Use of Letrozole Pretreatment with Misoprostol for Induction of Abortion in First Trimester : A Randomized Controlled Trial

Original Article

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ABSTRACT

Aim: This study aimed to compare the efficacy of using letrozole pretreatment before misoprostol versus using misoprostol alone for the medical termination of first trimester missed abortion.

Materials and Methods: This clinical trial was conducted at Ain-Shams University Maternity Hospital in the period between January 2020 and August 2020, and was registered at clinical trials.gov Identifier. NCT04590482. Patients that seem to be fulfilling the inclusion criteria were recruited, then, an informed written consent was taken from every patient before starting the examination. Followed by detailed history and examination of all the patients. Hemoglobin, hematocrit, blood group, RH, and trans- vaginal ultrasound were done for all patients before the study**.**

Results: The result of the study demonstrated an increase in complete abortion rate (primary outcome) at day 3 in group A (56.6%) more than group B (35.2%) which was statistically significant. Also there was an increase in the incidence of complete abortion at day 7 in group A (77.4%) more than group B (68.5%) but with no statistically significant difference between the two groups.

Conclusion: Using of letrozole pretreatment with misoprostol for induction of first trimester abortion is better than using of misoprostol alone, as there was an increase in complete abortion rate in group A more than group B.

Key Words: Abortion, letrozole, misoprostol

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INTRODUCTION

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 less than 49 days based on the last menstrual period (LMP)[1].

Missed abortion in 1st rimester is characterized by the arrest of embryonic or fetal development. The cervix is closed and there is no or only slight bleeding. Ultra sound shows a fetus without cardiac activity[2].

The most common early first-trimester medical abortion regimen consisted of mifepristone in combination with administration of misoprostol. The complete abortion rate was up to 95% in gestations up to 63 days[3].

However, Mifepristone is expensive and not registered in many countries[4]. Misoprostol is a synthetic analogue of naturally occurring prostaglandin E1, that has a uterotonic effect and can stimulate myometrial contraction and can cause cervical ripening and dilatation[5].

Misoprostol is rapidly absorbed orally, sublingually, rectally and vaginally. It is less expensive than the other preparations of prostaglandin and is simple to store[6].

With repeated doses (up to 3) of vaginal misoprostol alone, the success rate was only 65% when using dry misoprostol and 85% when using it moistened with water[7].

According to the FIGO protocol of induction of abortion 2017 (missed abortion 800ug misoprostol per vagina/3 hours with a maximum of 2 doses.

Letrozole is a highly specific non- steroidal aromatase inhibitor which suppresses the peripheral conversion of androgens to estrogens, as it competitively binds to the heme of the cytochromeP450 subunit of aromatase. It has been recently shown that the use of Letrozole combined

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with vaginal misoprostol was more effective than misoprostol alone in the termination of pregnancy[8].

The regimen of using Letrozole 7.5mg daily for 2 days combined with vaginal misoprostol 800mcg is associated with a complete abortion rate of 80% versus using misoprostol alone in subjects with gestations less than 63 days. In subjects with gestations less than 49 days, the complete abortion rate was higher (87.5%)[9].

The commonest side effects of letrozole are fatigue and nausea. Misoprostol may be associated with nausea, diarrhea and lower abdominal pain. Most of these side effects are already present during pregnancy before the administration of treatment and persist after letrozole pre-treatment and misoprostol administration[8].

AIM OF THE STUDY

The aim of this study is to compare the efficacy of using letrozole pretreatment before misoprostol versus using misoprostol alone for the medical termination of first trimester missed abortion.

PATIENTS AND METHODS

This study is a prospective, randomized, controlled trial which was conducted at Ain-Shams University Maternity Hospital.The study was started in January 2020.

The patients were recruited from women attending outpatient obstetric clinic or the emergency room of Ain-Shams University Maternity Hospital.

Sample size justification: Using PASS 11 program for sample size calculation and according to Javanmanesh *et al.*[10], the expected rate of complete abortion within 24 hrs in women who received letrozole followed by misoprostol is 78% and in women who received misoprostol alone is 13%, sample size of 50 women in each group can detect this difference with power > 99% and α-error 0.05. The sample was increased by 10% for any dropouts, so 55 women in each group was needed.

Primary outcome: Incidence of complete miscarriage (complete expulsion of the products of conception with no need for surgical intervention within the first 24 hours from the first dose of misoprostol.

