Caspian J Reprod Med, 2018, 4 (2): 17-22

Caspian Journal of Reproductive Medicine

Journal homepage: www.caspjrm.ir

Original article

Investigating the comparative effect of combined regimens of letrozole with misoprostol alone for first trimester medical abortion

Shahla Yazdani [1, 2], Mahtab Zeinalzadeh1[2], Zinatossadat Bouzari[3,] *, Zeinab Azmodeh fard [4]

[1]Infertility and Reproductive Health Research Center, Health Research Institute, Babol University of Medical Science, Babol, Iran
[2]Clinical Research Development Unit of Rouhani Hospital, Babol of University of Medical Science, Babol, Iran
[3]Cellular & Molecular Biology Research Center, Babol University of Medical Sciences, Babol, Iran
[4] Students' Research Committee, Babol University of Medical Sciences, Babol, Iran

Received: 14 Aug 2018 Accepted: 20 Oct 2018

Abstract

Background: Medical management of miscarriage in the first trimester is performed with multiple-medication regimens. We aimed to compare the efficacy and complications of combined regimen of letrozole and misoprostol with misoprostol alone for first trimester medical abortion.

Methods: A retrospective cohort study was conducted at Babol University of Medical Sciences for medical abortion at gestational age less than 12 weeks. All pregnant women in the first trimester with indications for abortion between 2014 and 2015 and treated by the combined regimen of letrozole and misoprostol or misoprostol alone were included in this study. The successful complete abortion, the frequency need for curettage, the induction-abortion interval, drug complications, hemoglobin, and hematocrit ratio were all retrieved from the patients' documents.

Results: During the study period, 110 pregnant women were admitted to our hospital for medical abortion at the first trimester and were considered for medical management. Of these, 40 women received letrozole 7.5 mg for two days, followed by misoprostol 800 mcg vaginally. Seventy women received only misoprostol 800 mcg vaginally. Follow-up for abortion was usually done 24 hours after the medical management. The successful complete abortion rate in the combined regimen of letrozole and misoprostol was more than that of the misoprostol alone group (75.0% vs. 31.4%; P= 0.001). The frequency need for curettage (P=0.001) and the mean induction-abortion interval (P= 0.021) were lower in combined regimen of letrozole than misoprostol alone group. The drug complications, hemoglobin ratio and hematocrit ratio were similar between the groups.

Conclusion: Our study suggested that letrozole enhances the misoprostol effect in the first trimester of pregnancy termination and decreases some of its complications.

Keywords: Abortion, adverse effects, Letrozole, Misoprostol, Pregnancy trimester

Introduction

Miscarriage may occur in up to 12%–15% in each pregnancy, and it is a common pregnancy complication. For early medical abortion management, multiple-medication regimens are recommended by current clinical guidelines. The effect of prostaglandins on preparing the cervix to induce labor has been proven (1-5). Misoprostol is a synthetic analogue of prostaglandin E1, causing uterotonic activities and cervical ripening (5), but it has different effects on inducing labor with different methods and different doses (1, 6). As this prostaglandin is a good alternative for dilatation and curettage and can alleviates the risks of surgery and anesthesia (7), it is used to induce abortion in the first and second trimesters of pregnancy (3, 7). However, different therapeutic effects of misoprostol are reported when it is used alone or in combination with other medications with different doses and different methods (1, 3, 8-11).

Letrozole inhibits the production of estrogen and when it is used with misoprostol, it has synergistic effects on medical abortion (5). A study on the mechanism of letrozole with gestational age less than 63 days showed that the pulsatility index (PI) and the resistance Index (RI) of uterine artery after three and

*Correspondence author: Dr. Bouzari Zinatossadat, Cellular & Molecular Biology Research Center, Ganafrouz Street, Babol University of Medical Sciences, Babol, Iran Tel: +989111131229 Fax:+9832238284 Email: z_b412003@yahoo.com

[DOI: 10.22088/caspjrm.4.2.17]

seven days of intervention in a group who received letrozole were reduced significantly compared to those of the control group who did not receive letrozole and their uterine blood flow and the risk of vaginal bleeding increased as a result. In addition, a significant decrease was observed in serum estradiol levels compared to the control group (12). Studies in which letrozole was used in combination with other medications such as misoprostol for the first trimester abortion reported a greater proportion of women with complete abortion (12, 13).

Unlike the above studies, Rezai and et al (2014) reported no significant difference in the combined use of letrozole and misoprostol compared to misoprostol alone for abortions under nine weeks of pregnancy (14). Lee and et al (20110) examined the combined use of letrozole and misoprostol compared to misoprostol alone for medical abortions in the second trimester of pregnancy and reported no significant difference in the two groups (15), which is inconsistent with Young's studies (12, 16). Given the different results of the above studies for the combined use of Letrozole and misoprostol and for decreasing complications of abortion, this study aimed to compare the efficacy and complications of combined regimen of letrozole and misoprostol with misoprostol only for the first trimester medical abortion.

