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# Comparative Study Between the Effect of Letrozole Before Misoprostol and Misoprostol Alone in Cases of Missed Abortion

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## Abstract

**Background:** Missed abortion is characterized as the presence of dead products of conception inside the uterus. Incidence: once the fetus is dead, spontaneous abortion occurs in 80 % of women within 2 weeks and only 10 % remain undelivered for more than 3 weeks, interestingly found evidence of delayed spontaneous labor when fetal death was due to Rh-isoimmunization, 50 % of mothers remaining undelivered after 5 weeks.

**Aim:** To assess the impact of letrozole combined with misoprostol on induction of abortion compared with usage of misoprostol alone.

**Patients and methods:** This was a comparative study that was performed on 150 women diagnosed with missed abortion at Al-Hussein University Hospital in February 2021. All patients were randomly divided into two groups: group A: 75 women (were induction of abortion by letrozole 7.5 mg (Femara) once daily for 3 days, followed by misoprostol 400 mcg vaginally every 4 h up to a maximum of five doses/day). Group B: 75 women (were induction of abortion by misoprostol (misotac) 400 mcg vaginally every 4 h up to five doses per day).

**Results and conclusion:** In instances with first-trimester miscarriages, a 3 days courses of letrozoles (7.5 mg/day) followed by misoprostols (400 mg) was associated with significantly greater complete abortion rates (81.3 % vs. 53.3 %); however, prescribing letrozoles before misoprostol was successful in improving the effectiveness of misoprostol for provoking abortion without increasing adverse reactions. Finding the ideal treatment plan to accomplish the greatest proportion of effectiveness and the lowest number of side-effects may require doing more, larger studies over longer durations and using a variety of doses.

**Keywords:** Abortion, Letrozole prior, Misoprostol

## 1. Introduction

The reason that some abortions do not terminate after fetal death is not clear. If the missed abortion terminates spontaneously and most do the process of expulsion is the same in the other abortions. If retained several weeks after death, it becomes a shriveled sac containing a macerated fetus.<sup>1</sup>

Consequently, medical management has been considered as an alternative for miscarriages treatment. The effectiveness of prostaglandins with or without mifepristones has been the subject of many

research. The suggested dosage is 200 mg of mifepristone accompanied by 800 mcg of vaginal misoprostol 36–48 h later. Up to a maximum of four further dosages, 400 mcg of misoprostol could be administered orally every 3 h.<sup>2</sup>

The combination treatment had an abortion frequency of 97–100 % within 24 h and an interval between inducement and abortion of roughly 5–10 h. Misoprostol alone treatment, for instance, recurrent dosages of 400 mcg, with an abortion rate of 73–81 % within 24 h and an inducement to abortion interval of 13–15 h, could be employed in nations where mifepristone is not accessible.

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Misoprostol, an antiprogesterone, may make the uterus more susceptible to prostaglandins.<sup>3</sup> Comparing with pretreatment protocols without misoprostol, pretreatment with misoprostol resulting in a shortened onset to abortion interval. The reality that misoprostol is costly and not accessible in several nations, though, restricts the wide adoption of the sequential regimens of misoprostol and a prostaglandin analogue. It is necessary to find a more affordable and accessible substitute.<sup>4</sup>

Compared with prostaglandin E2 counterparts, misoprostol is less expensive, has a more prolonged shelf life at room temp, and has less adverse effects. Misoprostol is the preferred prostaglandin since it can be administered via oral, vaginal, and sublingual methods in addition to others. Misoprostol vaginally is preferable to misoprostol by oral methode in terminating pregnancies in the first trimester. Mifepristone has been explored for this purpose.<sup>5</sup>

Alternative treatment options include surgical uterine evacuation, which was once the usual treatment but is linked to complications such infections, uterine perforation, or Asherman syndrome. Progesterone and oestrogen are both crucial hormones for maintaining pregnancy. The evidence for estrogen's part in primates' ability to maintain gestation comes from Albrecht et al.<sup>6</sup> study.

