

Letrozole vs. Placebo Pretreatment in the Medical Management of First Trimester Missed Miscarriage: a Randomized Controlled Trial

Vorbehandlung mit Letrozol vs. Placebo in der medizinischen Behandlung von Fehlgeburten im 1. Trimenon: eine randomisierte, kontrollierte Studie



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Key words

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Schlüsselwörter

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ABSTRACT

Introduction Misoprostol is used for the medical management of miscarriage as it is more effective in the early stages of pregnancy. Letrozole has an anti-estrogen effect and is used for the pretreatment of miscarriage with misoprostol.

Aim The aim of this study was compare the efficacy and safety of letrozole with placebo pretreatment in the medical management of first trimester missed miscarriage.

Design This was a prospective randomized case-control study.

Patients and Methods Four hundred and thirty-eight women were randomly divided into two groups of 219; the placebo group received placebo tablets twice daily for 3 days, followed by 800 micrograms of misoprostol vaginally on the fourth day of enrolment, while the letrozole group received letrozole 10 mg twice daily for three days followed by 800 micrograms misoprostol administered vaginally. Symptoms and side effects were recorded, and the women advised to return to hospital if they experienced severe pain or bleeding or intolerable side effects and to report to hospital for a check-up one week after misoprostol administration. Ultrasound was done seven days after misoprostol administration to monitor outcomes. Surgical evacuation was carried out if medical management failed.

Results There were significant differences between the two groups, with better outcomes found for the letrozole group in terms of rates of complete miscarriage, onset of vaginal bleeding, and interval between induction and onset of expulsion ($p < 0.001$). A higher rate of nausea and vomiting was reported for the letrozole group ($p = 0.002$). Differences between groups with regard to pre- and post-termination hemoglobin levels, fever, severe pain and severe bleeding needing evacuation were not statistically significant.

Conclusion Adding letrozole to misoprostol improves the success rate and decreases the interval between induction and expulsion in cases of first trimester miscarriage; however, nausea and vomiting is higher with letrozole.

ZUSAMMENFASSUNG

Einleitung Misoprostol wird für die medizinische Behandlung von Fehlgeburten eingesetzt, da es sich in der Frühschwangerschaft als effektiver erwiesen hat. Letrozol hat eine anti-östrogene Wirkung und wird für die Vorbehandlung von Fehlgeburten mit Misoprostol eingesetzt.

Ziel Ziel dieser Studie war es, die Effektivität und Sicherheit einer Vorbehandlung mit Letrozol mit Placebo zu vergleichen, bei der medizinischen Behandlung einer Fehlgeburt im 1. Trimenon.

Studiendesign Es handelte sich um eine prospektive randomisierte Fallkontrollstudie.

Patientinnen und Methoden 438 Frauen wurden in 2 Gruppen mit je 219 Teilnehmerinnen randomisiert; die Placebo-Gruppe erhielten Placebotabletten 2-mal täglich über 3 Tage, gefolgt von 800 Mikrogramm Misoprostol, die am 4. Tag nach Aufnahme in der Studie vaginal verabreicht wurden; die Letrozol-Gruppe erhielt 10 mg Letrozol 2-mal täglich über 3 Tage, gefolgt von 800 Mikrogramm Misoprostol vaginal verabreicht. Symptome und Nebenwirkungen wurden aufgezeichnet. Den Frauen wurde geraten, sich im Krankenhaus zu melden, falls sie starke Schmerzen oder Blutungen bzw. unerträgliche Nebenwirkungen verspüren sollten, und sich 1 Wo-

che nach der Verabreichung von Misoprostol beim Krankenhaus für eine Nachuntersuchung einzustellen. Sieben Tage nach der Verabreichung von Misoprostol wurde eine Ultraschalluntersuchung durchgeführt, um das Ergebnis zu kontrollieren. Falls die medizinische Behandlung der Fehlgeburt fehlschlug, wurde ein chirurgischer Abbruch durchgeführt.

