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# Mifepristone-misoprostol versus misoprostol alone for second trimester termination of pregnancy in a tertiary hospital in Hong Kong

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***Objective:*** To compare the mifepristone-misoprostol regimen with the misoprostol-alone regimen in terms of safety and effectiveness in women who underwent second trimester medical termination of pregnancy (MTOP).
***Methods:*** Medical records of all women with singleton pregnancy who underwent MTOP during the second trimester at Queen Elizabeth Hospital between 1 January 2018 and 31 December 2019 were reviewed. Patients were prescribed with misoprostol 400 μg every 3 hours up to a maximum of five doses per day orally or vaginally, or with mifepristone 200 mg followed by misoprostol after 36 to 48 hours. The primary outcome was the time from first misoprostol dose to fetal expulsion.
***Results:*** Of 94 patients (mean age, 33.5 years) included, 48 received the mifepristone-misoprostol regimen and 46 received the misoprostol-alone regimen. The mean gestational age was 16 weeks 4 days. Compared with the misoprostol-alone group, the mifepristone-misoprostol group had shorter time to fetal expulsion (7.3 hours vs 11.3 hours, p=0.017), shorter time to placental expulsion (7.9 hours vs 12.2 hours, p=0.026), higher proportion of successful abortion within 10 hours (71.7% vs 43.8%, p=0.005) and 24 hours (95.7% vs 79.2%, p=0.016), and lower number (3 vs 5, p<0.001) and dosage (1200 μg vs 1600 μg, p<0.001) of misoprostol administered. Complication rate was similar between the two groups.
***Conclusion:*** The mifepristone-misoprostol regimen is effective and safe for second trimester MTOP, with a shorter time to fetal expulsion.

*Keywords: Abortion, induced; Mifepristone; Misoprostol; Pregnancy trimester, second*

## Introduction

Termination of pregnancy can be performed medically or surgically. In the past, dilatation and evacuation was the primary way for abortion, even for second trimester abortion up to 14 weeks. Second trimester abortions constitute 10% to 15% of all induced abortions worldwide but account for two-thirds of major abortion-related complications[1]. Dilatation and evacuation for second trimester abortion requires specialised skills and instruments. It is at risk of surgical complications such as uterine perforation and cervical injury and precludes fetal post-mortem examination.

Over the past 20 years, with the increasing availability of prostaglandin and the introduction of mifepristone, medical termination of pregnancy (MTOP) has been increasingly used for second trimester abortion[2-4]. Prostaglandin is the principal agent, and its actions may be augmented by prior administration of mifepristone[5-10]. Pretreatment with mifepristone before misoprostol administration has been reported to increase the success rate, shorten the induction-to-abortion interval, and reduce the dosage of misoprostol required[11,12]. According to various international guidelines, mifepristone followed by a prostaglandin analogue for MTOP is considered appropriate, safe, and effective[13-15].

In Hong Kong, termination of pregnancy can be performed legally up to 23 weeks 6 days of gestation. In 2019, a total of 8272 abortions took place[16]. Because of improved ultrasound technology and prenatal diagnostic techniques, prenatal detection of fetal structural anomalies during the second trimester has improved substantially, and thus the demand for MTOP during the second trimester has increased. Because of the potential risk of serious complications, patients requesting second trimester abortion are often referred to the public sector. MTOP is now generally the standard of care in Hong Kong.

Mifepristone was registered in Hong Kong in April 2014. Only institutions (including public and private hospitals) listed in the Gazette as legal abortion providers

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can purchase mifepristone for abortion. However, mifepristone was not widely used in the public sector and was considered as second-line treatment. Since late 2017, Queen Elizabeth Hospital has started using mifepristone for second trimester abortion. This study aims to compare the mifepristone-misoprostol regimen with the misoprostol-alone regimen in terms of safety and effectiveness in women who underwent second trimester MTOP in a tertiary hospital in Hong Kong.

