

Medical Induction of First Trimester abortion by Misoprostol or Misoprostol with Letrozole

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Abstract

Background: Managing of abortion is an important subject in gynecology. Millions of patients had suffered from spontaneous abortions that occur per year.

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.

Patients and Methods: In a single –blind clinical trial ,128 female applicants for legal abortion within the first trimester of pregnancy that referred to AL-Batool hospital , were divided in to two groups: intervention (misoprostol with letrozole) and control groups (misoprostol alone). The complete abortion, drug-induced side effects of misoprostol and letazole were noted and evaluated.

Results: The complete abortion rate was 93.2% in intervention group and in 68.7% in the control group (misoprostol) only, which was significantly higher in intervention group ($p = 0.001$).

Abdominal pain in the intervention group is also significantly lower than that of the control group ($p = 0.013$). Intervention group also had significantly lower duration of bleeding rather than control group ($p = 0.006$).

Conclusions: Based on our results, pretreatment with letrozole plus Misoprostol was more effective for prompting abortion in the first trimester of pregnancy without increasing side effect compared to misoprostol alone.

Keywords: Letrozole; Abortion, Induced; Misoprostol, Pregnancy, First trimester;

Introduction

Regarding 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 managing is an important subject in gynecology. Millions of spontaneous abortions happen, and more than a million of induced abortions are occur yearly either by drugs or surgical techniques. Definitive treatment for abortion is a surgical practice yet it is

invasive and costly, is not required for all females.

According to the American college of obstetricians and gynecologists (2005), medical abortion is an suitable alternative for surgical techniques in pregnant women with gestational age of less than 49 days founded on the last menstrual period (LMP)⁽³⁾. Spontaneous abortion happens in 10% - 20% of whole pregnancies, while, 80% of abortions occur earlier the 12th week of pregnancy.⁽⁴⁾

In medical therapy, abortion done by various drugs, considering mifepristone drugs has limited access, its high cost, it is not available in most of the countries and alternative drugs are used to induce abortion⁽⁵⁾. One

of these drugs which used both vaginally and orally is prostaglandin E1 analogue, misoprostol, which is Known as Cytotec trade mark. Misoprostol is a cheap drug which could be kept in room temperature and usually used as vaginally and orally ⁽⁶⁾. Misoprostol is widely used for induce of labor, softening of the cervix, curettage, hysteroscopy, therapeutic abortion, endometrial biopsy, early termination of pregnancy, treatment of incomplete abortion or missed abortion and treatment of postpartum hemorrhage ⁽³⁾ Use of 800 mcg of vaginal misoprostol results in abortion by exciting the myometrium ⁽⁷⁾. Oral or vaginal route of administration of misoprostol cause complete abortion in nearly 85% of cases within seven days before the 12th week ^(6,7).

Letrozole is a non-steroidal aromatase inhibitor for the treatment of estrogen-dependent breast cancer. Estrogens are required for continuation of the pregnancy. Letrozole is competitive reversibly bonds with cytochrome P450 and inhibits the production of estrogen by the enzyme aromatase. Aromatase inhibitors are commonly used to treat patients with breast cancer ⁽⁸⁻⁹⁾.

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. ⁽⁷⁾

Materials and Methods

In a single-blind randomized, 128 women were included in our study, study protocol was approved by the Ethics Committee of Diyala university, Diyala medical college, during June 2016 to April 2018, Considered as two groups of intervention and control after consent of patient and her spouse to participate in the study, who age above 18 years old were referred to AL Batool Teaching hospital .

Inclusion criteria were involved:

1-Age of patient over 18 years old.

2-Gestational age less than 64 days gestation, missed abortion. (<9 wks).

3-Hemoglobin >10 g/dL.

4- Absence of any maternal illnesses such as: heart disease, asthma, past history of thromboembolism, cancer, renal failure, and liver illnesses,

Where exclusion criteria as followed: any medical problematic in patient which necessity to interfere and emergency management, history of allergy to misoprostol or letrozole drugs or Coagulopathy problem.