Secondary outcome: Need for surgical evacuation of the products of conception: Incomplete expulsion of the products of conception. Severe bleeding necessitating immediate surgical evacuation.

Inclusion criteria: Maternal age more than 18 years old. The gestational age less than 13 weeks confirmed by ultrasound scan on day 1 of the study. The hemoglobin was >10 g/dl. Missed abortion according to Royal College for Obstetrics and Gynaecology (RCOG) 2011 guidelines state that: If the crown rump length is >7mm and there is no embryonic cardiac activity. If the mean gestational sac diameter is >25mm and there is no yolk sac. Crown Rump length (CRL)<18mm as there is positive association with subsequent missed abortion.

Exclusion criteria: Mullerian Uterine anomalies as septate, bicornuate uterus. Fibroid uterus. Coagulopathy. Medical disorder that contraindicate induction of abortion. Allergy to misoprostol or letrozole.

Recruitment: Patients that seem to be fulfilling the inclusion criteria was recruited, then an informed written consent was taken from each patient before starting the examination and subjected to personal history; name, age, occupation, special habits of medical importance

Obstetric history: Parity, last delivery, last abortion, contraception method, first day of last menstrual period, estimated gestational age by date.

Past history: History of diabetes mellitus, hypertensive disorder, blood disease or bleeding tendency.

Examination of the patient: General examination: Vital data (blood pressure-pulse-temperature). Presence of pallor or jaundice. Presence of ecchymosis of skin to exclude coagulopathy. Chest and heart examination.

Abdominal examination: Size of uterus, scars for previous operation, previous laparotomies. ***Vaginal examination:*** Cervical assessment includes dilatation, position, length and consistency.

Investigations: Complete blood picture, blood group, RH, PT, PTT. Trans-vaginal ultrasound to confirm gestational age and missed abortion and to exclude molar pregnancy, fibroid, or uterine anomalies.

Randomization: Patients fulfilling inclusion and exclusion criteria were randomized into two groups. Randomization was done using computer generated randomization sheet using MedCalc© version 13 ; group A included 55 patients received letrozole one tablet each 12 hours for 2 days before the starting of misoprostol and group B included 55 patients received placebo (Folic acid) one tablet each 12 hours before the starting of misoprostol.

Allocation and concealment: One hundred and ten opaque envelops were numbered serially. In each envelope the corresponding letter which denotes the allocated group (A or B) was put according to a computer generated randomization table. All envelopes were put in one box.

When the first patient arrives the first envelope was opened and the patient was allocated according to the letter inside.

Procedures: Induction of abortion was carried according to the FIGO protocol of induction 2017 (missed abortion 800ug misoprostol per vagina/3 hours with a maximum of 2 doses. Group (A): Women received one tablet of letrozole 2.5 mg (Femara NOVARTIS) each 12 hours for two days at home and told to bring back the empty packs followed by 4 tablets of vaginal misoprostol (200mcg) (Misotac, SIGMA) soaked with saline and another dose per vagina after 4 hours if needed. Group (B): Women received one tablet of(folic acid, THE NILE) as a placebo each 12 hours for two days at home and told to bring back the empty packs, followed by 4 tablets of vaginal misoprostol (200 mcg) soaked with saline and another dose per vagina after 4 hours if needed.

Patients in both groups A,B was come after 24 hours of the last dose of misoprostol, or come at any time if considerable bleeding similar to that of the second day of menses occurs. Monitor minor side effects (fever, nausea, vomiting). Hemoglobin (Hb) and hematocrit (HCT) levels are recorded after 24 hours from abortion to estimate the decrease in Hb level. Excessive vaginal bleeding necessitates immediate evacuation under anesthesia. Remnants>3cm was assessed individually for either redosing of misoprostol or surgical evacuation. Patients who failed to respond to medical abortion was candidate for surgical evacuation under anesthesia.

Ethical considerations: All patients participating in the study was informed about the procedure and the reason of doing it. They were all sign a written consent for the procedure in accordance to the ethical committee regulation.

STATISTICAL ANALYSIS

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 21. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with normal distribution and median with inter-quartile range (IQR) for data with abnormal distribution.

