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A pilot study on the combined use of letrozole, mifepristone and misoprostol in termination of first trimester pregnancy up to 9 weeks' gestation

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ABSTRACT

Objective: To assess the feasibility of adding letrozole to the standard regimen of mifepristone and misoprostol for termination of pregnancy up to 63 days.
Study design: We recruited 50 subjects who had requested legal termination of pregnancy up to 63 days. Medical abortion was performed with a singe dose of 200 mg mifepristone and 10 mg of letrozole daily for 3 days followed by 800 mcg vaginal misoprostol.
Results: The complete abortion rate was 98% (95% CI: 94–100%). The median induction-to-abortion interval of the regimen was 5.1 h (range 1.2–56 h). No serious adverse effects were reported.
Conclusions: The results of this pilot study suggest that a regimen of mifepristone, letrozole and misoprostol is associated with a high complete abortion rate without major adverse events.

1. Introduction

After mifepristone was approved by the United States Food and Drug Administration in 2000, the combination of mifepristone and vaginal use of misoprostol became almost a standard of care in early medical abortion up to 63 days of gestation [1,2]. Misoprostol, a synthetic analogue of naturally occurring prostaglandin E_1, has a uterotonic effect and it can stimulate myometrial contraction and cause cervical ripening and dilatation. Progesterone maintains the uterus in a quiescent state by inducing hyperpolarization of the membrane of the myometrial cells, and a greater change in electric potential is necessary before contractions can occur [3]. Mifepristone is an anti-progestin that binds to the progesterone receptors and prevents endogenous progesterone from exerting its effects [4]. It can also increase the sensitivity of the uterus to prostaglandins. The complete abortion rate achieved with this sequential regimen has been found to be up to 93–95% [5,6], which is higher than the rate achieved with either mifepristone or misoprostol alone.

Oestrogen is another important hormone for the maintenance of pregnancy. Albrecht et al. showed that 50% of baboons miscarried when maternal oestrogen synthesis was suppressed using aromatase inhibitors whereas all maintained their pregnancy when concomitant estradiol was given [7]. Letrozole is a third-generation aromatase inhibitor which suppresses the production of oestrogen; at clinical doses there is no effect on basal levels of cortisol and aldosterone [8]. Shi et al. found that a combination of anti-progestin with aromatase inhibitor acted synergistically to induce a 100% abortion rate in rats, while there was little effect when the antiprogestin or aromatase inhibitor was administered alone [9]. Recently, the effect of pretreatment with letrozole prior to misoprostol was studied for early medical abortion. The efficacy was 80% and 86.9% when 7.5 mg letrozole was given for 2 days before treatment with 800 mcg vaginal misoprostol and 10 mg for 3 days before treatment with 800 mcg misoprostol respectively [10,11]. When 10 mg letrozole was given for 7 days followed by 800 mcg vaginal misoprostol, the complete abortion rate increased to 95% [12].

Letrozole probably facilitates medical termination by suppressing the synthesis of oestradiol, which is an important factor in the maintenance of early pregnancy. Although the combination of mifepristone and misoprostol is highly effective, complete abortion rates are lower with pregnancies more than 7 weeks. It is postulated that by combining both letrozole and mifepristone, together with misoprostol, a synergistic effect will be exerted as the depleted oestrogen and progesterone level will be insufficient to support the pregnancy, and the uterotonic effect of misoprostol will hasten the abortion process, hence improving the complete abortion rate. As the combination of these three drugs has not been used before, it is uncertain whether this regimen will lead to

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untoward side effects or complications. Therefore, we conducted a pilot study to assess the profile of side effects and the complete abortion rate of vaginal misoprostol when given with mifepristone and letrozole for termination of first trimester pregnancy up to 9 weeks' gestation.

2. Materials and methods

We conducted this pilot study at Queen Mary Hospital, Hong Kong. Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Written consent was obtained from all participants before participation in the study.

A total of 50 pregnant women aged 18 years or older with gestation up to 63 days requesting legal termination of pregnancy were recruited. The medical history was obtained, and a clinical examination including gynaecological and breast examination was performed by the gynaecologist. The research nurse recruited suitable women at the outpatient clinic after assessment by the medical staff. Exclusion criteria included (i) any contraindications or allergies to letrozole, mifepristone or misoprostol; (ii) an intrauterine contraceptive device in utero; (iii) breastfeeding; (iv) abnormal baseline liver/renal function tests or (v) multiple pregnancy. Following recruitment at the outpatient clinic, blood was taken for haemoglobin and liver/renal function tests. An ultrasound examination was performed to confirm the duration of pregnancy.

