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Letrozole And Misoprostol Vs. Misoprostol Alone In Management of First Trimester Missed Abortion, A Randomized Controlled Trial At Banha University Hospitals.

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Abstract

Foundation: Miscarriage occurs when a pregnancy ends before 20 weeks of gestation or when an embryo is conceived that weighs less than 500 grams. Inducing early termination with drugs is a medical treatment mediation option with financial benefits but lower outcomes, and a 60 to 95 percent success rate. The aim of this study was to determine the efficacy and safety of letrozole pretreatment with misoprostol versus misoprostol alone in the treatment of missed first-trimester abortions. The outpatient clinic and emergency division of the obstetrics and gynecology department at Banha university hospitals were the focus of this investigation. For each patient, an itemized history was taken and a careful review was completed. Basic tests such as hemoglobin, blood collection, RH, and trans-vaginal ultrasound were also performed on patients prior to the investigation First group, the patients were given 600 mcg of misoprostol (three tablets, each 200 mcg) orally as a single dose. second group, the patients were given letrozole 10 mg (4 tablets, each 2.5 mg) as a single dose for three days, followed by 600 mcg misoprostol orally. Results and end: When letrozole is used before misoprostol for the termination of a missed abortion in the first trimester, the full fetus removal rate is higher than when misoprostol is used alone. Along these lines, in cases of first trimester missed abortion, it is recommended to use letrozole accompanied by misoprostol instead of misoprostol alone for enlistment of early termination.

Keywords: Letrozole, Misoprostol, Missed abortion**.**

1. Introduction

Abortion causing medications are commonly used around the world, and their use has grown since 1950. In the 1960s, the preferred method for terminating pregnancy was vacuum yearning, a surgical procedure, and after the development of mifepristone in the 1980s, drug-assisted pregnancy termination increased [1].

Prompting foetus removal with drugs is a medical procedure mediation choice with monetary benefits but lower outcomes, and a 60 to 95 percent success rate. Various drugs could be used in a clinical treatment plan to cause the foetus to be removed. Due to a lack of access to mifepristone drugs and their high cost, it isn't available in the vast majority of countries, so elective medications are used to induce early termination [2].

Prostaglandin E1 simple, misoprostol, also known as Cytotec exchange label, is one of these drugs that can be used both vaginally and orally. Misoprostol is a small pill that can be stored at room temperature and is commonly used vaginally and orally. Misoprostol has lower results and does not need special attention during use, aside from being moderate and competent. This drug is well tolerated by patients and significantly reduces hospital costs, as well as curettage and the need for careful medication [3].

Letrozole is also an aromatase inhibitor and is used to stimulate ovulation in infertile women suffering from ovulatory dysfunction. With a relatively short 45-hour half-life, this drug is dynamic orally and reversibly inhibits aromatase Estrogen blockade causes an increase in endogenous gonadotropin, which then stimulates the growth of ovarian follicles. This drug can also play a role in foetus removal care by preventing oestrogen amalgamation. This drug is also used to treat estrogen-related breast cancer [4].

Misoprostol is a prostaglandin that induces myometrial contractions, cervical relaxation, and dilation. It's used to cause early termination of jobs and to treat peptic ulcers and atonic baby blues. It has the advantage of being realistic and stable, with a slow rate of results, which has led to it being remembered for the WHO's list of basic prescriptions In Egypt, misoprostol is approved for use in the event of a failed labour. It is not allowed to start work or deliver babies prematurely in some countries, such as Germany, but it is used under a different name to start work in the UK and Germany. Misoprostol is used alone for the clinical management of failed labour as an alternative to a surgical procedure, with a success rate of between 65 and 93 percent. It's more attractive in the early stages of pregnancy, when it's also less costly, less obtrusive, and removes the need for careful consideration. Misoprostol is also used in combination with other prescriptions, such as mifepristone and methotrexate, to increase the success rate [5].

Mifepristone in combination with misoprostol achieved up to 95 percent higher rates of completed foetus removals and is recommended for pretreatment in early termination and clinical unnatural birth cycle, but a less expensive and widely accessible alternative is needed, particularly in developing countries [6].

