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Pretreatment With Letrozole Plus Misoprostol Versus Misoprostol Alone in Induction of Missed Miscarriage

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Abstract

Background: Abortion, also known as miscarriage, is a common pregnancy problem that can happen naturally or be induced to terminate a pregnancy before the fetus has a chance to survive outside the uterus. Ten to 20 % of all clinically confirmed pregnancies end in a missed miscarriage.

Aim and objectives: To compare between repercussions of letrozole plus misoprostol also misoprostol alone by means of inducing missed miscarriage.

Patients and methods: This comparative trial was performed on 74 cases who were recruited from the patients presenting in the outpatient obstetric clinic or the Emergency Department in Al-Hussein and Sayed Galal Hospitals, Al-Azhar University.

Result: Time (h) among first misoprostol dose as well as onset of vaginal spotting changed significantly among each of the groups ($P = 0.04$), with the amount of time it took for the bleeding to stop after taking the first misoprostol dose (h) ($P < 0.001$). Univariate correlation regression between the outcomes and age, BMI, gravidity, previous cesarean sections, and gestational age and multivariate correlation regression between the outcomes and age, BMI, gravidity, previous cesarean sections, and gestational age. There was no statistically significant alteration among both groups as regard demographic data, side effects, and outcome.

Conclusion: When letrozole along with misoprostol were used together, the time during induction and expulsion of conception products was shortened in women with delayed miscarriage without substantial problems, in addition the rate of complete miscarriage was increased.

Keywords: Abortion, Letrozole, Miscarriage, Misoprostol

1. Introduction

Abortion, which can happen either naturally (miscarriage) or artificially (induced abortion), occurs when a pregnancy ends before the fetus has a chance to survive outside the uterus. Ten to 20 % of all clinically confirmed pregnancies end in a missed miscarriage.¹ During 1990 and 1994, it was estimated that ~50 million women had abortions as a result of being induced annually worldwide; between 2010 and 2014, that figure rose to 56 million. Also, it has been calculated that almost half of all abortions are unsafe and may result in a high

number of maternal deaths. Thus, the safe and a major focus of gynecology is the safe and humane operation of abortion.² In the 1960s, vacuum aspiration operation became the preferred method of abortion, whereas today, mifepristone is used on a massive scale all over the world to convince women to have abortions.³ Abortions that are induced by medicine rather than operation have a rate of success of between 60 and 95 % and a lower risk of complications. While mifepristone is effective in encouraging abortions, it is not available in the vast majority of republics due to its restrictive availability and prohibitive cost. Instead, other drugs are

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used to achieve the same goal. Misoprostol is an equivalent of prostaglandin E1, which is one of these drugs.⁴

Letrozole is a vital aromatase inhibitor that is used to infertile females who suffer from ovulatory problems to induce ovulation. It is active when taken orally, has a half-life of 45 h, as well as inhibits aromatase enzymes in an anticatalytic fashion.⁵

Letrozole may be useful in the treatment of abortions because it inhibits estrogen synthesis, which in turn increases endogenous gonadotropin and stimulates follicle growth in the ovaries.⁶ Furthermore, it has been stated that letrozole may substitute for mifepristone 'which is overpriced as well as not obtainable in many countries' for the treatment of estrogen-related breast cancer.⁷

With the purpose of increase in the efficacy of management regimens and reduce the need for operation, several researchers have proposed prescribing aromatase inhibitors before to the use of the main medicine 'such as misoprostol or mifepristone' for inducing medical abortions.⁶

2. Patients and methods

This comparative trial was performed on 74 cases who were recruited from the patients presenting in the outpatient obstetric clinic or the Emergency Department in Al-Hussein and Sayed Galal Hospitals, Al-Azhar University.

Seventy-four participants were included in this research that fulfilled the inclusion criteria. Participants were split into two separate groups: 40 patients in both group. Group A: given letrozole every day for 3 days, take 10 mg previously start of induction with misoprostol and group B: given misoprostol only.

Misoprostol was given according to the RCOG guidelines. For all gestations, misoprostol 800 µg were given by the vaginal route, followed by misoprostol 400 µg every 6 h until abortion occurs.

