Comparison between Effect of Letrozole plus Misoprostol and Misoprostol Alone in Terminating Non-Viable First Trimester Pregnancies: A Randomized Controlled Trial

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Abstract

BACKGROUND: Abortion is one of the most common complications of pregnancy. One type of abortion; missed abortion, occurs in 15%–20% of clinically diagnosed pregnancies and is the retention of pregnancy products in the uterus for several days or weeks after death of the fetus. Many medications registered had been described to terminate pregnancy replacing the surgical procedure avoiding considerable perioperative complications.

AIM: This study aimed to evaluate the effect of letrozole plus misoprostol to terminate non-viable pregnancies in first trimester compared with the use of misoprostol alone.

METHODS: This study included two groups: Group I, (Misoprostol group) received 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 1st day of enrolment (3 tablets twice, 4 hours apart).Group II, (Letrozole + Misoprostol group) received letrozole 2.5mg (Femara®, Tab. 2.5- mg, Novartis company, Egypt) , one dose 10 mg (4 tablets) on the 1st day of enrolment followed by 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 2nd day of enrolment (3 tablets twice, 4 hours apart). All women underwent detailed history, physical examination including local examination to assess the cervix. Investigations included: Complete blood count, Blood group analysis, Rh typing, Ultrasound.

RESULTS: 90 women were enrolled, divided into 45 women in letrozole + Misoprostol and 45 women in Misoprostol group. Four women from Misoprostol group and 2 women from Letrozole + Misoprostol group were lost to follow-up. Baseline characteristics regarding age, parity, gestational age and BMI revealing non significant difference between studied groups. The mean interval time of start of bleeding, induction to expulsion interval and abortion time were significantly lower in Letrozole + Misoprostol women compared to Misoprostol group. The most common side-effects in both groups were abdominal pain and headache. The incidence of side-effects was comparable for the two groups ($P > 0.05$),

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also the severity of side-effects was not significantly different between groups (P > 0.05). Complete abortion was observed in 36 subjects in Letrozole +Misoprostol group which was significantly more frequent than 26 subjects in Misoprostol subjects (83.7% and 63.4%, respectively, P < 0.05). No statistical significance was seen regarding Hb levels before and after treatment, while Hct levels showed significant difference before and after treatment concerning women underwent complete abortion only in the 2 studied groups.

CONCLUSION: The use of letrozole in addition to misoprostol was associated with shorter induction to complete expulsion interval, higher complete abortion rate and less curettage rate compared to misoprostol group in patients undergoing induction of first trimesteric missed abortion (less than 14 weeks). Further larger studies are needed to determine the optimum treatment protocol to achieve the highest success rate, and the lowest rate of side effects and the most cost-effective.

Introduction

According to the National Center for Health 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].

Missed abortions have been managed surgically and medically using a variety of techniques. Vacuum aspiration, dilatation, and curettage are surgical techniques. However, medical methods are typically chosen over surgical methods for abortion because they are more costly and require anesthesia. Medical approaches include prostaglandins, either alone or in conjunction with other medications. Misoprostol, or prostaglandin E1, is one of the prostaglandins that has drawn the most attention due to its high level of safety and potential for outpatient use. Misoprostol is commonly used for curettage, therapeutic abortion, inducing labor in the second trimester, and treating postpartum hemorrhage following term delivery [2].

With a success rate ranging from 65 to 93%, misoprostol is used alone as a medical alternative to surgery in the management of miscarriages. Early in pregnancy is when it works best, and it also has the benefits of being less expensive, less invasive, and preventing surgical complications. To boost the success rate, misoprostol is also used in combination with other drugs like methotrexate and mifepristone [3].

Letrozole is an important aromatase inhibitor that is used to stimulate ovulation in infertile female suffering from ovulatory dysfunctions. It is active when taken orally, has a 45-hour half-life, and inhibits aromatase enzymes in the opposite way. In abortion therapies, letrozole may be useful because it inhibits the synthesis of estrogen, which raises endogenous gonadotropin and stimulates the growth of ovarian follicles. Furthermore, letrozole has reportedly been used to treat estrogen-related breast cancer and has the potential to replace mifepristone, which is costly and unavailable in many countries [4].

Some Studies have shown that adding aromatase inhibitors before taking the main medication, such as mifepristone or misoprostol, to induce a drug abortion improves treatment effectiveness and reduces the need for surgery [5].

