Comparison between clomiphene citrate and letrozole pretreatment with misoprostol versus misoprostol alone for induction of missed abortion in first trimester

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Abstract
Background: Missed Abortion is non-viable intrauterine pregnancy with either an empty gestational sac or a gestational sac contains an embryo without fetal heart activity.
Objectives: The aim of this study was to compare effect of misoprostol with clomiphene citrate, misoprostol with letrozole and misoprostol alone in terminating first trimester missed abortion.
Patients and methods: This randomized clinical trial was included patients with missed abortion attending to our outpatient clinic at South Valley University Hospital, Department of Obstetrics and Gynecology. Fifteen patients were excluded during the follow-up period; hence, 37 patients per group were included in the final analysis. They divided into three groups: Interventional group (A): received 5mg letrozole ; Group (B): received 100 mg clomiphene citrate and Group (C): Control group received calcium carbonate . Then all patients received two doses of 800 microgram misoprostol orally.
Results: As regard outcome among the three studied groups. The results showed that 21.6% cases in group (A) showed failure in management with six cases needed surgical evacuation and two cases completed treatment on misoprostol, 32.4% cases in group(B) showed failure in management with ten cases needed surgical evacuation and two cases completed treatment on misoprostol and 37.8% cases in group(C) showed failure in management with ten cases needed surgical evacuation and four cases completed treatment on misoprostol.
Conclusion: Letrozole pre-treatment with misoprostol increases efficacy of misoprostol in induction of complete abortion of non-viable first trimester pregnancy with no evident side effects.
Keywords: Misoprostol; Abortion; Clomiphene citrate; Letrozole; Outcome.
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Introduction

Abortion is non-viable intrauterine pregnancy with either an empty gestational sac or a gestational sac contains an embryo or fetus without fetal heart activity. It is considered one of the most common complications of pregnancy with about 53 million cases annually according to WHO reporting and accounts for 10% of clinically diagnosed pregnancies **(Sedgh et al,. 2017).**

Missed miscarriage is retention of products of conception in the uterus after death of fetus , The management of missed abortion varies from medical induction to surgical methods **(Hamoda et al., 2010; Kim et al,. 2017) .**

Letrozole is an aromatase inhibitor used in cases of infertility due to ovulatory dysfunction, it inhibits aromatase enzyme leading to block of estrogen synthesis which increase endogenous gonadotropins ,Letrozole recently used in induction of abortion in the first trimester with considerable efficacy and minimal side effect **(Kopp et al., 2012).**

Clomiphene Citrate is a powerfully effective anti-estrogen officially classified as a Selective Estrogen Receptor Modulator (SERM), it has the ability to oppose the negative feedback of estrogens on the Hypothalamic-Pituitary-Ovarian-Axis. it also carries strong anti-estrogen properties.

This study aimed to compare effect of misoprostol with clomiphene citrate, misoprostol with letrozole and misoprostol alone in terminating first trimester missed abortion

Patients and methods

This study was a randomized controlled clinical trial curried out at South valley University Hospital ,Department of Obstetrics and Gynecology.

Ethical approval code : OBG024

Inclusion criteria: All patients with missed abortion attending to our outpatient clinic and fulfilled the following criteria: Age more than 18 years old, missed abortion less than 12 weeks confirmed by ultrasonography and hemoglobin 11 g/l or more

Exclusion criteria: Any abnormality in the coagulation profile**,** any of these medical maternal diseases (heart disease, asthmatic renal failure, cancer, liver disease), history of well-known drugs allergy, gestational age more than 12 weeks and any previous attempt for induction of abortion in current pregnancy

Sample size: This work was conducted on pregnant women attended to our outpatient clinic with non-viable first trimetric pregnancy less than 12 weeks based on last menstrual period from January 2021 to January 2022.

Study design:

All patients were be subjected to:

An informed consent was taken from every patient. Complete history taking and Complete physical examination. Investigations', CBC, Serum creatinine, Prothrombin Time (PT) and ABO.

Transabdominal and Transvaginal U/S to confirm missed abortion. All patients in the study were divided randomly by closed envelope into three groups, two interventional groups (A), (B) and one control group (C). Interventional group (A) received 5 mg letrozole (in form of 2 tabs of femara 2.5 mg of Novartis international AG) for three days. Interventional group (B) received 100 mg clomiphene citrate (in form of 2 tabs clomid 50 mg of global NAPI Pharmaceutical for Sanofi) for three days. group (C) [Control group] received calcium carbonate for three days, all patients received two doses of (800) microgram of oral misoprostol (in form of 4 tabs Cytotec spaced by 4 hours in the fourth day . The patient was evaluated on day 3 before use of misoprostol; patients who were already aborted were excluded from the study. All patients were given the first dose of misoprostol and monitor for 4 hours for any severe abdominal cramps, vaginal bleeding if no patient discharges. The First ultrasound was done after one week of last does of misoprostol.