## Methods

This study was approved by the Kowloon Central/ Kowloon East Research Ethics Committees (KC/KE-21-0193/ER-4). Medical records of all women with singleton pregnancy who underwent MTOP during the second trimester (13 weeks 0 days to 21 weeks 6 days of gestation) at Queen Elizabeth Hospital between 1 January 2018 and 31 December 2019 were reviewed through the Clinical Management System. Women were excluded if they had miscarriage, active bleeding or abdominal pain, premature rupture of membrane, multiple pregnancies, ectopic pregnancy, history of prior Caesarean section or uterine perforation, use of fetocide, hypersensitivity to mifepristone or misoprostol, bleeding tendency, inherited porphyria, chronic adrenal failure, chronic steroid use, renal or liver impairment, cardiovascular disease, epilepsy, severe asthma. Women who underwent MTOP at 22 weeks 0 days to 23 weeks 6 days were also excluded, as most of them received fetocide (fetal intracardiac potassium chloride).

Medical practitioners were required to certify the ground for termination of pregnancy. Depending on the clinician's decision and the patient's preference, patients were prescribed with misoprostol 400 μg every 3 hours up to a maximum of five doses per day orally or vaginally (as recommended by the World Health Organization), or with mifepristone 200 mg followed by misoprostol after 36 to 48 hours. Further courses of misoprostol were given until abortion. Oral paracetamol or intramuscular injection of pethidine was provided as pain relief when requested. Blood pressure, pulse, and body temperature were monitored every 4 hours until the abortion.

After the expulsion of the fetus and placenta, patients were assessed by the attending clinician. Intravenous oxytocin infusions were given as prophylaxis for haemorrhage. Abortuses and placentas were examined for completeness. Physical examinations and ultrasound scans of the pelvis were performed. Retained production of gestation (RPOG) was suspected if the endometrial thickness was >10 mm, and medical or surgical evacuation was performed. Patients were followed up until complete abortion. Psychological support and assessment was provided by clinical psychologists if necessary.

Data retrieved for analysis included demographics (age, weight, height, obstetric history, and gestational age), the time of fetal and placental expulsion, the number, dosage, and route of misoprostol administration, analgesic requirement, the length of hospital stay, and complications including RPOG, heavy bleeding, infection.

The primary outcome was the time from first misoprostol dose to fetal expulsion. Secondary outcomes included the time to placental expulsion, the proportion of successful abortion within 10 hours and 24 hours, the rate of complete abortion, the proportion of women requiring analgesics, the rate of complications, the length of hospital stay, and the readmission rate.

Statistical analyses were performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US). The mifepristone-misoprostol regimen and the misoprostol-alone regimen were compared using the Chi-squared test for categorical variables and the Mann-Whitney *U* test or independent t-test for continuous variables. Kaplan-Meier survival curve, with log-rank testing of the null hypothesis, was used to analyse the time to fetal expulsion between groups. Hazard ratio was calculated after adjusting for women's age, prior miscarriage or abortion, parity, gestational age, and route of misoprostol administration. A p value of $<0.05$ was considered statistically significant.

## Results

Of 94 patients (mean age, 33.5±5.05 years) included, 48 received the mifepristone-misoprostol regimen and 46 received the misoprostol-alone regimen (Table). 46 patients were nulliparous and 48 were multiparous. The mean gestational age was 16 weeks 4 days (standard deviation, 2 weeks 3 days). The reason for abortion was fetal abnormalities in 80 patients and maternal anxiety in 14 patients. The mifepristone-misoprostol group and the misoprostol-alone group were comparable in terms of women's age, height, prior miscarriage or abortion, parity, gestational age, and route of misoprostol administration.

All women had successful fetal expulsion. One woman failed to have placental expulsion and required surgical evacuation. Compared with the misoprostol-alone group, the mifepristone-misoprostol group had shorter time to fetal expulsion (7.3 hours vs 11.3 hours, p=0.017, Table),

