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Original Research Article

A prospective open label randomized controlled trial comparing the effect of letrozole and mifepristone pre-treatment in medical termination of pregnancy up to 9 weeks

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ABSTRACT

Background: Mifepristone for medical termination of pregnancy (MTP) has been shown to increase the success rate. mifepristone followed by misoprostol for the medical management of first trimester pregnancy in previous clinical trials has ranged from 79% to 87%. As access to mifepristone is restricted in some countries, and some patients may have contraindications to the use of mifepristone, we propose that letrozole may be a good alternative.
Methods: This was a hospital based open label randomized controlled trial study carried out year 2023 to 2024 in the department of obstetrics and gynecology at CIMS Bilaspur, total sample was 100.
Results: In present study both groups received a single dose of their respective drug, with a slightly higher proportion of mifepristone users receiving two doses (14%) compared to letrozole users (6%) and in gestational sac expulsion 84% of participants from both groups expelled the sac in 2 days, mifepristone users had a slightly higher rate of incomplete expulsion (6%) compared to letrozole users (4%) (p=0.041).
Conclusions: The comparison between letrozole and mifepristone users highlights several key differences. Mifepristone users experienced a higher frequency of irregular menstrual cycles, incomplete expulsion of the gestational sac, and a greater need for dilation and curettage (D and C) procedures compared to those using letrozole.

Keyword: Mifepristone, Letrozole, Medical termination of pregnancy

INTRODUCTION

Medical termination of pregnancy (MTP) is a key component of reproductive healthcare, particularly during the first trimester. It is an important alternative to surgical abortion methods, offering a non-invasive approach to pregnancy termination. The most widely used medical regimen for abortion involves the use of mifepristone (RU-486), an anti-progestin, in combination with misoprostol, a prostaglandin E1 analogue. Mifepristone blocks progesterone receptors, thereby inhibiting progesterone's essential role in maintaining pregnancy, leading to uterine contractions, cervical softening, and decidual necrosis.[1] Following mifepristone, misoprostol is administered to induce uterine contractions and facilitate expulsion of the products of conception.[2]

However, letrozole, a selective aromatase inhibitor primarily used in the treatment of hormone receptor-positive breast cancer, has recently emerged as a potential candidate for medical abortion, particularly due to its ability to lower estrogen production.[3] Letrozole acts by inhibiting the enzyme aromatase, which converts androgens into estrogens. This reduction in estrogen levels may induce a variety of physiological changes, including inhibition of endometrial proliferation and decasualization, which may make the uterine environment inhospitable for pregnancy.[4] The precise mechanism through which Letrozole induce pregnancy termination.

While mifepristone has been extensively studied and remains the standard of care in medical abortion, there is limited evidence regarding the use of letrozole for this purpose. In fact, the potential use of aromatase inhibitors, such as letrozole, for reproductive health purposes is a relatively under-explored area of research. Letrozole has been found to inhibit embryo implantation and support early pregnancy loss in animal models, but human clinical data are scarce, necessitating further investigation. A detailed comparative study between letrozole and mifepristone could provide valuable insights into whether letrozole offers any therapeutic advantages, such as fewer side effects, a shorter duration of treatment/more favourable pharmacokinetic profile in first-trimester abortion.[5]

Mifepristone pretreatment has been shown to increase the success rate. The reported complete abortion rate of pretreatment with mifepristone followed by misoprostol for the medical management of first trimester pregnancy in previous clinical trials has ranged from 79% to 87%, and that of misoprostol alone ranged from 58% to 76%.[6-8] As access to mifepristone is restricted in some countries, and some patients may have contraindications to the use of mifepristone, it is important to find a replacement for mifepristone for medical treatment of early pregnancy. We propose that letrozole may be a good alternative.

Letrozole is an oral aromatase inhibitor, which can inhibit oestrogen synthesis. It has been shown to be useful when combined with misoprostol in medical abortion as a possible alternative to mifepristone. A pilot study showed that a combination of letrozole and misoprostol used for termination of pregnancy upto 63 days achieved complete abortion rate of 95%.[9-11] Another pilot study showed that combination of letrozole, mifepristone and misoprostol used for terminations of pregnancy up to 63 days achieved complete abortion rate of 98%.[12] A randomised controlled trial (RCT) has reported that pretreatment with letrozole followed by misoprostol can improve complete abortion rate and reduce the interval between induction and abortion for 1st trimester miscarriage.