Ergebnisse Es gab signifikante Unterschiede zwischen den beiden Gruppen: die Ergebnisse der Letrozol-Gruppe waren besser hinsichtlich der Rate vollständiger Fehlgeburten, des Beginns der vaginalen Blutung und des Zeitabstands zwischen Induktion und Beginn der Austreibung ($p < 0,001$). Übelkeit und Erbrechen traten häufiger in der Letrozol-Gruppe auf ($p = 0,002$). Es gab keinen statistisch signifikanten Unterschied zwischen den beiden Gruppen hinsichtlich der Hämoglobin-Werte vor und nach dem Abbruch bzw. des Auftretens von Fieber, starken Schmerzen oder starken Blutungen, die eine chirurgische Intervention erforderlich machten.

Schlussfolgerung Die Gabe von Letrozol vor einer Behandlung mit Misoprostol erhöht die Erfolgsrate und verringert den Zeitabstand zwischen medizinischer Induktion und Austreibung bei Fehlgeburten im 1. Trimenon; Übelkeit und Erbrechen kommen häufiger nach Letrozol-Gabe vor.

Introduction

Misoprostol is a prostaglandin that causes myometrial contractions, cervical softening and dilatation. It is used to induce abortion and labor and to treat atonic postpartum hemorrhage and peptic ulcers [1]. It has the advantage of being cost-effective and stable with a low rate of side effects, which has led to it being included in the World Health Organization list of essential medications [2]. Misoprostol is licensed for use to induce miscarriage in Egypt. It has not been licensed to induce labor or miscarriage in certain countries such as Germany, but it is used off-label to induce labor in the UK [3] and in Germany.

Misoprostol by itself is used for the medical management of miscarriage as an alternative to surgery, with a success rate of between 65 and 93%. It is more effective in the early stages of pregnancy, where it also has the advantage of being cheaper, less invasive and avoiding surgical complications. Misoprostol is also used in combination with other medications such as mifepristone and methotrexate to increase the success rate [4].

Mifepristone used in combination with misoprostol achieved higher rates of completed abortions of up to 95% [5] and is recommended for pretreatment in abortion and medical miscarriage, but a cheaper and widely available alternative is needed, especially in developing countries.

Cesarean section (CS) rates are increasing worldwide, and many patients with a scarred uterus will need management of miscarriage. Uterine rupture is one of the complications which can occur in women with uterine scarring and this risk increases with the use of prostaglandins such as misoprostol but is very rare in first trimester miscarriage. There are different protocols for different doses of misoprostol used in women with previous CS. This

includes reducing the dose of misoprostol to 100 µg, administering doses less frequently or changing the administration route of misoprostol from vaginal to oral. However, there is no evidence-based protocol on adjusting the dose for women with previous CS [6]. The use of misoprostol to induce labor is contraindicated in many international guidelines because the risk of uterine rupture was found to increase by up to 18% in one study, even when a very low dose of 25 µg was administered [7].

Letrozole is an oral aromatase inhibitor which has been approved by the FDA [8]. Its anti-estrogen effect has been shown to be useful in the pretreatment of pregnancy terminations when combined with misoprostol. It can therefore replace mifepristone, which is expensive and not available in many countries [9].

The use of letrozole in combination with misoprostol to obtain higher rates of completed abortion was evaluated by Lee et al. [10]. In their study letrozole was administered for 3 days followed by misoprostol and achieved a success rate of 86.9%. In a pilot study by Yeung et al., a letrozole protocol was used for 7 days and achieved a 95% success rate [11]. In another pilot study [12] by Chai and Ho, mifepristone and letrozole were administered prior to misoprostol and achieved a 98% rate of complete abortion. But larger trials are needed to establish the clinical efficacy of pretreatment with letrozole to achieve complete miscarriage.

This randomized case control study aimed to compare the safety and efficacy of misoprostol alone or in combination with letrozole in the medical management of first trimester missed miscarriage.

Materials and Methods

This prospective randomized study was carried out in Al-Azhar University Hospitals, Al-Galaa Teaching Hospital, October 6th University Hospital and Airforce Specialized Hospital.

Ethical approval

The Ethical Committee of Al-Azhar University approved this study on June 9th, 2015. All women recruited to the study gave their informed consent prior to enrolment in the study. Women with previous CS were counseled about the risk of uterine rupture associated with misoprostol.