Chi-square test was used to compare between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell was less than 5. The comparison between two independent groups with quantitative data and normal distribution were done by using Independent t-test while the comparison between two independent groups with quantitative data and abnormal distribution data were done by using Mann-Whitney test. The confidence interval was set to be 95% and the margin of error accepted was set to be 5%. So, the p-value was considered significant as the following: $P > 0.05$: Non significant (NS). $P < 0.05$: Significant (S). $P < 0.01$: Highly significant (HS).

RESULTS

Table 1 showed that there was no statistically significant difference found between the two studied groups regarding age, weight, height, BMI and GA (weeks) with *p-value = 0.130, 0.053, 0.174, 0.201* and *0.098* respectively.

Also, there was no statistically significant difference found between the two studied groups regarding gravidity, parity, abortion and number of previous abortion with *p-value = 0.625, 0.239, 0.751* and *0.330* respectively (Table 1).

Table 2 showed that there was no statistically significant difference between the two studied groups regarding the hemoglobin level before treatment with *p-value = 0.731* while there was statistically significant difference between them after treatment with *p-value* = 0.005. The drop in the hemoglobin level was higher in group B (1.43± 0.42 than group A (1.19 ± 0.43) with *p-value = 0.004*.

Table 3 showed that there was statistically significant increase in the cases of complete abortion at day 3 in group A (56.6%) than group B (35.2%) with *p-value = 0.026*. Also, there was an increase in the incidence of complete abortion at day 7 in group A (77.4%) than group B (68.5%) but with no statistically significant difference between the two groups with *p-value = 0.304*. The incidence of surgical intervention was lower in group A (22.6%) than group B (31.5%) but with no statistically significant difference between the two groups with *p-value = 0.304*.

Table 4 showed that there was no statistically significant difference found between the two studied groups regarding results of US at day 7.

Table 5 showed that there was no statistically significant difference found between the two studied groups regarding the side effects after treatment.

Table 1: Demographic and characteristics of the two studied groups

		Group A No. = 53	Group B No. = 54	Test value	*P-value*	Sig.
Age	Mean ± SD	27.92 ± 4.69	29.35 ± 4.99	-1.525•	0.130	NS
	Range	20 – 35	19 – 35			
Wt (kg)	Mean ± SD	61.28 ± 5.13	59.50 ± 4.28	1.955•	0.053	NS
	Range	54 – 69	50 – 68			
Ht (cm)	Mean ± SD	155.62 ± 4.07	154.33 ± 5.54	1.370•	0.174	NS
	Range	149 – 162	140 – 165			
BMI	Mean ± SD	25.30 ± 1.85	24.84 ± 1.84	1.286•	0.201	NS
	Range	22.19 – 30.67	20.81 – 28.44			
Gestational age by US (weeks)	Mean ± SD	9.23 ± 1.81	9.83 ± 1.94	-1.670•	0.098	NS
	Range	6 – 12	6 – 12			
Gravidity	1	15 (28.3%)	19 (35.2%)	1.752*	0.625	NS
	2	21 (39.6%)	23 (42.6%)			
	3	11 (20.8%)	9 (16.7%)			
	4	6 (11.3%)	3 (5.6%)			
Parity	Median (IQR)	2 (1 – 3)	2 (1 – 3)	1.178≠	0.239	NS
	Range	0 – 4	0 – 5			
History of abortion	Negative	45 (84.9%)	47 (87.0%)	0.101*	0.751	NS
	Positive	8 (15.1%)	7 (13.0%)			
No. of previous abortion	1	4 (50.0%)	1 (14.3%)			
	2	3 (37.5%)	4 (57.1%)	2.219*	0.330	NS
	3	1 (12.5%)	2 (28.6%)			

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
•: Independent t-test; *: Chi-square test; ≠: Mann-Whitney test

Table 2: Hemoglobin level before and after treatment in the two studied groups

		Group A No. = 53	Group B No. = 54	Test value	*P-value*	Sig.
HGB before treatment	Mean ± SD	11.30 ± 0.63	11.26 ± 0.59	0.344•	0.731	NS
	Range	10.3 – 12.4	10.3 – 12.4			
HGB after treatment	Mean ± SD	10.11 ± 0.51	9.83 ± 0.51	2.898•	0.005	HS
	Range	9.2 – 11.5	9 – 10.7			
HGB drop	Mean ± SD	1.19 ± 0.43	1.43 ± 0.42	2.984•	0.004	HS
	Range	0.5 – 2.5	0.8 – 2.3			