Inclusion criteria: all women presenting with missed miscarriage, gestational age equal to or less than 20 weeks confirmed by ultrasound scan and singleton pregnancy.

Exclusion criteria: patients managed by surgical evacuation from the first (e.g. inevitable miscarriage), known allergy to letrozole and/or misoprostol, severe impairment of liver functions, bronchial asthma, and maternal morbidity due to nonsurgical management (i.e. sepsis, severe vaginal bleeding).

2.1. Methods

Every single individual underwent: complete history taking, physical examinations, investigational

studies (routine laboratory investigations, abdominal ultrasound examination, and transvaginal ultrasound).

2.2. Procedures

Group A (letrozole + misoprostol group): given letrozole 10 mg once daily for 3 days before start of induction with misoprostol. Group B (misoprostol group): misoprostol will be given according to the RCOG guidelines. Received 800-mg misoprostol vaginally followed by misoprostol 400 µg every 6 h until abortion occurs.

Letrozole was administrated by oral route.

After misoprostol administration, the participants shall stay in the hospital for at least 3–6 h to observe for bleeding, tissue passage, and severe adverse effects.

2.3. Outcome measurements and follow-up

Primary outcome: the time from start of induction of abortion till successful medical abortion without needing for rescue by operating room within 7 days of taking misoprostol.

Secondary outcome parameters: the requirement for operative removal of any remaining traces of conception due to either. Considerable vaginal bleeding leading to hemodynamic instability necessitating immediate surgical evacuation or unfinished expulsion of products of conception confirmed by ultrasound scan.

Delayed miscarriage: asymptomatic or missed death of the embryo or fetus without sufficient uterine contractions to push out the products of conception.

This study base on study carried out by Khodary and colleagues used to calculate the sample size by considering the following assumptions: 95 % two-sided confidence level, with a power of 80 % and α error of 5 %. The final maximum sample size taken from output was 78. Thus, the sample size was increased to 80 participants to assume any drop out cases during follow up.⁸

$$\left(\frac{Z_{\alpha/2} + Z_B}{P_1 - P_2}\right)^2 (p_1q_1 + p_2q_2)$$

n = sample size.

$Z_{\alpha/2}$ = the critical value that divides the central 95 % of the Z distribution.

Z_B = the critical value that divides the central 20 % of the Z distribution.

P_1 = accuracy prevalence in TCD group.

P_2 = accuracy prevalence in FL group.

Ethical consideration: the trial protocol was approved after it was submitted by the Ethical Committee of the Obstetrics and Gynecology Department of the Faculty of Medicine at Al-Azhar University. After providing each participant with an explanation of the objectives and methods of the trial, informed verbal in addition written agreement was gained from the participant's participation in the research. At every stage of the investigation, measures were taken to safeguard participants' right to privacy and confidentiality.

2.4. Medical management

According to NICE guidelines on April 2019, offer vaginal misoprostol for the medical treatment of missed or incomplete miscarriage. Oral administration is an acceptable alternative if this is the woman's preference. In missed miscarriage, use a single dose of 800 µg of misoprostol then advise the woman that if bleeding has not started 24 h after treatment, she should contact her healthcare professional to determine ongoing individualized care.

2.5. Statistical analysis

Using the SPSS program (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois, USA), version 23.0, we tabulated and statistically evaluated the data that we collected.

For numerical parametric information, descriptive statistics were premeditated as mean ± SD. In addition to the minimum as well as maximum of the range; for numerical nonparametric data,

calculations of descriptive statistics included the median, the first and third interquartile ranges, and the range from the median to the third interquartile. Calculations of descriptive statistics for categorical data included the calculation of numbers as well as percentages. Inferential analyses of quantitative parameters were carried out by using the independent *t*-test in situations involving two distinct groups that possessed parametric data also the Mann–Whitney *U* in scenarios involving two independent groups that possessed nonparametric data.

The χ^2 test for two-sample inferences was used on qualitative data with the assumption of independence. *P* values under 0.050 were regarded to have a significant impact statistically; values above 0.050 were deemed inconclusive. A study's *P* value indicates how likely it is that the results were produced by random chance.

