.78, whereas for gestational age, the values were 9.15 weeks (±1.25) and 9.03 weeks (±1.09), respectively, with P-value being 0.65.

Majority of patients were primipara, had education up to secondary level, and belonged to lower middle class without any significant difference between the two groups (Table 1).

Induction-abortion time was less in the letrozole group (11±0.79 h) than the misoprostol group (13.23±0.81 h) and the difference was statistically significant, P-value being 0.0001. Complete abortion rate was significantly higher in the letrozole group compared to misoprostol group (84.62% and 64.10%, respectively, P=0.03). 15.38% patients in the letrozole group and 35.90% patients in the misoprostol group had excessive vaginal bleeding and the difference was statistically significant, P-value being 0.03. The duration of vaginal bleeding was also significantly less in the letrozole group (2.45±0.29 days) than the misoprostol group (2.82±0.37 days), P<0.0001 (Table 2).

About 84.61% patients in the letrozole group and 64.10% patients in the misoprostol group did not need any surgical intervention and the difference was statistically significant, P-value being 0.03. Length of hospital stay for letrozole



Patient Recruitment Process

*Patients who did not give consent for the study (43 cases)
**Patients whose active vaginal bleeding started (6 cases)
***Patients who declined participation (6 cases)

Table 1: Sociodemographic characteristics

Characteristics	Group A (N1=39)	Group B (N2=39)	χ^2 value	P-value
	No (%)	No (%)		
BMI				
Underweight	4 (10.25)	5 (12.82)	0.56	0.90
Normal	25 (64.10)	22 (56.41)		
Overweight	8 (20.51)	9 (23.07)		
Obese	2 (5.12)	3 (7.69)		
Educational status				
Primary	8 (20.57)	7 (17.94)	0.68	0.87
Secondary	20 (51.28)	18 (46.15)		
Higher secondary	10 (25.64)	12 (30.76)		
Graduate	1 (2.56)	2 (5.12)		
Socioeconomic status				
Upper middle	1 (2.56)	2 (5.12)	0.69	0.87
Middle	13 (33.33)	15 (38.46)		
Lower middle	20 (51.28)	18 (46.15)		
Lower	5 (12.82)	4 (10.25)		
Gravida				
One	14 (35.89)	12 (30.76)	1.41	0.70
Two	20 (51.28)	18 (46.15)		
Three	4 (10.25)	7 (17.94)		
Four	1 (2.56)	2 (5.12)		
Parity				
Nullipara	14 (35.89)	12 (30.76)	1.40	0.49
Primipara	20 (51.28)	18 (46.15)		
Multipara	5 (12.82)	9 (23.08)		

BMI: Body mass index

group was 1.16±0.37 days and for misoprostol group, it was 1.57±0.49 days but the difference was not statistically significant, P-value being 0.08 (Table 2).

Pre-abortion hemoglobin level was similar in both groups; in letrozole group, it was 10.53±0.23 gm/dL and in the misoprostol group, it was 10.54±0.24 gm/dL, P=0.85. Post-abortion fall in hemoglobin level in the letrozole group (0.34±0.19 mg/dL) was less than the misoprostol group (0.37±0.13 mg/dL) but the difference between these two groups was not statistically significant, P-value being 0.42 (Table 2).

Majority of patients in both groups had nausea and vomiting but dizziness, constipation, fever, and rigor were present in a few women in both the groups. The incidence of side effects was comparable and also the severity of side effects was not significantly different between the groups (Figure 1).

DISCUSSION

The sequential regimen of mifepristone, an antiprogesterone followed by a prostaglandin preparation

Table 2: Comparison of outcomes between the two groups of study participants

Outcomes expressed in continuous terms			
Outcomes	**Group A (N1=39)**	**Group B (N2=39)**	**P-value (95% CI)**
	Mean (SD)	**Mean (SD)**	
Induction-abortion time (h)	11 (±0.79)	13.23 (±0.81)	<0.0001* (1.87–2.59)
Duration of vaginal bleeding (in days)	2.45 (±0.29)	2.82 (±0.37)	<0.0001* (0.22–0.52)
Length of hospital stay (in days)	1.16 (±0.37)	1.57 (±0.49)	0.08 (0.06–0.88)
Post-abortion fall in hemoglobin level (%)	0.34 (±0.19)	0.37 (±0.13)	0.42 (0.04–0.10)
Outcomes expressed in categorical terms			
Outcomes	**Group A (N1=39)**	**Group B (N2=39)**	**P-value (χ^2 value)**
	No (%)	**No (%)**	
Occurrence of complete abortion	33 (84.62)	25 (64.10)	0.03* (4.30)
Occurrence of excessive vaginal bleeding	6 (15.38)	14 (35.90)	0.03* (4.30)
Need for surgical intervention	6 (15.38)	14 (35.90)	0.03* (4.30)

*P-value is significant, SD: Standard deviation, CI: Confidence interval

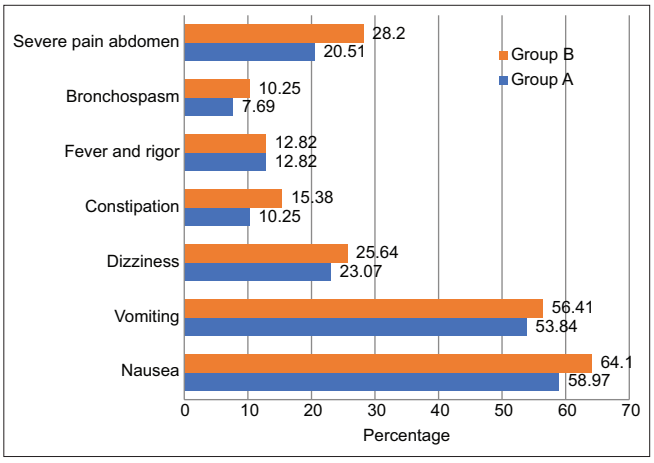


Figure 1: Reported side effects in the two groups

such as vaginal misoprostol, is the regimen of choice for medical abortion in the first trimester as it is more effective than the use of misoprostol alone. However, mifepristone is not available in many parts of the world. Therefore, we conducted this study to assess the feasibility of using letrozole, an antiestrogen to improve the efficacy of misoprostol compared to misoprostol alone for induction of complete abortion in the first trimester of pregnancy.