**Table. Clinical characteristics and outcomes of patients who underwent medical termination of pregnancy**

| | Misoprostol-only (n=48) | Mifepristone-misoprostol (n=46) | p Value |
|---|---|---|---|
| Age, y | 34.06±5.51 | 33.02±4.46 | 0.112 |
| Weight, kg | 57.42±10.21 | 58.29±8.41 | 0.327 |
| Height, cm | 158.54±4.70 | 159.90±6.38 | 0.235 |
| Prior miscarriage or abortion | | | 0.082 |
| 0 | 14 (29.2) | 20 (43.5) | |
| ≥1 | 34 (70.8) | 26 (56.5) | |
| Parity | | | 0.065 |
| 0 | 20 (41.7) | 26 (56.5) | |
| ≥1 | 28 (58.3) | 20 (43.5) | |
| Gestational age, weeks | 15.77±2.16 | 16.86±2.71 | 0.058 |
| Route of misoprostol | | | 0.164 |
| Oral | 19 (39.6) | 12 (26.1) | |
| Vaginal | 29 (60.4) | 34 (73.9) | |
| Time to fetal expulsion, hours | 11.3 (5.3-94.6) | 7.3 (2.4-103.3) | 0.017 |
| Time to placental expulsion, hours | 12.2 (5.8-95.6) | 7.9 (2.6-103.5) | 0.026 |
| Successful abortion in 10 hours | 21 (43.8) | 33 (71.7) | 0.005 |
| Successful abortion in 24 hours | 38 (79.2) | 44 (95.7) | 0.016 |
| No. of doses of misoprostol | 4 (2-20) | 3 (1-15) | 0.001 |
| Total dosage of misoprostol, mg | 1600 (800-6000) | 1200 (400-6000) | 0.001 |
| Any analgesics use | 39 (81.3) | 39 (84.8) | 0.649 |
| Heavy bleeding | 1 (2.1) | 5 (10.9) | 0.107 |
| Infection | 1 (2.1) | 0 (0) | 0.325 |
| Complete abortion | 4 (8.3) | 6 (13.0) | 0.459 |
| Surgical evacuation for suspected retained production of gestation | 35 (72.9) | 32 (69.6) | 0.72 |
| Medical evacuation for suspected retained production of gestation | 7 (14.6) | 5 (10.9) | 0.59 |
| Histological proven retained production of gestation | 28/42 (66.6) | 28/37 (75.7) | 0.802 |
| Hospital stay, days | 4 (2-17) | 5 (4-8) | <0.001 |
| Hospital stay since the first dose of misoprostol, days | 3 (2-17) | 3 (2-6) | 0.109 |
| Readmission | 6 (12.5) | 5 (10.9) | 0.806 |

* Data are presented as mean ± standard deviation, median (range), or No. (%)

which was confirmed by the Kaplan-Meier survival curves and log-rank tests (p=0.001, Figure) and by Cox proportional models after adjusting for potential confounders (hazard ratio=2.63, 95% confidence interval=1.66-4.16, p<0.001). In addition, the mifepristone-misoprostol group had shorter time to placental expulsion (7.9 hours vs 12.2 hours, p=0.026), higher proportion of successful abortion within 10 hours (71.7% vs 43.8%, p=0.005) and 24 hours (95.7% vs 79.2%, p=0.016), and lower number (3 vs 5, p<0.001) and dosage (1200 $\mu$g vs 1600 μg, p<0.001) of misoprostol administered. Nonetheless, the mifepristone-misoprostol group had longer length of hospital stay (5 days vs 4 days, p<0.001), but the length of hospital stay from the time of the first dose of misoprostol was similar in both groups (3 days).

79 (84.0%) of women required further surgical or medical evacuation for suspected RPOG. Five of them did not receive treatment initially after diagnosis: one was later found to have complete abortion; one underwent surgical

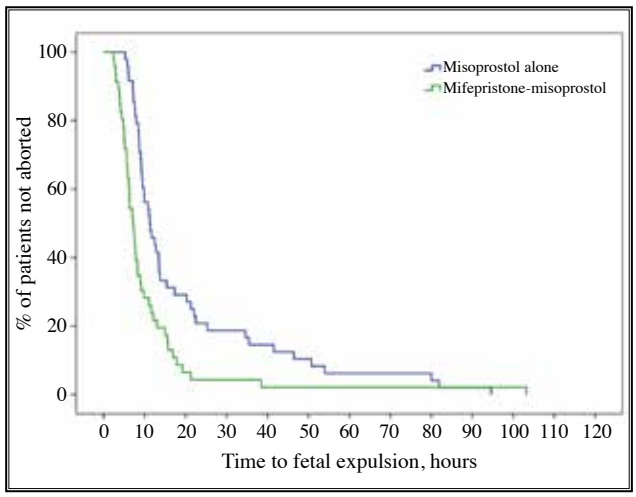


*Figure. Kaplan-Meier curves for the time to fetal expulsion in the mifepristone-misoprostol group and the misoprostol-alone group*

evacuation and one underwent medical evacuation; and the remaining two were lost to follow-up. 10 women were readmitted for management of RPOG and one was readmitted for post-abortal endometritis.

