The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 2112- 2118

Efficacy of Adjunctive Use of Letrozole and Misoprostol in the Medical Induction of First Trimester Abortion

Ahmed Mohamed Nofal[1], Nasser Kamal Abd El All[1], Alaa ElDeen Fathallah El Halaby[1], Fatma Fathy Mahmoud*[2], Osama Ali El-Kelani[1]

[1]Department of Obstetrics and Gynecology, Menoufia University, Menoufia, Egypt

[2] Department of Obstetrics and Gynecology, El Sadat Central Hospital, El-Sadat, Menoufia, Egypt

***Corresponding author:** Fatma Fathy Mahmoud, **Mobile:** (+20)1273927944, **E-mail:** drfatmatota@gmail.com

ABSTRACT

Background: Misoprostol is not only economical and effective, but it also has less adverse effects and doesn't require special handling when being used. Patients tolerate this medication well, and it greatly lowers treatment expenses, curettage, and the necessity for surgical intervention.

Objective: This work aimed to compare the use of misoprostol and letrozole in combination versus misoprostol alone for medical termination of first-trimester abortions.

Patients and methods: This prospective cohort study included 260 patients. This study was conducted at Menoufia University & El-Sadat Central Hospitals after being approved by the Committee of Medical Ethics. With a GA of age from 6 - ≤ 12 weeks, those who were candidates for abortion were selected and divided into two groups. **Group A** received 7.5 mg of Letrozole daily (3 tablets of 2.5 mg) for 3 days before taking Misoprostol and **group B** received Misoprostol only.

Results: Successful abortion rate was significantly higher in group A (69.2%) than in group B (57.7%); p=0.0001. There was a significant difference between the two groups regarding time from induction to abortion as group A has a shorter duration from the start of Misoprostol doses to complete abortion than group B with mean 6.2±2.18 vs 9.11±1.92 hours respectively (p value 0.001). Also, there was a significant difference between both groups as regards doses of misoprostol needed for complete abortion as group A needed lower dose of misoprostol than group B. There was no significant difference between both groups regarding hemoglobin level before and after abortion or side effects of treatment.

Conclusion: It could be concluded that using 7.5 mg daily Letrozole for three days, followed by vaginal Misoprostol, leads to a considerably greater rate of complete abortion than misoprostol alone in women with a GA of less than 12 weeks.

Keywords: Letrozole, Misoprostol, Induced Abortion.

INTRODUCTION

One frequent pregnancy complication is abortion, whether it is induced or spontaneous. According to data from the WHO[(1)], there are over 46 million induced abortions performed globally each year, and approximately 79 million unwanted pregnancies worldwide (excluding miscarriages) [(1,2)]. Estimating the overall number of abortions is challenging, particularly in underdeveloped nations where reporting of the procedure is typically restricted by law [(3)]. Both surgical and medicinal techniques can be used to conduct an induced abortion. When an early abortion is achieved without the need for any surgical intervention, it is referred to as a successful medical abortion. Medical abortions are induced by the ingestion of certain drugs. Furthermore, the medicinal technique has a high degree of patient satisfaction and is a safe and effective substitute for surgical treatments [(4)].

Misoprostol is an analog of prostaglandin E1, which is frequently used for early abortion. It is a better option than other prostaglandin compounds because it is less expensive, easier to administer, stable at room temperature, and has less systemic adverse effects [(5)]. Misoprostol is commonly administered sublingually and vaginally, both of which have distinct pharmacokinetic profiles and levels of efficacy. The vaginal method has less side effects after administration, and sublingual misoprostol achieves its maximal concentration quickly [(6)]. Various studies have shown varying success rates for abortion induction using misoprostol, ranging from 37% to 86%, contingent on the dose, method of administration, and regimen employed. Nevertheless, it worked better when used with other medications [(7)].In order to induce a medical abortion, misoprostol can be taken in conjunction with methotrexate and tamoxifen. Nevertheless, it has been shown through randomized controlled studies that there is no advantage to utilizing methotrexate-misoprostol or tamoxifen-misoprostol regimens over misoprostol alone [(8)].

