Feasibility and effectiveness of unintended pregnancy prevention with low-dose mifepristone combined with misoprostol before expected menstruation

Cui-Lan Li,*, Dun-Jin Chen, Yi-Fan Deng, Li-Ping Song, Xue-Tang Mo, and Kai-Jie Liu

1The Third Affiliated Hospital of Guangzhou Medical University & Key Laboratory for Major Obstetric Diseases of Guangdong Province & Key Laboratory of Reproduction and Genetics of Guangdong Higher Education Institutes, Guangzhou 510145, P. R. China

2Education and Developmental Psychology, The Hong Kong Institute of Education, Hong Kong SAR, P. R. China

*Correspondence address. The Third Affiliated Hospital of Guangzhou Medical University & Key Laboratory for Major Obstetric Diseases of Guangdong Province & Key Laboratory of Reproduction and Genetics of Guangdong Higher Education Institutes, 63 Duobao Road, Liwan District, Guangzhou 510145, China. Tel: +86-20-81266937; Fax: +86-20-81292949; E-mail: cuilanli@gzhmu.edu.cn

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STUDY QUESTION: What is the efficacy of maintaining or restoring non-pregnant status with low-dose mifepristone combined with misoprostol administered before expected menstruation?

SUMMARY ANSWER: Low-dose mifepristone and misoprostol administered at the time of expected menstruation was effective and safe in maintaining or restoring non-pregnant status, with no obvious menstrual disturbance.

WHAT IS KNOWN ALREADY: Menstrual regulation involves the medical or mechanical stimulation of uterine sloughing in women with up to 2–3 weeks of menstrual delay. Low-dose mifepristone plus misoprostol is efficacious for termination of ultra-early pregnancy (≤35 days of amenorrhoea) with no obvious menstrual disturbance.

STUDY DESIGN, SIZE, DURATION: A total of 678 women fulfilled all criteria and were recruited. Seventeen women dropped out after deciding to remain pregnant and 11 others were lost to follow-up. Thus, data from 650 women who completed the procedure were included in analyses. Participants were enrolled at any time during their menstrual cycle and administered medication 1 day before expected menstruation. The end of the study was defined on a per-patient basis as the date of completion of the post-treatment menstrual cycle. The primary outcome was the efficacy of abortion induction (for pregnant women) or menstrual regulation (for non-pregnant women).

PARTICIPANTS, SETTING, METHODS: Women with regular menstrual cycles (25–35 days) were voluntarily recruited for this study between February 2012 and December 2014. Serum β-hCG was measured before mifepristone intake. Mifepristone (50 mg) was administered orally 1 day before expected menstruation and 200 μg misoprostol was administered orally on the day of expected menstruation. Efficacy, disturbance in bleeding patterns in the treatment and post-treatment cycles, satisfaction with the treatment, and subsequent contraception preference were analysed.

MAIN RESULTS AND THE ROLE OF CHANCE: Retrospective analysis of serum β-hCG levels at admission indicated that 23.3% (158/678) of the women were pregnant. The success rate for pregnancy termination was 98.6% (136/138). Two women (1.5%, 2/138) had ongoing pregnancy that was subsequently terminated surgically. The overall bleeding induction rate within 7 days was 98.3% (639/650), with 100% (138/138) in pregnant participants and 97.9% (501/512) in non-pregnant participants. Most pregnant and non-pregnant participants experienced no significant menstrual disturbance during the treatment [96.3% (131/136) versus 97.6% (489/501)] or post-treatment [97.8% (133/136) versus 98.4% (493/501)] menstrual cycle. The general rate of satisfaction with the treatment was 96.7% (618/639). Generally, 36.0% (230/639) of participants preferred to use the regimen as a routine contraception method versus the 64.0% (409/639) who preferred to use it as a remedy for pregnancy prevention after unprotected sex (P < 0.001).
Introduction

Unintended pregnancy is a serious problem worldwide; more than half of all pregnancies are unintended, and half of these unintended pregnancies result in abortion, miscarriage or unplanned births without suitable prenatal care (Sedgh et al., 2014). Unintended pregnancy and its outcomes can result in serious physical, psychological, financial, and/or ethical stressors on women and families, especially in countries and regions where abortion is not legally available (Sedgh et al., 2014).