Third-generation aromatase inhibitors letrozole is approved as a therapy of advanced breast cancer that is oestrogen reliant. It prevents the conversion of androstenedione to oestrogen and testosterone to estradiol. Third-generation aromatases inhibitors may significantly reduce oestrogen levels without changing progesterone or cortisol levels. Ovarian granulosa cells and the placental both have higher levels of aromatases expression.<sup>7</sup>

Aromatase inhibitors treatment increases gonadotropin output in premenopausal women due to decreased oestrogen feedback to the brain and pituitary. As a result, it has also been utilised in ovulation stimulating programs for *in vitro* and intrauterine insemination as well as ovulation inducement.<sup>8</sup>

The goal of the current descriptive investigation is to contrast the effectiveness of the sequentially letrozole and misoprostol regimens with that of misoprostol alone in missing abortions during the first trimester.

## 2. Patients and methods

In February 2021, 150 women who had missed abortions were the subject of a comparison study at Al-Hussein University Hospital. All patients were

divided into two samples at rando: group A: 75 females (were induction of abortion by letrozole 7.5 mg (Femara) once daily for 3 days, followed by misoprostol 400 mcg vaginally every 4 h up to maximum five dosages per day). Group B: 75 women (were induction of abortion by misoprostol (misotac) 400 mcg vaginally every 4 h up to five doses per day).

### 2.1. Inclusion criteria

Pregnant women with: Good medical general condition, Age between 20 and 40 years old and A gestation of 13 weeks or less of missed abortion as demonstrated by ultrasonic imaging on research day 1 (i.e. day of letrozole intake).

### 2.2. Exclusion criteria

Bronchial asthma, Regular usage of any drug before the enrollment in the research, Heavy smoking, and Abnormal values in blood tests.

The following procedures were applied to all study participants: History taking (full history), and Clinical assessment of the patient (general assessment) 3-Investigation: Obstetric ultrasound examination and Laboratory assessment.

### 2.3. Statistical analysis

The findings were reviewed, processed, and processed into version 20 of the Statistical Package for Social Science. Once their distribution was found to be proportional, quantitative statistics were given as averages, standard deviations, and ranges, whereas qualitative data were provided as numbers and percentages.

Once the predicted number in any cell was less than 5, the contrast between the two samples with qualitative approach was made using the Tian analysis or the Fisher exact analysis.

## 3. Results

As illustrated in (Table 1); the average age in group A were;  $26.81 \pm 5.43$ , while average age in group B were  $27.39 \pm 5.98$ , the average BMI ( $\text{kg}/\text{m}^2$ ) in group A were;  $27.03 \pm 6.04$ , while average BMI ( $\text{kg}/\text{m}^2$ ) in group B were  $26.03 \pm 6.38$  and the average Gestational age (days) in group A were;  $60.56 \pm 12.90$ , while average Gestational age (days) in group B were  $61.31 \pm 14.36$ .

Age-wise, there was no statistically significant distinction between groups A and B., as well as BMI ( $\text{kg}/\text{m}^2$ ) and Gestational age (days).

Table 1. Contrast between group A (no. = 75) and group B (no. = 75) according to age, BMI (kg/m<sup>2</sup>) and gestational age (days).

	Group A No. = 75	Group B No. = 75	Test value●	P-value	Sig.
Age					
Mean ± SD	26.81 ± 5.43	27.39 ± 5.98	−0.615	0.540	NS
Range	20–40	20–40			
BMI (kg/m <sup>2</sup> )					
Mean ± SD	27.03 ± 6.04	26.03 ± 6.38	0.986	0.326	NS
Range	19–38	16–35			
Gestational age (days)					
Mean ± SD	60.56 ± 12.90	61.31 ± 14.36	−0.335	0.738	NS
Range	45–85	45–90			

Table 2. Comparison between group A (no. = 75) and group B (no. = 75) regarding gravidity.

