Misoprostol With or Without Letrozole Pretreatment for Termination of Pregnancy

A Randomized Controlled Trial

Vivian Chi Yan Lee, FHKAM(OG), Ernest Hung Yu Ng, MD, FRCOG, William Shu Biu Yeung, PhD, and Pak Chung Ho, MD, FRCOG

OBJECTIVE: To compare the success rate and side effects of letrozole and misoprostol versus misoprostol alone for medical termination of early pregnancy.

METHODS: Patients requesting termination of pregnancy up to 63 days of gestation were randomized into two groups. The letrozole group received letrozole 10 mg daily for 3 days followed by 800 micrograms of vaginal misoprostol, while the placebo group received placebo for 3 days followed by the same dosage of misoprostol. The complete abortion rate and the side effects profiles of the two groups were compared. The primary outcome measure was the complete abortion rate.

RESULTS: A total of 168 women were recruited. The complete abortion rate of the letrozole group was significantly higher than that of the placebo group (86.9% compared with 72.6%, relative risk [RR] 1.20, 95% confidence interval [CI] 1.03–1.40). The complete abortion rate in gestations up to 49 days was significantly higher in the letrozole group than in the placebo group (93.3% compared with 78.7%, RR 1.19, 95% CI 1.002–1.40), while the corresponding rates for gestation between 50 and 63 days were not significantly different between the two groups. There were significantly fewer women complaining of vomiting in the letrozole group than those in the placebo group (8.3% compared with 19.0%, *P*=.043, RR 2.29, 95% CI 1.005–5.27).

CONCLUSION: The use of letrozole and misoprostol is associated with a higher complete abortion rate.

CLINICAL TRIAL REGISTRATION: HKClinicalTrials.com, http://www.hkclinicaltrials.com, HKCTR-349.

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LEVEL OF EVIDENCE: I

The sequential regimen of mifepristone followed 36 hours later by misoprostol is now the standard regimen for medical abortion in the first trimester. The complete abortion rate was quoted up to 95%.[1,2] However, the widespread use of the sequential regimen is limited because mifepristone is expensive and unavailable in many countries. There is a need to find a cheaper and easily available alternative.

Our pilot study using a regimen of letrozole 7.5 mg for 2 days followed by vaginal misoprostol 800 micrograms resulted in a complete abortion rate of 80% in gestations up to 63 days.[3] Complete abortion rate was lower than that of the sequential regimen of mifepristone and misoprostol but was higher than that of the misoprostol alone in our previous study.[4] We postulated that with the use of a higher dosage of letrozole, 10 mg daily, which has a greater suppression of estrogen synthesis, the complete abortion rate would be higher especially in later gestation when the estradiol (E2) concentration is higher.

This randomized double-blinded controlled trial is to compare the complete abortion rate and the side effect profiles of letrozole combined with misoprostol with those using misoprostol alone in first trimester medical termination of pregnancy at gestation up to 63 days.

METHODS

Women attending the Department of Obstetrics and Gynecology, the University of Hong Kong for legal termination of pregnancy at gestational age up to 63

From the Department of Obstetrics and Gynecology, the University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China.

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Corresponding author: Vivian Chi Yan Lee or Pak Chung Ho, Department of Obstetrics and Gynecology, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong; e-mail: v200lee@hku.hk.

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days were recruited. The inclusion criteria were: good general health; older than the age of legal consent (ie, older than 18 years); the duration of pregnancy not more than 63 days as confirmed by ultrasound scanning on day 1 of the study (ie, day of letrozole administration); and hemoglobin higher than 10 g/L. The exclusion criteria included 1) history or evidence of adrenal pathology, steroid-dependent cancer, porphyria, diastolic pressure over 95 mm Hg, bronchial asthma, arterial hypotension; 2) history or evidence of thromboembolism, severe or recurrent liver disease or pruritus of pregnancy; 3) regular use of prescription drugs before admission to the study; 4) presence of an intrauterine device; and 5) any abnormal values in pretreatment blood tests, namely complete blood picture, renal and liver function tests (which include serum urea, creatinine, electrolytes, albumin, globulin, and liver enzymes). Women were excluded from a secondary analysis if any of the following was present: an acute illness requiring immediate treatment of any nature during the treatment period; use of drugs other than those prescribed by the investigators for the treatment of possible therapy-related side-effects; any violation of the study protocol; essential data missing from the participants' records making it impossible to judge treatment outcome.