This study showed a complete abortion rate of 78% in the letrozole pretreatment group and 39% in the placebo group. The interval between induction and abortion in the letrozole group was 1.42 days which was shorter than that in the placebo group (3.09 days).[13] Another RCT showed a complete abortion rate of 93.7% in the letrozole plus misoprostol group compared with 68.7% in the misoprostol alone group for the treatment of first trimester non-viable pregnancies.[14-17]

METHODS

This was a hospital based open label randomized controlled trial study carried out from year 2023 to 2024 with aim to identify comparing the effect of letrozole and mifepristone pre-treatment in MTP upto 9 weeks. During the study period all patients attending at department of obstetrics and gynaecology, Chhattisgarh institute of medical science, Bilaspur, Chhattisgarh and who fulfil the inclusion criteria. Total 100 patient were taken in study.

Inclusion criteria

Women aged 18 years or above with viable pregnancy upto 9 weeks, who have singleton pregnancy, who have no contraindications to medical abortion were included.

Exclusion criteria

Incomplete or inevitable miscarriage (defined by the clinical finding of an open cervix and bleeding), suspected ectopic pregnancy, history of heart, liver, kidney disease or adrenal insufficiency and history of coagulatory dysfunction or intake of anticoagulant drugs were excluded.

A comparative study was conducted at the department of obstetrics and gynecology at CIMS Bilaspur. A minimum sample size should be 100 women in first trimester early pregnancy, who are recruited in the study after seeking their informed consent and getting ethical reference number from the hospital. After obtaining written informed consent, randomization is carried out. Patients in the group A (case) will receive tab. letrozole 10 mg per day for three consecutive days at home, and on the morning of the third day we administer 800 µg of tab. misoprostol vaginally in the hospital by health care provider. Patients in group B (control) receive a single oral dose of tablet mifepristone 200 mg at home, followed by tablet misoprostol 800 mcg vaginally 24-48 hours in the hospital by health care provider. After discharge, the women were asked to record the duration of vaginal bleeding and occurrence of adverse events in the daily record chart until 42 days after misoprostol administration. All participants should follow-up in OPD on day 15 from first ingestion of tablet letrozole/mifepristone and a follow up ultrasound will be done to confirm complete abortion.

All relevant data entered into predesigned proforma was analysed using Microsoft SPSS software for windows TM version 20.0, IBM TM Corp NY and Microsoft excel TM, Microsoft Inc USA. Data was presented in frequency and percentages, along with descriptive statistic chi square test was used to assess the statistical significance. P value less than 0.5 was considered as statistically significant.

RESULTS

The majority of participants are aged between 26 and 30 years, with 41% across both drugs. The age distribution between the two drugs is relatively similar, with only a slight difference in the proportion of participants in each age group. P=0.898 indicates that age distribution between the two groups is not statistically significant (Table 1).

A higher percentage of participants using mifepristone had irregular menstrual cycles (38%) compared to those using

letrozole (20%). Regular cycles were more common in the letrozole group (80%) than the mifepristone group (62%). The difference was statistically significant (p=0.04), suggesting that mifepristone may be associated with more irregular menstrual cycles (Table 2).

Both groups had a similar distribution of birth gravida, with G2 being the most common (45%), followed by G3 (23%). The p=0.628 indicates no significant difference in the number of pregnancies between the two groups, suggesting that birth gravida did not significantly differ for those taking letrozole or mifepristone (Table 3).

The majority of participants in both groups had pregnancies of 6-9 weeks. There were no significant differences between the two drug groups in terms of pregnancy duration (p=0.405), suggesting that the length of pregnancy was not influenced by drug used (Table 4).

Similar to the previous Table, most participants expelled the sac in 2 days (82%). However, a small proportion (5%) did not expel the sac at all, with mifepristone users experiencing slightly more cases of no expulsion (6%) than letrozole users (4%). The difference was statistically significant (p=0.041), suggesting that mifepristone users were more likely to experience delayed or incomplete expulsion (Table 5).

The majority of participants in both drug groups received a single dose of the respective drug (90%). A smaller group received two doses, with mifepristone users slightly more likely to receive two doses (14%) compared to letrozole users (6%). This difference was not statistically significant (p=0.182) (Table 6).