Research outcome measures: Primary (main): Complete expulsion of product of conception with no need for surgical intervention within one week from first does of misoprostol. **Secondary:** Need for surgical intervention, hemoglobin and Hematocrit deficit and maternal morbidity as (nausea, vomiting, lower abdominal pain, severe vaginal bleeding).

Administrative Design: The protocol was applied for approval of Research Ethics Committee with ethical approval code, Informed consent was obtained from the patients before enrollment of the study.

Statistical Analysis: Data were checked, entered and analyzed using SPSS version 23 . Data were tested for normal ,distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square

test ($\chi 2$) to calculate difference between two or more groups of qualitative variables, Quantitative data were expressed as mean ± SD (standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant

Results:

The mean ages in group A, B & C were28.65±6.71 years, 29.71±6.97 years and 28.70±6.42 years. respectively. There was no statistically significant difference between the Three studied groups regarding age. The mean gestational ages in the three groups were 8.35± 1.46 weeks, 8.70± 1.81 weeks and 8.89± 1.52 weeks respectively. The mean BMI was 28.70± 2.61 Kg/m2, 8.70± 1.81 Kg/m2 and 8.89± 1.52 Kg/m2 respectively. There was no statistically significant difference between the three groups regarding gestational age and BMI, height, parity or previous CS (p>0.05) as we can see in (**Table 1**).

Table (1): Comparison between the studied groups regarding demographic characteristics

Variables		Group (A) (No. = 37)		Group (B) (No. = 37)		Group (C) (No. = 37)		Test value	P-value
		No.	%	No.	%	No.	%		
Age (years)	Mean± SD	28.65±6.71		29.71±6.97		28.70±6.42		KW = 0.618	0.734
	Median	28.0		29.0		29.0			
	Range	18.0- 42.0		18.0- 43.0		19.0- 40.0			
Gestational age (weeks)	Mean± SD	8.35± 1.46		8.70± 1.81		8.89± 1.52		KW = 1.646	0.439
	Median	9.0		9.0		8.0			
	Range	5.0- 11.0		5.0- 11.0		7.0- 11.0			
BMI (Kg/m^2)	Mean± SD	28.70± 2.61		28.88± 2.58		28.78± 2.44		KW = 0.447	0.800
	Median	28.93		28.96		28.93			
	Range	22.04- 35.65		22.04 – 35.65		22.04 – 35.65			
Parity	P0	7	18.9%	6	16.2%	5	13.5%	X^2= 11.401	0.495
	P1	8	21.6%	5	13.5%	7	18.9%		
	P2	10	27.0%	12	32.4%	11	29.7%		
	P3	5	13.5%	7	18.9%	8	21.6%		
	P4	6	16.2%	2	5.4%	6	16.2%		
	P5	1	2.7%	4	10.8%	0	0.0%		
	P6	0	0.0%	1	2.7%	0	0.0%		
Previous CS	No	19	51.4%	15	40.5%	13	35.1%	X^2= 11.671	0.166
	Previous 1 CS	6	16.2%	7	18.9%	12	32.4%		
	Previous 2 CS	6	16.2%	12	32.4%	9	24.3%		
	Previous 3 CS	3	8.1%	3	8.1%	3	8.1%		
	Previous 4 CS	3	8.1%	0	0.0%	0	0.0%		

Table (2) shows US findings among the three studied groups. In the first US done, there was 75.7% patients in group A, B & C had fetal pole with no pulsation. In the second US done, there was 78.4% patients in group A and 75.7% in group B & C had fetal pole with no pulsation. In the third US done, there was 78.4% patients in group A, 67.6% patients in group B & 62.2% patients in group C had empty uterus with no content. There was no statistically significant difference between the three groups regarding US finding in the first, second and third US (p>0.05).