An aromatase inhibitor with no androgenic, progesterone, or estrogenic properties is letrozole. Aromatase inhibitors appear to be a promising new therapeutic option for the treatment of female patients [(9)]. Multiple daily injections of letrozole followed by 800 micrograms of misoprostol administered vaginally may be an additional successful method of medical abortion, according to small trials [(10)].

There is ongoing debate on the effectiveness of letrozole supplementation in medical abortion. a study to investigate the impact of letrozole supplementation on medical abortion [(11)]. Overall, letrozole

Received: 25/12/2023
Accepted: 25/02/2024

supplementation was found to significantly increase complete abortion and decrease estradiol in comparison to the control group [(11)].

This study aimed to compare the use of misoprostol and letrozole in combination versus misoprostol alone for medical termination of first-trimester abortions.

PATIENTS AND METHODS

This prospective cohort study included a total of 260 patients as sample size which was calculated using open EPI program with confidence level 95% and power 80%. This study was conducted at Menoufia University Hospitals & El-Sadat Central Hospital, during the period from April 2020 to December 2021.

Inclusion criteria: Maternal age above eighteen (legal consent age), GA: six to twelve weeks, hemoglobin levels >10 g/dL. BMI ranging from 25 to 35 kg/m^2 and Loss of pregnancy early on or fetal death: When a fetus with a fetal pole measuring more than 7 mm had no fetal heart, transvaginal ultrasonography was used to diagnose fetal death. If there was no yolk sac or embryo and the mean gestational sac diameter was more than 20 mm, a diagnosis of pregnancy loss was established. Scanning the whole sac in a longitudinal and vertical plain requires special attention. Three diameters were used to measure and average the mean sac diameter.

Exclusion criteria: < 18 years of age, less than 6 or more than 13 weeks gestation, hemoglobin levels <10 g/dL, fibroid uterus, BMI between 25 and 35 kg/m^2, coagulopathy, history of misoprostol or letrozole allergies, medical conditions that make induction of abortion contraindicated (such as heart failure), uterine anomalies, and molar pregnancy.

The study population was divided into 2 groups: Group (A): 130 patients received misoprostol pretreated with letrozole. **Group (B):** 130 patients received misoprostol without pretreatment with letrozole.

Patients were admitted to the Department of Obstetrics and Gynecology at El Sadat Central Hospital and Menoufia University Hospital for 1st 48 hours of procedures to follow up on bleeding and vital signs then discharged to home (when bleeding was minimized, and vital measures were stable) and returned after 1 week to assess history of vaginal bleeding.

All patients were subjected to:

1-Careful and detailed history:

- **A.** ***Personal history****:* Name, age, employment, address, socioeconomic level, and important medical habits.
- **B.** ***Obstetric history:*** First day of the last menstrual cycle, estimated GA by date, and history of vaginal bleeding during this pregnancy.
- **C.** ***Past history:*** History of DM, hypertension, cardiac problems, chest diseases, renal diseases, blood diseases or bleeding tendency.
- **D.** ***Surgical history:*** Previous uterine scarring and prior laparotomies.

2- Examination of the patients:

- **A.** ***General examination:*** Maternal body weight, height and BMI. BMI =Weight (Kg) / Height (m)^2, Petechiae or ecchymosis of the skin to rule out the presence of a coagulation problem or blood illness, Cardiac and chest examinations Vital statistics (BP, pulse, temperature) Presence of pallor or jaundice.
- **B.** ***Abdominal examination****:* Size of the uterus, scar from prior laparotomies.
- **C.** ***Vaginal examination:*** The cervical examination comprises dilatation, location (posterior, middle, or anterior), length, and consistency (soft, firm, or hard).

3-Investigations: CBP, RH, PT, and PTT. Trans-vaginal ultrasound to confirm GA, missed abortion, and to eliminate molar pregnancy, fibroid, or uterine malformations.