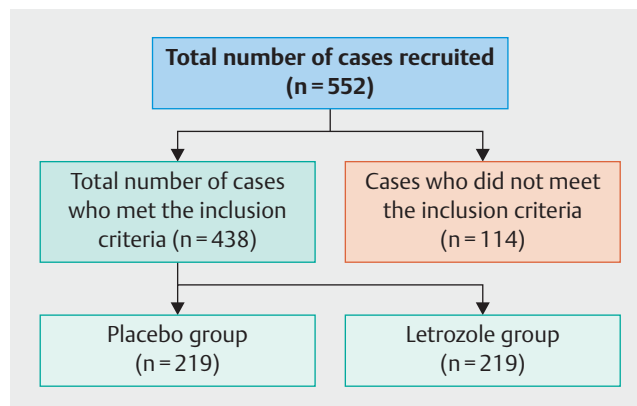
All women (n = 552) (► **Fig. 1**) who were diagnosed with unexplained first trimester miscarriage between July 2015 and June 2016 were approached for enrolment into the study. Missed miscarriage was diagnosed by the ultrasound finding of no fetal cardiac activity in the fetal pole. Women with a closed cervix and no products of conception in the cervical canal were included in the study. Exclusion criteria included a previous attempt to terminate the pregnancy, abnormal uterine lesions such as fibroids or congenital malformations, pregnancy despite an intrauterine contraceptive device (a known cause of miscarriage), medical disorders such as cardiac or hemorrhagic disease, and known hypersensitivity to any of the medications used. A total of 114 women were excluded from the study.

A detailed medical history was taken of all women included in the study (n = 438) and included the date of the first day of the last menstrual period to calculate gestational age. All women underwent physical examination including local examination to assess the cervix. Investigations performed included blood group analysis, Rh typing, screening for thrombophilia, karyotyping of both partners and ultrasound to confirm the diagnosis.

Women were divided into 2 groups with 219 in each group. The first group (placebo group) received a placebo of inert material twice daily for 3 days, followed by 800 micrograms of misoprostol administered vaginally on the 4th day of enrolment. The second group (letrozole group) received letrozole 10 mg twice daily for 3 days followed by 800 micrograms of misoprostol administered vaginally on the 4th day of enrolment. The misoprostol dose was not changed for women with prior CS as there is no recognized protocol to adjust the dose for women with previous CS, and also so as not to affect the study results.

All women were told to record the date of the first vaginal bleeding; the date of first passage of tissue pieces; lower abdominal pain of any degree, with pain assessed using a pain visual analog score; vaginal bleeding of any degree; any side effects such as nausea, vomiting, fever and shivering; any return to hospital for severe pain, bleeding or intolerable side effects; and to return to hospital on the 7th day after administration of misoprostol. An ultrasound scan was done on the 7th day after misoprostol administration to monitor the outcome. Surgical evacuation was performed if there was missed or incomplete miscarriage.

Primary outcome measures were the rate of complete miscarriages achieved and the induction-to-abortion interval in each group. Secondary outcome measures were the start of vaginal bleeding and any side effects (nausea, vomiting, fever, severe pain and severe bleeding) in both groups.



► **Fig. 1** Consort flow-chart of the cases.

Randomization and blinding

Patients allocated into the study were randomized into either of two groups using a computer-generated list at a 1:1 ratio. Concealment was achieved using opaque envelopes, to blind the physicians, while to blind the patients, the placebo tablet was methylcellulose resembling letrozole in shape.

Sample size calculation

The sample size was calculated with 219 subjects in each arm of the study, using the formula for comparison of proportion with $\alpha = 0.01$, $\beta = 0.05$, and power = 95%. The aim was to increase the percentage of complete miscarriages achieved with letrozole pretreatment before misoprostol in women with first trimester missed miscarriage.

Statistical analysis

Data were analyzed using the Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Independent t-test of significance was used to compare 2 means. Chi-square (χ^2) test was used to compare proportions of 2 qualitative parameters. Probability (p-value): $p > 0.05$ was considered insignificant, $p \leq 0.05$ was considered significant, and $p < 0.001$ was considered highly significant.

Results

This study compared two treatment modalities for the medical management of missed miscarriage. The first group was given placebo and misoprostol, while the second group received pretreatment with letrozole followed by misoprostol. There were no significant differences in age and gestational age between the two groups (► **Table 1**).

Comparison of gravidity

The distribution of gravidity in the placebo group was 46 primigravida, 61 gravida 2, 22 gravida 3, 4 gravida 4, and 86 gravida 5. Distribution in the letrozole group was 54 primigravida, 55

► **Table 1** Comparison of demographic data.