Emergency contraception (EC) has been characterized as a last resort approach to avoiding unintended pregnancy after unprotected sex (Trussell et al., 2014). Mifepristone, the most commonly prescribed anti-progesterone EC medication, has drawbacks including a narrow administration window, intermenstrual bleeding, delayed onset of subsequent menstruation, gastrointestinal side effects, and reduced efficacy with repeated sexual intercourse and re-use within the same menstrual cycle (Koyama et al., 2013; Li et al., 2014).

One recent study found that intrauterine devices (IUDs) were highly effective for EC at any time in the menstrual cycle (Turok et al., 2013). However, concerns about potential insertion difficulties, the need for local anaesthesia or prophylactic antibiotics, the requirement for administration by specialized medical staff in a medical setting, and the lack of need for long-term contraception among the majority of women limit the widespread acceptance and usage of IUDs (Wu et al., 2010; Turok et al., 2013).

Menstrual delay can be an intense stressor on women worried about unintended pregnancy. Menstrual regulation involves the medical or mechanical stimulation of uterine sloughing in women with up to 2–3 weeks of menstrual delay (Swahn et al., 1999; Bygdeman, 2003; Xiao et al., 2003). A positive pregnancy test result is not a prerequisite for menstrual regulation, and it can be conducted in countries or regions where medical abortion is legally restricted. Menstrual regulation and medical abortion may have different medical, psychological, and legal impacts on women.

Clinically, regimens for avoiding unintended pregnancy between the last effective EC and expected menstrual onset are urgently needed. A method for maintaining or achieving non-pregnant status during this period of time, regardless of current pregnancy status, is needed. Mifepristone is the only medication that can be used alone for EC (Ho, 2001; Narvekar et al., 2006), be used in combination with prostaglandin for menstrual regulation (Swahn et al., 1999; Bygdeman, 2003; Xiao et al., 2003), ultra-early pregnancy (≤35 days of amenorrhoea, Takahama et al., 1989) termination (Li et al., 2007, 2012, 2015), or termination in the first and second trimesters of pregnancy (Hausknecht, 2003; Borgatta et al., 2011), and be used in combination with methotrexate for the conservative treatment of ectopic pregnancy. Theoretically and practically, menstrual regulation achieved as close as possible to the time of expected menstrual onset is an appealing remedy for suspected pregnancy, with no menstrual disturbance.

One study attempted to explore the efficacy of menstrual regulation with monthly administration of a combination of 200 mg oral mifepristone 1 day before expected menstruation and 400 μg oral misoprostol 48 h later in volunteer participants for up to 6 months, but the study was terminated prematurely due to low efficacy of the treatment [4.0% (5/125 cycles) ongoing pregnancy and 12% (15/125 cycles) irregular bleeding] (Swahn et al., 1999). Curiously, the efficacy of ≤200 mg oral mifepristone combined with ≤400 μg misoprostol for early (≤56 days of amenorrhoeae) medical abortion (Creinin et al., 2001; WHO, 2001; Jerbi et al., 2005) and menstrual regulation (Xiao et al., 2003) has been confirmed convincingly. The low efficacy observed in the terminated study of Swahn et al. (1999) may represent a discrepancy in the outcome criteria. Interpretation of these results might be facilitated by dividing the failure rate into failure to induce abortion (ongoing pregnancy), the rate of which was acceptable, versus the rate of the adverse secondary effect of irregular bleeding, which was unacceptably high. The reason for irregular bleeding may be related to mifepristone being administered at a relatively high dosage 1 day before expected menstruation or repeated use of the regimen.

In this study, we explored the efficacy of a regimen consisting of low-dose mifepristone administered 1 day before the expected menstruation day combined with misoprostol administered on the day of expected menstruation for menstrual regulation. We further examined the impacts of this combined regimen on the treatment and post-treatment menstrual cycles.

