MEDICAL ABORTION WITH MIFEPRISTONE AND MISOPROSTOL: A CLINICAL TRIAL IN TAIWANESE WOMEN

Eing-Mei Tsai, Cheng-Hui Yang, and Jau-Nan Lee

Background and Purpose: Medical abortion was not officially approved in Taiwan until the end of 2001. We investigated the efficacy of combination mifepristone and misoprostol therapy for medical abortion (which has now been approved) in early pregnant Taiwanese women and whether the attitudes of women who received this treatment affected the clinical outcome of medical abortion.

Methods: Eighty healthy women in early pregnancy (<49 d of gestation) were enrolled into two studies of medical abortion using mifepristone and misoprostol regimens. The outcomes were evaluated based on complete expulsion of intrauterine contents, with or without surgical intervention. Study 1 used treatment with mifepristone (200 mg or 600 mg) and misoprostol (400 µg), and the decision to perform surgical intervention was made mainly on the basis of the patient's request. Study 2 used treatment with mifepristone (200 mg or 600 mg) and misoprostol (600 µg) where the decision to perform surgical intervention was made exclusively by the physician. Serum or urinary human chorionic gonadotropin (hCG) concentration was measured serially after abortion.

Results: In general, the success rate was 95% as judged by complete expulsion of intrauterine contents without surgical intervention. However, the success rate in Study 1 was only 62.5%. The mean duration of bleeding after abortion was 16.7 to 21.7 days. Serum or urinary hCG concentration remained positive in one woman (1.2%) studied during 43 to 60 days after abortion.

Conclusion: A combination of mifepristone and misoprostol for medical abortion in Taiwanese women during early pregnancy can achieve a high success rate. Our study showed that a mifepristone dose of 200 mg and a misoprostol dose of 400 µg were most effective. Our results suggest that sufficient physician and patient communication regarding medical abortion affects the clinical outcome.

Mifepristone (RU 486) is a potent antiprogestin. Its combination with misoprostol, a prostaglandin E₁ compound, has been widely used for medical termination of early pregnancy during the past decade [1–3]. The rationale for the combination of these two drugs is that misoprostol increases uterine contractility [4]. The efficacy of this combination regimen is high, with success rates ranging from 90 to 98% [5–7].

Of the 1.18 million legal abortions performed in the USA in 1997, medical abortion accounted for only 0.25% [8]. On the other hand, up to 0.2 million women die annually in developing countries of complications after illegal abortion [9]. Data on illegal abortion in Taiwan are not available and this practice remains an important problem in women's healthcare. An antecedent abortion is associated with an increased risk of molar pregnancy, possibly due to retention of trophoblastic cells within the uterine tissues. The prevalence of molar pregnancy varies from 1 per 100 deliveries among Asian women to 1 per 1,000 to 1,500 deliveries in the USA [10]. The association between gestational trophoblastic disease and medical abortion remains
controversial, especially in oriental women. There are no data on human chorionic gonadotropin (hCG) concentration after abortion using mifepristone and misoprostol regimens.

Medical abortion was not officially approved in Taiwan until the end of 2001. This study aimed to determine the efficacy of combination mifepristone and misoprostol therapy in medical abortion for Taiwanese women in early pregnancy. Factors that may affect the clinical outcome, physician–patient interactions and post-abortion hCG concentrations were also investigated.

Subjects and Methods

This prospective, randomized, single-blind study comparing different doses of mifepristone and misoprostol combination therapy was conducted between March and July 2000 to investigate the efficacy and safety of this treatment for early pregnancy termination in Taiwanese women. This investigation was officially approved by the Department of Health of Taiwan. The drugs were supplied by Lotus Medical Supply Inc., Taiwan.

The inclusion criteria were early pregnancy (<49 d of gestation, positive pregnancy test, and positive ultrasonographic findings), and fulfillment of the criteria for legal abortion. All participants gave written informed consent for participation in the trial. Using computerized randomization, all women were allocated to one of two studies. In Study 1 (n = 40), the participant’s feelings and decision to opt for surgical intervention served as the primary basis for the intervention (patient domination), while in Study 2 (n = 40), women were asked to follow the physician’s judgment. Study 1 was further divided into two groups: group A (n = 20) received mifepristone 200 mg and misoprostol 400 µg, while group B (n = 20) received mifepristone 600 mg and misoprostol 400 µg. Study 2 was also divided into two groups: group C (n = 20) received mifepristone 200 mg and misoprostol 600 µg, while group D (n = 20) received misoprostol 600 µg.

Exclusion criteria were as follows: age less than 18 or more than 35 years; smoking more than 10 cigarettes/day; cardiovascular risk factors; hepatic, renal, endocrine or hematologic disorders; asthma; breast-feeding; ectopic pregnancy; and intrauterine device in situ. Seventy-seven women (96.3%) had had a previous surgical abortion before enrollment into this study. All participants were given extensive information about medical abortion using the combination of mifepristone and misoprostol.