Demographic data	Group 1 (placebo)	Group 2 (letrozole)	p-value
Age			0.863
Mean ± SD	26.62 ± 4.30	26.52 ± 3.87	
Range	19–40	19–35	
Body mass index			0.0163
Mean ± SD	25.81 ± 2.7	25.12 ± 3.3	
Range	16.53–33.33	19.37–37.46	
Gestational age			0.065
Mean ± SD	48.83 ± 8.00	50.19 ± 7.478	
Range	35–62	35–63	
Gravidity			0.742
Gravida 1	46	54	
Gravida 2	61	55	
Gravida 3	22	22	
Gravida 4	4	7	
Gravida 5	86	81	
Parity			0.891
Para 0	59	66	
Para 1	57	52	
Para 2	20	19	
Para 3	3	4	
Para 4	80	78	
Previous cesarean section (CS)			0.117
No previous CS	92	116	
1 previous CS	92	77	
2 previous CS	21	19	
3 previous CS	11	4	
4 previous CS	3	3	

gravida 2, 22 gravida 3, 7 gravida 4, and 81 gravida 5. There was no significant difference between groups ($p = 0.742$).

Comparison of previous cesarean sections

The distribution of women with previous cesarean section (CS) in the placebo group was 92 women with no previous CS; 92 with 1 previous CS; 21 with 2 previous CS; 11 with 3 previous CS; and 3 with 4 previous CS. In the letrozole group 116 women had no previous CS; 77 had 1 previous CS; 19 had 2 previous CS; 4 had 3 previous CS; and 3 had 4 previous CS. There was no significant difference between groups ($p = 0.117$). There was no reported case of uterine rupture.

Comparison of hemoglobin levels before and after termination

Mean hemoglobin before treatment in the placebo group was 10.90 g/dl (range: 9–12 g/dl). Mean hemoglobin in the letrozole group was 10.86 g/dl (range: 9–12 g/dl). There was no significant difference between groups ($p = 0.676$). Mean hemoglobin after treatment was 10.41 g/dl in the placebo group (range: 8.5–

11.5 g/dl) and 10.49 g/dl (range: 8.8–11.9 g/dl) in the letrozole group, with no significant difference between groups ($p = 0.495$).

Significant clinical data

► **Table 2** shows that more women had complete miscarriage in the letrozole group than in the placebo group. The difference was highly significant ($p < 0.001$).

Women in the letrozole group had a shorter time to induction and complete miscarriage after misoprostol than women in the placebo group; the difference was highly significant ($p < 0.001$) (► **Table 3**).

Vaginal bleeding started earlier in the letrozole group compared to the placebo group, and the difference was highly significant ($p < 0.001$) (► **Table 3**). Women in the letrozole group also started to pass products of conception earlier than women in the placebo group, and the difference was highly significant ($p < 0.001$) (► **Table 3**).

► **Table 2** Comparison of failure rates between groups.

Failure rate	Group 1 (placebo)		Group 2 (letrozole)		Chi-square test
	n	%	n	%	p-value
No (complete miscarriage)	85	39	171	78	<0.001
Yes (incomplete miscarriage)	134	61	48	22	

► **Table 3** Comparison of onset and duration of vaginal bleeding and onset of passing products of conception (clinical data).

Clinical findings	Group 1 (placebo)	Group 2 (letrozole)	p-value
Time to 1st vaginal bleeding after administration of misoprostol, days			<0.001
Mean ± SD	2.30 ± 0.64	1.33 ± 0.29	
Range	1–4	1–3	
Time to induction of abortion after administration of misoprostol, days	3.09 ± 0.99	1.42 ± 0.50	<0.001
Mean ± SD	2–7	1–2	
Range			
Time to 1st product of conception passed after administration of misoprostol, days	3.50 ± 1.55	2.09 ± 0.70	<0.001
Mean ± SD	2–9	1–7	
Range			

► **Table 4** Comparison of side effects of medication.

Side effects	Group 1 (placebo)		Group 2 (letrozole)		Chi-square test
	No	%	No	%	p-value
Nausea and vomiting	7	3	37	17	0.002
Fever	16	7	9	4	0.152
Severe pain	15	7	24	11	0.132
Severe bleeding needing evacuation	48	22	36	16	0.141

Comparison of side effects

More women experienced nausea and vomiting in the letrozole group than in the placebo group, and the result was significant ($p = 0.002$) (► **Table 4**). There were no significant differences between groups with regard to the incidence of fever, severe pain, and severe bleeding needing surgical management (► **Table 4**).

