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Induction of Abortion in the First Trimester by Misoprostol or Misoprostol With Letrozole

Ezzatossadat Haj Seyed Javadi [1]; Masoomeh Mohammadi [1]; Ameneh Barikani [1,*]

[1]Children Growth Research Center, Qazvin University of Medical Sciences, Qazvin, IR Iran
[*]*Corresponding author*: Ameneh Barikani, Children Growth Research Center, Qazvin University of Medical Sciences, Qazvin, IR Iran. Tel: +98-2833328709, Fax: +98-2833344088, E-mail: barikani.a@gmail.com

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Background: Management of abortion is an important issue in gynecology. Several millions of spontaneous abortions occur yearly and more than a million induced abortions are performed in the USA.
Objectives: The aim of this study was to compare the effect of misoprostol alone and misoprostol with letrozole in the induction of abortion in the first trimester of pregnancy in the Qazvin city of Iran.
Patients and Methods: Seventy female candidates for legal abortion within the first trimester of pregnancy were divided to two groups: misoprostol alone and misoprostol with letrozole. The complete abortion, time to open the internal os of the cervix, time to complete the abortion, and drug-induced side effects of misoprostol and letrozole were recorded and analyzed.
Results: The complete abortion rate was 69.7% in the misoprostol and letrozole group and 30.3% in the misoprostol group. Incomplete abortion was 32.4% in the misoprostol and letrozole group, and 67.6% in the misoprostol group ($P = 0.004$). Bleeding, cervix os opening time, and time to complete abortion from induction of drugs were similar in both groups ($P > 0.05$). There were no medical complications in both groups.
Conclusions: Misoprostol plus letrozole was more effective for inducing abortion in the first trimester of pregnancy compared to misoprostol alone.

Keywords: Letrozole; Abortion; Induced; Misoprostol; Pregnancy Trimester; First

1. Background

According to the national center of vital statistics, centers for disease control and prevention and the world health organization definition, abortion is the termination of a pregnancy before the 20th week of pregnancy or termination of pregnancy before the fetus weighing 500 g (1, 2).

Abortion management is an important issue in gynecology. Several millions of spontaneous abortions occur yearly and more than a million induced abortions are annually performed in the USA. Induced abortion is one of the most common surgical procedures in gynecology and is amongst topics that are commonly investigated (2).

Definitive treatment for abortion is a surgical procedure yet it is invasive and is not necessary for all females. Curettage may not be needed via expectation and medical treatment (1). According to the American college of obstetricians and gynecologists (2005), medical abortion is an acceptable alternative for surgical procedures in pregnant women with gestational age of less than 49 days based on the last menstrual period (LMP) (1).

Spontaneous abortion occurs in 10% - 20% of total pregnancies. Furthermore, 80% of abortions occur before the 12th week of pregnancy. The mean gestational age of spontaneous abortion is nine weeks (2). Misoprostol is extensively used for induction of labor in the second trimester of pregnancy, softening the cervix before using devices, curettage, hysteroscopy, therapeutic abortion, endometrial biopsy, early termination of pregnancy, treatment of incomplete abortion or missed abortion, treatment of postpartum hemorrhage and induction of labor at term (3). Misoprostol abortion rate is less than 90% in most studies and it has different side effects (4-7).

Application of 800 mcg of vaginal misoprostol results in abortion by stimulating the myometrium (1). Oral or vaginal misoprostol cause complete abortion in almost 85% of cases within seven days before the 12th week (1). Mifepristone and a prostaglandin analogue for induction of abortion are preferred in nonsurgical methods. Using a combination of mifepristone and misoprostol is limited due to unavailability (8).

Letrozole is a non-steroidal aromatase inhibitor for the treatment of estrogen-dependent breast cancer. Estrogen is produced by aromatase enzyme activity from androgens. Estrogens are necessary for continuation of the pregnancy. Letrozole reversibly and competitively bonds with the iron in cytochrome P450 and prevents the production of estrogen by the enzyme aromatase. Aroma-

tase inhibitors such as letrozole are widely used to treat patients with breast cancer (9-11).