3. Results

Table 1 displays that mean age of groups A, B was 26.9 ± 5.26 and 26.1 ± 5.45 , respectively. The mean BMI of the two groups was 24.9 ± 2.09 and 24.49 ± 2.3 , respectively. There is no statistically significant change among each group according to age ($P = 0.83$) and BMI ($P = 0.56$).

Table 2 shows that mean time passed later first misoprostol dose till the begin of vaginal spotting (h) was 7.1 ± 0.42 for group A and 8.2 ± 0.8 for group B, and the mean. The length of time that a woman will bleed after taking their first dose of misoprostol (h) was 6.1 ± 0.5 for group A and was 7.1 ± 0.8 for group B.

There was a statistically significant variance among the two groups when compared to the amount of time that passed after the initial misoprostol dose until the start of vaginal spotting (h) ($P = 0.001$) and the amount of time that passed until the start of vaginal bleeding after the initial misoprostol dose (h) ($P < 0.0001$).

Table 3 shows evaluation between studied groups as regard side effects; as regard group A; we found

Table 1. Comparison among each group relative to demographic data.

	Group A	Group B	Test	<i>P</i> value
Age				
Mean ± SD	26.9 ± 5.26	26.1 ± 5.45	1.07	0.83
Minimum—maximum	27 (19–36)	25 (19–36)		
BMI (kg/m ²)				
Mean ± SD	24.9 ± 2.09	24.49 ± 2.3	1.21	0.56
Minimum—maximum	24 (21–28)	24 (21–28)		

Table 2. Comparison among studied groups in contrast to time from initial misoprostol dose to vaginal spotting (in h) and time from first misoprostol dose to end of vaginal bleeding (in h).

	Group A	Group B	Test	<i>P</i> value
Time passed after 1st misoprostol dose till the start of vaginal spotting (h)				
Mean ± SD	7.1 ± 0.42	8.2 ± 0.8	2.89	0.001
Minimum—maximum	6.5 (5–8)	7 (6–10)		
Duration of vaginal bleeding after the 1st misoprostol dose (h)				
Mean ± SD	6.1 ± 0.5	7.1 ± 0.8	6.431	<0.0001
Minimum—maximum	6.3 (5–8)	7 (6–8)		

Table 3. Comparison among studied groups in accordance with side effects.

	Group A	Group B	Test	P value
Side effects				
No	13	11	0.23	0.62
Pain	4	4	–	1
Severe bleeding needing evacuation	9	5	1.38	0.32
Hyperpyrexia	4	5	0.12	0.72
Nausea and vomiting	10	16	2.05	0.15

no SE in 13 cases, pain in four cases, severe bleeding needing evacuation in nine cases, hyperpyrexia in four cases, and nausea and vomiting in 10 persons. Regarding any and all adverse effects, there was not a statistically significant distinction among the two groups.

Table 4 demonstrate comparison among studied groups in accordance with outcome; in group A 27 cases ended with complete abortion, four cases ended with incomplete abortion, and nine cases needed emergency D and C. In group B 30 cases ended with complete abortion, five cases ended with incomplete abortion, and five cases needed emergency D and C.

There was no statistically significant variance among the researched groups according to the outcome ($P = 0.49$).

Table 5 shows significant univariate correlation regression between the outcomes and age, BMI,

Table 4. Comparison among two groups according to outcome.

	Group A	Group B	Test	P value
Outcome				
Complete abortion	27	30	1.412	0.49
Incomplete abortion	4	5		
Emergency D and C	9	5		

Table 5. Univariate correlations between outcomes and different factors.

	Value
Age	
Correlation	0.348
Significance	<0.0001
BMI	
Correlation	0.471
Significance	<0.0001
Gravidity	
Correlation	0.412
Significance	<0.0001
Previous cesarean sections	
Correlation	0.357
Significance	<0.0001
Gestational age (days)	
Correlation	0.462
Significance	<0.0001

Table 6. Multivariate correlations between outcomes and different factors.