On Day 1, each woman received a single oral dose of mifepristone after an overnight fast. Misoprostol was given on Day 3 (approximately 48 hr after mifepristone). All women were under close observation in the clinic for at least 6 hours after misoprostol administration. All participants were told that bleeding would occur about 3 to 4 hours after taking misoprostol. They were advised to visit the clinic again if abortion did not occur or bleeding did not stop or decrease within 1 week. In general, all women were asked to visit the clinic every 2 weeks after misoprostol administration. Vaginal ultrasonography was performed to confirm complete expulsion of the conceptus and an hCG test was carried out. A diary card was used to record adverse events such as abdominal pain, nausea, vomiting, and diarrhea. Vaginal bleeding was recorded as spotting (without using pad), normal (using pad similar to normal menses), and heavy (more than normal menstrual flow).

First treatment outcome, complete expulsion of the intrauterine conceptus diagnosed ultrasonographically, was assessed on Day 3 after misoprostol administration. Second treatment outcome was assessed after 2 weeks. Success for the second treatment outcome was defined as complete expulsion of intrauterine conceptus identified ultrasonographically and no surgical intervention to evacuate intrauterine contents [7, 11]. A third outcome assessment was made after 4 weeks, with success defined as complete expulsion of intrauterine conceptus, no surgical intervention and a negative blood or urine hCG test [12]. Failure implied an ongoing pregnancy, incomplete expulsion of products, or any other condition requiring surgical intervention. If the hCG concentration was persistently raised, weekly follow-up was arranged until a negative result was achieved.

The Kaplan-Meier test was used to estimate the success rate of abortion at different times after mifepristone administration and a negative hCG test was included in the definition of success. Chi-square test or Fisher’s exact test was used to analyze differences in rates of success or side effects between groups using various dosages of mifepristone and misoprostol.

Results

Complete expulsion of the intrauterine conceptus had occurred on Day 3 (first assessment) in 97.5% of cases in Study 1 and 92.5% of cases in Study 2, with an average of 95% overall. The success rate at the second assessment was 62.5% (25/ 40) in Study 1, where women were allowed to request surgical intervention, and 92.5% (37/ 40) in Study 2, where only physicians were allowed
Medical Abortion with Mifepristone and Misoprostol

Discussion

Medical abortion using a mifepristone and misoprostol regimen offers an alternative for women seeking termination of early pregnancy and is popular in developed countries. In general, women receive mifepristone (200–600 mg) followed by misoprostol (400 µg) 48 hours later. Bleeding occurs within 3 to 4 hours after misoprostol administration, accompanied by the expulsion of the conceptus. The doses of mifepristone and misoprostol do not appear to affect outcome. This is probably explained by the saturation of alpha-acid glycoprotein, the serum protein binding mifepristone, resulting in similar serum concentrations following administration of 100 to 800 mg [13]. Another possible explanation is that, since plasma concentrations of progesterone (which is mainly secreted by the corpus luteum) change little between conception and week 10, 200 mg of mifepristone could result in sufficient concentrations to compete successfully for progesterone receptors at the endometrial level.

Table 1. Clinical outcomes of mifepristone and misoprostol for medical abortion (<49 d of gestation) in Taiwanese women

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (misoprostol 400 µg)</th>
<th>Study 2 (misoprostol 600 µg)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mifepristone</td>
<td>Mifepristone</td>
<td>Subtotal</td>
</tr>
<tr>
<td></td>
<td>200 mg</td>
<td>600 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 20)</td>
<td>(n = 20)</td>
<td></td>
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<tr>
<td>Rate of complete expulsion of conceptus at Day 3 (1st assessment)</td>
<td>19</td>
<td>20</td>
<td>97.5%</td>
</tr>
<tr>
<td>Success rate at 2nd week:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUP(–) and intervention(–)</td>
<td>12</td>
<td>13</td>
<td>62.5%</td>
</tr>
<tr>
<td>*Success rate at 4th week:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUP(–), intervention(–) and hCG(–) (3rd assessment)</td>
<td>–</td>
<td>–</td>
<td>18.3%</td>
</tr>
<tr>
<td>Failure rate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>8</td>
<td>7</td>
<td>37.5%</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incomplete abortion</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Medical indication</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Patient’s request</td>
<td>5</td>
<td>6</td>
<td></td>
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</tbody>
</table>

In Study 1, women could request surgical intervention for personal reasons, while in Study 2, the intervention was decided by physician’s judgment. IUP = intrauterine pregnancy; *Kaplan-Meier analysis.
The mean duration of vaginal bleeding in the present study was similar to that of 16 days reported in a multicenter study of Chinese women [14]. The total duration of bleeding (14.2–21.7 d) appears to be longer than reported in the western literature, for example, 13 days (600 mg) was reported by Spitz et al [7], 9 days (600 mg) by Peyron et al [11], and 10 days (600 mg) by Aubeny et al [15]. A possible explanation for more prolonged bleeding after mifepristone treatment in the present study is that mifepristone’s longer half-life in the circulation of Asian women than in Caucasians inhibits the ability of estrogen to stimulate endometrial regeneration [16]. Moreover, it has been reported that premenopausal Asian women have significantly lower plasma concentrations of sex steroid hormones than Caucasian women [17]. This lower sex steroid hormone level, in turn, might predispose to delay in endometrial restoration after abortion.