These compounds directly inhibit estrogen biosynthesis, lead to an increase in FSH secretion from the pituitary gland, yet don't have the side effects of anti-estrogen on the endometrium and cervix. Non-steroidal aromatase third generation inhibitors such as letrozole have potent and reversible effects. The absence of anti-estrogenic effects of aromatase inhibitors, such as letrozole, is another advantage. It prevents the interference of endometrium morphology and the cervix.

Aromatase inhibitors have no androgenic, progesterone and estrogenic effects. It seems that aromatase inhibitors, such as letrozole, can open a new path and be a significant therapeutic option in the treatment of females. Letrozole is an aromatase inhibitor that can amplify the effect of misoprostol in first trimester abortions.

Aromatase is an enzyme that is secreted from the placenta, ovarian granulosa cells and other tissues, such as fat, muscle, brain and breast tissue. Letrozole has been used in the treatment of estrogen-dependent breast cancers (9-11).

In a clinical trial by Lee et al. (2011), complete abortion in the first trimester, in the misoprostol alone and the misoprostol with letrozole group was 72.6% and 86.9%, respectively (P = 0.021) (12).

2. Objectives

The aim of this study was to compare the effect of misoprostol alone and misoprostol with letrozole for induction of abortion in the first trimester of pregnancy in the Qazvin city of Iran.

3. Patients and Methods

This randomized double-blind study was conducted during year 2013. All females that had referred to the Kowsar hospital of Qazvin and were candidates for therapeutic abortion with gestational age (GA) of less than 12 weeks were considered as the target population. Seventy women with nonliving pregnancy were randomly allocated to the control or intervention group (35 in the control group and 35 in the intervention group). Inclusion criteria were as follow:

1. Gestation age of less than 12 weeks, based on ultrasound results, on the first day of letrozole administration.
2. Mother's age being more than 18 years.
3. Hemoglobin concentration (Hb) ≥ 10 gr/dL.

Exclusion criteria were as follow:

1. History of previous cesarean section.
2. History of adrenal disease, steroid-dependent cancer, liver disease, severe or recurrent, bronchial asthma, evidence or history of thromboembolism, history of renal disease, blood pressure > 95 mmHg, history of smoking.

The patients received letrozole 10 mg as an oral dose (four tablets of 2.5 mg for three days) in the letrozole group. Four placebo tablets were given to the control group with the same instructions. Patients in both groups on the third day of the study were hospitalized and received a third dose of 800 μg of vaginal misoprostol in a single dose.

The patients were examined for opening of the internal os of the cervix every hour after the onset of uterine contractions (the time between administration of medication and opening of internal os was recorded). Two other duration times were recorded including the time between drug use and discharge initiation of pregnancy products and tissue, and time between drug use and complete abortion (with completing the tissue rejection).

Vital signs were recorded every six hours. The patient side effects including fever, chills, nausea, vomiting, diarrhea, headache and abdominal pain were recorded in a form. Finally, vaginal sonography revealed the extent of the need for curettage.

Patient information was collected using a questionnaire. Data were analyzed using the student's t-test, chi-square test and Fisher's exact test. P values of < 0.05 were considered significant. Before the study, the researcher described the trend of the study and the patients who were willing to participate in the study signed a consent form.

4. Results

A total of 70 patients were enrolled. Two patients in the letrozole group had curettage before receiving misoprostol (second day) due to incomplete abortion. The mean age of patients in the letrozole and misoprostol, and misoprostol alone group was 26 ± 5.7 and 27.7 ± 5.6 years, respectively. Furthermore, 32.9% and 67.1% of patients had gestational age of less than seven weeks, and seven to twelve weeks, respectively.

Mean duration time of drug administration to open the os of the cervix was 6.0 ± 1.3 hours in all patients. Mean duration time to start prescribing tissue rejection was 8.9 ± 2.0 hours in all patients. The mean duration time to complete abortion medication was 9.0 ± 2.0 hours in the patients. The complete abortion rate was 47.14% and curettage rate was 52.86% in all patients.