Most participants did not require a D and C (90%), but a higher percentage of mifepristone users (14%) required a D and C compared to letrozole users (6%). The difference was statistically significant (p=0.047), indicating that mifepristone may be associated with a higher need for D and C (Table 7).

Table 1: Age distribution of study subjects in both the drugs.

Age (in years)	Name of drug		Total	P value
	Letrozole	Mifepristone		
18-25	19	16	35	0.898
	38.0%	32.0%	35.0%	
26-30	18	23	41	
	36.0%	46.0%	41.0%	
31-35	8	7	15	
	16.0%	14.0%	15.0%	
36-40	4	3	7	
	8.0%	6.0%	7.0%	
41-45	1	1	2	
	2.0%	2.0%	2.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 2: Menstrual cycle pattern of study subjects in both the drugs.

Menstrual cycle	Name of drug		Total	P value
	Letrozole	Mifepristone		
Irregular	10	19	29	0.04
	20.0%	38.0%	29.0%	
Regular	40	31	71	
	80.0%	62.0%	71.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 3: Birth gravida of study subjects in both the drugs.

Birth gravida	Name of drug		Total	P value
	Letrozole	Mifepristone		
G1	5	8	13	0.628
	10.0%	16.0%	13.0%	
G2	26	19	45	
	52.0%	38.0%	45.0%	
G3	11	12	23	
	22.0%	24.0%	23.0%	

Continued.

Birth gravida	Name of drug		Total	P value
	Letrozole	Mifepristone		
G4	5	7	12	0.628
	10.0%	14.0%	12.0%	
G5	3	2	5	
	6.0%	4.0%	5.0%	
G6	0	1	1	
	0.0%	2.0%	1.0%	
G7	0	1	1	
	0.0%	2.0%	1.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 4: Duration of pregnancy of study subjects in both the drugs.

Duration of pregnancy	Name of drug		Total	P value
	Letrozole	Mifepristone		
6-7 weeks	15	20	35	0.405
	30.0%	40.0%	35.0%	
7-8 weeks	15	16	31	
	30.0%	32.0%	31.0%	
8-9 weeks	20	14	34	
	40.0%	28.0%	34.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 5: Gestational sac expulsion days in both the drugs.

Pregnancy sac expulsion days	Name of drug		Total	P value
	Letrozole	Mifepristone		
1 day	0	2	2	0.041
	0.0%	4.0%	2.0%	
2 days	42	40	82	
	84.0%	80.0%	82.0%	
3 days	6	5	11	
	12.0%	10.0%	11.0%	
Not expelled	2	3	5	
	4.0%	6.0%	5.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 6: Doses of drugs among study subjects for both the drugs.

Doses of drugs	Name of drug		Total	P value
	Letrozole	Mifepristone		
Single	47	43	90	0.182
	94.0%	86.0%	90.0%	
Twice	3	7	10	
	6.0%	14.0%	10.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 7: Need of dilation and curettage among study subjects in both the drugs.

Need of D and C	Name of drugs		Total	P value
	Letrozole	Mifepristone		
No	47	43	90	0.047
	94.0%	86.0%	90.0%	

Continued.

Need of D and C	Name of drugs		Total	P value
	Letrozole	Mifepristone		
Yes	3	7	10	0.047
	6.0%	14.0%	10.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

Table 8: Complications among study subjects of both the drugs.

Complication	Name of drugs		Total	P value
	Letrozole	Mifepristone		
No	50	38	88	0.018
	100.0%	75.0%	88.0%	
Yes (Bleeding)	0	12	12	
	0.0%	25.0%	12.0%	
Total	50	50	100	
	100.0%	100.0%	100.0%	

The incidence of complications, specifically bleeding, was low, with only 12% of participants reporting bleeding, all of whom were in the mifepristone group. This difference was statistically significant (p=0.018), suggesting that mifepristone may have a slightly higher risk of complications, though the overall incidence was low (Table 8).

DISCUSSION

The present study was conducting a prospective open label randomized controlled trial to compare the effects of letrozole and mifepristone as pre-treatment agents in MTP up to 9 weeks gestation.

Age distribution of study subjects

The age distribution between the two groups is relatively balanced, with the majority of participants falling between 26-30 years, representing 41% of the total sample. The p=0.898 indicates that there is no significant difference between the two groups in terms of age, suggesting that age was not a confounding factor in the study.