Individuals who fulfilled the selection criteria and were willing to participate gave their informed written consent. The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster. The study was registered on HKClinicalTrials.com with the trial number HKCTR-349.

The participants were randomized into the two groups by the hospital pharmacists according to computer-generated random numbers. The packages of letrozole (10 mg daily for 3 days) and packages of similar number of placebo tablets, which had the same appearance and taste, were prepared by the hospital pharmacy according to the randomization schedule. Until the completion of the study, both patients and the clinicians were blinded to the group assigned.

Ultrasound examination was performed on eligible women to confirm intrauterine pregnancy and the gestational age. After a detailed history and a full body examination, complete blood count, renal, and liver function were checked.

Women in the letrozole group were given 10 mg letrozole orally on days 1–3, whereas women in the placebo group were given placebo tablets on days 1–3. A designated research nurse supervised the participants to take the first dose of letrozole or placebo on day 1 and the participants took the second dose themselves on day 2. The third dose of letrozole or placebo together with 800 micrograms of vaginal misoprostol together was given on the morning of day 3 when the women were admitted into the hospital. Blood for serum E2 and progesterone concentrations was collected on day 1 and day 3.

Women stayed in the hospital for 4 hours after the administration of misoprostol. Side effects, the amount of bleeding, and the time of expulsion of tissue mass were recorded. Women were allowed to go home after the 4-hour observation period if bleeding was not heavy and abdominal pain was not severe. Upon discharge from hospital, participants were given diary cards to record days and amount of vaginal bleeding and side effects.

The first follow-up visit was on day 15 during which a pelvic ultrasound examination was performed and blood was taken for hemoglobin level. In participants with ongoing pregnancies on the day 15 follow-up visit, vacuum aspiration was performed. In those with incomplete or missed abortion, vacuum aspiration was also done if there was heavy bleeding or on patient's request. Otherwise, no further action was taken. In these women the final judgment on the outcome of therapy was made at the follow-up on days 43. If no emergency or elective curettage was necessary during the period up to the first menstruation, the outcome of treatment was classified as "complete abortion." The remaining cases in whom curettage was done were classified as "incomplete abortion" or "missed abortion" according to the ultrasound findings. Women were classified as having missed abortion when the pelvic ultrasound examination just before curettage showed the demised fetus staying inside the gestation sac inside the uterine cavity, while incomplete abortion was diagnosed when the ultrasound before curettage showed the absence of a gestational sac but only some products of conception left. The tissues removed by curettage were sent for histologic examination.

The primary outcome measure was the complete abortion rate. Secondary outcome measures included the duration of vaginal bleeding and the incidences of side effects, including nausea, vomiting, diarrhea, fatigue, dizziness, headache, lower abdominal pain, fever, rash and chills or shivering. The induction-to-abortion interval was defined as the interval between misoprostol administration and the passage of product of conception.

The difference in complete abortion rates was used to calculate the sample size. Our pilot study using a similar regimen of letrozole and misoprostol showed that the complete abortion rate was 87.5% in those with pregnancies up to 49 days. The complete abortion rate after a single dose of 800 micrograms of vaginal misoprostol alone was 68% in the previous study conducted

in our department.[4] Therefore, a sample size of 80 in each arm will have a power of 0.8 at 5% significance level to detect such a difference (Sigmastat). Allowing for 5% dropouts, a total of 168 participants were required.