Lee et al evaluated the use of letrozole in combination with misoprostol to achieve higher rates of completed early termination [7]. In their study, letrozole was given for three days and then misoprostol, with an overall success rate of 86.9%. A letrozole convention was used for 7 days in a pilot study by Yeung et al. [8] and obtained a 95 percent success rate. The aim of this study was to see whether letrozole pretreatment with misoprostol and

misoprostol alone in the clinical administration of first trimester missed abortions is viable and safe.

2. Patients and methods

This is a prospective randomised interventional controlled study that included 44 patients with missed abortion who attended the Obstetrics and Gynecology department's outpatient clinic and emergency unit at Banha university hospitals between May and December 2020. The participants were randomly assigned to one of two groups: intervention and control or placebo group. All patients were given a full medical history and a detailed clinical review.

Patients in the intervention category received 10 mg oral letrozole daily for three days before receiving 600 microgram single dose oral misoprostol to induce drug abortion.

Patients in the control group were given a normal placebo of letrozole, like the intervention group, and then 600 micrograms of single-dose oral misoprostol.

Patients in both groups who had a spontaneous abortion within the first three days of taking misoprostol would be removed from the study. The haemoglobin levels of patients in both groups were determined at the start and end of the study. Single blinding was used in the study, and patients were unaware of the study groups. After receiving a single dose of misoprostol, both groups were monitored for 4 hours for potential side effects such as stomach cramps or bleedingand in terms of a lack of abdominal cramps or serious bleeding, after describing the risks and warning signs, such as bleeding beyond usual menstruation, was published.

Repeated doses of misoprostol or curettage candidates underwent surgery if complete disposal of pregnancy remnants or termination failed, and patients in all groups of monitoring and intervention were divided into two categories of response to treatment and failure in response to treatment.

2.1Sample size:

Two groups of 44 patients were created. There were 22 participants in the intervention group and 22 participants in the control or placebo group.

2.2Inclusion criteria:

• First trimester of pregnancy (less than 13 weeks based on LMP).
• Non-living embryo.
• Mothers over the age of 18.
• No maternal disorders such as heart disease, asthma, thromboembolism, cancer, renal failure, or liver disease, as well as the patient's and her husband's agreement to participate in the study.

2.3Exclusion Criteria

Any medical condition that requires immediate medical attention in the patient, as well as a history of misoprostol or letrozole drug allergies.

2.4Study Outcome

The primary outcome was the full evacuation of the uterine contents without the need for anaesthesia.

Hemoglobin and hematocrit values before and after evacuation, medication side effects, surgical evacuation complications, dose required to achieve complete evacuation, and hospital stay were all secondary outcomes.

2.5Statistical methods

SPSS vs.25 was used for data management and statistical analysis (IBM, Armonk, New York, United states). Means and standard deviations were used to summarise numerical results. Numbers and percentages were used to summarise categorical results. P values were all two-sided. Significant P values were described as those less than 0.05.

3. Results

The research was carried out at Banha university hospitals' outpatient clinic and emergency department of obstetrics and gynaecology, with demographic data in Table (1).

Table (1): Comparison between groups as regard demographic data.

	Group		t-test	p- value	Difference (95% CI)
	Misoprostol	Misoprostol -Letrozole			
	Mean ± SD	Mean ± SD			
Age (years)	25.26 ± 5.25	25.44 ± 5.44	0.072	0.943	-0.08 (-2.44 -2.27)
Weight (kg)	69.82 ± 8.76	68.93 ± 8.48	0.128	0.899	0.25 (-3.69 -4.19)
Height (cm)	161.33 ±6.54	162.77 ±6.42	1.206	0.231	-1.43 (-3.8 - 0.93)
BMI (kg/m2)	25.57 ± 3.08	25.04 ± 3.48	0.753	0.453	0.54 (-0.88 -1.95)
Gestational age (weeks)	8.99 ± 1.97	8.96 ± 2.01	-0.113	0.911	-0.05 (-0.91 -0.81)

In misoprostol-letrozole, bleeding began faster and lasted less time, as shown in table 2.

Table (2) Comparison between groups as regard onset and duration of vaginal bleeding.