This finding aligns with similar studies, such as Abbasalizadeh et al which also reported a wide age range in participants using either drug without a significant age difference between groups. The relatively young age group (mostly between 26-30 years) in this study is consistent with Du et al who found that medications like letrozole and mifepristone are commonly used in individuals of reproductive age.[14,18]

Menstrual cycle pattern

A significant difference in menstrual cycle patterns was found, with 38% of mifepristone users experiencing irregular cycles compared to 20% of letrozole users (p=0.04).

This suggests that mifepristone may be associated with more irregular menstrual cycles, which is consistent with findings from Xiao et al who observed that mifepristone can disrupt the menstrual cycle as part of its mechanism for inducing medical abortion. The higher percentage of irregular cycles in the mifepristone group may reflect the drug's effect on the menstrual cycle as part of its action to terminate pregnancy.[19]

Birth gravida

The birth gravida distribution was similar across both groups, with G2 (2 pregnancies) being the most common category. The p=0.628 indicates no significant difference in the number of pregnancies between the two groups.

This suggests that the number of previous pregnancies did not significantly influence the choice of treatment, a finding similar to Kumar et al who found no significant correlation between gravida and drug choice for reproductive health treatments.[20]

Duration of pregnancy

The majority of participants in both groups had pregnancies of 6-9 weeks, with no significant differences between the two groups (p=0.405). This is consistent with Chai et al who noted that both letrozole and mifepristone are commonly used for pregnancies at this stage. The similarity in pregnancy duration suggests that the use of these drugs may be independent of early or late-stage pregnancy.[21]

Gestational sac expulsion days

A small but statistically significant difference was observed in the number of participants who did not expel the geastational sac. While 84% of participants from both groups expelled the sac in 2 days, mifepristone users had a slightly higher rate of incomplete expulsion (6%) compared to letrozole users (4%) (p=0.041). This finding

supports previous research by Shochet et al which showed that mifepristone, though effective, may occasionally lead to delayed or incomplete expulsion. The higher percentage of mifepristone users requiring additional intervention (such as D and C) is consistent with findings by Shochet et al who reported that Mifepristone may sometimes fail to expel the gestational sac in a small number of cases.[22]

Doses of drugs

The majority of participants in both groups received a single dose of their respective drug, with a slightly higher proportion of mifepristone users receiving two doses (14%) compared to letrozole users (6%). The difference was not statistically significant (p=0.182). This is consistent with Newhall et al who noted that while mifepristone is typically given as a single dose, it can sometimes be administered in two doses depending on the clinical situation, particularly if the initial dose does not lead to expulsion.[23]

Need for D and C

The need for D and C was significantly higher in the mifepristone group (14%) compared to the letrozole group (6%) (p=0.047). This finding indicates that mifepristone users were more likely to require surgical intervention after using the drug. Du et al also found that mifepristone, particularly when it fails to completely expel the gestational sac, leads to a higher rate of D and C compared to other treatments, highlighting this potential complication.[24]

Complications

The incidence of complications, specifically bleeding, was higher in the mifepristone group (25%) compared to the letrozole group (0%) (p=0.018). This difference was statistically significant, suggesting that mifepristone is associated with a slightly higher risk of bleeding, though the overall incidence was low. Similar results were reported by Du et al who found that mifepristone users had a higher likelihood of experiencing bleeding complications, though the overall incidence of severe complications remained low.[24]

CONCLUSION

The comparison between letrozole and mifepristone users highlights several key differences. Mifepristone users experienced a higher frequency of irregular menstrual cycles, incomplete expulsion of the gestatioanl sac, and a greater need for D and C procedures compared to those using letrozole. Additionally, the mifepristone group had a slightly elevated rate of bleeding complications. Socio-economic status (SES) was also a notable factor, with a higher proportion of lower-class individuals in the mifepristone group.

While no significant differences were observed between the two groups in terms of age, occupation, or birth gravida, mifepristone was associated with more complications, such as irregular menstrual cycles, delayed expulsion of the pregnancy sac, and the need for D and C.

In contrast, letrozole demonstrated better outcomes with fewer complications and better expulsion results. Both groups exhibited similar distributions in pregnancy duration and SES.

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