Procedures: The abortion was induced using the FIGO protocol, which calls for administering 800 μg of misoprostol per vagina over the course of three hours, with a maximum of three doses [(12)].

Group (A): Women were given 3 oral tablets of letrozole (Femara®,NOVARTIS) as a single dosage, each tablet 2.5 mg (total dose 7.5 mg per day) for 2 days at home and were instructed to return the empty packets. The 3rd dosage was administered upon admission to the hospital on day three, and it will be followed by four tablets of vaginal misoprostol (200 mcg) (Misotac ®, SIGMA) soaked in saline every three hours, for a maximum of three doses.

Group (B): Women were given four tablets of vaginal misoprostol (200 mcg) (Misotac®, SIGMA) soaked in saline every three hours, up to a maximum of three doses.

Temperature, blood pressure and pulse were recorded hourly for the two groups.

Patients were strictly instructed to come back to the hospital once they developed rigors, considerable vaginal bleeding, and offensive vaginal discharge or fever more than 38º C.

The follow-up appointment occurred on day 7, during which a transvaginal ultrasound was conducted and a blood sample was collected to determine hemoglobin levels. Surgical evacuation will be performed at any moment throughout the 7-day follow-up period if there is significant bleeding or at the patient's request. The outcome of therapy is categorized as "complete miscarriage" if no emergency or voluntary curettage is required within 7 days. If there was incomplete abortion or any complications happened in the period of follow up dilation and curettage was done

for termination of unviable pregnancy. According to **NICE** guidelines [13].

Data recording:
Vital data (temperature, blood pressure and pulse) during hospital stay, **hemoglobin** and hematocrit before treatment and after miscarriage to estimate the decrease in hemoglobin and hematocrit levels, **monitoring minor side effects** (fever, rigor, nausea, vomiting and headache), **recording major side effects** (considerable vaginal bleeding or sepsis), **Patients who had three doses** of misoprostol and did not abort within seven days following the final dosage were regarded failure to produce complete miscarriage; surgical evacuation under anesthesia will be conducted; and profuse vaginal bleeding requires rapid evacuation under anesthesia.

Outcome measures:

- ***Primary outcome:*** Clinical as well as sonographic evidence of completeness of abortion and induction to abortion interval.
- ***Secondary outcome:*** Necessity of surgical evacuation in case of incomplete miscarriage, undesired side effects of given medication, the impact of BMI on induction to delivery interval.

Ethical approval:
This study was ethically approved by Menoufia University Faculty of Medicine's Institution Research Board. Written informed consent of all the participants was obtained. At every stage of the study, personal privacy and confidentiality were upheld. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Microsoft Excel is used for the coding, entering, and analysis of historical data, basic clinical examinations, laboratory studies, and outcome measurements. Then, SPSS version 20.0 was opened with the data loaded. Using the Shapiro Walk test, data were examined for normal distribution. Relative percentages and frequencies were used to display the qualitative data. The statistical information was presented as Mean±SD. The significance and correlation of the differences were assessed using the following tests: Pearson's correlation and Spearman's. The study employed the student t-test to compare two groups under investigation using quantitative data that was normally distributed, while the X^2-test was utilized for categorical variables to compare between several groups. P-values were established at less than 0.05 and less than 0.001 for outcomes that were considered significant.

RESULTS

The demographic information; mean age, weight, height, GA, BMI, parity, and prior ultrasound abortions, did not significantly differ between the two groups (P>0.05) **(Table 1).**

Table (1): Demographic data of the study group.