Gravidity	Group A No. (%)	Group B No. (%)	Test value	P-value	Significance
PG	21 (28.0 %)	19 (25.3 %)	0.800*	0.938	NS
G2	16 (21.3 %)	17 (22.7 %)			
G3	13 (17.3 %)	11 (14.7 %)			
G4	9 (12.0 %)	8 (10.7 %)			
G5	16 (21.3 %)	20 (26.7 %)			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

As illustrated in (Table 2); in group A; 28.0 % of them were PG, 21.3 % were G2, 17.3 % were G3, 12.0 % were G4, and 21.3 % were G5, while the group B; 25.3 % of them were PG, 22.7 % were G2, 14.7 % were G3, 10.7 % were G4, and 26.7 % were G5.

Considering Gravidity, there was no statistically significant distinction comparing group A and group B.

As illustrated in (Table 3); in group A; 76.0 % of them were previous cesarean sections (CSs) 0, 14.7 % were previous CSs 1, 4.0 % were previous CSs 2, 2.7 % were previous CSs 3, and 2.7 % were previous CSs 4, while the group B; 80.0 % of them were previous CSs 0, 12.0 % were previous CSs 1, 2.7 % were previous CSs 2, 2.7 % were previous CSs 3, and 2.7 % were previous CSs 4.

For Prior CSs, there was no statistically noteworthy variation between Group A and Group B.

As shown in (Table 4), the mean number of hours after the first dosage of misoprostol until the onset of

vaginal spotted in group A was  $33.81 \pm 5.83$ , whereas the average number of hours after the first dosage of misoprostol until the onset of vaginal spotting in group B was  $57.01 \pm 9.80$ , The mean length of time that vaginal bleeding persisted after taking the first dosage of misoprostol was  $36.17 \pm 7.82$  h in group A and  $73.88 \pm 13.49$  h in group B and the average number of hours between the first misoprostol dosage and the first product of conception (POC) passage in group A was  $53.62 \pm 10.19$ , whereas the average number of hours between the first misoprostol dosage and the first POC passage in group B was  $76.71 \pm 18.47$ .

As illustrated in (Table 5); in group A; 12.0 % of them had immediate examination required due to excruciating pain or bleeding, including one women who Remnant on the third day U/S and 1 women who Remnant on the seventh day U/S, while the group B; 25.3 % of them had immediate examination required due to excruciating pain or bleeding, including 19 women who Remnant on the third day

Table 3. Comparison between group A (no. = 75) and group B (no. = 75) regarding previous Cesarean sections.

Previous CSs	Group A No. (%)	Group B No. (%)	Test value	P-value	Significance
0	57 (76.0 %)	60 (80.0 %)	0.477*	0.976	NS
1	11 (14.7 %)	9 (12.0 %)			
2	3 (4.0 %)	2 (2.7 %)			
3	2 (2.7 %)	2 (2.7 %)			
4	2 (2.7 %)	2 (2.7 %)			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

Table 4. Comparing group A (no. = 75) and group B (no. = 75) regarding clinical findings.

Clinical findings	Group A No. = 75	Group B No. = 75	Test value●	P-value	Significance
Time passed before the first POC passing (hrs.) following the initial misoprostol dosage					
Mean ± SD	53.62 ± 10.19	76.71 ± 18.47	-9.478	0.000	HS
length of vaginal bleeding following the first dosage of misoprostol (hrs.)					
Mean ± SD	36.17 ± 7.82	73.88 ± 13.49	-20.942	0.000	HS
time passed before the onset of vaginal spotting (hrs.) after the initial misoprostol dosage,					
Mean ± SD	33.81 ± 5.83	57.01 ± 9.80	-17.619	0.000	HS
Range	25–45	38–70			
Range	25–50	50–95			
Range	38–70	45–110			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance. POC, product of conception.