Materials and Methods

After ethical committee approval and informed consent from the patients, this randomized controlled trial was performed on 90 pregnant women diagnosed with non-viable first trimester pregnancy (less than 14 weeks based on Last Menstrual Period (LMP) or according to dating scan), recruited from the obstetric outpatient clinic at Ain Shams

University, Maternity hospital between January 2022 and July 2022. Participants included in this study were 20-40 years old pregnant ladies in the first trimester, diagnosed as non-viable first trimester pregnancy. 1. CRL ≥ 7 mm without fetal pulsations. 2. MSD ≥ 25 without fetal pole inside. 3. Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac. 4. Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac [6, 7].Exclusion criteria included patients who need interference and emergency treatment, with history of known allergy to misoprostol or letrozole drugs, pregnancy ≥ 14 weeks of gestation, any maternal diseases such as heart disease, asthma, thromboembolism, cancer, renal failure, and liver diseases, previous attempt to terminate the pregnancy, abnormal uterine lesions such as fibroids or congenital malformations, or pregnancy on top of intrauterine contraceptive device.

All women included are subjected to detailed medical history including the date of the first day of the LMP to calculate gestational age. They also underwent physical examination including local examination to assess the cervix. Obstetric ultrasound was done to all of them to confirm the diagnosis and to exclude the presence of any uterine lesions or congenital malformations in addition to CBC and blood and Rh grouping. 90 eligible women were randomly allocated to one of 2 groups . ▪ Group I (Misoprostol group): received 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 1st day of enrolment, (3 tablets twice, 4 hours apart) [8]▪ Group II (letrozole group): received letrozole 2.5mg (Femara®, Tab. 2.5-mg, Novartis company, Egypt) , one dose 10mg (4 tablets) on the 1st day of enrolment followed by 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 2nd day of enrolment (3 tablets twice, 4 hours apart). Randomisation was conducted using a computer-generated table of random numbers with allocation concealment. Once allocation has been done, it will not be changed. The misoprostol dose was not changed for women with prior CS as there is no recognized protocol to adjust the dose for women with previous CS, and also so as not to affect the study results. All women were told to record the date of the first vaginal bleeding; the date of first passage of tissue pieces; lower abdominal pain of any degree, with pain assessed using a pain visual analog score; vaginal bleeding of any degree; any side effects such as nausea, vomiting, fever and shivering; any return to hospital for severe pain, bleeding or intolerable side effects; and to return to hospital on the 7th day after administration of misoprostol. An ultrasound scan was done on the 7th day after misoprostol administration to ensure complete evacuation of the uterine contents. Surgical evacuation was only performed if there was inevitable or incomplete miscarriage. Primary Outcome Measure was success of medical approach (Full evacuation of the uterine contents without the need for operative intervention). Secondary outcome Measures were 1. Hemoglobin and hematocrit values before and after evacuation. 2.Medication side effects e.g. nausea, vomiting, fever and shivering. 3. Surgical evacuation complications. 4.Dose required to achieve complete evacuation. 5.Hospital stay. 6. Pain using visual analog scale.

Results

One hundred forty two women were assessed for eligiblility and randomly assigned into two intervention groups. During follow up period, 14 women weren't meeting inclusion criteria , 33 declined to participate, 5 were excluded for other reasons. Finally, 90 women were enrolled, divided into 45 women in letrozole + Misoprostol group and 45 women in Misoprostol group. Four

women from Misoprostol group and 2 women from Letrozole + Misoprostol group were lost to follow-up or continuation of pregancy (Figure 1).

Baseline characteristics regarding age, parity, gestational age and BMI were shown in (Table 1) revealing non significant difference between studied groups. The mean interval for time of start of bleeding, induction to expulsion interval and abortion time were significantly lower in Letrozole + Misoprostol women compared to Misoprostol group (P< 0.001) (Table 2). The most common side-effects in both groups were abdominal pain and headache. The incidence of side-effects was comparable for the two groups (P > 0.05), also the severity of side-effects was not significantly different between groups (P > 0.05) (Figure 2). Complete abortion was observed in 36 subjects in Letrozole +Misoprostol group which was significantly more frequent than 26 subjects in Misoprostol subjects (83.7% and 63.4%, respectively, P < 0.05) (Table 3). No statistical significance was seen regarding Hb levels before and after treatment, while Hct levels showed significant difference before and after treatment; concerning women underwent complete abortion only in the 2 studied groups (Figures 3, 4).