Variables	Value
Age	
Correlation	71.305
Significance	<0.0001
BMI	
Correlation	20.495
Significance	<0.0001
Gravidity	
Correlation	25.595
Significance	<0.0001
Previous cesarean sections	
Correlation	72.35
Significance	<0.0001
Gestational age (days)	
Correlation	21.49
Significance	<0.0001

gravidity, previous cesarean sections, and gestational age.

Table 6 shows significant multivariate correlation regression between the outcomes and age, BMI, gravidity, previous cesarean sections, and gestational age.

4. Discussion

A spontaneous or induced abortion is one of the most common types of abortion complications that can arise during pregnancy. According to the WHO, there are around 79 million unplanned pregnancies happening each year around the world. This number does not include miscarriages. In addition, there are around 46 million abortions that are induced each year around the world. It is extremely challenging to provide an accurate estimate of the total number of abortions, particularly in developing nations. Furthermore, the number is typically underreported because of the legal constraints, and a significant proportion of medically induced abortions are carried out in unsanitary environments. An unintended financial burden on families and the healthcare system could result from the abortion. Abortions performed in the absence of medical supervision increase the risk of serious consequences, including maternal mortality, uterine rupture, and infection. The procedure's safety is of utmost importance if the desired outcome is not life-threatening.⁸

The main results of this study were as following:

Regarding demographic data; mean age of groups A, B was 26.9 ± 5.26 and 26.1 ± 5.45 , respectively, the mean BMI of the two groups was 24.9 ± 2.09 and 24.49 ± 2.3 , respectively. There is no statistically significant variance among the two groups as regard age ($P = 0.83$) and BMI ($P = 0.56$).

Our outcomes were compatible with trial of Elbareg and Essadi Fathi. According to their findings, 60 individuals in the letrozole/misoprostol group along with 56 participants in the misoprostol group were able to finish the research as well as their data reviewed. The average age of patients in the letrozole/misoprostol group was 28.3 ± 3.4 years old, whereas those in the misoprostol group averaged 29.8 ± 4.5 years old. There was no statistically significant change among the two groups as regard age and BMI.⁹

The current study showed that time passed after first misoprostol dose till the start of vaginal spotting (h) was 7.1 ± 0.42 for group A and 8.2 ± 0.8 for group B, and the mean duration of vaginal bleeding after the first misoprostol dose (h) was 6.1 ± 0.5 for group A and was 7.1 ± 0.8 for group B. There was a statistically significant disparity among both groups in terms of the amount of time that passed after the first misoprostol dose until the start of vaginal spotting (h) ($P = 0.001$) and the amount of time that passed after the first misoprostol dose until the start of vaginal bleeding (h) ($P < 0.0001$), respectively. After taking the initial dose of misoprostol, the average amount of time that transpired until the first POC passing (h) was 7.1 ± 0.78 for group A and 8.66 ± 1.4 for group B, and the number of cases that need for urgent evaluation owing to severe discomfort or bleeding were nine in group A and five in group B. There were statistically significant alterations among the two groups as regard time passed after first misoprostol dose till the first passage of POC (h) ($P = 0.04$), but there were no statistically significant distinctions among the two groups as regard need for urgent evaluation due to severe pain or bleeding ($P = 0.32$). The mean induction to abortion interval (h) was 7.5 ± 0.93 for group A and 8.89 ± 1.45 for group B. There was statistically significant change among both groups as regard the induction to abortion interval ($P = 0.01$). According to third day US, we found no remnant in 23 cases and remnant in the other 17 persons in group A, while in group B five cases showed no remnant and 35 cases showed remnants. According to seventh day US, we found no remnant in nine cases and remnant in the other 31 cases in group A, while in group B five cases showed no remnant and 35 cases showed remnant. There was statistically significant alteration among the two groups as regard the third day US ($P < 0.001$), but there was no statistically significant alteration among the two groups as regard the seventh day US ($P = 0.32$).