Mean duration time of drug administration to open the os of the cervix was 5.9 ± 1.5 hours in the letrozole and misoprostol group yet this was 6.1 ± 1.2 hours in the misoprostol alone group; this difference was not significant (P = 0.59) (Table 1).

Mean duration time between drug administration and opening of the os of the cervix was 5.2 ± 1.7 hours in patients with GA of less than seven weeks, and 6.1 ± 1.4 hours in patients with GA of between seven and twelve weeks from the misoprostol with letrozole group; this difference was not significant (P = 0.18) (Table 2).

From the total of 12 cases with complete abortion (GA of less than seven weeks), 41.7% were in the letrozole and misoprostol group and 85.3% were in the misoprostol alone group (P = 0.22). From the total of 21 cases with GA of between 7 and 12 weeks and complete abortion, 85.7% of the patients were in the letrozole plus misoprostol group and 14.3% were in the misoprostol group (P = 0.001).

Table 1. Time Span to Open the Cervix, Tissue Rejection, and Complete Abortion by Misoprostol With and Without Letrozole in the First Trimester of Pregnancy [a]

Observed Time	Misoprostol	Letrozole + Misoprostol	P Value
Induction to opening of internal os time, h	6.1 ± 1.2	5.9 ± 1.5	0.59
Induction to abortion time, h	9.0 ± 1.7	8.9 ± 1.4	0.8
Induction to complete abortion time, h	9.0 ± 1.7	9.0 ± 2.4	1.0

[a] Data are presented as mean ± SD.

Table 2. Comparison of Misoprostol Alone or in Combination With Letrozole in Inducing Abortion During the First Trimester of Pregnancy by Pregnancy Age [a]

Observed Time	Misoprostol		P Value	Letrozole + Misoprostol		P Value
	< 7, w	7 - 12, w		< 7, w	7 - 12, w	
Induction to internal os time, h	5.53 ± 1.24	6.6 ± 1.02	0.007	5.2 ± 1.7	6.1 ± 1.43	0.18
Induction to abortion time, h	8.13 ± 1.30	9.7 ± 1.70	0.006	7.8 ± 2.7	9.2 ± 2.2	0.19
Induction to complete abortion time, h	8.13 ± 1.3	1.7 ± 9.7	0.006	7.8 ± 2.7	9.3 ± 2.3	0.16

[a] Data are presented as mean ± SD.

The success rate of excretion products in the first trimester of pregnancy was higher in patients treated with misoprostol and letrozole, compared to misoprostol alone (69.7% vs. 30.3%, and P = 0.004). Complete abortion rate was 69.7% for the misoprostol and letrozole group, and 30.3% for the misoprostol alone group. This difference was statistically significant (P = 0.004). Drug side effects (e.g. nausea, dizziness, fatigue, abdominal pain, and chills) were not found in the study subjects.

5. Discussion

This study compared the effects of misoprostol combined with letrozole, and misoprostol alone for the induction of abortion in the first trimester of pregnancy. Based on our observations, letrozole administration with misoprostol raised the rate of complete abortion in pregnancies under 12 weeks in comparison with misoprostol alone.

The results of our study showed a 69.7% success rate of complete abortion with misoprostol and letrozole compared to 30.3% with misoprostol alone (P = 0.004). In the study of Yeung et al. complete abortion, side effects, and the duration between induction and abortion (complete abortion induction interval) were studied. The results proved that the overall rate of complete abortion was 95%, and one case (5%) had incomplete abortion and had to undergo curettage (13). The overall rate of complete abortion in patients with GA of less than 49 days was 100% (13). In contrast to our study, Yeung et al. used letrozole in combination with misoprostol regimen for seven days. The mean induction to abortion interval was not significant in our study, similar to the findings of Yeung et al. Drug side effects such as nausea, dizziness, fatigue, abdominal pain and chills were not found in our study. Lee et al. studied the use of letrozole in combination with letrozole, misoprostol and mifepristone (14), and complete abortion was higher in the letrozole plus misoprostol group, while in this group, the interval between induction and abortion was shorter than the other group. The success rate in the study of Lee et al. was 86.9% vs. 69.7% in our study with similar drug administration. In our study, the sample size was greater than the study of Lee et al. (70 vs. 40), and they studied patients with gestational age of less than 63 days. In our study, there were a total of 12 cases of complete abortion with GA of less than seven weeks (41.7%); five patients were in the letrozole and misoprostol group (85.3%), and seven cases were in the misoprostol alone group (P = 0.22).