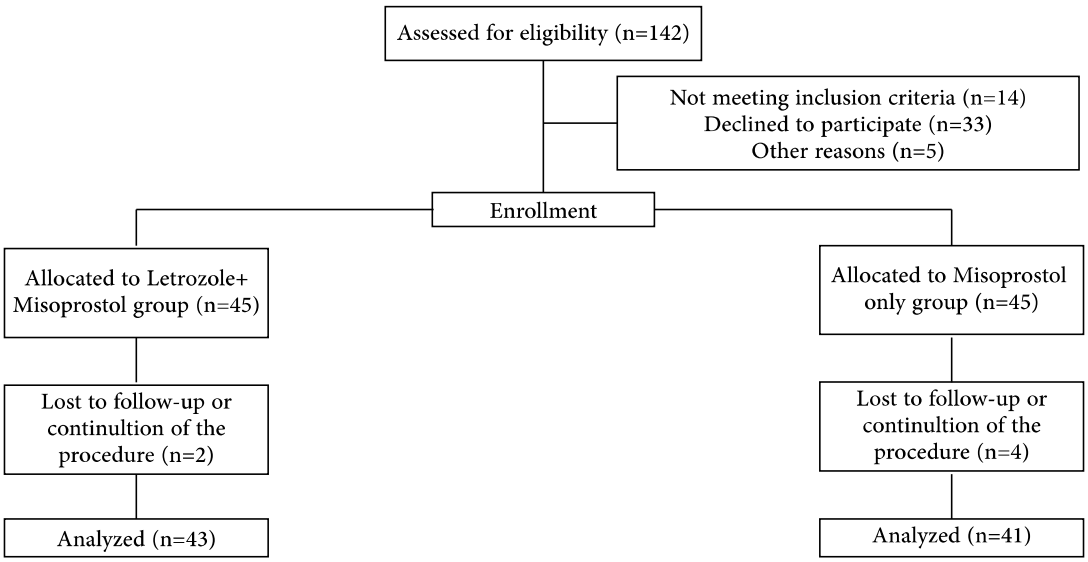

Figure (1): Patients study flow diagram

Table (1): Comparison between Misoprostol and Letrozole Misoprostol group regarding demographic data of the studied patients.

		Misoprostol group	Letrozole+ Misoprostol group	Test value	P-value	S.
		No. =45	No. =45			
Age (years)	Means ± SD Range	29.60 ± 5.84 19 - 45	29.64 ± 6.37 19 - 10	-0.035*	0.973	NS
Parity	PG MP	9 (20.0%) 36 (80.0%)	13 (28.9%) 32 (71.1%)	0.963*	0.327	NS
GA (weeks)	Means ± SD Range	9.13 ± 2.26 6 - 14	8.38 ± 1.66 7 - 13	1.808*	0.074	NS
BMI (Kg/m^2)	Means ± SD Range	29.82 ± 3.91 22 - 37	30.11 ± 4.79 22 - 38	-0.313*	0.755	NS

*S.: Significance. P-alue>0.05: Non significant (NS); Chi-square test; *: independent t-test. No. Number*

Table (2): Comparison between Misoprostol and Letrozole Misoprostol group regarding time of start of bleeding, time of start of expulsion, abortion time in hours of the studied patients.

		Misoprostol group	Letrozole+ Misoprostol group	P-value	S.
		No. =45	No. =45		
Time to start bleeding (hours)	Means ± SD Range	6.4 ± 1.2 4 - 9	4.49 ± 1.5 3 - 8	< 0.001	HS
Time to expulsion (hours)	Means ± SD Range	15.44 ± 2.29 10 - 20	10.44 ±3.12 7 - 18	< 0.001	HS
Abortion time (hours)	Means ± SD Range	23.58 ± 2.43 19 - 28	17.73 ± 4.58 12 - 28	< 0.001	HS

S.: Significance. P-alue>0.05: Significant (S); P-value<0.01: highly significant(HS). No. Number