Demographic data	Group A (n=130)	Group B (n=130)	t-test	p-value
Age (years)	26.87±2.38	26.5±2.35	1.6	0.06
BMI(kg/m2)	23.56±3.5	24±4 .7	1.9	0.08
Gravidity			1.89	0.09
One	37	34		
Two	51	56		
More than 2	42	40		
Parity			1.7	0.09
Once	40	46		
Twice	52	48		
More than 2	38	36		
Previous abortion			1.92	0.078
No	37	35		
Once	39	36		
Twice	35	37		
More than 2	31	32		
Gestational age by ultrasonography (weeks)	8.83±0.5	9.2±0.44	1.4	0.077
US criteria of gestational sac			1.8	0.098
Belighted ovum	77	82		
Missed abortion	53	48		
Cervical effacement			0.99	0.08
Yes	67	71		
No	63	59		

Regarding the total abortion rates at 12 hours, there was no statistically significant difference between the two research groups (P>0.05). However, there was a statistically significant difference in the two groups' complete abortion rates at 24 and 48 hours (P<0.05 and P<0.01, respectively) **(Table 2).**

Table (2): Comparison between group A and non-group A groups as regard the complete abortion rate of the patients

		Group A (n=130)		Group B (n=130)		X^2	P.value
		No	%	No	%		
Complete abortion 12 h	No	62	47.7%	75	53.4%	1.26	0.261
	Yes	68	52.3%	45	47.6%		
Complete abortion 24 h	No	45	42.3%	68	52.3%	6.54	0.011*
	Yes	75	57.7%	62	47.7%		
Complete abortion 48 h	No	40	30.7%	55	42.3%	39.3	0.001**
	Yes	90	69.2%	75	57.7%		
Complete abortion 7days	No	40	30.7%	55	42.3%	39.3	0.001**
	Yes	90	69.2%	75	57.7%		

Regarding the number of patients who underwent full abortions, there was a statistically significant difference between the two groups: 90 cases in Group A and 75 cases in Group B underwent complete abortions. Regarding the number of women who had unsuccessful attempts at inducing abortion or who had incomplete abortions, there was no statistically significant difference between the two groups **(Table 3).**

Table (3): Results of Ultrasound at day 7 in the two studied groups

	Group A (n=130)		Group B (n=130)		X^2	P.value
	No	%	No	%		
No of complete abortion	90	69.2	75	57.7	3.90	0.033*
No of incomplete abortion	31	23.8	40	30.7	2.9	0.087
Failed induction	9	7	15	11.5	2.88	0.081

Regarding the induction to abortion time, there was a statistically significant difference between the two groups, as Group A has shorter time than group B with mean 6.2±2.18 vs 9.11±1.92 hours respectively (p value 0.001)**.** Also, there was a significant difference between both groups as regards doses of Misoprostol needed for complete abortion as group A needed lower dose of Misoprostol than group B with mean 625±26.9 vs 775±31.2 respectively (p value 0.05**) Table (4)**.

Table (4): Outcome of treatment among patients with complete abortion after 48 hours