Materials and Methods

Enrolment of participants

The study was approved by the local Ethics Committee of Guangzhou. Between February 2012 and December 2014, subjects were recruited...
from our hospital, three other teaching hospitals, and three teaching clinics affiliated with our medical university, all located in the same region. The recruited women had visited these facilities seeking emergency or medical contraception after unprotected sexual intercourse, post-abortion care, or scientific education materials about healthy contraception. Healthy women aged 15–45 years with regular menstrual cycles (duration of 25–35 days) and regular sexual activity, who agreed not to use any other contraception method during the study period, were recruited. Exclusion criteria were significant end-organ (cardiac, lung, liver, kidney or adrenal) disease, hormone treatment, haematological disease (haemolytic or thrombotic disease, coagulation disorder), allergy to mifepristone or misoprostol, IUD use, and history of abnormal pregnancy or labour (Caesarean section, incomplete/ongoing medical abortion, ectopic pregnancy, threatened/spontaneous abortion). Only volunteers who planned to terminate any resulting pregnancy during the study period and who consented to surgical termination in the event of treatment failure were recruited.

**Sample size calculation**

Based on the sample size calculation, a total sample of 216 subjects, at least 108 each in the pregnant and non-pregnant groups, would achieve 90% power to detect an effect size of 0.10 with chi-squared analysis of a fourfold table at a significance level (alpha) of 0.05. To compensate for subjects’ refusal to participate or failure to complete the study, a minimum of 158 participants per group were recruited. Data from a single treatment administration per participant were included in the final statistical analyses.

**Treatment procedure**

Volunteers were enrolled at any time during their menstrual cycle. General information, including age, length of menstrual cycle, marital status, histories of pregnancy and delivery, and history of contraceptive use, was recorded at the initial visit. Gynaecological examination was routinely performed at this visit. The recruitment procedures were explained to all enrolled participants, who provided written consent before enrolment.

All participants were asked to fill out an anonymous questionnaire consisting of two parts, Parts 1 and 2, which referred to the treatment cycle and post-treatment cycle, respectively. Information obtained in Part 1 included the recruitment date, patient age, history of pregnancy or labour, date of last menstrual cycle, date of misoprostol administration, bleeding start and termination dates, daily bleeding amount (compared with regular menstrual flow), urine hCG level on Day 10 after treatment, and items assessing the convenience of medication administration and obvious menstrual disturbances. Information obtained in Part 2 included the onset and completion dates of the first menstrual cycle after treatment, bleeding amount, future contraception preference, and items assessing obvious post-treatment menstrual disturbances, role of the regimen (as routine or EC), and general satisfaction with the treatment.

The study flow is illustrated in Fig. 1. Participants with regular cycles of 25–35 days were asked to visit our hospital or clinic 1 day before the expected date of menstruation. This date was either predicted exactly or estimated as the median of a maximum 2-day range of expected menstruation dates. Blood was collected for serum β-hCG detection and 50 mg mifepristone (Zizhu Pharmaceutical, Beijing, China) were orally administered under the supervision of Drs C.-L.L., D.-J.C. and L.-P.S. Participants were instructed to self-administer 200 μg oral misoprostol (Zizhu Pharmaceutical) 24 h later. They were instructed not to eat or drink within 2 h before or 2 h after taking the medications. One urine hCG test stick, a daily log card to record side effects (i.e., GI side effects, abdominal pain, vaginal bleeding, amount and duration, tissue expulsion), and an anonymous questionnaire were distributed to each participant.

The final follow-up was conducted by telephone and/or return visit to our hospital after completion of the post-treatment menstrual cycle. Daily logs were returned by mail, fax or e-mail. Medical students recorded treatment effectiveness and side effects, conducted follow-up, and collected daily logs and questionnaires. All results were computerized and statistically analysed by Y.-F.D.