After admission into the study, all women were given 200 mg of mifepristone (Hua Lian Parmaceutical Co., Shanghai, China) and 10 mg of letrozole orally in the presence of medical or nursing staff. This was designated as day 1 of the study. Women were instructed to return on day 2 for a second dose of 10 mg of letrozole. On day 3 the patient was admitted into the hospital in accordance with our local laws. After admission the patient was given the third dose of 10 mg of letrozole, and 800 mcg of misoprostol (Cytotec; Pfizer, New York, USA) was given vaginally. Women stayed in the hospital for 4 h. Temperature, blood pressure and pulse rate were recorded hourly by a nurse. Women were interviewed by a nurse at the end of 4 h regarding the side effects experienced. Vaginal examination was done at the end of 4 h. If a woman did not have heavy bleeding or severe pain, she was allowed to go home with a diary card to record the days of vaginal bleeding.

The women came back on day 7 for clinical assessment, ultrasound examination of the pelvis and blood sampling for haemoglobin level. The intention was to determine whether the abortion was complete and to review the bleeding pattern. If the pelvic ultrasound examination showed the presence of an ongoing pregnancy, vacuum aspiration would be arranged without a further attempt with misoprostol. If the pelvic ultrasound examination showed that there was incomplete abortion or missed abortion, the woman would be observed unless there was heavy bleeding. The women were followed up again on day 43 for duration of bleeding and return of menses. If no vacuum aspiration was necessary during the period up to the first menstruation, the outcome was classified as complete abortion.

The primary outcome measures were the proportion of complete abortion and the induction-to-abortion interval. Secondary outcome measures included the incidence of side effects and the duration of bleeding.

3. Results

Fifty-four women were invited to this pilot study. Four were not eligible due to two cases of silent miscarriage, and two cases of abnormal liver function tests.

Table 1
Baseline demographics of the study population.

	Study group ($n = 50$)
Age (years)	34.1 (6.8)
Weight (kg)	57.1 (10.0)
Height (cm)	159.4 (4.6)
Gestational age by ultrasound (days)	51.1 (6.0)
Previous pregnancy	42 (84)
Previous abortion (s)	13 (26)
Parity	38 (76)

Data are expressed as *n* (%) or mean (SD).

Table 2
Abortion outcomes of the study population.

	Study group ($n = 46$)[a]
Median induction-to-abortion interval in hours (range)	5.1 (1.2–56)
Success rate in 4 h (%)	9 (19.6)
Success rate in 8 h (%)	39 (84.8)
Success rate in 12 h (%)	44 (95.7)
Success rate in 16 h (%)	44 (95.7)
Success rate in 20 h (%)	44 (95.7)
Success rate in 24 h (%)	44 (95.7)
Success rate in >48 h (%)	46 (100)
Mean haemoglobin level, g/dl (SD)	
Before	12.3 (1.0)
After	12.5 (0.9)
Median duration of bleeding in days (range)	14 (7–33)

[a] 4 women were unsure of the timing.

The baseline demographics of the study group are presented in Table 1. The characteristics of the abortion process are shown in Table 2. Forty-nine women (98%) had complete abortion (95% confidence interval: 94–100%). One woman had incomplete abortion requiring emergency vacuum aspiration due to heavy bleeding. She was a 42-year-old nulliparous woman with a history of one spontaneous miscarriage. Dating ultrasound confirmed a gestational age of 59 days on day 1 of the study. Bleeding started at 4 h after the administration of misoprostol and a piece of tissue was expelled an hour later. Ongoing bleeding was noted 2 h after expulsion of the tissue mass with total blood loss of 400 ml. On examination the cervical os was open with continuous bleeding from the uterine cavity. Emergency suction evacuation was arranged for incomplete abortion, and haemostasis was achieved at the end of operation. Histology of the tissue mass and uterine evacuates both confirmed products of gestation.

The median induction-to-abortion interval (defined as the interval between the administration of misoprostol and the abortion) was 5.1 h (1.2–56 h). Of the 46 women who noted the timing of passage of products of gestation, 44 (95.7%) aborted within 12 h of misoprostol administration.

The incidence of side effects after the administration of medications is shown in Table 3. The incidence of side effects after mifepristone and letrozole were comparable to those of baseline, while bleeding, diarrhoea, abdominal pain, and fever developed after misoprostol administration in most women.

4. Comments

Medical abortion became an alternative method of abortion with the availability of prostaglandin analogues in the early 1970s and the anti-progestin mifepristone in the 1980s. The most common early first-trimester medical abortion regimen consisted of mifepristone in combination with administration of misoprostol [1,2]. The complete abortion rate was up to 95% in gestations up to 63 days [5,6].