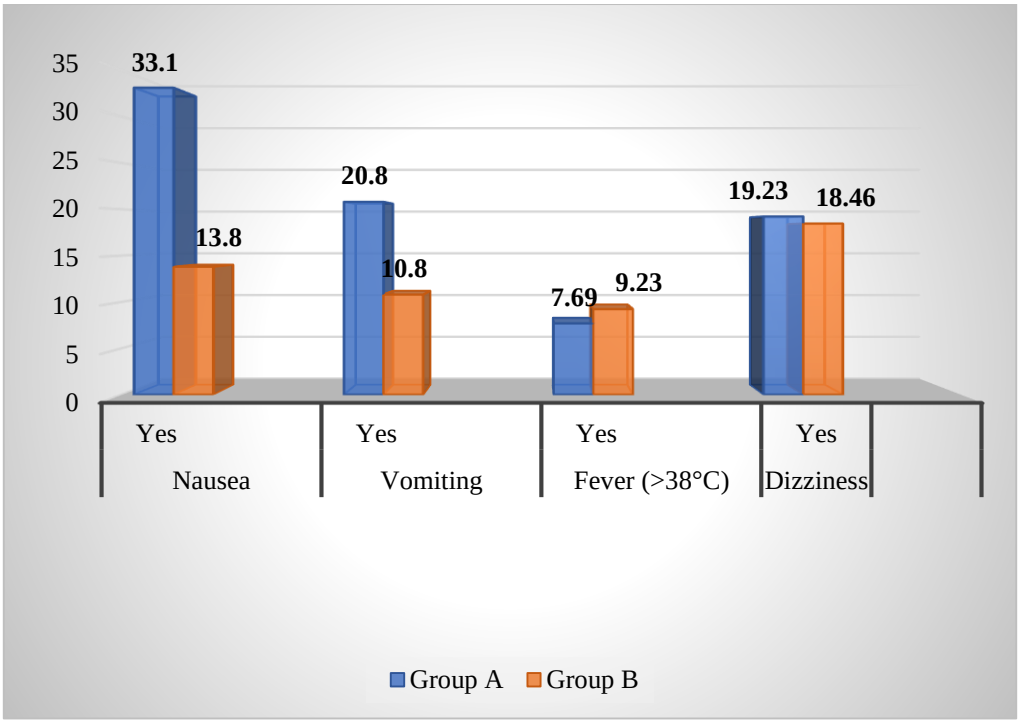
	Group A (n=130)	Group B (n=130)	t. test	p. value
Induction to abortion time in hours	6.2±2.18	9.11±1.92	3.38	0.001
Misoprostol dose (mcg)	625±26.9	775±31.2	3.54	0.05

Regarding the hemoglobin level before and after the abortion induction, there was no statistically significant difference between the two groups (P >0.05) **(Table 5).**

Table (5): Hemoglobin level before and after abortion.

vital measures	Group A (n=130)	Group B (n=130)	t.test	p.value
Hemoglobin level before induction of abortion (g/dl)	10.8±0.83	11.5±0.8	2.4	0.051
Hemoglobin level after abortion (g/dl)	9.86±0.73	10.05±0.82	1.7	0.061

When it came to nausea and vomiting, there was a statistically significant difference between the two groups; nevertheless, there were negligible changes when it came to other side effects, including: diarrhea, dizziness, fatigue, headache, breast tenderness and post abortive bleeding. **(Figure 1)**