There were a total of 21 cases of complete abortion with GA of between seven and twelve weeks (85.7 %); 18 patients in the letrozole and misoprostol group (14.3%) and three patients in the misoprostol group (P = 0.001). The success rate in use of letrozole and misoprostol, in patients with GA of seven to twelve weeks, was 85.7% at the disposal of pregnancy products, similar to the results of Lee et al. (14).

In another study that was conducted by Lee et al. (2011) (14), complete abortion was 86.9% with misoprostol and letrozole yet this was 72.6% in the misoprostol alone group, and the difference was statistically significant (P = 0.021). Common side effects (abdominal pain, nausea and vomiting) were found in 3.8% of cases in the letrozole and misoprostol group, and 19% in the misoprostol alone group; the difference being statistically significant (P = 0.043) (12). In contrast to this study, our success rate was lower, yet no side effects were recorded, and the difference in our study was not statistically significant.

In the study of Chai et al. complete abortion rate was 98% with the addition of letrozole to mifepristone and misoprostol, and the interval from induction to abortion was 5.1 hours. In our study no adverse effects were report-

ed yet in the study of Chai et al. (15), 2% of cases needed suction due to massive bleeding.

Differences in studied populations, genetic diversity and distribution of receptors, the application of medications, PH of the vagina, drug manufacturers, GA and sample size were confounding factors that must be considered.

Letrozole is an aromatase inhibitor that has an effect on the production of estrogen in the mitochondria, ovaries and the placenta (16, 17). Previous studies have shown that letrozole is effective in reducing estrogen and does not affect progesterone (13, 17). Furthermore, recent studies have shown that letrozole has no effect on uterine contractions (18). The mechanism of action of letrozole is different from that of more expensive drugs such as mifepristone.

The mechanism of action of letrozole could explain the number of days prescribed for maximum efficacy. Another factor that was noted was that letrozole reduces bleeding after abortion, which makes it a good therapeutic option, since bleeding is one of the major concerns (19, 20). Loss of pregnancy during the first trimester is one of the most common pregnancy complications. Its incidence is 50% (21). Surgical termination of pregnancy is very effective yet has many complications such as infection, uterine perforation, Asherman's syndrome and future infertility of women (22). Expectant management may also be useful in some individuals yet it is unpredictable (23). Medical termination of pregnancy is a safer method. Medical termination of pregnancy by mifepristone was recommended, yet mifepristone is an expensive drug and is not available everywhere (8). On the basis of this study, we recommend the use of letrozole plus misoprostol for the treatment of abortion due to lower costs and greater chances of complete abortion (without special effects). As far as we know, in our country, this was the first study on the combination of letrozole with misoprostol in comparison with misoprostol alone to terminate pregnancies under 12 weeks.

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Authors' Contributions

Study concept and design: Ameneh Barikani and Ezzatossadat Haj Seyed Javadi. Analysis and interpretation of data: Ameneh Barikani. Drafting of the manuscript: Ameneh Barikani and Ezzatossadat Haj Seyed Javadi. Critical revision of the manuscript for important intellectual content: Masoomeh Mohammadi. Acquisition of data: Ezzatossadat Haj Seyed Javadi and Masoomeh Mohammadi. Statistical analysis: Ameneh Barikani. Administrative, technical and material support: Ezzatossadat Haj Seyed Javadi and Masoomeh Mohammadi. Study supervision: Ameneh Barikani and Ezzatossadat Haj Seyed Javadi.

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This study was officially registered as a gynecology and obstetrics specialty thesis at the School of Medicine, Qazvin University of Medical Sciences and was registered as a clinical trial with the following code IRCT201505011903N8.

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