**Serum β-hCG and urine hCG detection**

Serum β-hCG levels were measured in the clinical laboratory in our hospital using chemiluminescence microparticle immunoassays (Abbott Ireland Diagnostics Division, Longford, Ireland) according to the manufacturer’s instructions. Serum β-hCG values of 0–10 mIU/ml were considered not pregnant and those of > 10 mIU/ml were considered positive. Participants self-detected urine hCG levels on the 10th day after taking misoprostol using the One Step hCG Urine Pregnancy Test (Colloidal Gold, Blue Cross Bio-Medical Co. Ltd., Beijing, China). As indicated in the product instructions, self-detection was based on the appearance of a positive detection line that was distinct from the control line.

**Follow-up procedure**

Subjects experiencing any of the following conditions or any discomfort were advised to seek medical attention after taking the treatment, to exclude the possibility of ongoing pregnancy, ectopic pregnancy, or incomplete abortion: continued morning sickness (including nausea or vomiting), continued breast tenderness, urine hCG positivity on the 10th day after taking misoprostol, spotting for > 10 days, severe abdominal pain, or severe vaginal bleeding (more than menstrual flow for > 3 h). Hospital visits involved transvaginal ultrasonic examination (Voluson S8 Pro; GE Healthcare, USA) or serum β-hCG detection to screen pregnancy outcomes and guide further

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**Figure 1** Flow diagram of the study protocol for treatment with low-dose mifepristone combined with misoprostol before expected menstruation. EM = day of expected menstruation, D1: Day 1.
treatment. All participants were followed by telephone until completion of the post-treatment cycle.

**Study outcomes**

The primary outcome was the efficacy of abortion induction (for pregnant women) or menstrual regulation (for non-pregnant women). Complete medical abortion with no surgical requirement was defined as a successful outcome for pregnant women, and was assessed by the disappearance of morning sickness, cessation of bleeding, and negative urine hCG result. Serum β-hCG detection and/or vaginal ultrasound were conducted when incomplete abortion, ongoing pregnancy or ectopic pregnancy was suspected. Secondary outcomes were the impacts of the treatment on bleeding patterns in the treatment and post-treatment cycles, participants’ satisfaction with the treatment, and contraception preference.

**Statistical analysis**

All the statistics were calculated using the Statistical Package for the Social Sciences 19.0 (IBM, Chicago, IL, USA). Numerical data were expressed as mean ± SD, and categorical data were recorded as proportions. All data were normally distributed. The two-sample t-test was used to examine means for independent samples. The fourfold table chi-squared test was used for comparison of categorical variables, such as some proportional data. P-values <0.05 were considered statistically significant.

**Results**

A total of 762 volunteers were screened for the study; 678 of these women fulfilled all inclusion criteria and were enrolled in the study. Of them, 17 dropped out because they decided to remain pregnant after obtaining positive self-detected urine hCG test results. Eleven participants (three pregnant and eight non-pregnant women) were lost to follow-up. Thus, data from 650 participants who completed the entire procedure were included in the analyses (Fig. 1).

Participants’ baseline data, including age, menstrual duration, and obstetric and gynaecological histories, are stated in Table I. No significant difference in baseline characteristics between pregnant and non-pregnant women was observed.

The rate of pregnancy, based on retrospective analysis of β-hCG measurement at admission, was 23.3% (158/678). The efficacy of pregnancy termination was 98.6% (136/138). Ongoing pregnancy occurred in 1.5% (2/138) of participants, and these pregnancies were terminated by surgical means. No ectopic pregnancy or incomplete abortion occurred among study participants. All outcomes are stated in Table II.

The overall rate of bleeding induction within 7 days was 98.3% (639/650): 100% (138/138) in pregnant participants and 97.9% (501/512) in non-pregnant participants. Participants were excluded from the statistical analysis if they reported bleeding induction 7 or more days after misoprostol administration. According to the pharmacokinetics of mifepristone and misoprostol, the serum blood concentration of the medications would have been metabolically undetectable or have disappeared 7 days after oral administration (Heikinheimo, 1989; Kekkonen et al., 1996; Aronsson et al., 2007).