Table 2. Comparison between the studied groups regarding US findings

Variables		Group (A) (No. = 37)		Group (B) (No. = 37)		Group (C) (No. = 37)		Test value	P-value
		No.	%	No.	%	No.	%		
1st U.S	Blighted ovum	9	24.3%	5	13.5%	9	24.3%	X^2= 0.0	1.00
	Fetal pole with no pulsation	28	75.7%	32	86.5%	28	75.7%		
2nd U.S	Blighted ovum	8	21.6%	9	24.3%	9	24.3%	X^2= 0.100	0.951
	Fetal pole with no pulsation	29	78.4%	28	75.7%	28	75.7%		
3rd U.S	Blighted ovum	3	8.1%	5	13.5%	8	21.6%	X^2= 9.60	0.294
	Empty uterus with no content	29	78.4%	25	67.6%	23	62.2%		
	Fetal pole with no pulsation	1	2.7%	1	2.7%	1	2.7%		
	product of conception remnants	4	10.8%	3	8.1%	5	13.5%		
	Sever vaginal bleeding, cervical abortion	0	0.0%	3	8.1%	0	0.0%		

Table (3) shows side effect of misoprostol among the three studied groups. Nausea and vomiting were found in 8.1% cases in group A, 29.7% cases in group B and 29.7% cases in group C. Dizziness was found in 2.7% cases in group B. Abdominal cramps was found in 2.7% cases in group A, 21.6% cases in group B and 24.3% cases in group C. There was high statistically significant difference between the three groups regarding side effect of misoprostol (p=0.002) as group A was the least group having side effect

Table 3. Comparison between the studied groups regarding side effect of misoprostol

Variables	Group (A) (No. = 37)		Group (B) (No. = 37)		Group (C) (No. = 37)		Test value	P-value
	No.	%	No.	%	No.	%		
No	33	89.2%	17	45.9%	17	45.9%	X^2= 21.1	0.002
Nausea & vomiting	3	8.1%	11	29.7%	11	29.7%		
Dizziness	0	0.0%	1	2.7%	0	0.0%		
Abdominal cramps	1	2.7%	8	21.6%	9	24.3%		

Table (4) shows induction abortion interval among the three studied groups. The mean days between misoprostol doses and abortion.in group A, B & C was 2.97±1.14 days, 3.69±1.14 days and 4.39± 0.99 days. Induction abortion interval was significantly lower in group A compared to group B and group C (p=0.024 &<0.001 respectively).

Table 4. Comparison between the studied groups regarding days between misoprostol doses and abortion

Variables		Group (A) (No. = 37)	Group (B) (No. = 37)	Group (C) (No. = 37)	Test value	P-value	P-value between groups
Days between misoprostol doses and abortion (days)	Mean± SD	2.97±1.14	2.69±1.14	4.39± 0.99	KW = 16.2	**<0.001**	**P_{A-B}=0.024**
	Median	3.0	3.0	4.0			P_{A-C}=0.082
	Range	1.0- 6.0	1.0- 6.0	3.0- 6.0			**P_{B-C}<0.001**

Table (5) shows outcome among the three studied groups. The results showed that 13.5% cases in group A showed failure in management with three cases needed surgical evacuation and two cases completed treatment on misoprostol 1×3, 21.6% cases in group B showed failure in management with six cases needed surgical evacuation and two cases completed treatment on misoprostol 1×3and 37.8% cases in group C showed failure in management with ten cases needed surgical evacuation and four cases completed treatment on misoprostol 1×3. There was statistically significant difference between the three groups regarding

outcome as higher rate of success was observed in group A (p=0.046).

Table 5. Comparison between the studied groups regarding outcome

Outcome	Group (A) (No. = 37)		Group (B) (No. = 37)		Group (C) (No. = 37)		Test value	P-value
	No.	%	No.	%	No.	%		
Passed	32	86.5%	29	78.4%	23	62.2%	X^2= 6.167	0.046
Failed	5	13.5%	8	21.6%	14	37.8%		

Discussion

The mean age in group A, B & C was 28.65±6.71 years, 29.71±6.97 years and 28.70±6.42 years. The mean gestational age in the three groups was 8.35± 1.46 weeks, 8.70± 1.81 weeks, and 8.89± 1.52 weeks respectively. The mean BMI was 28.70± 2.61 Kg/m2, 8.70± 1.81 Kg/m2 and 8.89± 1.52 Kg/m2 respectively which is not statically significant, Likewise, there was no statistically significant difference between the two groups regarding height, parity, and previous CS (p>0.05).

Our results were supported by study of **Afifi et al., 2021** included a number of 200-cases who were randomly classified to 2 equal groups: Group-I "Misoprostol" which included 100 cases received 800-mg of misoprostol at once of diagnosis vaginally and group-II "Letrozole + Misoprostol" which included 100 cases received 10-mg letrozole 2 times a day for 3 days as pre-treatment then 800-mg of vaginal misoprostol. The results showed that nonsignificant changes were found among groups regarding ages (P-value=0.48), BMI (P-value=0.62), gestational age (P=0.32), gravidity (P=0.84) and previous CSs (P=0.83).