The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Results of continuous variables were given as mean plus or minus standard deviation (SD) if normally distributed, and as median (range) if not normally distributed. Statistical comparison was carried out by Student *t* test, Mann-Whitney *U*-test, Wilcoxon signed ranks test for continuous variables, and χ^2 test or Fisher exact test for categorical variables, where appropriate. Statistical analysis was performed using the SPSS 17.0. The two-tailed value of $P<.05$ was considered statistically significant.

RESULTS

During the study period between September 1, 2008, and September 30, 2009, 193 women requesting legal termination of pregnancies were approached and 26 patients were excluded or declined to participate in the study. Thus, 168 participants were recruited. Individuals were randomized into the letrozole and placebo groups with 84 participants in each group (Fig. 1).

The demographic data are shown in Table 1. There were no significant differences in age, parity, history of miscarriages, height, weight, and gestational age between the letrozole group and the placebo group.

The complete abortion rate in the letrozole group was significantly higher than that in the placebo group (86.9% compared with 72.6%, RR 1.20, 95% confidence interval [CI] 1.03–1.40), as shown in Table 2. The difference in complete abortion rates was 14.3% (95% CI 2.3%–26.2%). The rate of incomplete abortion requiring surgical treatment was significantly lower in the letrozole group when compared with the placebo group. There were 10 participants (11.9%) in the letrozole group who required surgical treatment: seven for ongoing pregnancies and three for incomplete abortions; 23 individuals (27.4%) in the placebo group needed surgical treatment: nine for ongoing pregnancies, three for missed abortions, 10 for incomplete abortions, and one at the request of the patient, whom we categorized into the group with undetermined outcome. Both the missed abortion rate and ongoing pregnancy rate were lower in the letrozole group but the difference was not statistically significant. One patient in the letrozole group was classified as having an undetermined outcome because she was lost to follow-up and we failed to reach her by whatever means.

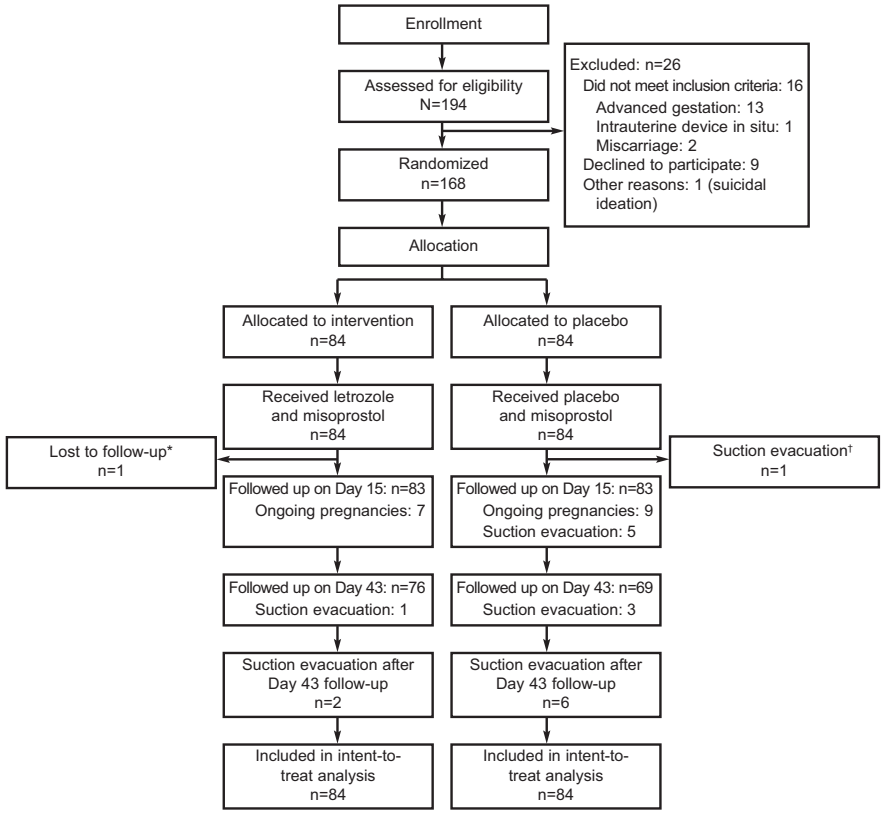

Fig. 1. CONSORT 2010 flow diagram. *Patient lost to follow-up was included in intent-to-treat analyses. †One patient received suction evacuation before the scheduled follow-up; this patient was also included in the intent-to-treat analyses.