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
•: Independent t-test

Table 3: Results of Ultra-sound scan at day 3 and day 7

Complete abortion (1ry outcome)	Group A		Group B		Test value	*P-value*	Sig.
	No.	%	No.	%			
Day 3	30	56.6%	19	35.2%	4.943	0.026	S
Day 7	41	77.4%	37	68.5%	1.058	0.304	NS
Surgical intervention	12	22.6%	17	31.5%	1.058	0.304	NS

Table 4: Results of US at day 7 in the two studied groups

	Group A		Group B		Test value*	*P-value*	Sig.
	No.	%	No.	%			
Incomplete miscarriage	4	7.5%	7	13.0%	0.851	0.356	NS
Missed miscarriage (no change in TVUS picture 7 days after misotac)	2	3.8%	3	5.6%	0.191	0.662	NS
Inevitable miscarriage (E & C was done)	6	11.3%	7	13.0%	0.068	0.794	NS
Complete miscarriage	41	77.4%	37	68.5%	1.058	0.304	NS

P-value > 0.05: Non significant; *P-value < 0.05:* Significant; *P-value < 0.01*: Highly significant
*: Chi-square test

Table 5: The side effects after treatment in the two studied groups

Side effects	Group A No. = 53	Group B No. = 54	Test value	*P-value*	Sig.
Pyrexia	6 (11.3%)	9 (16.7%)	0.634*	0.426	NS
Nausea/ vomiting	8 (15.1%)	7 (13.0%)	0.101*	0.751	NS
Severe abdominal pain	10 (18.9%)	12 (22.2%)	0.184*	0.668	NS
Diarrhea	5 (9.4%)	7 (13.0%)	0.335*	0.563	NS
Headache	4 (7.5%)	6 (11.1%)	0.401*	0.527	NS

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
*: Chi-square test

DISCUSSION

Abortion, spontaneous or induced is a common complication of pregnancy. Induced abortion can be performed by medical and surgical methods.

The most widely used regimen for induction of the medical abortion involves the use of oral mifepristone 200 milligram followed by vaginal misoprostol 800 microgram 24-48 hours later[11].

Misoprostol is a synthetic prostaglandin E1 analogue that causes uterine contraction and ripening of the cervix, used for inducing medical abortion as it is a cheap and safe drug. However mifepristone is expensive and only available in 44 countries[12].

Letrozole (a third- generation selective aromataze inhibitor) used for the treatment of local or metastatic breast cancer that is hormone receptor positive in postmenopausal women[13]. Its anti-estrogenic effect has been shown to be useful in the induction of abortion when combined with misoprostol[9].

The present study is aiming to compare the efficacy of using letrozole pretreatment before misoprostol versus using misoprostol alone for the medical termination of first trimester missed abortion.

Our study was carried on 110 patients divided into 2 groups; Group A included women who received one tablet of letrozole 2.5 milligram (Femara NOVARTIS) each 12 hours for 2 days followed by 4 tablets of vaginal misoprostol (800 microgram) (Misotac, SIGMA) soaked with saline and another dose per vagina after 4 hours if needed.

Group B included women who received one tablet of folic acid 5mg (Folic acid, The Nile) as a placebo each 12 hours for 2 days followed by 4 tablets of vaginal misoprostol (800 microgram) (Misotac, SIGMA) soaked with saline and another dose per vagina after 4 hours if needed.

In group A, 55 patients were recruited of which 2 patients did not attend the follow up visits and where excluded from the analysis of the study, so 53 patients were analyzed of which 30 patients resulted in complete abortion (56.6 %) at day3 after the last dose of misoprostol and they were increased to 41 patients resulted in complete abortion (77.4%) at day 7. Another 4 patients resulted in incomplete abortion (7.5%),6 patients resulted in inevitable abortion (11.3 %) in which urgent evacuation and curettage was needed and 2 patients showed no change in the ultra sound scan (3.8%).

In group B, 55 patients were recruited of which 1 patient did not attend the follow up visits and where excluded from the analysis of the study, so 54 patients were analyzed of which 19 patients resulted in complete abortion (35.2%) at day 3 after the last dose of misoprostol and they were increased to37 patients resulted in complete abortion (68.5%) at day 7.Another 7 patients resulted in incomplete abortion (13.0%),7 patients resulted in inevitable abortion(13.0%) in which urgent evacuation and curettage was needed and 3 patients showed no change in the ultra sound scan (5.6%).