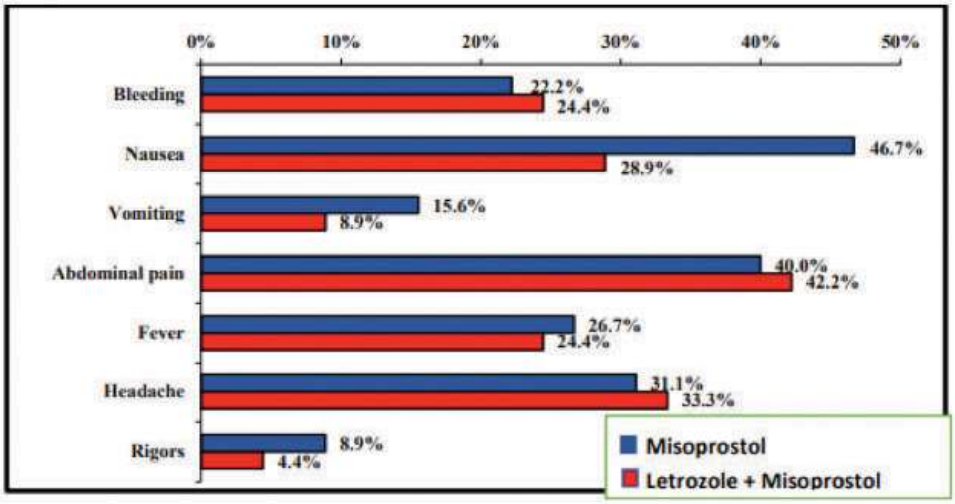

Figure (2): Side effects between the studied groups

Table (3): Complete abortion rate within 24 hours between the studied groups.

		Misoprostol group		Letrozole+ Misoprostol group		P-value	S.
		No.	%	No.	%		
Complete Abortion rate	Yes No	26 15	63.4% 36.6%	36 7	83.7% 16.3%	< 0.05	S

S.: Significance. P-alue>0.05: Significant (S); P-value<0.01: highly significant(HS). No. Number

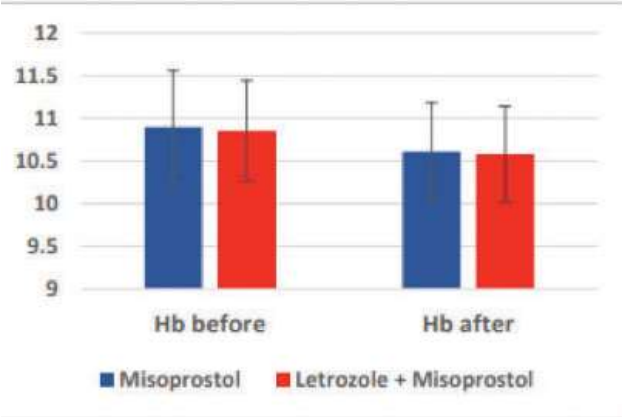

Figure (3): Hb levels before and after treatment in complete abortion only women in the studied groups (gm%).

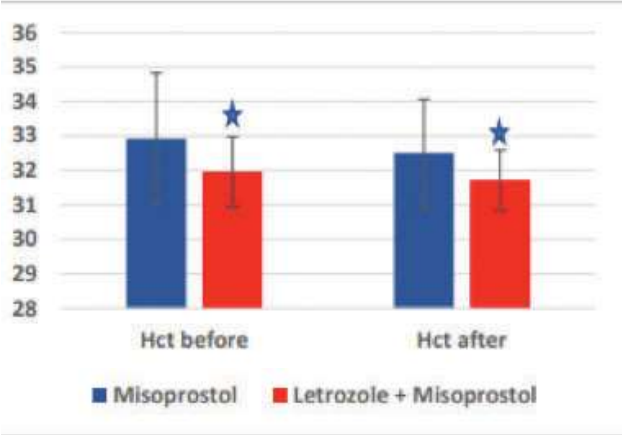

Figure (4): Hct levels before and after treatment in complete abortion only women in the studied groups (%). S: ★

Discussion

The current randomized controlled study that included two matched groups, had compared the effectiveness of misoprostol combined with letrozole versus misoprostol alone for the induction of abortion in the first trimester of pregnancy. It was found that the addition of letrozole for 24 hours prior to the administration of misoprostol has a higher rate of complete abortion in pregnancies less than 14 weeks of gestation in comparison with the administration of misoprostol alone.