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Table 1. Comparison of Demographic Data

	Placebo (n=84)	Letrozole (n=84)	*P*
Age (y)	30.6±6.9	30.4±7.2	.915
Primigravida	21 (25)	24 (28.6)	.601
History of miscarriage	11 (13.1)	13 (15.5)	.659
Height (cm)	158.5±5.0	159.2±4.9	.472
Weight (kg)	53.8±7.7	55.85±9.0	.119
Gestational age (d)	49.4±6.2	49.6±6.5	.903

Data are mean±standard deviation or n (%) unless otherwise specified.

Subgroup analysis showed that the complete abortion rate in participants with gestations up to 49 days was significantly higher in the letrozole group than that in the placebo group (RR 1.19, 95% CI 1.002–1.40). The incomplete abortion rate was comparable for the two groups. For gestations between 50 and 63 days, the complete abortion rate was not significantly different between the two groups, while the incomplete abortion rate was significantly lower in the letrozole group than the placebo group.

Both the induction-to-abortion interval (8.2 hours, range 3.3–711.6 hours in letrozole group, compared with 8.7 hours, range 3.9–937.3 hours in placebo group) and the duration of bleeding (15 days, range 6–63 days in the letrozole group, compared with 19 days, range 8–67 days in the placebo group) were comparable for the letrozole and placebo groups (Fig. 2A, B).

The most common side effects in both groups after ingestion of placebo or letrozole were lower abdominal pain and nausea, which were comparable in both groups. There were significantly fewer patients in the letrozole group reporting vomiting after the ingestion of medication than in the placebo group (8.3% compared with 19%, *P*=.043, RR 2.29, 95% CI 1.005–5.27). All other side effects were not significantly different between the two groups. There were also no significant differences in the side effects reported after the administration of vaginal misoprostol (Table 3). There was no difference in the use of analgesic (dologesic) among two groups (10.7% in the letrozole group compared with 15.5% in the placebo group, *P*=.362).

The results of the analysis of the serum levels of E2 and progesterone are shown in Table 4. There was a significant reduction in the serum E2 level after the administration of letrozole (*P*<.001) while there was no significant change after administration of placebo. The percentage of the suppression in serum E2 level (E2 concentration after administration of letrozole divided by the basal E2 level) was comparable in women with different gestational ages, 4.8% in gestation up to 49 days, and 4.4% in gestation of 50 to 63 days. There was no difference in the median serum progesterone level and in the change in serum progesterone level between the two groups.

Overall, the gestational age of women having ongoing pregnancies was significantly higher than those having complete abortion (53.2 days±6.3 days compared with 49.0 days±6.4 days respectively, *P*=.013). The result seemed to be confined to the letrozole group (55.4 days±7.1 days compared with 48.9 days±6.3 days, respectively, *P*=.019). The gestational age was not