Discussion

The present study showed a higher rate of complete miscarriages in the group which received additional letrozole (78%) compared to the control group (39%). The interval between induction and abortion was shorter in the letrozole group (1.42 days) compared to the placebo group (3.09 days) (► **Tables 2 and 3**). These results are similar to the success rates of other studies, with a success rate of 78% for the letrozole group in our study and a rate of 76.7%

reported for the letrozole group in the study by Naghshineh and colleagues [13].

The current study has the advantage of being a randomized study with a power of 95%. The main limitation in our study is the lack of long-term follow-up, and the need to test different misoprostol doses, especially in women who have had previous cesarean section.

In their study, Lee and co-workers [10] reported a significant difference in favor of the letrozole/misoprostol group; the rate of complete abortions in their study was higher than that found in our study, and amounted to 86.9% of pregnancies up to 7 weeks of gestation and 93.3% of pregnancies up to 9 weeks of gestation; however, their study included fewer numbers of women and they only administered letrozole 10 mg once daily, whereas in our study letrozole 10 mg was administered twice daily. Another pilot study [11] used a 7-day course of letrozole followed by vaginal

misoprostol and reported an even higher rate of complete abortions (95%), which could be explained by the longer period of administration of letrozole. A possible explanation for the difference in results could be the different treatment regimens and the differences in gestational age. In our study, letrozole 10 mg was administered twice a day and not once a day as in the study by Yeung et al. [11].

Our study showed a faster interval to onset of vaginal bleeding and a shorter duration in the letrozole group; the interval between administration of medication and onset of expulsion of the products of conception was also shorter in the letrozole group, which is similar to the results reported in other studies [10, 13].

In a study which attempted to determine the mechanism by which letrozole acts in medical abortions, Lee and co-workers [14] examined the effect of letrozole on the expression of steroid receptors in the placentas of 2nd trimester women undergoing medical termination of pregnancy. They concluded that the expression of progesterone receptor transcripts, estrogen receptor-alpha and estrogen receptor-alpha protein were all suppressed by letrozole in the placentas of women receiving letrozole; however, their study only examined second trimester terminations and not terminations in the first trimester of pregnancy. Yung et al. [15] evaluated the effect of letrozole-induced estradiol suppression on the reduction of progesterone receptor expression and apoptosis in the first trimester using immune-histochemical staining of progesterone receptors in a double-blinded randomized placebo-control trial and found no differences in the expression of progesterone receptors and apoptotic markers in decidual tissue after pretreatment with letrozole for 7 days before first trimester abortion. In a randomized controlled trial, Lee and co-workers [16] measured the effect of letrozole on uterine artery Doppler indices prior to surgical termination of first trimester pregnancy and found significant decreases in both pulsatility and resistance index in the letrozole group, which suggests that blood flow changes might play a role in the mechanism of action of letrozole.

The study of Lee et al. [10] showed that estradiol levels were significantly lower after the administration of letrozole in first trimester inductions of abortion. Estrogens are known to induce the expression of estrogen receptors (ER) and progesterone receptors (PR). This suggests that letrozole may act by suppressing ER and PR. The role of estradiol in supporting pregnancy had not yet been as clearly elucidated as the role of progesterone. A study by Albrecht and co-workers [17] on pregnant baboons showed that estradiol depletion using aromatase inhibitors induced abortion. This suggests a role for estrogen in placental development and function. Other studies such as those of Dunk et al. [18], Schiessl et al. [19], and Albrecht et al. [20], suggested that the endothelial growth factor family and the angio-protein family play a role in the remodeling of spiral arteries. Letrozole was found to suppress endothelial growth factor in those studies.