Table 5. Contrast between group A (no. = 75) and group B (no. = 75) regarding follow-up.

Follow-up.	Group A No. (%)	Group B No. (%)	Test value	P-value	Significance
Immediate examination required due to excruciating pain or bleeding	9 (12.0 %)	19 (25.3 %)	4.391	0.006	HS
Third day U/S					
No remnant	8 (88.9 %)	0	23.644	0.000	HS
Remnant	1 (11.1 %)	19 (100.0 %)			
Seventh day U/S					
No remnant	8 (88.9 %)	5 (26.3 %)	9.614	0.002	HS
Remnant	1 (11.1 %)	14 (73.7 %)			
Drop out failed to follow					
No	73 (97.3 %)	72 (96.0 %)	0.207	0.649	NS
Yes	2 (2.7 %)	3 (4.0 %)			

P-value greater then 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

U/S and 14 women who Remant on the seventh day U/S.

When it came to the following factors: requiring an urgent examination due to excruciating pain or hemorrhage, the third day's U/S, the seventh day's U/S, and the dropouts failure to follow, group A and group B differed significantly statistically.

As illustrated in (Table 6); in group A; 32.0 % of them had side effects, including 13 women who suffer from nausea and vomiting, 2 women with hyperpyrexia, 4 women with severe pain and 5 women with severe bleeding needing evacuation, while the group B; 38.7 % of them had side effects,

including 3 women who suffer from nausea and vomiting, 8 women with hyperpyrexia, 5 women with severe pain and 13 women with severe bleeding needing evacuation.

There was no significant disparity in the adverse reactions between group A and group B.

As illustrated in (Table 7); in group A; 81.3 % of them were complete abortion, 4.0 % were drop out, 10.7 % were emergency D and C and 4.0 % were incomplete abortion, while the group B; 53.3 % of them were complete abortion, 2.7 % were drop out, 24.0 % were emergency D and C and 20.0 % were incomplete abortion.

Table 6. Comparison between group A (no. = 75) and group B (no. = 75) regarding side effects.

	Group A No. (%)	Group B No. (%)	Test value*	P-value	Significance
Side effects	24 (32.0 %)	29 (38.7 %)	0.729	0.393	NS
Nausea and Vomiting	13 (54.2 %)	3 (10.3 %)	–	–	–
Hyperpyrexia	2 (8.3 %)	8 (27.6 %)			
Severe Pain	4 (16.7 %)	5 (17.2 %)			
Severe bleeding needing evacuation	5 (20.8 %)	13 (44.8 %)			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

Table 7. Comparison between group A (no. = 75) and group B (no. = 75) regarding outcome.

Outcome	Group A No. (%)	Group B No. (%)	Test value	P-value	Significance
Complete abortion	61 (81.3 %)	40 (53.3 %)	16.412	0.001	HS
Drop out	3 (4.0 %)	2 (2.7 %)			
Emergency D and C	8 (10.7 %)	18 (24.0 %)			
Incomplete abortion	3 (4.0 %)	15 (20.0 %)			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

There were very substantial statistical variations in the outcomes between group A and group B.

As illustrated in (Table 8); the average Induction to abortion interval (hrs) in group A were;  $60.35 \pm 9.02$ , while average Induction to abortion interval (hrs) in group B were  $100.18 \pm 11.09$ .

In terms of time from initiation to abortion, there was an extremely statistically significant distinction comparing group A and group B (hrs).