A 128 patient divided into two equal group, Sixty-four patients in intervention group and 64 patients in control group. In intervention group to encourage drug abortion, patients first received 10 mg letrozole per day orally for 3 days, then they received 600 microgram oral misoprostol as single dose, While in control group patients first daily established placebo of letrozole similar intervention group and then 600 microgram single dose oral misoprostol was used. In both groups, patient who had spontaneous abortion before starting treatment of misoprostol in the first three days of study, were excluded from the study.

Patients in both groups hemoglobin levels were examined at the beginning and end of the study. Serum estradiol levels were measured at the beginning in control group and measured at the beginning and before taking misoprostol in intervention group.

Both groups were checked for 4 hours after receiving single dose of misoprostol and were observed for probable side effects such as abdominal cramp or possible bleeding, and in terms of absence of abdominal cramp or severe bleeding, were released after explanation risk and threatening signs such as bleeding more than normal menstruation.

Subsequent visit and monitoring of patients in both groups was showed 15 days later and response to treatment and complete abortion, amount and period of bleeding, drug side effects such as nausea, vomiting, diarrhea, headache, dizziness, pain in the lower parts of the abdomen, and age all were detected and ultrasound to perform in both groups to check uterine cavity and measuring the hemoglobin level. If remnants of pregnancy or failure in termination of pregnancy,

repeated doses of misoprostol or curettage can be done. In both groups of control and intervention were put in two categories of response to treatment and failure in response to treatment.

Statistical analysis was done by SPSS, software package version 16.0 for windows (SPSS Quantitative data were accessible as mean ± standard deviation (SD), while qualitative data were established as frequency and

percent (%). To compare qualitative variables chi-square statistical test was used and to relate quantitative variables between two considered groups independent T-test was implemented. Also to associate intra-group quantitative variables such as hemoglobin, paired T-test was applied. Significance level was considered as $p < 0.05$

Results

	Intervention group (letrazole group) (N=)	Control group (N=)	P-value
Mean age of patients	29 ± 4.08 years	28.53±5.25years	0.402
Mean pregnancy age	7.74 ± 0.95 weeks	8.52 ± 1.29	0.103
BMI (KG\M2)	23.9±5.0	22.8±5.0	0.301

Table 1: Demographic data shows ,women age, body mass index and gestational age of pregnancy in both groups..

No significant difference were found in the women age, body mass index and gestational age of pregnancy.

	Intervention group Letrozole + Misoprostol	Control group Placebo + Misoprostol	P value
Before Intervention	13.29± 0.95	13.02± 0.86	0.080
After Intervention	12.55±1.01	12.14±0.97	0.015

Table2: Hemoglobin level (mg/dl) in both Intervention and Control groups

Decrease of Hemoglobin level in the intervention group was statistically significantly lower than control group

Table 3. Complet abortion in both groups

	Intervention group Letrozole + Misoprostol	Control group Placebo + Misoprostol	P value
Complet abortion (%_)	93.75%(n=(64)	68.55%(n=44)	P=0.001
Surgical interference %	6.25%(n=4)	31.25%(n=20)	P=0.012

In terms of response to treatment, two groups had statistically significant difference ($p = 0.001$)

And need for surgical curettage in intervention group was significantly lower than that of control group ($p = 0.012$).

Table 4. Complications in the period of study in individually in Intervention group and Control group

Intervention group Letrozole + Misoprostol		Control group Placebo + Misoprostol	P value
Nausea	59.3%	70.3%	0.218
Vomiting	29.6%	26.6%	0.710
Diarrhea	31.2%	43.8%	0.113
Dizziness	28.1%	25.0%	0.848
Headache	6.2%	4.7%	0.728
Abdominal pain	54.6%	76.6%	0.013
Fever	6.2%	1.6%	0.127
Chills	10.9%	9.4%	0.786

Drugs side effects in two studied groups during the study, have been obtainable in table 3. the abdominal pain in interventional group was significantly lower than that of control group. (P=0.013).

