Chapter 2

Advance in Mifepristone Combined With Misoprostol For Ultra-Early Pregnancy Termination (Amenorrhea ≤35 days)

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Abstract

There are several kinds of medical abortion methods available, among which mifepristone is widely used around the world. In the combined regimen, lower doses of mifepristone together with a lower fixed dose of misoprostol (200 mg, given 24 hours later) are as effective and safe as higher doses of mifepristone for termination of ultra-early pregnancy, which is clinical suggestion for safe and effective ultra-early termination pregnancy (less than 35 days of pregnancy). In addition, lower doses of mifepristone (50 or 75mg) offer the advantages of reducing vaginal bleeding and medication side effects. Vaginal administration is more effective than oral administration, and has less side effects than sublingual or buccal. Combined regimens are more effective than single agents.

Introduction

Since the 1960s, one of method of choice for early pregnancy termination might be surgical abortion by vacuum aspiration or dilatation and curettage. In the 1980s, another alternative method of first trimester pregnancy termination, medical abortion, showed up. Nowadays, the most widely researched drugs are mifepristone alone, prostaglandins (PGs) alone, methotrexate alone, mifepristone with misoprostol, mifepristone with prostaglandins and methotrexate with prostaglandins.

Previous studies showed that there were several ways to first trimester abortion, including combined regimen mifepristone, prostaglandin, mifepristone alone, prosta-
glandin alone, gemeprost, tamoxifen and methotrexate.

And higher effectiveness with the combined regimen can be observed among the researches. A system review [1] showed that 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. However, clinical outcomes with regimens containing mifepristone followed by misoprostol to terminate pregnancies beyond 63 days of gestation are urgently needed [1].

Termination of Ultra-Early Pregnancy

Determination in Ultra-Early Pregnancy

Nowadays whether ultra-early pregnancy (less than 35 days of pregnancy) is intrauterine or ectopic is still very difficult to be determined [2]. Clinicians are often faced with patients who need to terminate an undesired pregnancy at an ultra-early gestational age. The self-detection of ultra-early pregnancies can be detected by the high sensitivity of urine pregnancy tests. However, the majority of clinicians still prefer to confirm whether the pregnancy is intrauterine or ectopic before treatment. Therefore patients who had been pregnant less than 35 days were unavoidably included in these previous studies, and these patients were usually treated with standard doses of abortion drugs with expected outcomes and acceptable side effects.

Although medical abortion is a widely accepted method in the clinic to terminate pregnancy after its diagnosis, the confirmation of intrauterine pregnancy has seldom been explored to exclude ectopic pregnancy. The indications of medical abortion with mifepristone and misoprostol are limited to the termination of early, intrauterine pregnancy. Therefore, concerns about whether the pregnancy is ectopic or not show up.

To date, there were still no reference can prove that the menstrual induction can definitively stop an ectopic pregnancy, but it has been shown to be at least partially effective and safe [3,4]. One study reported the rate of ectopic pregnancy after medical abortion is only 0.02% (10 of 44,789), which is much lower than an overall incidence (1.15%-1.97%) [5,6]. Thus, they concluded that the medical abortion regimens do not lead to unusual complications in patients with ectopic pregnancy [7].

Research in the Use of Mifepristone and misoprostol

The regimens of mifepristone in combination with misoprostol are widely used as effective and safe regimens for medical termination of early confirmed intrauterine pregnancy both intrauterine and ectopic pregnancies [8-10]. One previous study demonstrated that 150 mg mifepristone together with 600 mg misoprostol can
effectively terminate ultra-early pregnancy, irrespective of its location (intrauterine or ectopic pregnancy). However, the study did not include proof of intrauterine location prior to treatment. This has the advantage of not requiring confirmation of the pregnancy location prior to medical abortion [11]. Several reports demonstrated that the effectiveness and side effects of mifepristone for early pregnancy termination may be dependent on the dose used [12-15]. One study demonstrated that the mifepristone+misoprostol regimen was as effective as the misoprostol only regimen for termination of pregnancy between 9 and 12 weeks of gestation [16].

Recently, increasing numbers of studies have stated that mifepristone is effective and safe in the treatment of conservative ectopic pregnancy [17,18]. These studies demonstrated that the issue of ectopic pregnancy should not be an obstacle to the exploration of termination of ultra-early pregnancies.