While, in the study of Haj Seyed Javadi and colleagues in all, all patients required a period of

medication administration time averaging 6.0 ± 1.3 h in order to open the os of the cervix. In total, there was a mean duration time of 8.9 ± 2.0 h until the first patient was prescribed tissue rejection. The patients took a total of 9.0 ± 2.0 h to finish the abortion medicine, which was the mean duration time. In the group that received letrozole plus misoprostol, the mean duration time of medication administration to open the os of the cervix was 5.9 ± 1.5 h, but in the group that received misoprostol alone, this was 6.1 ± 1.2 h; the difference between these two groups was not statistically significant ($P = 0.59$). This difference in duration time among drug administration in addition to opening of the os of the cervix was not statistically significant ($P = 0.18$). The mean duration time between drug administration as well as opening of the os of the cervix was 5.2 ± 1.7 h in patients with GA of lesser than seven weeks along with 6.1 ± 1.4 h in individuals with GA among 7 as well as 12 weeks from the misoprostol with letrozole group.¹⁰

Whereas, Nadim et al.¹¹ demonstrated that there was no statistically significant change observed among the two examined groups regarding outcomes of US at day 7.

In addition, Elbareg and Essadi Fathi demonstrated that the mean length of time from the administration of misoprostol to the expulsion of product of conception (induction-to-miscarriage time) was shorter in the letrozole/misoprostol group (6.1 ± 1.6 h) compared with the misoprostol group (9.4 ± 2.2 h). Furthermore, statistical analysis revealed that the variation was noteworthy.⁹

In the study in our hands, Comparison among studied groups as regard negative consequences; as regard group A; we found no SE in 13 cases, pain in four cases, severe bleeding needing evacuation in nine cases, hyperpyrexia in four cases, and nausea and vomiting in 10 cases. There was not any statistically significant distinction among both groups in any of the adverse effects that were observed.

Our findings were consistent with the findings of the research conducted by Nadim et al.,¹¹ who concluded that there was not a statistically significant distinction among both groups that were evaluated in terms of the adverse effects experienced after treatment.

While, in the study of Afifi and colleagues discovered that there was not a significant distinction among the groups in terms of the incidence of adverse effects (37 patients in group A vs. 32 individuals in group B, $P = 0.46$), however there was a substantially higher incidence of vomit and nausea in group B ($P < 0.01$).²

The present study showed that evaluation among examined groups as regard consequence; in group

A 27 cases ended with complete abortion, four cases ended with incomplete abortion, and nine cases needed emergency D and C. In group B 30 cases ended with complete abortion, five cases ended with incomplete abortion, and five cases needed emergency D and C. There was no statistically significant variance among the two groups as regard the outcome ($P = 0.49$).

While, in the study of Behroozi-Lak and colleagues case group, a successful abortion was seen in 30 (76.9 %) of the participants, whereas nine (23 %) of the cases were unsuccessful. In the control group, there were a total of 16 (41.03 %) successful abortions as well as a total of 23 (58.97 %) unsuccessful abortions. The percentage of women in the case group who had a successful abortion was completely different from the percentage of women in the control group ($P = 0.001$). In the case group, 58.97 % of patients received only letrozole, while the remaining 41.03 % received both letrozole and misoprostol. Patients in the case group one (2.6 %), two (5.1 %), two (5.1 %), one (2.6 %), and 33 (84/6 %) were each given 15, 20, 22.5, 25, and 30 mg of letrozole.¹²

Whereas, Elbareg and Essadi Fathi revealed that the probability of complete abortion was significantly greater in the letrozole/misoprostol group (48/60, 80 %) than it was in the misoprostol group (29/56, 51.8 %), as well as this variation was statistically significant ($P < 0.01$).⁸

In the trial of Nada et al.¹³ group B showed higher rate of incomplete abortion (22.2 %) than group A (8.9 %). P value was below 0.05.

Our outcomes presented that there is significant strong (+ve) connection among the outcomes and age, BMI, gravidity, previous cesarean sections, and gestational age. There is significant univariate correlation regression between the outcomes and age, BMI, gravidity, previous cesarean sections, and gestational age.

4.1. Conclusion

When letrozole along with misoprostol were used together, the time during induction and expulsion of conception products was shortened in women with

delayed miscarriage without substantial problems, in addition the rate of complete miscarriage was increased.

Conflicts of interest

There are no conflicts of interest.

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