Materials & Methods

This retrospective cohort study was conducted at Babol University of Medical Sciences for medical abortion at gestational age less than 12 weeks. All pregnant women in first trimester with indications for abortion between 2014 and 2015 and treated by the combined regimen of letrozole and misoprostol or misoprostol only were included in this research. Forty women received letrozole (Letrofem, 2.5 mg/tab, Iran Hormone Co.Tehran,Iran) 7.5 mg orally once daily for two days outpatient, and were hospitalized on the third day and received misoprostol 800 mcg in posterior fornix of vagina. Seventy women were hospitalized and received misoprostol 800 mcg in posterior fornix of vagina. Follow-up for abortion was usually done 2-7 days after the medical management by transvaginal sonography. If no residues were left or endometrial thickness was less than 15 mm, the treatment outcome was considered perfect abortion. Curettage was usually conducted in patients who failed to expel concepts, and those with residues or endometrial thickness over 20 mm in ultrasound.

Medical management is chosen according to each gynecologist's personal preference, either by combined regimen of letrozole and misoprostol or misoprostol only. All gynecologists use the common practice. They include women with gestational age less than 12 weeks with indications for abortion for the following reasons: missed abortion, fetal malformations, or maternal diseases. In addition, the women with pain and heavy bleeding, the history of sensitivity to misoprostol, severe anemia, coagulation disorders, using anticoagulants, active liver disease, cardiovascular diseases, uncontrolled seizures, adrenal diseases, or using corticosteroid are considered for vacuum aspiration.

We included successful complete abortion, the frequency need for curettage, induction-abortion interval, and drug complications such as fever, severe bleeding, diarrhea, vomiting, hemoglobin, and hematocrit ratio, which were all retrieved from the patients' documents.

Patients' information such as age, height (cm), weight (kg), and gestational age based on reliable LMP or ultrasound at early stages of pregnancy and the number of pregnancies was also retrieved from patients' documents.

This study was approved by the Ethics Committee of Babol University of Medical Sciences (No: MUBABOL.REC.1392.3609). Since the data were retrieved from the patients' documents, we did not require patients' written informed consent. The data were analyzed in SPSS-18 using t-test and chi-square test. P-value<0.05 was considered significant.

Results

The mean age (SD) of the participants was 26.58 ± 6.15 years, and the mean gestational age (SD) was 40.74 ± 10.38 days. There was no significant difference between the mean body mass index, age, gestational age, and the gravidity of pregnant women between the two groups (Table 1).

The successful complete abortion rate in the combined regimen of letrozole and misoprostol was significantly more than that of the misoprostol alone group (75.0% vs 31.4%; P= 0.001). The frequency need for curettage (P=0.001) and the mean induction-abortion interval

[DOI: 10.22088/caspjrm.4.2.17]

(P= 0.021) were lower in combined regimen of letrozole than the misoprostol alone group (table 2).

The hemoglobin level was not significantly different before and after the complete abortion between the two groups (Table 3). Most patients in both groups had no medication side effects, but fever was the most common complication in both groups.

In this study, the effects of age, height, weight, gravida, and the abortion history were investigated in the regression model. The results indicate that the combined regimen of letrozole and misoprostol and misoprostol alone were not significantly different.

Table 1. The clinical characteristics of both the cases and controls group

Variables	Misoprostol n=70 n (%)	Letrozole +misoprostol n=40 n (%)	P-value
Successful complete abortion	22 (31.4%)	30 (75.0%)	0.001
Need for curettage	50 (71.42%)	17 (42.5%)	0.001
Induction-abortion interval	129.11±69.16	77.28±79.10	0.021
Side effects Drugs	16 (22.85%)	10 (25.0%)	0.967

Table 2. Compare some variables of pregnant women in the intervention group and the control group

Variables	Misoprostol n=70 n (%)	Letrozole +misoprostol n=40 n (%)	P-value
Successful complete abortion	22 (31.4%)	30 (75.0%)	0.001
Need for curettage	50 (71.42%)	17 (42.5%)	0.001
Induction-abortion interval	129.11±69.16	77.28±79.10	0.021
Side effects Drugs	16 (22.85%)	10 (25.0%)	0.967

Table 3. Compare hemoglobin level before/ after medical abortion in both two groups

Variables	Before medical abortion Mean±SD	After medical abortion Mean±SD	P-value
Misoprostol group	10.87±0.90	10.64±0.95	0.334
Letrozole +misoprostol	10.53±0.76	10.45±1.06	0.425