Both regimens were tolerated by most women, with a few women reporting side effects such as low-grade fever and severe pain in addition to nausea and vomiting; this finding agreed with the results of other previous studies [21–24]. All the studies found that side effects were associated with the administration of misoprostol, with more side effects associated with the sublin-

gual route. They reported comparable rates of side effects for nausea, vomiting and fever for vaginally administered misoprostol [21–24]. There were no significant differences in side effects between groups, with the exception of rates of nausea and vomiting which were significantly higher in the letrozole group. This could be explained by the higher risk of developing side effects when using two medications (letrozole and misoprostol). The current study had a higher rate of nausea and vomiting than the rate reported by Lee et al. [10] because letrozole was given twice daily compared to once daily. The proportion of women with severe bleeding who needed surgical evacuation was lower in the letrozole group, but the difference was not statistically significant; none of the women had a marked drop in hemoglobin level or required blood transfusion.

Conclusion

The addition of letrozole to misoprostol improved the success rate and decreased the interval between induction and expulsion in women with first trimester miscarriage. However, the number of women complaining of nausea and vomiting increased. Further larger studies are needed to determine the optimum treatment protocol to achieve the highest success rate and the lowest rate of side effects.

Trial registration number: PACTR201701001973403 Pan African Clinical Trials Registry www.pactr.org

Conflict of Interest

The authors report that they neither have a conflict of interest nor have they received financial support for this work.

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Correction

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“Material and Methods”

Under the heading “Randomization and blinding” the sentence should read in full: Concealment was achieved using opaque envelopes, to blind the physicians, while to blind the patients, the placebo tablet was methylcellulose resembling letrozole in shape.

“Results”

In the 1st paragraph, the last sentence correctly reads: There were no significant differences in age and gestational age between the two groups (► **Table 1**).

Under the heading “Comparison of gravidity”, the p-value has been corrected in the last sentence of the 1st paragraph. Correct is: $p = 0.742$.

Under the heading “Comparison of previous cesarean sections”, the p-value has been corrected in the penultimate sentence. Correct is: $p = 0.117$.

► **Table 1** has been corrected. Correct is:

► **Table 1** Comparison of demographic data.

Demographic data	Group 1 (placebo)	Group 2 (letrozole)	p-value
Age			0.863
Mean ± SD	26.62 ± 4.30	26.52 ± 3.87	
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Mean ± SD	25.81 ± 2.7	25.12 ± 3.3	
Range	16.53–33.33	19.37–37.46	
Gestational age			0.065
Mean ± SD	48.83 ± 8.00	50.19 ± 7.478	
Range	35–62	35–63	
Gravidity			0.742
Gravida 1	46	54	
Gravida 2	61	55	
Gravida 3	22	22	
Gravida 4	4	7	
Gravida 5	86	81	
Parity			0.891
Para 0	59	66	
Para 1	57	52	
Para 2	20	19	
Para 3	3	4	
Para 4	80	78	
Previous cesarean section (CS)			0.117
No previous CS	92	116	
1 previous CS	92	77	
2 previous CS	21	19	
3 previous CS	11	4	
4 previous CS	3	3	

► **Table 2** has been corrected. Correct is:

► **Table 2** Comparison of failure rates between groups.

Failure rate	Group 1 (placebo)		Group 2 (letrozole)		Chi-square test
	n	%	n	%	p-value
No (complete miscarriage)	85	39	171	78	<0.001
Yes (incomplete miscarriage)	134	61	48	22	

► **Table 3** has been corrected. Correct is:

► **Table 3** Comparison of onset and duration of vaginal bleeding and onset of passing products of conception (clinical data).

Clinical findings	Group 1 (placebo)	Group 2 (letrozole)	p-value
Time to 1st vaginal bleeding after administration of misoprostol, days			<0.001
Mean ± SD	2.30 ± 0.64	1.33 ± 0.29	
Range	1–4	1–3	
Time to induction of abortion after administration of misoprostol, days	3.09 ± 0.99	1.42 ± 0.50	<0.001
Mean ± SD	2–7	1–2	
Range			
Time to 1st product of conception passed after administration of misoprostol, days	3.50 ± 1.55	2.09 ± 0.70	<0.001
Mean ± SD	2–9	1–7	
Range			

► **Table 4** has been corrected. Correct is:

► **Table 4** Comparison of side effects of medication.

Side effects	Group 1 (placebo)		Group 2 (letrozole)		Chi-square test
	No	%	No	%	p-value
Nausea and vomiting	7	3	37	17	0.002
Fever	16	7	9	4	0.152
Severe pain	15	7	24	11	0.132
Severe bleeding needing evacuation	48	22	36	16	0.141