Effectiveness and Safety of Lower Doses of Mifepristone Combined with Misoprostol for the Termination of Ultra-Early Pregnancy

In 2001, a report from the World Health Organization (WHO) stated that 50 mg mifepristone followed by 0.5 mg or 1.0 mg gemeprost is inadequate for early medical abortion. These dosages produced complete abortion in only 84.7% (combined with 0.5 mg gemeprost) and 89.8% (combined with 1.0 mg gemeprost) of cases. In that study, the duration of pregnancy was shorter than 56 days [14]. In 2010, another study from the WHO also reported that a 400 mg dose of misoprostol should not replace the 800 mg dose when administered 24 hours after 200 mg mifepristone for induction of abortion in pregnancies up to 63 days [19].

Early in 2010, a prospective randomized controlled trial [16] included 122 women seeking medical abortion at 9 to 12 weeks of gestation. 73 patients were given a fixed protocol of 200 mg of mifepristone which was followed 48 h later by 400 mcg oral misoprostol (Group 1). The second group of 49 patients was administered 800-mcg intravaginal single-dose misoprostol (Group 2). This study sought to compare safety, efficacy and acceptability of these two nonsurgical abortion regimens. The results showed for late first-trimester termination, a single 800-mcg vaginal dose of misoprostol seems to be as effective as the mifepristone+misoprostol regimen, with acceptable side effects.

One previous study [20] in 2012 showed that it was safe and effective treatment with the lowest dosages of mifepristone and misoprostol to terminate ultra-early pregnancies. One hundred cases in G1 group (minimized dosage) were orally administered 25 mg mifepristone once
a day for 2 days and combined with 200 ug misoprostol 48 hours later, while 150 mg mifepristone combined with 600ug misoprostol 48 hours later were given to 100 cases in G2 group (normal dosage). All cases were observed for 6 hours after taking misoprostol and returned for assessment three days later. Expulsion of conceptus: G1 and G2 group were 22 (22.0%, 22/100) and 25 (25.0% , 25/100 : P>0.05). Failure rate: Cases with incomplete abortion were 1(1.0%,1/100)and 2(2.0% . 2/100) in

G1 and G2 group, hospitalization for suspected ectopic pregnancies both was 1 (1.0%). Bleeding: bleeding cases during the administration of mifepristone in G1 and G2 group were 71 (71.0%.71/100) and 78(78.0%,78/100;P>0.05); the mean bleeding time were (5.3±1.4) days and (6.0±1.5) days (P<0.01). Other side effects ; in G1 group, majority showed light nausea (7.0%,7/100) and light abdominal pain (20.0%,20/100). Menses recovery 99 (99.0%,99/100) for G1 group and 98 (98.0%,98/100) for G2 group to recovery on scheduled time. Satisfactions: both were 99 (99.0%,99/100). Except mean bleeding days and side-effects, the differences above showed no significance (P>0.05).

To some extent, it is much safer for patients with possible ectopic pregnancies to undergo intervention under close supervision as early as possible rather than delaying treatment.

The standard dose of 150 mg mifepristone followed by 600mg misoprostol has been reported to be effective, but heavy or prolonged vaginal bleeding and medication side effects are significant challenges. Usually, it is believed that 200 mg of mifepristone can delay the return of menses by more than 1 week, especially after intrauterine pregnancy. This may be partially due to the gestational age or the lower dose of mifepristone used, and the underlying mechanism requires further investigation.

A recent study [21] in 2014 found that lower doses of mifepristone together with a lower fixed dose of misoprostol (200 mg) given 24 hours later are as effective and safe as higher doses for termination of early pregnancy and have the advantages of reducing or cutting down vaginal bleeding and fewer and less severe medication side effects when 50 or 75 mg mifepristone was used. It is the first study to assess the effectiveness and safety of lower doses of mifepristone in combination with misoprostol for medical abortion of ultra-early pregnancies when it is unknown whether the pregnancy is intrauterine or ectopic. This study originally aimed to investigate the effectiveness and safety of lower doses of mifepristone combined with misoprostol for the termination of ultra-early pregnancy. A total of 2500 women with ultra-early pregnancy (amenorrhea ≤35 days) were randomly divided into 5 groups with gradually decreased dose of oral mifepristone from 150 to 50 mg followed by 200 mg of oral misoprostol24
hours later. The primary end point was complete abortion without surgical intervention. Secondary end points were vaginal bleeding, return of menses, and side effects. Rates of complete abortion were high in all groups. Moreover, the lower doses of mifepristone led to shorter vaginal bleeding period, the return of menses on the expected date, and fewer side effects. Lower doses of mifepristone combined with 200 mg of misoprostol are as effective and safe as higher doses of this combination for the termination of ultra-early pregnancy with lower possibility of vaginal bleeding and side effects. Moreover the result may be explained by the idea that administration of mifepristone initiates degradation of the endometrium, the clinical sign is uterine bleeding, the lower the dosage, the shorter the bleeding [14].

References


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