Table 2. Comparison of the Pregnancy Outcomes

	Placebo	Letrozole	*P*
Gestation 63 d or less	n=84	n=84	
Complete abortion	61 (72.6), 61.8–81.8	73 (86.9), 77.8–93.3	.021
Incomplete abortion	10 (11.9), 5.9–20.8	3 (3.6), 0.7–10.1	.043
Missed abortion	3 (3.6), 0.7–10.1	0	.081
Ongoing pregnancy	9 (10.7), 5.0–19.4	7 (8.3), 3.4–16.4	.599
Undetermined	1 (1.2), 0.03–6.5	1 (1.2), 0.03–6.5	1.000
Gestation 49 d or less	n=47	n=45	
Complete abortion	37 (78.7), 64.3–89.3	42 (93.3), 81.7–98.6	.044
Incomplete abortion	4 (8.5), 2.4–20.4	2 (4.4), 0.5–15.1	.430
Missed abortion	2 (4.3), 0.5–14.5	0	.162
Ongoing pregnancy	3 (6.4), 1.3–17.5	1 (2.2), 0.06–11.8	.328
Undetermined	1 (1.2), 0.05–11.3	0	.325
Gestation 50–63 d	n=37	n=39	
Complete abortion	24 (64.9), 47.5–79.8	31 (79.5), 63.5–90.7	.154
Incomplete abortion	6 (16.2), 6.2–32.0	1 (2.6), 0.07–13.5	.040
Missed abortion	1 (2.7), 0.07–14.2	0	.301
Ongoing pregnancy	6 (16.2), 6.2–32.0	6 (15.4), 5.9–30.5	.921
Undetermined	0	1 (2.6), 0.07–13.5	.327

Data are n (%), 95% confidence interval unless otherwise specified.

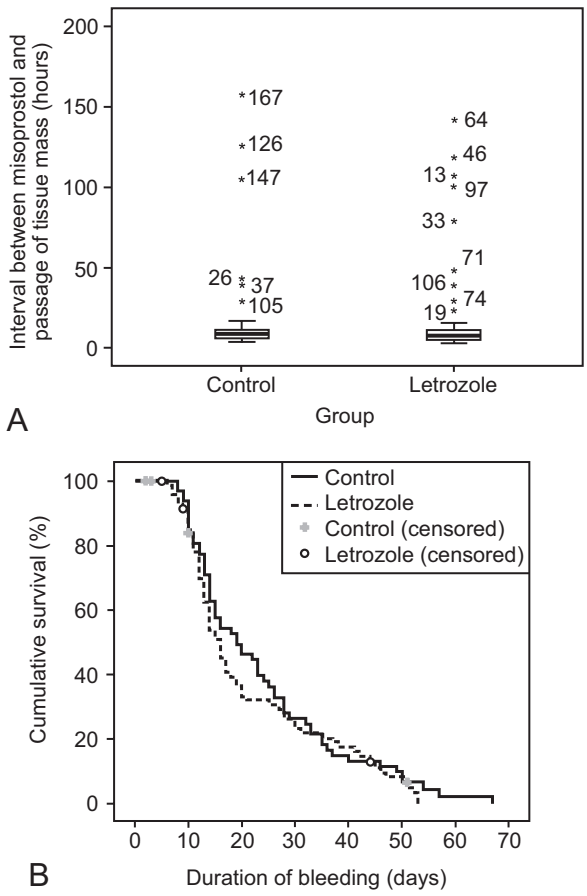

Fig. 2. A. Box plot graph representing the induction-to-abortion interval. The whiskers show the 95% confidence intervals, asterisks represent outliers. Numbers are patient numbers. **B.** Survival curve representing the duration of vaginal bleeding after abortion. **P* is not significant.

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significantly different between those with ongoing pregnancies and complete miscarriage in the placebo group. In the letrozole group, the baseline serum E2 level on day 1 in women with ongoing pregnancies was significantly higher than those with complete abortion (Fig. 3), but the percentage of suppression of serum E2 was comparable in both groups, 4.8% and 4.6%, respectively. Therefore, although the median reduction in serum E2 level was greater in those with ongoing pregnancies, the median E2 level on day 3 in these women was still significantly higher than that in women with complete abortion.

DISCUSSION

Over the past decade, medical termination of pregnancy in the first trimester gained popularity with the highly effective regimen combining mifepristone and misoprostol. The complete abortion rate was up to 95.7% in gestations up to 63 days.[5] The complete abortion rate of the misoprostol-alone regimen was reported to be less than 90% by most studies,[6] except one using misoprostol tablets soaked with normal saline with the abortion rate up to 94.2% in gestations up to 49 days.[5] However, the use of the sequential regimen is limited by the availability of mifepristone, available in just 44 countries (http://www.gynuity.org). We aimed at finding a new synergistic agent to be used with misoprostol to achieve a higher abortion rate than misoprostol alone.