	Group		t-test	p-value	Difference (95% CI)
	Misoprostol	Misoprostol -Letrozole			
	Mean± SD	Mean ± SD			
Onset of bleeding (hours)	6.39 ± 0.72	5.7 ± 0.95	3.828	<0.001	0.7 (0.34 - 1.07)
Duration of vaginal bleeding (days)	4.79 ± 1.81	3.79 ± 1.85	2.641	0.010	1.06 (0.26 - 1.87)

Fig. (1) indicates that there is no statistically significant difference between groups in terms of US review on day 3, but there is a statistically significant difference between groups on day 7 after the first misoprostol dose. This suggests that at the end of the trial, combined therapy was linked to a higher rate of full evacuation than single therapy.

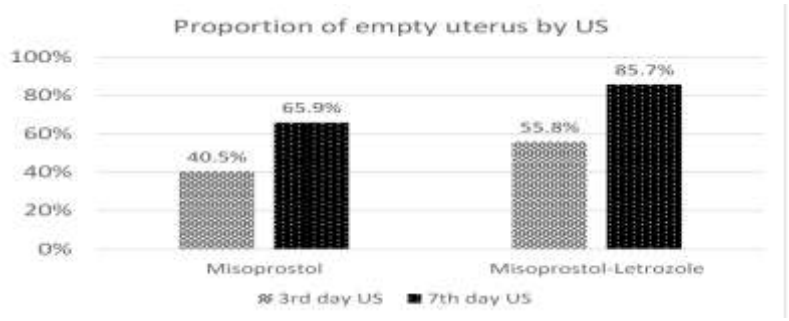

Fig. (1) Results of US examination at day 3 and 7 day in both study groups.

In terms of haemoglobin levels before the sample, there was no statistically significant difference between groups. Participants' Hb levels dropped statistically significantly in both groups, but the drop was greater in the misoprostol group, and the difference was statistically significant Table (3).

Table (3) Hemoglobin level in both study groups before and after study.

	Group		t-test	p-value	Difference (95% CI)
	Misoprostol	Misoprostol -Letrozole			
	Mean ± SD	Mean ± SD			
Hb before	10.86 ± 0.54	10.88 ± 0.50	-0.180	0.858	-0.02
Hb after	10.01 ± 0.46	10.20 ± 0.52	-2.235	0.028	-0.25
Hb Before - Hb after	0.94 ± 0.43	0.96 ± 0.30	2.468	0.016	0.226 (0.049-0.409)

At the end of the trial, combined therapy was linked to a higher rate of full evacuation than single therapy Fig. (2).

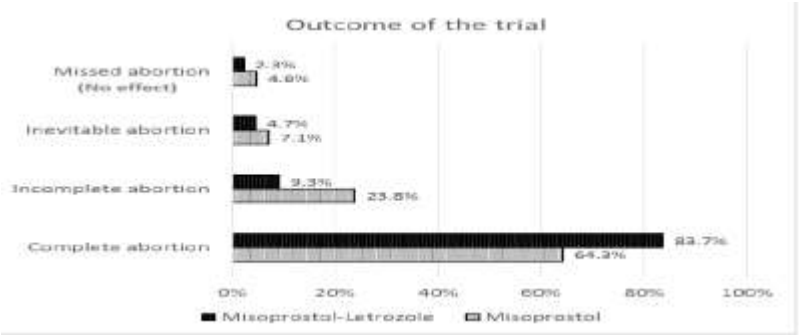

Fig (2) Outcome of abortion in both study groups.

In terms of the incidence of side effects, there was no statistically significant difference between groups fig. (3**).**

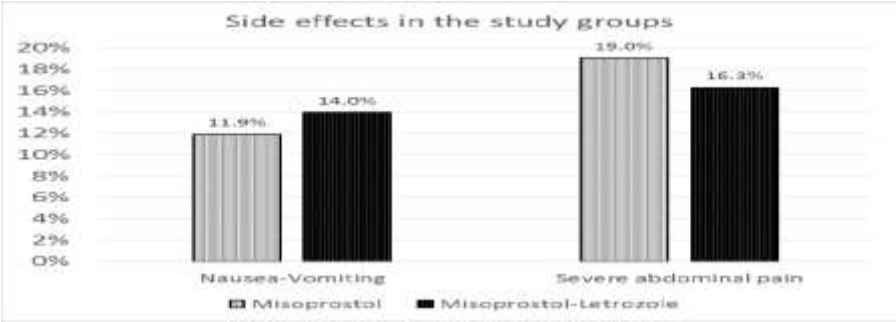

Fig (3) Incidence of side effects in both study group.