To the best of our knowledge, there were no previous study conducted to compare efficacy of misoprostol with clomiphene citrate, misoprostol with letrozole and misoprostol alone in induction of abortion in first trimester missed miscarriage.

However, in the study of **Amer et al., 2021,** the participants were randomly assigned to one of two groups: intervention and control or placebo group. 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. 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.

The current study showed that as regard US findings among the three studied groups. In the first US done, there was 75.7% patients in group A, B & C had fetal pole with no pulsation. In the second US done, there was 78.4% patients in group A and 75.7% in group B & C had fetal pole with no pulsation. In the third US done, there was 78.4% patients in group A, 67.6% patients in group B & 62.2% patients in group C had empty uterus with no content. There was no statistically significant difference between the three groups regarding US finding in the first, second and third US (p>0.05).

In contrary to our results study of **Amer et al., 2021,** as they revealed 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.

In contrast to our results study of **Allameh et al., 2020** as they reported that complete abortion was reported for 93 (77.5%) women: 48 (80.0%) and 45 (75.0%) women in the misoprostol plus letrozole and misoprostol only group, respectively (P=0.80). Correspondingly, the number of incomplete abortions was 27 (22.5%), of which 12 (20%) and 15 (25%) were in the misoprostol plus letrozole and misoprostol only group, respectively (P=0.65)

In the study in our hands, Nausea and vomiting were found in 8.1% cases in group A, 29.7% cases in group B and 29.7% cases in group C. Dizziness was found in 2.7% cases in group B. Abdominal cramps was found in 2.7% cases in group A, 21.6% cases in group B and group A24.3% cases in group C. There was high statistically significant

difference between the three groups regarding side effect of misoprostol (p=0.002) as group A was the least group having side effect .

Furthermore, **Torky et al.2018** who found a higher rate of nausea and vomiting in letrozole + Misoprostol group compared to Misoprostol alone group (17.0% vs. 3.0%, p = 0.002). However, they found that the occurrence of other complications (fever, severe pain and severe bleeding) didn't change significantly among groups.

The present study showed that as regard days between misoprostol doses and abortion among the three studied groups. The mean days between misoprostol doses and abortion.in group A, B & C was 2.97±1.14 days, 3.69±1.46 days and 4.39± 0.99 days. Days between misoprostol doses and abortion was significantly lower in group A compared to group B and group C (p=0.024 &<0.001 respectively).

Our results were supported by study of **Afifi et al., 2021** as they reported that misoprostol alone group (group, I) had significantly higher time passed after 1st misoprostol dose till the start of vaginal spotting compared to group-II (53.9 ± 14.2 vs. 33.4 ± 7.4 hrs., P-value&<0.01 for all).

In contrast to our results, study of **Allameh et al., 2021** as they reported that the mean induction duration in the misoprostol plus letrozole and misoprostol only groups was 7.35 ± 3.54 hours and 8.2 ± 3.84 hours, respectively. The difference was not statistically significant (*P*=0.21). The difference between their study and ours may be due to different route of administration.

The current study showed that as regard outcome among the three studied groups. The results showed that 21.6% cases in group A showed failure in management with six cases needed surgical evacuation and two cases completed treatment on misoprostol 1×3, 32.4% cases in group B showed failure in management with ten cases needed surgical evacuation and two cases completed treatment on misoprostol 1×3and 37.8% cases in group C showed failure in management with ten cases needed surgical evacuation and four cases completed treatment on misoprostol 1×3.There was no statistically significant difference between the three groups regarding outcome (p>0.05).

However, **Torky et al. 2018** who found that Letrozole + Misoprostol achieved a success rate of 78.0% in complete miscarriage versus a success rate of 39.0% that was achieved by Misoprostol alone (P<0.01). Also, the incomplete miscarriages rate was significantly higher in Misoprostol only group compared to the combined one (61.0% vs. 22.0%, P<0.01).

Similarly, **Javanmanesh et al. 2018** compared the use of Misoprostol with or with no Letrozole in management of miscarriage. They found that the rate of success was significantly high in the group received Letrozole+ Misoprostol than that of the group receiving Misoprostol only (78.3% vs.13.0%; p=0.001).

Conclusion:

Letrozole pre-treatment with misoprostol increases efficacy of misoprostol in induction of complete abortion of non-viable first trimester pregnancy with no evident side effects.

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