Letrozole is a selective and reversible aromatase inhibitor used to treat estrogen-dependent breast cancer.[7] Letrozole suppresses estrogen biosynthesis from peripheral androgen aromatization. Its successful use in ovulation induction and superovulation were reported.[8–17] At clinical doses, letrozole has no effect on basal levels of cortisol and aldosterone.[18–20]

Both estrogen and progesterone are important hormones for maintenance of pregnancy. Albrecht et al demonstrated the critical physiologic role of estrogen in the maintenance of primate pregnancy.[21] Shi et al demonstrated an abortion rate up to 100% when combining mifepristone with aromatase inhibitors in pregnant mice, rats or guinea pigs.[22]

Our pilot study[3] included 20 women using 2 days of 7.5 mg letrozole combined with vaginal misoprostol 800 micrograms and the complete abortion rate was 80% in pregnancies up to 63 days. We increased the dosage of letrozole to 10 mg for 3 days as we anticipated a higher dose may result in higher abortion rate. The results of this randomized controlled trial proved that our postulation was correct with a higher complete abortion rate resulted. It is worthwhile to mention that only one ongoing pregnancy was noted in a woman in the letrozole group with gestations up to 49 days, suggesting the possibility of the regimen for termination of pregnancy in early gestation.

Our results confirmed the importance of estrogen in the maintenance of pregnancy in humans. We postulate that there are two possible mechanisms of action for letrozole in termination of pregnancy. Letrozole may act directly on the corpus luteum in the early pregnancy, or placenta in later gestation. The suppressed E2 synthesis could be detrimental to their functions, which may cause abortion or exert a synergistic effect on the induction of abortion with misoprostol.

The percentage of E2 suppression is consistent across the gestational age studied. The serum E2 level was higher in women with ongoing pregnancies than those with complete abortions, which may be solely due to the more advanced gestational age with higher serum E2 levels. Letrozole was capable of suppressing the

Table 3. Comparison of Side Effects Profile

Side Effects	Placebo (n=84)	Letrozole (n=84)	*P*
After letrozole but before administration of misoprostol			
Nausea	45 (53.6)	35 (41.7)	.122
Vomiting	16 (19.0)	7 (8.3)	.043
Diarrhea	3 (3.6)	9 (10.7)	.072
Fatigue	27 (32.1)	28 (33.3)	.869
Dizziness	22 (26.2)	19 (22.6)	.590
Headache	8 (9.5)	11 (13.1)	.465
Lower abdominal pain	75 (89.3)	79 (94.0)	.601
During hospital stay for administration of misoprostol			
Nausea	14 (16.7)	12 (14.3)	.670
Vomiting	3 (3.6)	1 (1.2)	.311
Diarrhea	7 (8.3)	5 (6.0)	.549
Fatigue	2 (2.4)	5 (6.0)	.247
Dizziness	6 (7.1)	11 (13.1)	.201
Headache	4 (4.8)	10 (11.9)	.094
Lower abdominal pain	68 (81.0)	65 (77.4)	.569
Fever (38°C or higher)	—	3 (3.6)	.081
Rash	1 (1.2)	—	.316
Chills, shivering	5 (6.0)	11 (13.1)	.115

Data are n (%) unless otherwise specified.

estrogen biosynthesis very effectively up to 63 days. For more advanced gestations the percentage of suppression may not be satisfactory because of the higher basal E2 level, which requires properly designed trials to show the effect in later gestation. As the suppression of serum E2 level was substantial, further increase in the dosage of letrozole may not improve the complete abortion rate.