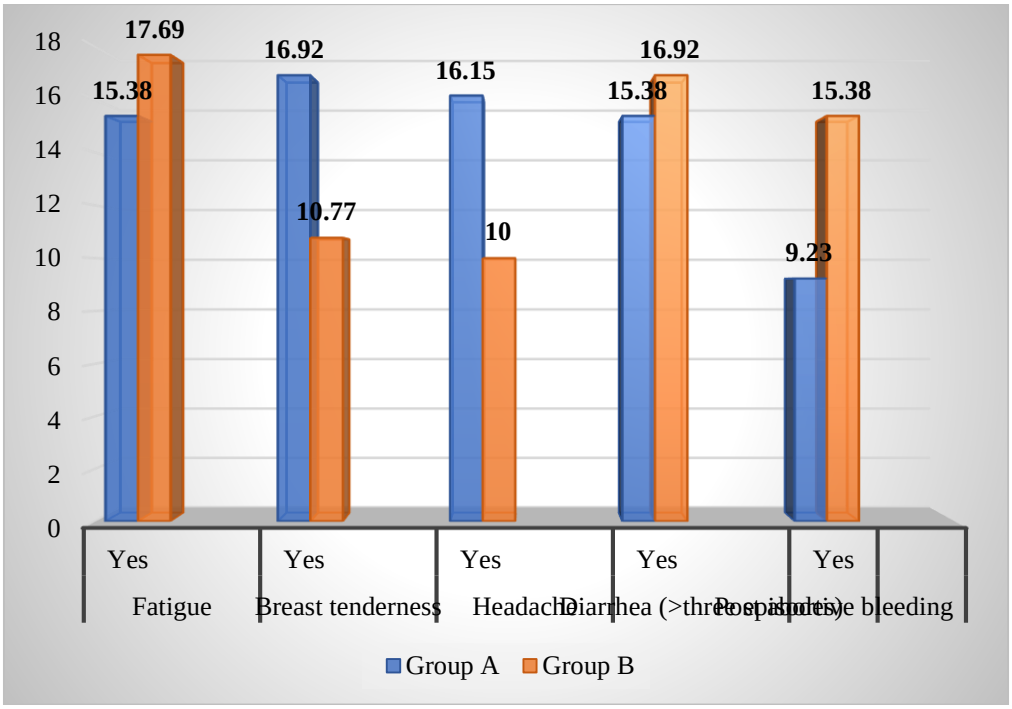


Figure (1): The appearance of side effects among the two studied groups.

DISCUSSION

As regards the complete abortion rates, the current investigation revealed no statistically significant difference between the two study groups at 12 h (52.3%vs. 47.6%, respectively, p 0.261), while there were statistically significant differences at 24 h (57.7% vs. 47.7%, p 0.0.011) and 48 h (69. 2 %vs. 57.7%, p 0.001). The complete abortions were confirmed by examination of the abortion products and post abortion pelvic ultrasound. This was consistent with research by **Javanmanesh *et al.*** [14] who showed a significant increase in success rate when Letrozole was used prior to Misoprostol for the induction of abortion without causing any major adverse effects. The results showed that letrozole had no discernible effect on the induction-abortion interval when compared to non-letrozole.

Naghshineh *et al.* [15] conducted a second randomized controlled experiment with 130 women to assess the effectiveness of letrozole in inducing abortions. According to the current study's findings, the letrozole group in this experiment had a greater risk of complete abortions. The non-letrozole group in this trial, however, got a higher dosage of misoprostol.

Yeung *et al.* [10] tested twenty women who were potential candidates for induction of abortion. Unlike the current trial, when patients began Letrozole 7 days before taking 800 mcg of vaginal Misoprostol on the 7th day, the subjects in this study were administered Letrozole 7 days before getting vaginal Misoprostol. They found a 95% overall completion rate of abortions with no significant side effects. These results were in line with the current study's findings.

Consistent with our research, **Shakir *et al.*** [16] discovered that the LTZ/Miso group experienced total expulsion of gestational products (70/58/83%), which was substantially greater than that of the placebo/miso group (62, 41, 64%) (p<0.001).

Contrary to our study, Nadim *et. al.* [17] discovered that there was no discernible statistical difference between the two groups with regard to number of complete abortion rate between both groups as there was 41(77.4%) cases had complete abortion in group A vs37 (68.5%) cases in group B p value 0.304. Also, **Allameh *et al.*** [18] stated that there was no statistically significant difference in the complete abortion rate between the two groups, with 93 women (77.5%) having complete abortions recorded: 48 (80.0%) in the group receiving misoprostol + letrozole, and 45 (75.0%) in the group receiving misoprostol alone (P=0.80).

Additionally, the research by **Rezai *et al.*** [19] discovered that the overall complete abortion rate was 81.3% and that the letrozole group's complete abortion rate (84.1% compared to 78.5%) was not statistically significantly greater than the placebo group's (P>0.05).

Vaginal bleeding began earlier in the letrozole group than in the non-letrozole group in the **Torky *et al.*** [20] trial, and the difference was statistically significant (p < 0.001).Additionally, letrozole-using women began to pass reproductive products earlier than non-letrozole-using women, and this difference was statistically significant (p<0.001).

Our study found that There was statistically significant difference between both groups regarding induction to abortion time as Group A has shorter time than group B with mean 6.2±2.18 vs 9.11±1.92hours between Group A and Group B respectively p value <0.001,and there was nearly significant difference between both groups as regards doses of Misoprostol needed for complete abortion as group A needed lower dose of Misoprostol than group B with mean 625±26.9 vs 775±31.2 in group A and group B respectively with p value 0.05**(Table 4)** .

