Chapter 1

Advance in Menstruation Inducement and Ultra-Early Pregnancy Termination (Amenorrhea ≤ 28 days)

Cui-Lan Li*, Li-Ping Song and Shi-Yan Tang

The Third Affiliated Hospital of Guangzhou Medical University, PR China
Key Laboratory for Major Obstetric Diseases of Guangdong Province, PR China
Key Laboratory of Reproduction and Genetics of Guangdong Higher Education Institutes, PR China

*Corresponding Author: Cui-Lan Li, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou 510145, P. R. China, Tel: +86-20-81266937; Fax: +86-20-81292949; E-mail: cuilanli@gzhmu.edu.cn

First Published January 13, 2016
Copyright: © 2016 Cui-Lan Li et al.

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source.

Abstract

There are several drugs used to prevent pregnancy shortly after unprotected intercourse, including mifepristone alone, prostaglandins (PGs) alone, methotrexate alone, mifepristone with mifepristone, mifepristone with prostaglandins and methotrexate with prostaglandins. Within the last 10 years, misoprostol use with mifepristone for medical abortion has become common place. Unintended pregnancy can lead to menstrual delay, recently a new method, using low-dose mifepristone combined with misoprostol before expected menstruation, proves that it’s possible to maintain menstrual regulation as well as achieve pregnancy termination (≤28 days) with no need of confirmation of pregnancy.

Introduction

Unintended pregnancy, a serious problem worldwide, can result in serious physical, psychological, financial, and/or ethical stresses on women and families, especially in regions and countries where there is no legally available abortion [1].

Emergency contraception (EC) is using several available interventions, including mifepristone, Levonorgestrel, Yuzpe, ulipristal acetate or copper intrauterine device (Cu-IUD) to prevent pregnancy shortly after unprotected intercourse. A report showed that intermediate-dose mifepristone (25-50 mg) was superior to LNG and Yuzpe regimens [2].
Menstrual delay can be an intense stressor leading to women's worries about unintended pregnancy. Menstrual regulation involves the mechanical or medical stimulation of uterine sloughing in women with up to 2–3 weeks of menstrual delay [3-5]. It is not a pre-condition for menstrual regulation to have a positive pregnancy test result, which can be conducted in countries or regions where medical abortion is legally restricted.

Different medical, psychological, and legal impacts on women can be seen between menstrual regulation and medical abortion. Clinically, regimens for avoiding unintended pregnancy between the last effective EC and expected menstrual onset at early time are urgently needed.

Menstrual Induction and Pregnancy Termination

Menstrual indocement, originally defined to be performed in women with a menstrual delay of up to 2-3 weeks without knowing if the women is pregnant or not, is a variant of suction aspiration. It is not new to use medical methods for menstrual induction. The initial studies, tested in a large multicenter study, were using prostaglandin analogues and sulprostone to induce menstrual. However the frequency of gastrointestinal side effects and, to a lesser extent, of strong abdominal pain showed the limitation of medical method for routine clinical use [6].

Prerequisites for a pharmacological method for menstrual induction are a high efficacy to induce a bleeding in non-pregnant women and an expulsion of the pregnancy in pregnant women. Treatment with prostaglandins, specifically intramuscular sulprostone, can be as effective as suction aspiration for menstrual induction. However, the administration of prostaglandin in therapeutically effective doses was associated with a high frequency of gastrointestinal side effects and, to a lesser extent, of strong abdominal pain, which limited their routine use [4]. One recent study found that intrauterine devices (IUDs) were highly effective for EC at any time in the menstrual cycle [7]. 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 [7,8].

Mifepristone Used in Menstrual Induction and Pregnancy Termination

A method for maintaining or achieving non-pregnant status during this period of time, regardless of current pregnancy status, is urgently needed. Mifepristone, the most commonly prescribed antiprogestrone EC medication, is the only medication that can be used alone for EC [9,10], be used in combination with prostaglandin for
menstrual regulation [4,5,11], ultra-early pregnancy (≤35 days of amenorrhoea [12]) termination [13-15], or termination in the first and second trimesters of pregnancy [16,17], 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.

Mifepristone, when used along or with vaginal suppository of the prostaglandin analogue in some early studies [18,19], had the efficiency of inducing menstrual but also 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 [20,21].

Recently the combined use of mifepristone with misoprostol arouse more attention. Since 600 mg mifepristone in combination with 0.4 mg misoprostol orally is highly effective in terminating early pregnancy (up to 49 days of amenorrhea) [22], oral administration might have been equally effective. 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 mg 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 [11]. Curiously, the efficacy of ≤200 mg oral mifepristone combined with ≤400 mg misoprostol for early (≤56 days of amenorrhoea) medical abortion [23-25] and menstrual regulation [5] has been confirmed convincingly. The low efficacy observed in the terminated study of [3] 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.