The safety profile of letrozole was reassuring. There was no serious adverse event. Significantly fewer women experienced vomiting after the administration of letrozole, which could be related to the suppressed level of human chorionic gonadotropins or estrogens.[23] Another concern is the possible teratogenicity of letrozole. All women should be counseled carefully before

Table 4. Comparison of Serum Estradiol and Progesterone Concentrations

	Placebo (n=84)	Letrozole (n=84)	*P*
Gestation 63 d or less			
Day 1 E2 level*	4,009 (302–16,200)	3,770 (811–18,102)	.775
Day 3 E2 level*	4,218 (471–15,394)	184 (73–1,061)	<.001
Drop in E2 level*	−159 (−4,222–−3,572)	3,570 (727–17,041)	<.001
Day 1 P4 level†	68.0 (24.7–170.9)	72.0 (1–180.9)	.726
Day 3 P4 level†	65.0 (29.1–147)	70.0 (1–145.9)	.391
Drop in P4 level†	5.6 (−29.9–−49.8)	1.9 (−36.7–−55.9)	.367
Gestation 49 d or less			
Day 1 E2 level*	2,821 (302–11,782)	3,131 (811–7,626)	.465
Day 3 E2 level*	2,923 (471–11,843)	151 (73–474)	<.001
Drop in E2 level*	−149 (−2,180–−3,572)	2,908 (727–7,205)	<.001
Day 1 P4 level†	66.0 (37.5–170.9)	72.0 (1–180.9)	.788
Day 3 P4 level†	62.0 (31–147)	68.0 (1–145.9)	.651
Drop in P4 level†	6.8 (−29.9–−49.8)	1.9 (−35.5–−55.9)	.371
Gestation 50–63 d			
Day 1 E2 level*	4,603 (1,517–16,200)	4,993 (1,810–18,102)	.946
Day 3 E2 level*	4,942 (1,857–15,394)	219 (73–1,061)	<.001
Drop in E2 level*	−274 (−4,222–−1,650)	4,627 (1,732–17,041)	<.001
Day 1 P4 level†	71.0 (24.7–128.7)	71.0 (42.2–173.9)	.905
Day 3 P4 level†	66.0 (29.1–145.7)	73.0 (37.6–145.9)	.519
Drop in P4 level†	2.9 (−29.1–−31.1)	1.8 (−36.7–−47.2)	.716

Data are median (range) unless otherwise specified.
* Estradiol level expressed in pmol/L.
† Progesterone level expressed in nmol/L.

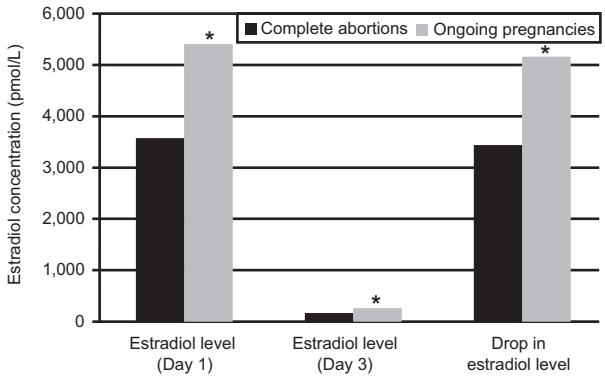

Fig. 3. The E2 concentration (pmol/L) of women with complete abortions and ongoing pregnancies. *P is significantly different when comparing the two groups.

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using this regimen for medical abortion as there were no data on the effect on human fetuses.

This study demonstrated that 10 mg letrozole for 3 days followed by 800 micrograms of vaginal misoprostol is more effective than misoprostol alone for first-trimester abortion. The current cost of the mifepristone with misoprostol is USD $54 while that of letrozole regimen is cheaper (USD $44). It is registered in more than 100 countries (www.femarainfo.com/country-sites.jsp). Therefore, in countries where mifepristone is not available, the combination of letrozole and misoprostol can be offered as a more effective alternative to using misoprostol alone. Further studies are needed to refine the regimen to improve its efficacy.

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