Our results showed an increase in complete abortion rate (primary out come) at day 3 in group A (56.6%) more than group B (35.2%) which was statistically significant.

Also there was an increase in the incidence of complete abortion at day 7 in group A (77.4%) than group B (68.5%) but with no statistically significant difference between the two groups.

The rate of incomplete, inevitable, and missed abortion that required surgical intervention (secondary outcome) was slightly higher in group B than group A but the difference was not statistically significant.

In a pilot study by Tang and his colleagues for inducing legal abortion in 40 cases who requested termination of pregnancy up to 63 days, divided into two equal groups in which 20 patients took letrozole 7.5 milligram daily for two days followed by 800 microgram vaginal misoprostol, the other 20 patients took letrozole 7.5 milligram for two days followed by 200 milligram mifepristone. The result in his study showed that in letrozole and misoprostol group the complete abortion rate was 80% compared to 71.4% in the other group[14].

The results of our study goes in line with his study as the combination of letrozole with misoprostol had a higher complete abortion rate, but it was different from our study in that mifepristone was used instead of misoprostol in the second group.

In another randomized controlled trial done by Naghshineh and his collegues on 130 patients eligible for legal abortion divided into two groups. Patients in this group received 10 milligrams of letrozole for 3 days followed by sublingual misoprostol. Patients in the other group received oral dose of placebo (inert material) for 3 days followed by sublingual misoprostol[15].

The dose of misoprostol was administrated according to ACOG guidelines based on the patients gestational age. The results in his study showed that in the letrozole group 46 patients had complete abortion (76.7%)

and 26 patients in the placebo group had complete abortion (42.6%) which goes on agreement to our study.

Also in his study, the placenta was not delivered in 14 patients in the letrozole group and in 35 patients in the placebo group, so curettage was done as a surgical intervention.The higher difference in the success rate might be attributed to the higher dose of letrozole.

In a pilot study performed by Yeung *et al*. on 20 patients requesting legal termination of pregnancies up to 63 days by giving them letrozole (10 milligrams) for 7 days followed by vaginal misoprostol (800 microgram) on day 7 showed a very high complete abortion rate 95%.This higher rate may be due to the longer duration of letrozole administration (7 days) compared to our study (2 days). This approach might jeopardize the economical value that many patients sought in the recent years[16].

In one study done by Lee and his colleagues on 168 women requesting termination of pregnancy up to 63 days of gestation randomized into two groups. The complete abortion rate of the Letrozole group was higher than that of the placebo group (86.9% compared with 72.6%).

Compared to our study the complete abortion rate was higher (86.9% compared to 77.4% in our study in the letrozole group,72.6% compared to 68.5% in the placebo group),however the previous study used different dose of letrozole than our study with the dose of 10 milligram daily for three days which may explain the higher complete abortion rate compared to our study, also this can be explained by the difference in gestational age between the two studies (90 days in our study compared to 63 days in his study).

There were 10 patients (11.9%) in the letrozole group and 23 patients (27.4%) in the placebo group who needed surgical treatment due to failed medical treatment[9].

Compared to our study more cases needed surgical intervention than that in his study for both groups, which may be due to the difference between the two studies in the doses and the duration of letrozole administration.

Our results goes in line partially with Abbasalizadeh and his colleagues results who performed a study on the use of letrozole combined with oral misoprostol and the use of misoprostol alone on 128 women for inducing abortion in first trimester of non viable pregnancies. After the use of letrozole (10 mg daily for 3 days) followed by 600 mcg misoprostol orally[8].

Complete abortion rate was 93.7 % and in the placebo group was 68.7%,this study goes in agreement to our study regarding the more complete abortion rate using letrozole with misoprostol but their success rate was higher than ours as they used higher dose of letrozole 10 mg daily for 3 days.

Our study showed statistically significant difference between both groups as regards the cost at which the letrozole group costs more.

In our study, the deficit in the hemoglobin level was significantly higher in group B (misoprostol only) than that of group A.

The most common side effects in our study were pyrexia, nausea and /or vomiting, diarrhea, headache and abdominal pain.

As regard pyrexia, it occurred in 6 patients (11.3%) of group A but it was higher in group B as it occurred in 9 patients (16.7%), but shows no statistically significant difference.