4. Discussion

A total of 44 patients were used in our study. The main gathering received 600 mcg of misoprostol orally without delay. The next group was given letrozole 10 mg orally once a day for three days as a pretreatment, followed by 600 mcg of misoprostol orally.

Our findings revealed that there were no significant differences between bunches in terms of segment data.

22 patients were broken down in the main gathering (misoprostol only), with 64.3 percent having a full unnatural birth cycle, 23.8 percent having an inadequate premature delivery, 7.1 percent having an inevitable early termination requiring pressing clearing and curettage, and 4.8 percent having no differentiation in the ultrasound scan.

In the following gathering (letrozole pretreatment accompanied by misoprostol), 22 patients were tested, with 83.7 percent causing a full unnatural birth period, 9.3 percent causing a defective premature delivery, and (4.7 percent) causing an inevitable early termination requiring earnest clearing and curettage., In the ultrasound check, (2.3 percent) of the patients showed no difference.

The most important finding of our study was that the finished premature delivery rate without careful intercession in pregnancies lasting up to 90 days (12 weeks incubation + 6 days) was 64.3 percent in the first group (misoprostol only) compared to 83.7 percent in the second group (letrozole pretreatment followed by misoprostol), As a result, the research reveals a measurably important distinction between bunches in terms of the rate of complete unsuccessful labour.

In the misoprostol study, the rate of insufficient, unavoidable, and missed premature births necessitating additional careful mediation was higher.

In a study by Elnashar and his colleagues in the department of Obstetrics and Gynecology Banha University, 320 patients with missed abortion up to 63 days were recruited and randomized into the letrozole and placebo groups with 160 participants in each group , the first group received pretreatment with letrozole 7.5 mg orally once daily for three days followed by misoprostol 800 mcg vaginally , while the second group was given placebo for three days followed by 800 mcg misoprostol vaginally. The complete abortion rate in the letrozole group was significantly higher than that in the placebo group (82.6% compared with 68.2%, p- Value < 0.001). [9]

Our study and Elnashar and his colleagues' study both agreed that using letrozole before misoprostol is associated with higher rate of complete miscarriage without the need of surgical intervention when compared to misoprostol alone, but the rate of complete miscarriage without surgical intervention in letrozole-misoprostol group was higher in our study (83.7% compared to 82.6% in ***Elnashar*** and his colleagues' study) this can be explained by the higher dose of letrozole given in our study (10 mg in our study compared to 7.5 mg in Elnashar and his colleagues).

The most commonly recognised symptoms in our study were queasiness or possibly heaving, stomach torment, or colic.

In terms of abdominal pain after misoprostol administration, it was slightly lower in the first (misoprostol only) group, occurring in (11.9 percent) of patients, while it occurred in (14 percent) of patients in the second (letrozole) group, indicating no statistically significant difference.

In terms of nausea and vomiting, it occurred in 19% of misoprostol patients and 16.3 percent of misoprostol-letrozole patients, but there was no discernible difference.

For excessive draining or sickliness affecting the overall condition in the two groups, none of our test subjects needed blood bonding.

The cost of 12 tablets of letrozole 2.5 mg, which was used as a pretreatment before misoprostol, was significantly higher in the second gathering.

When comparing the beginning and duration of vaginal seeping after the first misoprostol dose in both examination groups, there is a significant difference.

The start of vaginal draining was slower in the first (misoprostol-only) group than in the second (letrozole-only) group, implying that letrozole-only

patients start vaginal draining earlier than misoprostol-only patients.

The first (misoprostol only) group had significantly more vaginal drainage than the second (letrozole) group.

Similarly, haemoglobin deficiency was fundamentally higher in the first (misoprostol only) group than in the second (letrozole) group, implying that vaginal drainage was more in the first group.

Letrozole in combination with misoprostol is more effective than misoprostol alone in the enlistment of first trimester missed unnatural birth cycles, according to our research.

5. Conclusion

Letrozole pretreatment followed by misoprostol for early termination in the first trimester is associated with a higher rate of full foetus removal than misoprostol alone. In cases of first trimester missed abortion, it is recommended to use letrozole accompanied by misoprostol instead of misoprostol alone for foetus removal acceptance.

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