It was in line with the research conducted by **Naghshineh *et al.*** [15] which discovered that the letrozole group's mean interval for induction-to-abortion length was substantially shorter than that of the control group (5.1 ± 1.7 h and 8.9 ± 2 h, respectively, P < 0.001). They discovered that the length of the induction of abortion varied significantly between the two regimens. It was also discovered that, although the mean misoprostol dosage in the control group was larger than that of the letrozole group (922.6 ± 235.9 mcg and 853.3 ± 270.2 mcg, respectively, P = 0.13), it was not statistically significant.

Also, in line with our study **Shakir *et al.*** [16] found that The LTZ/MISO had a shorter miscarriage from the beginning (induction) to the end. In this group, patients miscarried after 6.1±1.6 hours, but in the placebo group, miscarriage occurred after 9.4±2.2 hours, which was considerably shorter (p < 0.003).

In contrast to **Allameh *et al.*** [18] who found that the groups who received misoprostol with letrozole had an induction period of 7.35 ± 3.54 hours, while the group that received misoprostol alone had an induction period of 8.2 ± 3.8 hours (P=0.21).

In our study we discovered that there was no statistically significant difference in hemoglobin levels before and after the abortion induction between the two research groups (P >0.05). **Javanmanesh *et al.*** [14] stated that the severity of vaginal bleeding did not differ substantially between the two groups, which is consistent with our findings. Not a single case in any group reported experiencing severe vaginal bleeding.

In contrast, **Nadim *et al.*'s** [17] study revealed that, although there was a statistically significant difference between the two groups under examination regarding their hemoglobin levels before treatment (p-value = 0.731), there was a statistically significant difference between them after treatment (p-value = 0.005). Group B showed a greater decrease in hemoglobin levels (1.43±0.42) compared to group A (1.19 ±0.43), with a p-value of 0.004.

Regarding the appearance of side effects in both groups our results showed that, the two groups did not differ statistically significantly in terms of most side effects, including: diarrhea, dizziness, fatigue, headache, breast tenderness and post abortive bleeding. The most commonly reported side effect in both groups

of the study was dizziness (19% & 18.5% respectively), while the least reported side effect was breast tenderness (16.9% & 10.8% respectively).

The results were nearly agreed with **Rezai *et al.*** [19] who reported that there were not appreciably fewer women reporting side symptoms in the letrozole group compared to the placebo group (P>0.05). Side effects such temperature, tachycardia, diarrhea, and discomfort were identical in the two groups. Every study revealed that there were negative effects connected to the misoprostol administration, with the sublingual route having the most side effects. They found that the incidence of nausea, vomiting, and fever associated with vaginally given misoprostol were similar [9].

The incidence of nausea and vomiting were considerably greater in the letrozole group, but other than that, there were no appreciable variations in side effects across the groups. This may be explained by the increased likelihood of adverse effects while taking two drugs (misoprostol and letrozole). Because letrozole was administered twice daily in this trial as opposed to once daily, the rate of nausea and vomiting was greater than that reported by Lee *et al.* [9]. According to **Torky *et al.*'s** [20] study, which is consistent with our research, a significant number of women in the letrozole group suffered nausea and vomiting compared to those in the non-letrozole group (p = 0.002). When comparing the two groups, there were no appreciable variations in the frequency of fever, excruciating pain, or serious bleeding that required surgical intervention. Furthermore, according to **Javanmanesh *et al.*** [14] there was no discernible difference in the two groups' unfavorable effects (p>0.05).

CONCLUSION

It could be concluded that using 7.5 mg daily Letrozole for three days, followed by vaginal Misoprostol, leads to a considerably greater rate of complete abortion than misoprostol alone in women with a GA of less than 12 weeks.