With over 30,000 women included in, a studies [22], examining mifepristone with buccal misoprostol for medical abortion since the first report using this regimen 10 years ago, demonstrated that outpatient medical abortion regimens with followed in 24–48 hours mifepristone by buccal misoprostol are highly effective for pregnancy termination through 63 days of gestation with the complete abortion rate with this protocol is higher than the 92% rate with the FDA-approved regimen [26].
Feasibility and Rationale of Low-Dose Mifepristone and Misoprostol Administration for Menstruation Regulation and Pregnancy Termination

The clinical sign of uterine bleeding is the result of initiation of endometrial degradation caused by the effects and side effects of mifepristone [23,27,28]. Early use of mifepristone increases the effectiveness of the drug, and use of a low dosage reduces side effects without compromising efficacy [14,15,29]. A World Health Organization report [29] 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 [23,25,30]. 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 [24]. 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.

Side-effect rates vary across previous studies, which may be related to different ways of defining these events or different patient populations. However, the side-effect profile of both regimens is comparable, and whether regimens with lower buccal misoprostol would be well tolerated and acceptable to participants was under questioned [31-34].

Previously, no obvious menstrual disturbance can be seen when 50 mg of mifepristone combined with 200 mg of misoprostol effectively terminated pregnancy within 35 days [14,15]. In the current study, the same regimen was administrated 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 ≤25 mg mifepristone daily, with a steady-state serum concentration of about 400 ng/ml, increases the serum concentration of mifepristone linearly [27]. Oral administration of 50 mg mifepristone daily results in a saturation concentration of about 1100 ng/ml mifepristone [35]. The plateau concentration does not rise in a dose-dependent manner for single doses exceeding 100 mg [27,28,35]. Thus, a single oral dose of 50 mg of mifepristone combined with misoprostol is pharmaco kinetically and clinically rational and sufficient for menstrual regulation, at least for very early stage menstrual delay.

A single oral dose of 150 mg mifepristone combined with 400 mg misoprostol administered vaginally 48 h later regulates menstruation within 7 days of menstrual delay, including cases of very early medical abortion [5]. The
failure rate in the present study was significantly lower than that reported for menstrual regulation by [5] [7.5% (37/492); x²=50.74, P < 0.001]. However, the evaluation of bleeding induction differed considerably between studies, with assessment conducted up to 44 days [5] and 7 days (present study) after misoprostol administration. Both studies showed high efficacy of the regimens for menstrual regulation, but [5] did not report on menstrual disturbance. It is 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 [36].

Feasibility and Effectiveness of Unintended Pregnancy Prevention with Low-Dose Mifepristone Combined with Misoprostol Before Expected Menstruation

Outpatient medical abortion regimens with mifepristone followed by buccal misoprostol in 24–48 hours are highly effective for pregnancy termination through 63 days of gestation [26]. Clinical outcomes with regimens containing mifepristone followed in 24 hours by buccal misoprostol and in pregnancies beyond 63 days of gestation are needed.

Specially,a recent study found that 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 safe and effective [36].

In this advanced study, participants with regular cycles of 25–35 days were asked to visit 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. Participants were instructed to self-administer 200 mg oral misoprostol 24 h later. Serum β-hCG detection, urine hCG test, a daily log card to record side effects (i.e. GI side effects, abdominal pain, vaginal bleeding, amount and duration, tissue expulsion) and final follow-up conducted by telephone and/or return visit to Hospital were needed. The final follow-up was after completion of the post-treatment menstrual cycle.

The general rate of satisfaction with the treatment was 96.7% (21/639), while 96.4% (133/138) of pregnant participants were satisfied with the regimen’s medical abortion capability and 97.6% (489/501) of non-pregnant participants were satisfied with its menstrual induction capability, with no difference between groups [36].
Generally, 36.0% (230/639) of participants indicated that they would like to use the regimen as a routine contraception method compared with the majority (64.0%, 409/639) who indicated that they would prefer to use this treatment for unintended pregnancy termination after contraception failure (P<0.001).

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 (≤28 day) [36].

Conclusion

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 [3]. Given the lack of convincing evidence confirming the efficacy of repeated regimen use, analysis included only the first treatment administration for each participant. 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 highly acceptable treatment, which showed high efficacy and menstrual regulation, may be a new method for suspected unintended pregnancy (≤28d) after unprotected sexual intercourse and before menstrual onset [36].

Whether this treatment can be used to routine contraception is still under evaluation, it is hopefully that this will be a new method in contraception for less than 28 days unintended pregnancy.

References

6. World Health Organization Task Force on Post Ovulatory Methods for Fertility Regulation. Phi...


18. Grimes DA, Mishell DR, David HP. A randomized clinical trial of mifepristone for induction of de-