The majority of pregnant and non-pregnant participants experienced no significant menstrual disturbance (i.e. a cycle shorter than 3 days longer than 7 days), in the treatment [96.3% (131/136) versus 97.6% (489/501)]

**Table I Baseline characteristics of participants in a study of treatment with low-dose mifepristone combined with misoprostol before expected menstruation (N0 = 678).**

<table>
<thead>
<tr>
<th>Characteristic/Outcome</th>
<th>Pregnant (N = 158)</th>
<th>Non-pregnant (N = 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.2 ± 7.4 (14–45)</td>
<td>26.9 ± 7.1 (14–45)</td>
</tr>
<tr>
<td>Menstrual cycle (days)</td>
<td>27.7 ± 1.2 (25–30)</td>
<td>28.2 ± 1.1 (25–30)</td>
</tr>
<tr>
<td>Number of deliveries</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>1 (1–3)</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>23.3% (158/678)</td>
<td>76.7% (520/678)</td>
</tr>
</tbody>
</table>

SD or median (range).
No significant differences in baseline characteristics were observed between groups.

**Table II Outcomes for participants who completed the whole procedure (N2 = 650).**

<table>
<thead>
<tr>
<th>Characteristic/Outcome</th>
<th>Pregnant (N = 138)</th>
<th>Non-pregnant (N = 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-HCG (mIU/ml)</td>
<td>107.4 ± 29.8 (10.8–624.7)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete abortion</td>
<td>98.6% (136/138)</td>
<td>93.0% (476/512)</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>1.5% (2/138)</td>
<td>2.9% (15/512)</td>
</tr>
<tr>
<td>Bleeding induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 h after ms</td>
<td>98.6% (136/138)</td>
<td>93.0% (476/512)</td>
</tr>
<tr>
<td>&lt;72 h after ms</td>
<td>1.5% (2/138)</td>
<td>2.9% (15/512)</td>
</tr>
<tr>
<td>&lt;7 days after ms</td>
<td>0</td>
<td>2.0% (10/512)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>0</td>
<td>2.2% (11/512)</td>
</tr>
<tr>
<td>Menstrual disturbance in TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As expected</td>
<td>96.3% (131/136)</td>
<td>97.6% (489/501)</td>
</tr>
<tr>
<td>Shorter than 3 days</td>
<td>0</td>
<td>1.4% (7/501)</td>
</tr>
<tr>
<td>Longer than 7 days</td>
<td>3.6% (5/136)</td>
<td>0.1% (5/501)</td>
</tr>
<tr>
<td>Menstrual disturbance post-TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As expected</td>
<td>97.8% (133/136)</td>
<td>98.4% (493/501)</td>
</tr>
<tr>
<td>Shorter than 3 days</td>
<td>0.7% (1/136)</td>
<td>0.6% (3/501)</td>
</tr>
<tr>
<td>Longer than 7 days</td>
<td>1.5% (2/136)</td>
<td>1.0% (5/501)</td>
</tr>
<tr>
<td>Satisfaction regarding the regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory</td>
<td>96.4% (133/138)</td>
<td>97.6% (489/501)</td>
</tr>
<tr>
<td>No obvious menstruation disturbance</td>
<td>92.0% (127/138)</td>
<td>95.4% (478/501)</td>
</tr>
<tr>
<td>Convenient administration</td>
<td>81.2% (112/138)</td>
<td>80.6% (404/501)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concern for pregnancy</td>
<td>3.6% (5/138)</td>
<td>3.2% (16/501)</td>
</tr>
<tr>
<td>Contraception preference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine use</td>
<td>39.1% (54/138)</td>
<td>35.1% (176/501)</td>
</tr>
<tr>
<td>As remedy**</td>
<td>60.9% (84/138)</td>
<td>64.9% (325/501)</td>
</tr>
</tbody>
</table>

TC, treatment cycle; ms, misoprostol.
**P < 0.001 for As remedy versus Routine use.
serum concentration of about 400 ng/ml, increases the serum concentration of about 1100 ng/ml mifepristone (Heikinheimo, 1989). The plateau concentration does not rise in a dose-dependent manner for single doses exceeding 100 mg ($t_{1/2} = 1.2–1.4$ h, $t_{1/2} = 24.2–47.8$ h) (Heikinheimo, 1989; Kekkonen et al., 1996; Danielsson et al., 2003). Thus, a single oral dose of 50 mg of mifepristone combined with misoprostol is pharmacokinetically and clinically rational and sufficient for menstrual regulation, at least for very early stage menstrual delay.