Discussion

The present study aimed to investigate and compare the effect of misoprostol with/without letrozole in the termination of the first-trimester pregnancy and demonstrated that complete abortion was significantly higher in combined regimen of letrozole and misoprostol group than the misoprostol only group. Similar results were found in a study by Lee et al. (2011) on 40 pregnant women with gestational age less than 63 days. They reported the rate of complete abortion 86.9% in the combined regimen of letrozole and misoprostol group, which was slightly higher than our results. In our study, the successful complete abortion rate was 57.5% in the intervention group and 32.2% in the control group [13]. The dose of letrozole was 7.5 mg in our study, which was slightly lower than that in Lee's study. Our participants were younger and had lower gestational age than their patients. Differences in the methods used might explain the difference in complete abortion rates in the two studies. In another study (2012), with an increase in letrozole from three to seven days followed by 800 mcg misoprostol, the complete abortion rate reached 95%,

[DOI: 10.22088/caspjrm.4.2.17]

which is comparable to the standard protocol of mifepristone and misoprostol for the termination of pregnancy in early pregnancy (12).

Chai et al. (2013) used letrozole, mifepristone, and misoprostol and reported the complete abortion rate of 98% (17). It can be concluded that these abortion medications have synergistic effects and their combined administration can improve the therapeutic outcome of abortion.

Rezai et al. examined pregnancies less than nine weeks and reported that the rate of complete abortion in both the intervention and control groups after receiving letrozole and misoprostol was lower than that in the present study, with no significant difference between the two groups. The difference may be due to different gestational age in the two groups (14). Similar to the study conducted by Rezai, we observed less need for abortion in the group receiving combined regimen of letrozole and misoprostol than in the misoprostol only group.

The mean induction-abortion interval was about two hours less in treatment with the combined regimen of letrozole and misoprostol group than that in treatment with misoprostol alone, which is less than what Yeung et al. in Hong Kong had reported. Yeung and Chai et al. reported the median of this interval 7.5 hours (12) and 5.1 hours (17), respectively, which is shorted than our study results.

The reduction in the induction-abortion interval in the combined treatment group can be attributed to the role of letrozole in facilitating the function of misoprostol (10) and inhibiting the synthesis of estradiol (5, 17). This was cited in all previous studies, which highlighted reduced induction time.

In general, in terms of medication side effects including fever, nausea and diarrhea, no significant difference was seen in the misoprostol group and combined regimen of letrozole and misoprostol group. A large percentage of cases in both groups had no complications. In our study, the incidence of fever in the two groups with/without letrozole was estimated 11.43% and 12.5%, respectively. Similarly, Rezai et al. reported fever in the two groups with/without letrozole 8.4% and 5.6%, respectively, which was not statistically significant (14). Even though Lee (2011) reported no fever in the misoprostol group, it was 3.6% in the combined group [13]. In Yazdani et al. and our study, the rate of nausea was higher in the combined group than in the group without letrozole (2). Lee et al, nonetheless, reported significantly lower rates of nausea in the combined group than in the misoprostol only group (14.3% vs. 16.7%) (13). In the same vein, Rezai reported a lower rate of nausea in the combined group than in the misoprostol only group (14).

In this study, the need for curettage in the misoprostol group was significantly higher in those treated with combined regimen of letrozole and misoprostol, which is inconsistent with the findings of Rezai's study in which no significant difference was found between the two groups (14).

Estrogen and progesterone are hormones for maintaining pregnancy (18). Previous studies showed the success of anti-progesterone medications such as mifepristone in combination with prostaglandins for the termination of early pregnancy (19-21). Due to the fact that it was not available (15), letrozole was used instead, which can inhibit estradiol synthesis and lead to the cessation of progesterone activities by reducing serum estradiol (16), in combination with misoprostol for abortion (12, 14, 16). The differences between the results in these studies and the present study could be due to the difference in dose and duration of administering letrozole with misoprostol and the gestational age. However, further studies are needed to determine the mechanism of letrozole in facilitating medical abortion, especially when it is used with misoprostol (16).

The present study has several limitations. It is a retrospective study, and this may cause data fault. The short time of monitoring cases and illegal factors were the limitations in our study. Moreover, we failed to identify the risk factors for abortion and monitor the possible long-term complications in both groups.

Conclusion

The results of the current study demonstrated that 7.5mg of daily letrozole for two consecutive days, followed by vaginal misoprostol 800 mcg proved more effective in terminating pregnancy in the first trimester than vaginal 800 mcg misoprostol alone.

Acknowledgements

We truly appreciate Babol University of Medical Sciences and the Clinical Research Development Unit of Rouhani Hospital for their cooperation and all the sincere support.

[DOI: 10.22088/caspjrm.4.2.17]

Conflicts of Interest

The authors have no conflicts of interest.