This finding is in accordance with most of the studies [3, 4, 7, 9-12] performed in this context although different doses, regimens and routes were used among different studies. The rate had ranged between 76-88% vs 41-56% in the letrozole + misoprostol group vs misoprostol only group respectively; while the rate was as low as 69% vs 30% in Javadi et al. study [1] and as high as 93% vs 69% in Abbasalizadeh et al. study [5] in the two groups respectively.

One of the pilot studies that initiate the use of letrozole as a neoadjuvant to misoprostol was that held by Yeung et al. [9].They conducted this case series in 2012 on 20 women candidate for induction of abortion. They started a long preparatory phase with letrozole for 7 days prior to receiving vaginal misoprostol, which ended in a 95% abortion with no major adverse effects, which was higher than their previous pilot randomized controlled study Lee et al. [13] that showed complete abortion in 89%.

The only study that negated the difference in abortion rate was that held by Allameh et al. [2] who had studied 120 cases with a complete abortion rate of 80% and 75% in the letrozole+misoprostol group and misoprostol only group respectively.

As regard Lee et al [14], the rate of abortion that vary apparently between several studied groups could be attributed to the different doses, the treatment duration of the medication, and to the different 9 9.5 10 10.5 11 11.5 12 Hb before Hb after Misoprostol Letrozole + Misoprostol 28 29 30 31 32 33 34 35 36 Hct before Hct after Misoprostol Letrozole + Misoprostol 9 gestational age range. No one can tell definitely for how long this pregnancy had been in a missed state (i.e. fetal demise); probably longer durations of fetal demise could give fair periods of downregulation.

As regards the dose of letrozole in the current study, we had used a new dose of 10 mg for only 24 hours; in contrary, the other studies used from 7.5 mg once per day Elnashar et al [11] to 10 mg twice daily Afifi et al. [4] while the others used 10 mg once daily Yeung et

al. [9]; Javadi et al. [1]; Naggshineth et al. [7]; Beehrozi-Lak et al. [10]; Abbasalizadel et al. [5]; Torky et al. [3]; and Amer et al. [12], all for three consequetive days. Although different studies used different regimens of Letrozole, the abortion rate was still significantly different between the two groups in theirs and ours.

The dose and the route of misoprostol were different between the current study and the other studies as well as in-between other studies. We opted to use the sublingual route with two doses of 600 mcg 4-hour apart on the next day to letrozole dose. While other studies had used doses ranging from single dose 600 or 800 mcg either sublingually, vaginally or orally for one dose or two doses or even three doses with 4 to 12-hours apart. The difference that had not ultimately affected the significant difference in the rate of abortions among groups.

Actually, many studies had been held to explore the best route for administration of misoprostol for induction of abortion with contradictory results, no single regimen had considered to have best results Zhang et al. [15].

In the current study, we were confined to the 14 week-duration, although other studies had extended the duration to 17 weeks Naggshineh et al. [7] and to 20 weeks Javanmanesh et al. [17], and on the other hand; some studies confined the pregnancy duration to 9 weeks only Chai and Ho [16].

The present study reported that time between induction of abortion to start bleeding was significantly shorter among letrozole+misoprostol group than among misoprostol only group. This was in contrary to the studies of Javadi et al. [1] and Amer et al. [12] who reported no significant difference between the two groups. Other studies had not commented on this duration.

The current study reported that the time between induction of abortion to start of expulsion of pregnancy products was shorter in the letrozole+misoprostol group compared to misoprostol only group. This was in convenience to Torky et al. study in which they reported a time to start passage of products of conception following administration of misoprostol was 2.09 hours in letrozole+ misoprostol group vs 3.05 hours in misoprostol only group Torky et al. [3]; as point of obvious difference the current study reported longer periods for staring the passage of products of conception ((7.8 hours vs 11.2 hours respectively). Torky et al. [3] had investigated 438 women in their huge comparative study that entailed 219 women in each arm. They had used letrozole 10mg orally daily in two divided equal doses for three days followed by 800mcg misoprostol vaginally and the doses were the apparent difference between their study and the current one (viz.letrozole for 24 hours only and the misoprostol given sublingually with two doses of 600 mcg).