We retrospectively analysed serum $\beta$-hCG levels to determine pregnancy status (Swahn et al., 1999; Xiao et al., 2003) and confirmed pregnancy in about one-quarter of patients. A single oral dose of 150 mg mifepristone combined with 400 µg misoprostol administered vaginally 48 h later regulates menstruation within $<7$ days of menstrual delay, including cases of very early medical abortion (Xiao et al., 2003). The failure rate in the present study was significantly lower than that reported for menstrual regulation by Xiao et al. (2003) [7.5% (37/492); $\chi^2 = 50.74$, $P < 0.001$]. However, the evaluation of bleeding induction differed considerably between studies, with assessment conducted up to 44 days (Xiao et al., 2003) and 7 days (present study) after misoprostol administration. Both studies showed high efficacy of the regimens for menstrual regulation, but Xiao et al. (2003) did not report on menstrual disturbance. We suspect that the difference in efficacy between the studies is due to the difference in amenorrhoea duration, as early administration appears to increase the efficacy. Overall, the findings in the present study indicate that this regimen can rationally be used for menstrual regulation, and for preventing or terminating unintended pregnancy after unprotected sexual intercourse and before menstrual onset.

Feasibility and rationale of low-dose mifepristone + misoprostol administration for menstruation regulation

The effects and side effects of mifepristone are attributable to the initiation of endometrial degradation, the clinical sign of which is uterine bleeding (Kekkonen et al., 1996; Creinin et al., 2001; Danielsson et al., 2003). Early use of mifepristone increases the effectiveness of the drug, and use of a low dosage reduces side effects without compromising efficacy (WHO, 2000; Li et al., 2012, 2015). A World Health Organization report (WHO, 2000) stated that 200- and 600-mg doses of mifepristone showed similar efficacy for early medical abortion, with less failure risk in the cases with less gestational weeks or cases where menstruation was delayed slightly. The standard mifepristone dose for medical abortion is 150–200 mg, although some studies have demonstrated a 100-mg dose to be an effective alternative (Creinin et al., 2001; Jerbi et al., 2005; Goel et al., 2010). A multicentre study showed that a further reduction of the mifepristone dose to 50 mg compromised efficacy, with termination of 84.7–89.8% of pregnancies of $<57$ days (WHO, 2001). Cases of failure were not further examined in that paper. Thus, it is uncertain whether the main cause of failure was related to longer pregnancy duration. Efficacy may be associated mainly with cases of shorter amenorrhoea. We previously demonstrated that 50 mg of mifepristone combined with 200 µg of misoprostol effectively terminated pregnancy within 35 days, with no obvious menstrual disturbance (Li et al., 2012, 2015). In the current study, the same regimen was administered to women with suspected pregnancy 1 day before or on the date of expected menstruation, with promising efficacy and minimal side effects.

Oral administration of $\leq 25$ mg mifepristone daily, with a steady-state serum concentration of about 400 ng/ml, increases the serum concentration of mifepristone linearly (Kekkonen et al., 1996). Oral administration of 50 mg mifepristone daily results in a saturation concentration of about 1100 ng/ml mifepristone (Heikinheimo, 1989). The present study indicates that this regimen can rationally be used for menstrual regulation, at least for very early stage menstrual delay.