#### 4. Discussion

Abortion is the termination of a pregnancy before the fetus can develop in the uterus. This could happen accidentally (miscarriage) or by design (induced abortion). In about 10 % and 20 % of clinically diagnosed gestations, a missed miscarriage occurs. It was anticipated that there would be over 50 million provoked abortions annually between 1990 and 1994, which rose to 56 million annually between 2010 and 2014.<sup>9</sup> Effective therapy for abortion is a critical issue in gynecology because it is believed that about 50 % of abortions.<sup>10</sup>

In the 1960s, hoover aspiration operation was the preferred procedure for ending pregnancies. Later, the production of mifepristone allowed for the widespread use of medication-assisted abortions throughout the globe. Medication-assisted abortion is an alternative to surgical abortion, which has reduced costs, fewer side effects, and a satisfactory result of between 60 % and 95 %.<sup>11</sup> Many drugs can be used to induce abortions, but mifepristone isn't accessible in most nations because of accessibility issues and cost concerns. Thus, replacement drugs are used instead. Among these drugs is the prostaglandin E1 analog misoprostol.<sup>12</sup>

Misoprostol causes myometrial cervical softness, contractions, and dilatations. It is used to induce

labor and induce abortions as well as to treat ulcerative colitis and atonic postpartum hemorrhage.<sup>10</sup> It has the advantage of being affordable, reliable, and having a low rate of adverse effects, which has led to its inclusion on the WHO list of essential pharmaceuticals.<sup>13</sup> Misoprostol is inexpensive and effective, does not require special handling while being used, and can be administered in various ways, including vaginally, orally, and sublingually. Patients absorb misoprostol well, and its costs are much lower than other therapies. Moreover, it significantly lowers the need for surgery and curettages.<sup>14</sup>

A significant aromatase inhibition called letrozole is used to stimulate ovulation in infertile women who have ovulatory dysfunctions. Letrozole is effective orally, has a relatively short 45 h half-life, and inhibits aromatase activities in the reverse direction. Letrozole can be used to treat abortions by limiting the production of estrogen, which raises endogenous gonadotropin and, in turn, stimulates the development of ovaries' follicles.<sup>15</sup> Also, letrozole is reportedly used to manage estrogen-related breast cancer and can take the place of mifepristone, which is "expensive and unavailable in several regions," according to reports.<sup>8</sup>

Several studies contend that prescribing aromatase inhibitors prior to the use of powerful drugs, "such misoprostol or mifepristone," to induce medicated abortions increases the efficacy of treatment plans and also lessens the need for surgeries. When misoprostol was administered after letrozole for three days, a success rate of 86.9 % was attained. Further research used the letrozole treatment for seven days with a 95 % success rate.<sup>16</sup> Whereas letrozole and mifepristone, which were used before to misoprostol and achieved a 98 % success rate for total abortion.<sup>8</sup>

Table 8. Contrast between group A (no. = 75) and group B (no. = 75) regarding induction to abortion interval (hrs).

Induction to abortion interval (hrs)	Group A No. = 75	Group B No. = 75	Test value	P-value	Significance
Mean $\pm$ SD	$60.35 \pm 9.02$	$100.18 \pm 11.09$	24.128	0.000	HS
Range	45–75	85–120			

P-value greater than 0.05 indicates non significance, P-value less than 0.05 indicates significance, and P-value less than 0.01 indicates very significance.

Several investigations assessed the effectiveness of misoprostol and letrozole in treating silent miscarriages, but more research is necessary before definitive conclusions can be drawn.

This trial's objective was to examine the effectiveness of using misoprostol alone against letrozole and misoprostol together for abortion initiation.

At the Al-Hussein University Hospital in February 2021, 150 women who had missed abortions were the subject of a comparison study. All individuals were assigned to two groups at random: group A: 75 female (were given misoprostol 400 mcg intravaginally every 4 h up to a maximum of five dosages a day) underwent abortion initiation with letrozole 7.5 mg (Femara) once daily for three days. 75 females in group B underwent abortion initiation using Misoprostol (Misotac) 400 mcg intravaginally every 4 h up to five dosages daily.

The findings from this research showed that there were no statistically significant variations in age, BMI (kg/m<sup>2</sup>), or gestational age between two group (days).

The present investigation did not identify any statistically significant differences in earlier CSs or gravidity between group A and group B.