Demographic characteristics such as maternal age, BMI, parity, gestational age, socioeconomic status, educational status, and pre-abortion hemoglobin level were similar in both the groups.

Induction-abortion time was less in the letrozole group (11±0.79 h) than the misoprostol group (13.23±0.81 h) and the difference was statistically significant, P-value being 0.0001. Naghshineh et al., showed that the mean interval for induction-to-abortion duration in letrozole group was significantly lower than in control group (5.1±1.7 h and 8.9±2 h, respectively, P<0.001).[20] Torky et al., showed that women in the letrozole group had a shorter time to induction (1.42±0.50 vs. 3.09±0.99 days, P=0.05) than women in the placebo group.[21] Zhuo et al., in his meta-analysis showed that letrozole supplementation has no remarkable effect on induction-abortion time (std. MD=−1.03; 95% CI=−2.99–0.93; P=0.30).[22]

Incidence of complete abortion was 84.62% in the letrozole group compared to 64.10% in the misoprostol group and the difference was statistically significant, P-value being 0.03. Naghshineh et al., showed that complete abortion was significantly more in letrozole group compared to misoprostol only group (76.7% and 42.6%, respectively, P<0.001).[20] Abbasalizadeh et al., showed that complete abortion rate in the intervention group was 93.7%, and in control group was 68.7% which was significantly higher in intervention group (P=0.001).[23] Torky et al., showed that more women had complete miscarriage in the letrozole group than in the placebo group (78% vs. 39%) and the difference was highly significant (P=0.05).[24,25]

Duration of vaginal bleeding was less in the letrozole group (2.45±0.29 days) than the misoprostol group (2.82±0.37 days) and the difference was statistically significant, P-value being 0.0001. Mohammed AL-Taie et al., Abbasalizadeh et al., in their study showed that letrozole group had significantly lower duration of bleeding than misoprostol group, a finding similar to our study.[23,26]

Need of surgical intervention was significantly less in the letrozole group compared to misoprostol group (15.38% vs. 35.90%, respectively, P=0.03). Several studies got similar results showing that misoprostol had a significantly higher number of cases needed for urgent surgical intervention due to severe pain or bleeding compared to letrozole plus misoprostol group.[20-23,27,28]

Length of hospital stay for letrozole group was 1.16±0.37 days and for misoprostol group, it was 1.57±0.49 days but the difference was not statistically significant, P-value being 0.08. Behroozi-Lak et al., showed that the time form admission to discharge in letrozole groups was significantly shorter than those in misoprostol group (P=0.001).[29]

Post-abortion fall in hemoglobin level in the letrozole group (0.34±0.19 mg/dL) was less than that in the misoprostol group (0.37±0.13 mg/dL) but the difference between the two groups was not statistically significant, P-value being 0.42.

Majority of patients in both groups had nausea, 58.97% in letrozole group, and 64.10% in misoprostol group and the difference between these two groups was not statistically significant, P-value being 0.64. Torky et al., Afifi et al., in their study, showed that more women experienced nausea in the letrozole group than in the misoprostol group, and the difference was statistically significant.[21,30] Zhuo et al., in their meta-analysis, showed that letrozole supplementation has no remarkable effect on nausea.[22]

Vomiting was present in 53.84% women of letrozole group and 56.41% of the misoprostol group and the difference between these two groups was not statistically significant, P-value being 0.81. Lee et al., Torky et al., Afifi et al., in their study, showed that more women experienced vomiting in the letrozole group than in the misoprostol group, and the difference was significant (P< 0.05).[13,21,30] Zhuo et al., in a meta-analysis showed that letrozole supplementation has no remarkable effect on vomiting.[22]

Dizziness, bronchospasm, constipation, fever, and rigor were present in few women of both the groups without any statistically significant difference in our study.

Majority of patients in both groups in this study did not suffer from severe abdominal pain, 79.48% in letrozole group, and 71.79% in misoprostol group and the difference between these two groups was not statistically significant, P-value being 0.43. Abbasalizadeh et al., showed that abdominal pain in the letrozole group is significantly lower than that of the misoprostol group (P=0.013).[23] Naghshineh et al., Javanmanesh et al., in their study, showed that the incidence of side effects was comparable in two groups; also, the severity of side-effects was not significantly different between the groups.[20,24]

Limitations of the study

It is a single-center, non-randomized study.

We did not include patients with severe medical or surgical disorders such as severe or recurrent liver disease, history or evidence of bronchial asthma, porphyria, hypertension (DBP>95 mmHg), and heart disease.

We did not include patients who had uterine distortion like fibroid uterus.

Study sample including different ethnic groups would have been better.

CONCLUSION

Results of this study suggest that letrozole and misoprostol combination regimen leads to significant increase in complete abortion rate than misoprostol-alone regimen.

This combination regimen also reduces the duration of vaginal bleeding, induction-abortion time, and need for surgical intervention and the difference is statistically significant when compared to misoprostol regimen.

Post-abortion fall in hemoglobin percentage, duration of hospital stay, and incidence of side effects are lower in letrozole group than misoprostol group but the difference is not statistically significant.

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