Low-dose mifepristone + misoprostol causes no significant menstrual disturbance

In this and our previous studies (Li et al., 2007, 2012, 2015), no obvious menstrual disturbance was observed. Most participants experienced normal menstrual duration and normal menstrual flow during the treatment cycle and restoration of the post-treatment cycle within 1 week of treatment. In contrast, IUD or EC medication use at any point in the menstrual cycle has been reported to cause significant menstrual disturbance (Task Force on Postovulatory Methods of Fertility Regulation, 1998; Wu et al., 2010; Turok et al., 2013; Trussell et al., 2014). In the current study, the regimen was administered 1 day before expected menstruation to induce menses with high efficacy and only slight menstrual disturbance, possibly because endometrial degradation caused by mifepristone coincided with spontaneous menstrual onset. Although the difference in administration timing prevents direct statistical comparison of the abnormal bleeding rate, the method tested in this study achieved expected menstrual onset.

Data from other published studies present a less optimistic picture than ours. Swahn et al.’s (1999) study was terminated prematurely due to high rates of abnormal bleeding, which made accurate determination of the treatment day for the next cycle difficult. The regimen used in that study was similar to those used in more recent studies (Creinin et al., 2001; WHO, 2001; Jerbi et al., 2005), in which irregular bleeding was assumed to be acceptable for abortion induction. The mifepristone dose used in an abortion-inducing regimen, however, may be unnecessarily high for menstrual regulation, especially for short menstrual delay. A lower dose may be more suitable, having less risk of adverse secondary effects without sacrificing treatment efficacy. Two other
Menstrual regulation studies (Bygdeman, 2003; Xiao et al., 2003) did not include data on the duration of bleeding induction in relation to the mifepristone dosage used. Pharmacokinetically, higher mifepristone doses have longer cleavage times and more profound endometrial side effects, producing clinically relevant menstrual disturbances. Low-dose mifepristone is easily cleared from the endometrium and results in only a slight disturbance in menstrual bleeding. The minor menstrual disturbance observed in the treatment and post-treatment cycles in the present study may be due, at least in part, to the timing of administration and the low dose of mifepristone used.

Our previous large-scale study demonstrated that the efficacy of low-dose mifepristone for termination of ultra-early pregnancy (≤35 days of amenorrhoea) was similar to that observed with a higher dose and that with higher doses used in a combination treatment, but with a much lower likelihood of altered bleeding patterns in the treatment and post-treatment cycles (Li et al., 2012, 2015). Further studies are needed to explore whether repeated use of the regimen in consecutive cycles or the dose of mifepristone being too high was the main reason for the high abnormal bleeding rate reported by Swahn et al. (1999).

Concern about ectopic pregnancy in menstruation regulation

When a woman presents to the hospital for medical abortion, intrauterine pregnancy is typically confirmed by vaginal ultrasonic scan, assuming that the patient is in the amenorrheic period when such confirmation is possible. However, ectopic pregnancy remains a common concern and an obstacle for the exploration of menstrual regulation when pregnancy is not a precondition, as well as for exploration of medical abortion strategies for ultra-early pregnancy, when ectopic pregnancy is too early to be excluded by any strategy. Nevertheless, the overall reported incidence of ectopic pregnancy in the UK [1.15% (11.5/1000 pregnancies)] (Tay et al., 2000), the USA [1.97% (19.7/1000 pregnancies)] (Saraiya et al., 1999), and France [1.6% (16/1000 pregnancies)] (Coste et al., 2000) is quite low. However, even when intrauterine pregnancy is diagnosed before medical abortion, there remains a nonzero incidence of ectopic pregnancy among medical abortion patients, ranging from 0.006% (5/80 000) to 0.02% (10/44 789) (Hausknecht, 2003; Shannon et al., 2004). Thus, intravaginal ultrasonic scanning for ectopic pregnancy before medical abortion is an efficacious, but imperfect, strategy.