This agrees with Afifi et al.<sup>17</sup> We sought to compare the safety and efficacy of two methods of treatment (Letrozol plus Misoprostol vs Misoprostol) in the clinical treatment of missed miscarriages in the first trimester. In terms of ages, they showed that there weren't any significant differences between groups.

These findings are consistent with those of Torky et al.,<sup>18</sup> Naghshineh et al.,<sup>10</sup> and Abbasalizadeh et al.<sup>11</sup>

To guarantee the homogeneity of the researched groups and obtain accurate findings from their comparisons, these minimal changes in categorical variables between the samples analyzed are crucial.

According to the findings from this research, there were strongly statistically significant differences between group A and group B in regards to the length of vaginal bleeding after the first misoprostol dosages, the moment after the first misoprostol dosages until the first passage of POC, and the duration after the first misoprostol doses until the beginning of vaginal spotting (hrs.).

The present findings showed that there were exceptionally significant decreases in need for urgent evaluation due to severe pain or bleeding, third day U/S, seventh day U/S, but no statically meaningful differences concerning drop out failure to continue amongst group A than group B.

This agrees with Afifi et al.<sup>17</sup> who demonstrated that Comparing with the Letrozol + Misoprostol

group, the Misoprostol's group had a considerably higher amount of cases that required immediate examination "because to severe discomfort or bleeding" (22 cases vs. 10 cases).

Similar to our findings, Abbasalizadeh et al.<sup>11</sup> Comparing with the Letrozol + Misoprostol group, the Misoprostol monotherapy group had a considerably higher amount of cases that required immediate examination "because to severe discomfort or bleeding" (22 cases vs. 10 cases).

Moreover, Lee et al.,<sup>4</sup> Naghshineh et al.<sup>10</sup> and Javanmanesh et al.<sup>14</sup> confirmed comparable results.<sup>14</sup>

Abbasalizadeh et al.<sup>11</sup> reported, When making comparisons bleeding times, the letrozole able to receive group had an average shorter bleeding period. When comparing haemoglobin levels, the two groups did not differ significantly before the intervention, but following the abortion, the letrozole able to receive group's haemoglobin frequency was significantly greater than the control group's. Moreover, letrozole recipients experienced less stomach pain than the control group.

On the contrary, a review research has demonstrated that sublingual misoprostol 600 mg single dosage or intravaginal misoprostol 800 mg single dosage are appropriate alternatives to operation for the therapy of failed abortion in the first pregnancy trimester. This research additionally showed that there was no requirement for hospitalisation following the prescription of misoprostol, and cases should be referred in the event of severe bleeding or infection. It is also advised to conduct a second examination and monitoring patients after 1–2 weeks following the prescription of misoprostol.<sup>19</sup>

There was no statistically significant distinction between group A and group B concerning adverse events in the current investigation. In group A, 32.0 % of the participants experienced adverse effects, including 13 women who experienced nausea and vomiting, 2 women who experienced hyperpyrexia, 4 women who experienced severe pain, and 5 women who required evacuation due to severe bleeding. In group B, 38.7 % of the participants experienced adverse effects, including 3 women who experienced nausea and vomiting, 8 women who experienced hyperpyrexia, 5 women who experienced severe pain, and 13 women who experienced severe bleeding.

This agrees with Afifi et al.<sup>17</sup> who reported that, There was not any discernible disparity between the two groups in respect to the incidence of negative impacts (37 patients in group I vs. 32 patients in group II,  $P = 0.46$ ), whereas nausea and vomiting were significantly more frequent in group II ( $P < 0.01$ ).

This is in consistent with Torky et al.<sup>18</sup> who discovered that the letrozole + Misoprostol group had a greater rate of nausea and vomiting than the Misoprostol only group (17.0 % vs. 3.0 %,  $P = 0.002$ ). Nevertheless, they discovered that there were no appreciable differences in the incidence of other problems (fever, excruciating pain, and serious hemorrhage).