In developed countries, the physician’s decision in medical management is usually unchangeable by the patient. This is supported by the findings of the present trial that patients in Study 2 could not request surgical intervention, resulting in a higher success rate similar to most reports from western countries. However, in the majority of Asian countries, traditional and herbal medicines still represent an important alternative for patients receiving medical management. This different cultural background may influence the results obtained by Asian and Caucasian women seeking medical abortion. For example, surgical intervention at the patient’s request is infrequent in reports from western countries [11, 18–21]. A recent large-scale clinical study found that 7% (5/65) of surgical interventions were performed at the patient’s request [7]. In our study, 73.5% (11/15 cases) of surgical interventions were at the patient’s request despite extensive pretreatment communication.

The role of hCG determination after medical abortion with a mifepristone/misoprostol regimen has seldom been mentioned in the literature [11]. This might be due to previous poor experience with methotrexate treatment in medical abortion where determination of hCG concentrations is not helpful for monitoring efficacy and diagnosis of incomplete abortion [22] because hCG may be detectable in the blood for up to 3 months [23]. Similarly, in this study, hCG tests remained positive in 78.7% of all women at

<table>
<thead>
<tr>
<th>Time by which hCG test became negative after abortion (d)</th>
<th>Study 1 (n = 40)</th>
<th>Study 2 (n = 40)</th>
<th>Total (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>9 (22.5%)</td>
<td>8 (20.0%)</td>
<td>17 (21.3%)</td>
</tr>
<tr>
<td>28</td>
<td>28 (70.0%)</td>
<td>26 (65.0%)</td>
<td>54 (67.5%)</td>
</tr>
<tr>
<td>42</td>
<td>38 (95.0%)</td>
<td>38 (95.0%)</td>
<td>76 (95.0%)</td>
</tr>
<tr>
<td>60</td>
<td>40 (100%)</td>
<td>39 (97.5%)</td>
<td>79 (98.8%)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>–</td>
<td>40 (100%)</td>
<td>80 (100%)</td>
</tr>
</tbody>
</table>

In Study 1, women could request surgical intervention for personal reasons while, in Study 2, the intervention was decided by physician’s judgment.
15 days after mifepristone treatment and 1.2% remained positive between the sixth and the tenth week, despite the occurrence of bleeding as normal menstrual flow. In Study 2, one woman was classified as having a successful abortion and menstruation occurred on day 46. However, serial serum hCG concentration in this patient was 1,343 mIU/mL 23 days after abortion, 470 mIU/mL 28 days after abortion, 722 mIU/mL 35 days after abortion, 676 mIU/mL 42 days after abortion, 150 mIU/mL 55 days after abortion, 13 mIU/mL 62 days after abortion, and 3 mIU/mL 77 days after abortion. The urinary pregnancy test became negative 62 days after abortion. One patient showed a serum hCG concentration of 493 mIU/mL 33 days after mifepristone treatment, menstruation occurred 39 days after mifepristone treatment, and serum hCG concentration became negative 57 days after mifepristone treatment. Another woman had serum hCG concentrations of 153 and 59 mIU/mL 40 and 49 days after misoprostol treatment, and her serum hCG was negative 56 days after misoprostol treatment. Intermittent vaginal spotting was the only complaint in these two patients. These results, however, imply that the variable presence of circulatory hCG indicates that trophoblastic cells have unexpectedly remained in the uterus after mifepristone and misoprostol treatment for medical abortion. This is of great concern not only because of the higher prevalence of molar pregnancy among Asian women than in western women [10], but also because we have previously demonstrated that choriocarcinoma can occur in women 2 years after a molar pregnancy [24]. Thus, follow-up of hCG concentration should be performed until hCG disappears from the circulation after medical abortion. The risk of undetermined gestational trophoblastic diseases should be borne in mind, especially in high-risk groups of women.

In conclusion, although the success rate is variable, the combination of mifepristone and misoprostol is an effective and safe method for medical abortion in early pregnancy. The results of this study suggest that sufficient physician-patient interaction and careful psychologic considerations will achieve a better clinical outcome in medical abortion. Concerning the high prevalence of molar pregnancy associated with antecedent abortion, apart from the complete evacuation of intrauterine conceptus, follow-up of hCG concentrations should be monitored carefully. Thus, complete disappearance of hCG is essential for the assurance of safety following medical abortion in Oriental women.

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References

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