As regard abdominal pain after the administration of misoprostol, it was higher in group B as it occurred in 12 patients (22.2%), while in group A it occurred in 10 patients (18.9%), but it also shows no statistically significant difference. There were fewer women complaining of vomiting in group B than those in group A.

Lee and his co-workers showed that the most common side effects in both groups after ingestion of placebo or letrozole were lower abdominal pain and nausea, which were comparable in both groups, there were more patients in the letrozole group reporting vomiting after the ingestion than in the placebo group which goes in line with our study[9].

No one of our study patients suffered from sever complication as uterine perforation, or needed blood transfusion for severe bleeding in both groups.

So, combining letrozole with misoprostol is effective in the induction of first trimestric missed abortion but with increase in the cost. The safety profile of letrozole was reassuring. There was no serious adverse event.

CONCOLUSION

Using of letrozole pretreatment with misoprostol for induction of first trimester abortion is better than using of

misoprostol alone, as there was an increase in complete abortion rate in group A more than group B.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams obstetrics, 24th ed. Mcgraw-hill; 2014.

2. Gemzell-Danielsson K, Ho PC, Gómez Ponce de León R, Weeks A, Winikoff B. Misoprostol to treat missed abortion in the first trimester. International Journal of Gynecology & Obstetrics. 2007;99:S182-5.

3. Kapp N, Eckersberger E, Lavelanet A, Rodriguez MI. Medical abortion in the late first trimester: a systematic review. Contraception. 2018 Nov 13.

4. Sneeringer RK, Billings DL, Ganatra B, Baird TL. Roles of pharmacists in expanding access to safe and effective medical abortion in developing countries: a review of the literature. Journal of public health policy. 2012;33(2):218-29.

5. Deshmukh VL, Rajamanya AV, Yelikar KA. Oral misoprostol solution for induction of labour. The Journal of Obstetrics and Gynecology of India. 2017 Apr 1;67(2):98-103.

6. Ayati S, Vahidroodsari F, Farshidi F, Shahabian M, Aghaee MA. Vaginal versus sublingual misoprostol for labor induction at term and post term: a randomized prospective study. Iranian journal of pharmaceutical research: IJPR. 2014; 13(1):299.

7. Yilmaz B, Kelekci S, Ertas IE, Kahyaoglu S, Ozel M, Sut N, Danisman N. Misoprostol moistened with acetic acid or saline for second trimester pregnancy termination: a randomized prospective double-blind trial. Human Reproduction. 2005;20(11):3067-71.

8. Abbasalizadeh F, Sahhaf F, Sadeghi-Shabestari P, Mirza-Aghazadeh-Attari M, Naghavi-Behzad M. Comparison Between Effect of Letrozole Plus Misoprostol and Misoprostol Alone in Terminating Non-Viable First Trimester Pregnancies: A Single Blind Randomized Trial. Journal of family & reproductive health. 2018;12(1):27.

9. Lee VC, Ng EH, Yeung WS. Misoprostol with or without letrozole pretreatment for termination of pregnancy: a randomized controlled trial. Obstet Gynecol. 2011;117:317–323.

10. Javanmanesh F, Kashanian M, Mirpang S. Comparison of Using Misoprostol with or without Letrozole in Abortion Induction: A Placebo-Controlled Clinical Trial. Journal of Obstetrics, Gynecology and Cancer Research (JOGCR). 2018 Jun 15;3(2):0-.

11. Chai J and Ho PC. 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):291-4.

12. Robson SC, Kelly T, Howel D, Deverill M, Hewison J, Lie ML, Stamp E, Armstrong N, May CR. Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation. Health Technology Assessment. 2009; 13(53):1-148.

13. Long BJ, Jelovac D, Handratta V, Thiantanawat A, MacPherson N, Ragaz J, Goloubeva OG, Brodie AM. Therapeutic strategies using the aromatase inhibitor letrozole and tamoxifen in a breast cancer model. Journal of the National Cancer Institute. 2004; 96(6):456-65.

14. Tang OS, Chan CC, Kan AS, Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12-20 weeks gestation. Hum Reprod. 2005;20:3062–6.

15. Naghshineh E, Allame Z, Farhat F. The effectiveness of using misoprostol with and without letrozole for successful medical abortion: A randomized placebo-controlled clinical trial. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2015; 20(6):585.

16. Yeung TW, Lee VC, Ng EH, 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;86:763–9.