Also, Javanmanesh et al.<sup>14</sup> found that regarding side effects, there wasn't a statistically significant difference between the Letrozole and Misoprostol groups.

Moreover, Naghshineh et al.<sup>10</sup> discovered that both the frequency and the severity of side effects were comparable between the Letrozole + Misoprostol group and the Misoprostol alone group ( $P = 0.9$ ).

Furthermore, Lee et al.<sup>4</sup> and Milani et al.<sup>20</sup> identified related findings. Presently, the heightened likelihood of experiencing side effects when taking 2 drugs may be employed to explain the much higher incidence of nausea and vomiting in the combined group.<sup>21</sup>

Our research supported previous investigations' findings, which revealed that same adverse effects of letrozole and misoprostol administered vaginally.<sup>20,22</sup>

Behroozi-Lak et al.<sup>23</sup> revealed that, The treatment regimen utilised in their trial was well accepted, with no serious side effects or unusual side effects, and its effectiveness was similar to that of the control group.

The disparities in results may warrant the conduct of additional randomised trials to assess the efficacy of the letrozole and misoprostol combination.

Nevertheless, Abbasalizadeh et al.<sup>11</sup> discovered that Letrozole Plus Misoprostol adverse reactions were significantly less common when contrasted to Misoprostol monotherapy ( $P$ -value = 0.013).

The findings demonstrate that there was a very significant variation in outcomes between group A and group B. As opposed to group B, which had 53.3 % Full abortions, 2.7 % dropouts, 24.0 % emergency D and C, and 20.0 % incompletely abortions, group A had 81.3 % complete abortions, 4.0 % dropouts, 10.7 % emergency D and C, and 4.0 % incompletely abortions.

This is in consistent with Afifi et al.<sup>17</sup> who indicated that compared with the group using only misoprostol, the combined group had a considerably higher success rate for complete abortions (81.0 % vs. 54.0 %,  $P < 0.01$ ). Moreover, the group receiving only misoprostol experienced considerably more emergency D and C cases and incomplete abortions ( $P < 0.01$ ).

These outcomes are consistent with those of Torky et al.,<sup>18</sup> who discovered that Misoprostol only performed at a degree of 39.0 % of overall miscarriages,

while Letrozole + Misoprostol performed at a rate of 78.0 %. ( $P < 0.01$ ). In addition, the rate of partial miscarriages was higher in the group receiving only misoprostol than in the group receiving both (61.0 % vs. 22.0 %,  $P < 0.01$ ).

Parallel to this, misoprostol with or without Letrozole was tested by Javanmanesh et al.<sup>14</sup> for the management of miscarriage. They found that the combination of Letrozole and Misoprostol resulted in a significantly better outcomes than Misoprostol monotherapy.

Similar findings were made by Abbasalizadeh et al.<sup>11</sup> who discovered that effective abortion rates were 93.75 % in the sample that included both letrozole and misoprostol as opposed to 68.75 % in the cohort that included only misoprostol ( $P = 0.001$ ). Also, they found that fewer cases in the combination group failed to end in an entire abortion than in the misoprostol group.

Furthermore, a different study by Behroozi-Lak et al.<sup>23</sup> showed that the combination of Letrozole and Misoprostol resulted in a completed abortion rate of 76.7 % especially in comparison with 42.6 % when Misoprostol was used alone, raising the overall abortion rate and decreasing the time between induction and abortion in women with a gestational age of 4 months.

Furthermore, misoprostol alone failed to produce a better success rate of completed abortions than Letrozole for 3 days accompanied by Misoprostol (86.9 % vs. 72.6 %) by Lee et al.