Table5:-Bleeding duration in both interventional and Control group s

Intervention group Letrozole + Misoprostol		Control group Placebo + Misoprostol	value
Within a few hours	0.00%	7.81%	P=0.001
Within a day	60.93%	42.19%	P=0.001
More than a day	39.06%	50.00%	P=0.001

Generally comparing both groups in expressions of duration of bleeding, intervention group had significantly lower duration of bleeding rather than control group (p = 0.006)

Discussion

Medical abortion reduce side effects such as bleeding and infection, and also stress in patients, relating with surgery. In medical abortion technique it is possible to use several drug regimens to induce abortion. Misoprostol is a prostaglandin analog and a benign and cheap drug which is used for inducing medical abortion and frequent studies have shown its efficiency^(10, 11).

In a pilot study, in persuading abortion in 40 legal below r-63-day abortion cases, 7.5 mg letrozole for 2 days, and then usage of vaginal misoprostol leads to preform abortion in 80% of patients and comparing with Mifepristone, using of letrozole with misoprostol together was more efficient than combination of letrozole and mifepristone⁽¹²⁾. In the present study also success rate of complete abortion was higher in using misoprostol and letrozole comparing with using misoprostol alone (p = 0.001).^(11,12)

In a prospective study success rate in prompting abortion for 56-day or less pregnancies using single dose misoprostol vaginally, was informed 72%. Also this study claimed that in case of failure in access to mifepristone, using misoprostol only clinically could lead to suitable outcomes⁽¹³⁾. Also a evaluation of this study has revealed that in treatment of missed abortion in the first trimester of pregnancy by misoprostol, 800 microgram misoprostol as single dose per vagina or 600 microgram single dose sublingual misoprostol are good substitutes for surgery. This study also expressed that after advising misoprostol there was no necessity for hospitalization and patients would refer in case of severe bleeding or infection (14). In the current study also frequency of complete misoprostol for using misoprostol alone was 68.75%, and in case of lack of admission to another drug, using this drug had suitable outcomes similar other studies^(13,14)

In a pilot study, up to the ninth week of pregnancy in 50 person, a single dose of 200 mg mifepristone and 10 mg letrozole per day for 3 days, and lastly 800 microgram single dose 1 misoprostol per vagina, were used to persuade abortion rate of complete abortion in this study was 98%, and also no significant side effects were informed⁽¹⁵⁾

Similar to recent study, in a clinical trial, on 168 women below -63-day pregnancy age, letrozole treatment before misoprostol was examined. Success rate in complete abortion in letrozole getting group was significantly higher than that of group getting misoprostol alone. Between side effects, vomiting was significantly more in letrozole group than in control group⁽¹⁶⁾. In current study using letrozole did not lead to rise in side effects and even abdominal pain and bleeding time in intervention group was significantly lower than that of control group. Also another study presented that using letrozole for 7 days before using vaginal misoprostol also increases rate of complete abortion up to 96%⁽¹⁷⁾

While the effect of using letrozole with misoprostol for inducing abortion excluding the first trimester of pregnancy, in a clinical trial on outcome of using letrozole with misoprostol for inducing abortion in the second trimester of pregnancy, advising letrozole prior to misoprostol did not lead to significant change in success rate of inducing medical abortion in the second

trimester of pregnancy. Also in this study there was no significant change among two groups in rappers of side effects⁽¹⁸⁾. Related to the recent study, many studies have stated effectiveness of using letrozole

prior to misoprostol in increasing rate of success in complete drug abortion, without increase in side effects⁽¹⁸⁾. Also in current study, while comparing bleeding time, letrozole receiving group had mean lower bleeding time and about hemoglobin level, two groups didn't have significant difference before intervention, but after intervention and conducting abortion, hemoglobin rate of letrozole receiving group was significantly higher than that of control group. Also abdominal pain in letrozole receiving group was lower than that of control group. Finally numerous new studies express that, implementing effective drug regimens for inducing abortion is more affordable and risk free than methods such as vacuum aspiration^(19, 20), which should be paid attention by physicians.

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Department of anesthesia Bilad AL-Rafidein University College and all experiments were carried out in accordance with approved guidelines.

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