The best strategy for dealing with a possible unintended pregnancy is to induce menstrual onset on its original assumed date or to terminate the possible pregnancy as soon as possible. Mifepristone, alone or combined with prostaglandin, is increasingly being used for EC, menstrual regulation and medical abortion purposes. Mifepristone, in conjunction with methotrexate, was used to explore its effectiveness in ectopic pregnancy conservative treatment with conflicting findings, that it is promising (Gazvani et al., 1998; Perdu et al., 1998), or of no benefit (Rozenberg et al., 2003). At least, we have seen no indications suggesting that the use of mifepristone to terminate pregnancy is harmful to a patient who has an existing ectopic pregnancy, or that use of the drug increases the incidence or risk from ectopic pregnancy. Nevertheless, it should be stressed that use of mifepristone for treatment of ectopic pregnancy is not an approved clinical use of mifepristone and we are not recommending such use here.

Ectopic pregnancy was not decisively excluded in women participating in the current study because the medication was administered before the onset of menstruation. In this situation, taking the medication as soon as possible under close medical and/or self-supervision may be much safer than waiting for confirmation of pregnancy location by vaginal ultrasonic examination. Given that the incidence of ectopic pregnancy in studies of medical abortion is much lower than its overall incidence (Saraiya et al., 1999; Coste et al., 2000; Tay et al., 2000; Hausknecht, 2003; Shannon et al., 2004), concerns about ectopic pregnancy should not be an obstacle to the exploration of abortion induction or menstrual regulation with appropriate recruitment screening and procedure supervision, especially for women recruited before menstruation onset, as in this study. Given that risks remain that the medication may fail to terminate a pregnancy, may produce an incomplete abortion, or may perhaps result in an ectopic pregnancy, all subjects were advised to seek medical help if they had a post-treatment positive urine hCG test, experienced any symptoms of pregnancy, or felt any discomfort, such as abdominal pain. It is our belief that it is pertinent that clinicians continue to be attentive to such risks.

Satisfaction and contraception preference

Although satisfaction rates for abortion induction and menstrual induction were high, the participants indicated that they would prefer to use this regimen as a remedy after unprotected sexual intercourse rather than as routine contraception.

Study limitations

Menstrual regulation is not recommended as routine contraception. Previously reported efficacy estimates may have been influenced by the dosage and/or repeated use of medication in consecutive cycles (Swahn et al., 1999). Given the lack of convincing evidence confirming the efficacy of repeated regimen use, our analysis included only the first treatment administration for each participant. Repeated treatment, however, is inevitable in any study of menstrual regulation, regardless of the reason (abortion induction or menstrual regulation) or form (continuous or discontinuous) of re-administration. In the final statistical analysis, the assessment of efficacy was based solely on the first treatment administration, thereby avoiding this limitation. In addition, this limitation does not affect the efficacy of the treatment for abortion induction and/or menstrual induction for preventing unintended pregnancy after unprotected sexual intercourse. Studies with larger sample sizes and long-term follow-up may provide more data regarding whether repeated use of this regimen hampers its efficacy. All participants were from the same city, limiting the generalisability of study results. Contraceptive needs may differ among populations and geographic locations. Studies involving multiple centres from different nations, provinces and cities may be needed to resolve this limitation.

Conclusion

Menstrual regulation with oral administration of low-dose mifepristone 1 day before expected menstruation and low-dose misoprostol on the date of expected menstruation is effective and safe. This treatment, which was highly acceptable to patients due to its high efficacy and minor menstrual disturbance, may be the last remedy for suspected
unintended pregnancy after unprotected sexual intercourse and before menstrual onset.

Authors’ roles
C.-L.L. designed the study, clinically managed participants, drafted the manuscript and approved the final manuscript; D.-J.C. organized participants from different centres, clinically managed participants and approved the final manuscript; Y.-F.D. trained participants in medication and follow-up protocols, analysed and interpreted data, drafted the manuscript and approved the final manuscript; L.-P.S. clinically managed participants, analysed and interpreted data and approved the final manuscript; X.-T.M. clinically managed participants, trained participants in medication and follow-up protocols and approved the final manuscript; K.-J.L. clinically managed participants, trained participants in medication and follow-up protocols and approved the final manuscript.

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Conflict of interest
None declared.

References