The current results showed induction to complete expulsion interval that was significantly shorter in letrozole+misoprostol group than misoprostol only group which is in agreement to 10 other studies. One of them, that was held by Naghshineh et al. on 130 cases who showed figures of 5 and 9 hours between the groups Naghshineh et al. [7], whilst the current study concluded longer durations (although still statistically significant) viz. 17 and 23.5 hours in the two groups. One of the big differences between the current study as well as other studies and between Naghshineh et al. study is that they had administered variable doses of misoprostol changing with gestational age according to the FIGO guidelines (FIGO, 2017), this would be explained by the inclusion of women pregnant up to 17 weeks in their study.

Similar to our study, Behroozi-Lak et al. [10] reported that induction-to-abortion time in letrozole group was significantly shorter than the control group in a randomized trial conducted on 78 women with gestational age less than 14 weeks who received daily

oral dose of 10 mg of letrozole for three days followed by vaginal misoprostol.

Javanmanesh et al. [17] reported shorter induction-abortion intervals in the letrozole group although they held their study on only 46 women with a wide range of gestational age extended to 20 weeks.

Afifi et al. [4] showed an obvious difference in the induction-abortion interval from the current study and the other studies as well; they reported clear prolonged interval that was 61 and 99 hours in the two groups respectively. They had not explained on what basis they had extended the definition of this period in their study.

Letrozole has its appealing action on preparation for induction of abortion. It had been used as an adjuvant to mifepristone prior to misoprostol administration with an abortion rate of 98% Chai and Ho [16]

Recently, the study of Alabiad et al. [18] reported that letrozole in the treatment of ectopic pregnancy had markedly reduced expression of estrogen and progesterone receptors as well as the vascular endothelial growth factor (VEGF) with a significant elevation of the apoptotic index cleaved caspase-3. Letrozole probably cause a decline in the placental estrogen causing decrease in the signals for vascular network with subsequent marked apoptosis.

On the contrary, one decade before, Lee et al. [19] on two separate articles, had shown that letrozole increases the blood flow to the uterus, and it does not downregulate the progesterone receptors or affect the apoptotic factors in the placenta. Moreover, Kallner et al. [20] showed that letrozole did not affect uterine contractility or increase the sensitivity to misoprostol of the uterine myometrium.

Availability wise, letrozole could be easily obtained in the Egyptian market in contrary to mifepristone which is not legalized in Egypt.

The present study reported no significant differences between the study groups regarding adverse effects. This was in accordance with the results of similar studies Chai and Ho [16]; Lee et al. [14]; Javanmanesh et al. [17]; in which there were no significant differences between the study groups regarding side effects.

In contrast to the current study Javadi et al. [1] reported common side effects in 3.8% of cases in the letrozole+misoprostol group and in 19% in the misoprostol alone group; the difference being statistically significant (P= 0.043). No explanation for this result had been attributed to Javadi et al. [1]

Another study Torky et al. [3]showed that more women experienced nausea and vomiting in the letrozole group than in the misoprostol only group, and the result was significant (P= 0.002). There were no significant differences between groups with regard the incidence of fever, abdominal pain and vaginal bleeding that needed surgical management.

Logistically and administratively speaking, the inpatient treatment was disfavored, and the patients were followed up in the outpatient clinic. The hospitalization rate was low, saved for patients with considerable bleeding, pain or cannot readily reach a well occupied medical authority or those who ultimately failed to abort. Again, this was based on the safe, acceptable and effective home-based medical abortion especially during the last three years that witnessed the pandemic of COVID-19 and this was supported by the study conducted by Gambir et al. [21].

A point of strength in this study is the short duration of the pretreatment with letrozole viz. a 24-hour duration that possibly decreases the psychological and financial burden on women needing medical abortion especially if this protocol is generalized in the usual practice.

A limitation point in this study is the lack of estimation of the amount of blood loss, this issue is attributed to the low number of case

hospitalization. Other limitation is the failure to assess the visual analog scale (VAS); it was omitted from the evaluation of the patients in this study as the rate of hospitalization was low in both groups. Generally speaking, Letrozole could be added to the battery of medication used in induction of abortion with appealing good results as regards effectiveness and low adverse outcome.

Conclusion and Recommendations: The use of letrozole in addition to misoprostol was associated with shorter induction to complete expulsion interval, higher complete abortion rate and less curettage rate compared to misoprostol group in patients undergoing induction of first trimesteric missed abortion (less than 14 weeks). Further larger studies are needed to determine the optimum treatment protocol to achieve the highest success rate, and the lowest rate of side effects and the most cost-effective.

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