References

1. Yazdani SH, Bouzari Z, Farahi S, Monadi TA. Oral misoprostol with oxytocin versus oxytocin alone for labor induction in pre-labor rupture of membranes (PROM) at term pregnancy. J Babol Univ Medical Sci. 2012;14(3):7-12.
2. Yazdani S, Javadian M, Bouzari Z, Ghanbari S. Intracervical Foley Catheter Balloon Versus Prostaglandin E2 in Preinduction Cervical Ripening. Journal of Mazandaran University of Medical Sciences. 2010;20(79):56-61.
3. Bebbington MW, Kent N, Lim K, Gagnon A, Delisle MF, Tessier F, et al. A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination. American journal of obstetrics and gynecology. 2002;187(4):853-857.
4. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstetrics & Gynecology. 1997;89(5):768-772.
5. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. New England Journal of Medicine. 2001;344(1):38-47.
6. Yazdani S, Zeinalzadeh M, Bouzari Z, Golsorkhtabar-Amiri M. Effects of vaginal versus oral misoprostol to terminate second-trimester pregnancy. Clinical and experimental obstetrics & gynecology. 2012;39(4):529-531.
7. Beucher G, Baume S, Bekkari Y, Legrand-Horras M, Herlicoviez M, Dreyfus M. Medical treatment of early spontaneous miscarriages: a prospective study of outpatient management using misoprostol. Journal de gynecologie, obstetrique et biologie de la reproduction. 2004;33(5):401-406.
8. Blanchard K, Winikoff B, Ellertson C. Misoprostol used alone for the termination of early pregnancy: a review of the evidence. Contraception. 1999;59(4):209-217.
9. Ramin KD, Ogburn PL, Danilenko DR, Ramsey PS. High-dose oral misoprostol for mid-trimester pregnancy interruption. Gynecologic and obstetric investigation. 2003;54(3):176-179.
10. Lee VC-Y, Gao J, Lee K-F, Ng EH-Y, Yeung WS-B, Ho P-C. The effect of letrozole with misoprostol for medical termination of pregnancy on the expression of steroid receptors in the placenta. Human Reproduction. 2013:det345.
11. Shaw KA, Topp NJ, Shaw JG, Blumenthal PD. Mifepristone–misoprostol dosing interval and effect on induction abortion times: a systematic review. Obstetrics & Gynecology. 2013;121(6):1335-1347.
12. Yeung TWY, Lee VCY, Ng EHY, Ho PC. A pilot study on the use of a 7-day course of letrozole followed by misoprostol for the termination of early pregnancy up to 63 days. Contraception. 2012;86(6):763-769.
13. Lee VCY, Ng EHY, Yeung WSB, Ho PC. Misoprostol with or without letrozole pretreatment for termination of pregnancy: a randomized controlled trial. Obstetrics & Gynecology. 2011;117(2, Part 1):317-323.
14. Rezai Z, Bazardehi H, Sareh S, Ghasemi Nezhad A, Sadeghi AS, Ghorbani Yekta B. Letrozole and misoprostol versus misoprostol alone for termination of pregnancy: a randomized clinical trial. Tehran University Medical Journal TUMS Publications. 2014;71(11):700-706.
15. Lee VCY, Tang OS, Ng EHY, Yeung WSB, Ho PC. A prospective double-blinded, randomized, placebo-controlled trial on the use of letrozole pretreatment with misoprostol for second-trimester medical abortion. Contraception. 2011;84(6):628-633.
16. Lee V, Yeung T, Tang O, Ng E, Yeung W, Ho P. Effect of letrozole on uterine artery Doppler flow indices prior to first-trimester termination of pregnancy: a randomized controlled trial. Ultrasound in Obstetrics & Gynecology. 2012;40(4):392-397.
17. Chai J, Ho P-C. A pilot study on the combined use of letrozole, mifepristone and misoprostol in termination of first trimester pregnancy up to 9 weeks' gestation. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013;171(2):291-294.
18. Albrecht ED, Aberdeen GW, Pepe GJ. The role of estrogen in the maintenance of primate pregnancy. American journal of obstetrics and gynecology. 2000;182(2):432-438.
19. Bygdeman M, Swahn M-L. Progesterone receptor blockage: effect on uterine contractility and early pregnancy. Contraception. 1985;32(1):45-51.

[DOI: 10.22088/caspjrm.4.2.17]

20. Cameron I, Michie A, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU486 alone or in combination with prostaglandin analogue (gemeprost). Contraception. 1986; 34(5):459-468.
21. Schaff EA, Fielding SL, Eisinger SH, Stadalius LS, Fuller L. Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days. Contraception. 2000;61(1):41-46.

[DOI: 10.22088/caspjrm.4.2.17]