Financial support and sponsorship: Nil
Conflict of Interest: Nil

REFERENCES

1. **Sedgh G, Bankole A, Oye-Adeniran B *et al.* (2006):** Unwanted pregnancy and associated factors among Nigerian women. Int Fam Plan Perspect., 32:175-84.
2. **Sedgh G, Henshaw S, Singh S *et al.* (2007):** Induced abortion: Estimated rates and trends worldwide. Lancet, 370:1338-45.
3. **Shah I, Ahman E (2010):** Unsafe abortion in 2008: Global and regional levels and trends. Reprod Health Matters, 18:90-101.
4. **ACOG (2005):** ACOG practice bulletin. Clinical management guidelines of obstetrician- gynecologists. Number 67, October 2005. Medical management of abortion. Obstet Gynecol., 106:871-82.
5. **Schaub B, Fuhrer P, Saint e-Rose D (1995):** Randomized study of sulprostone versus misoprostol in the cervical preparation before elective abortion in nulliparous women. J Gynecol Obstet Biol Reprod., 24:505-10.
6. **Tanha F, Golgachi T, Niroomand N *et al.* (2013):** Sublingual versus vaginal misoprostol for second trimester termination: A randomized clinical trial. Arch Gynecol Obstet., 287(1):65-9.
7. **Von Hertzen H, Piaggio G, Wojdyla D *et al.* (2009):** Comparison of vaginal and sublingual misoprostol for second trimester abortion: Randomized controlled equivalence trial. Hum Reprod., 24:106-12.
8. **Wiebe E (1999):** Tamoxifen compared to methotrexate when used with misoprostol for abortion. Contraception, 59(4):265-70.
9. **Lee V, Ng E, Yeung W *et al.* (2011):** Misoprostol with or without letrozole pretreatment for termination of pregnancy: a randomized controlled trial. Obstet Gynecol., 117(2 Pt 1):317–23.
10. **Yeung T, Lee V, Ng E *et al.* (2012):** 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, 86(6):763-9.
11. **Zhuo Y, Cainuo S, Chen Y *et al.* (2021):** The efficacy of letrozole supplementation for medical abortion: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med., 34(9):1501-1507.
12. **Grimes D, Stuart G (2010):** Abortion jabberwocky: The need for better terminology. Contraception, 81(2):93-6.
13. **NICE Guideline (2021):** 2021 exceptional surveillance of ectopic pregnancy and miscarriage: diagnosis and initial management (NICE guideline NG126). London: National Institute for Health and Care Excellence (NICE). https://www.ncbi.nlm.nih.gov/books/NBK576876/
14. **Javanmanesh F, Kashanian M, Mirpangi S (2018):** Com-parison of Using Misoprostol with or without Letrozole in Abortion Induction: A Placebo-Cont-rolled Clinical Trial. Journal of Obstetrics, Gynecology and Cancer Research, 3(2):49-52.
15. **Naghshineh E, Allame Z, Farhat F (2015):** The effectiveness of using misoprostol with and without letrozole for successful medical abortion: A randomized placebo-controlled clinical trial. J Res Med Sci., 20(6):585-589.
16. **Shakir H (2022):** Cost Letrozole as pretreatment to misoprostol in the medical termination of early pregnancy miscarriage. Biochemical and Cellular Archives, 22(1): 1303-06.
17. **Nadim A, Ghanem R, Rady S (2022):** Use of Letrozole Pretreatment with Misoprostol for Induction of Abortion in First Trimester: A Randomized Controlled Trial. Evidence Based Women's Health Journal, 12(1): 125-32.
18. **Allameh Z, Goharian M, Eslamian M (2020):** Effect of misoprostol with and without letrozole on the induction of abortion for women with first-trimester missed abortion. Int J Gynaecol Obstet., 151 (2); 214-18.
19. **Rezai Z, Heydari Bazardehi S *et al.* (202014):** Letrozole and misoprostol versus misoprostol alone for termination of pregnancy: A randomized clinical trial. Tehran Univ Med J., 71(11): 700-706.
20. **Torky H, Marie H, ElDesouky E *et al.* (2018):** Letrozole vs. Placebo Pretreatment in the Medical Management of First Trimester Missed Miscarriage: a Randomized Controlled Trial. Geburtshilfe Frauenheilkd., 78(1):63-71.