Researchers observed that 92.4 % of complete abortions occurred when the second dosage of 800 mg misoprostol was administered vaginally, while 56.3 % occurred after the first dosage (1600 mg).<sup>24</sup> There have been reports of 82.9 % of complete abortions occurring within 24 h of misoprostol (800 mcg) vaginal treatment.<sup>25</sup> Others who use misoprostol alone have experienced a full abortion rate of 68 %–81 %.<sup>26</sup>

Many results have been reported from studies that looked at the use of letrozole in combination with vaginal misoprostol. In one study, letrozole (10 mg for three days) and a single dose of vaginal misoprostol were administered to 86.9 % of pregnancies up to week 7 of gestation, and the results showed that these treatments resulted in complete abortion rates in these pregnancies (800 mg).<sup>27</sup> Others claimed that a full abortion incidence of roughly 95 % was seen following a 7-day treatment of letrozole with vaginal misoprostol.<sup>16</sup> It has additionally been observed that the regimens of vaginal misoprostol (800 mg), pre-treatment with mifepristone (200 mg), and three days of letrozoles (10 mg/daily) results in a 98 % effective abortion rates.<sup>8</sup>



These variances could be attributed to changes in gestational age among the study subjects, letrozole exposure time, and administering dosage. Yet, similar to earlier research, letrozole plus misoprostol was more efficient than misoprostol separately.

Our study showed that, there were highly statistically significant increase among group A than group B regarding induction to abortion interval (hrs). The average induction to abortion interval (hrs) in group A were;  $60.35 \pm 9.02$ , while average Induction to abortion interval (hrs) in group B were  $100.18 \pm 11.09$ .

Lee et al.<sup>28</sup> found that Letrozole has the ability to alter development of therapeutic protein mRNA, oestrogen receptor $\alpha$ , and in the placenta's oestrogen receptor-protein of individuals taking it in an attempt to understand the process by which Letrozole induces abortion.

Furthermore, Lee et al.<sup>29</sup> Researchers looked at how Letrozole affected uterine artery Doppler indices prior to surgically terminating first-trimester pregnant women. They found that pulsatility and resistance indices decreased dramatically in the Letrozole group, which suggests that blood circulation variations could play a role in the drug's action of Letrozole.

Also, Lee et al.<sup>4</sup> reported that Estradiol concentrations were considerably lower following letrozole administration throughout the first stage of pregnancy induction, suggesting that letrozole acts by inhibiting both oestrogen and progesterone receptors.

Additional possibility is that letrozole has been shown to inhibit endothelial growth factor, which may have a role in the triggering of miscarriages.<sup>30</sup>

Behroozi-Lak et al.<sup>23</sup> revealed that, The case group's induction-to-abortion period was considerably shorter than that of the normal control. In another study, the letrozole group's median sleep time was estimated to be 9.7 h, whereas the control group's was 10.9 h.<sup>20</sup> Another study found that the letrozole group had a lower median induction-to-abortion rate than the control group. In other instances, the median time following delivery of the letrozole and misoprostol combinations was 5.1 h, 7.5 h, 8.2 h, and 8.7 h.<sup>8,16</sup>

#### 4.1. Conclusion

A course of letrozole (7.5 mg/day) 3 days duration followed by 400 mg of misoprostol vaginally resulted in significantly higher full abortion rates in instances of first-trimester miscarriages than misoprostol alone (81.3 % vs. 53.3 %). Prescribers found that putting letrozole first helped misoprostol

work more effectively to induce abortion without raising adverse effects. To determine the optimum treatment strategy to achieve the maximum success rate and the lowest number of adverse effects, larger studies using a variety of dosing and prolonged periods may be required.

#### Ethical approval

Ethical approval ID 00000501 with expiration date 19-2-2028.

#### Consent for publication

Not applicable.

#### Availability of data and materials

Data and materials were available.

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#### Authorship

The conception and design of the study was done by Prof. Dr. E M A, acquisition of data, or analysis were done by Dr. A M E S and interpretation of data was done by O A A A, drafting the article or revising it critically for important intellectual content or final approval of the version to be submitted were done by all authors.

#### Conflicts of interest

Authors claim to have no conflicts of interest.

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