Severe complications included six cases of heavy bleeding and one case of infection requiring intravenous antibiotics. There was no uterine perforation, scar rupture, severe allergic reaction, or death.

## Discussion

Pretreatment with mifepristone enables the use of lower dosage of misoprostol to achieve comparable efficacy, with a shorter induction-to-abortion interval for second trimester MTOP[17]. In the present study, the median time to fetal expulsion after the mifepristone-misoprostol regimen was 7.3 hours, which was similar to previous studies[9,18,19]. Mifepristone is a synthetic steroidal drug with anti-progesterone and anti-glucocorticoid actions. It binds with the progesterone receptors, which antagonises prostaglandin synthesis and metabolism, resulting in increased production and decreased deactivation of prostaglandins. It induces cervical softening and enhances the efficacy of the prostaglandins as an abortifacient[20,21]. It reduces the number and dosage of subsequent prostanglandin required for abortion.

Nonetheless, the use of mifepristone is not widely used in the public sector in Hong Kong. Possible reasons include its recent introduction (in 2014) and high cost (HK$440/tablet vs $1.6/200mcg for misoprostol). Although mifepristone is more expensive than misoprostol, it enables shorter abortion interval, which potentially improves patient satisfaction and reduces frustration and stress associated with the advancing of gestation or discomfort from repeated vagina suppositories.

The slightly more cases of heavy bleeding in the mifepristone-misoprostol group may be due to the small sample size and the rare occurrence of the complication[6]. There were one case of infection requiring intravenous antibiotics and one case of post-abortal endometritis; the infection rate was only 2.1%, which is consistent with a previous study[6]. Thus, antibiotic prophylaxis should not be offered routinely to women with MTOP[14].

Analgesic requirement was reported to be higher in women with prolonged induction to abortion interval and with an increased number of misoprostol doses[22]. However, in the present study, analgesic requirement was similar in women with or without mifepristone pretreatment. This may indicate that mifepristone pretreatment is unable to decrease the analgesic requirement, despite the reduction in the induction-to-abortion interval and misoprostol dosage. Thus, clinicians should provide adequate analgesics to women undergoing MTOP irrespective of abortion regimen.

The complete abortion rate was slightly higher in the mifepristone-misoprostol group than the misoprostol group (13.0% vs 8.3%, p=0.459), but the rate of RPOG of both groups remained high (89%), compared with 2.5% to 53% reported in previous studies[23,24]. The high rate of RPOG is likely to be contributed by over-reliance on ultrasound assessment immediately after abortion. This increases the early diagnosis rate of RPOG. Among those who received surgical or medical evacuation for RPOG, the histologically proven RPOG rate remained high (>60%-70%). Little evidence was available on the optimal timing and diagnostic criteria of post-MTOP ultrasound assessment in second trimester MTOP. Clinicians should make the diagnosis of RPOG based on both clinical findings and examination of abortus and placenta. Future research is needed to determine the role of ultrasound in post-MTOP assessment and to improve the complete abortion rate.

In the present study, 71.7% of women with the mifepristone-misoprostol regimen achieved abortion within 10 hours. This makes outpatient day service feasible. Day service for MTOP should be aimed for, as women with MTOP are generally younger and more active. However, the length of hospital stay was longer in the mifepristone-misoprostol group than in the misoprostol-alone group

(5 days vs 4 days). As a safe practice during the initial phase of the introduction of mifepristone to our unit, mifepristone was not given in an outpatient setting. Further study on outpatient administration of mifepristone is warranted to determine its effect on the length of hospital stay.

Limitations to the present study are its retrospective nature and small sample size. Nevertheless, this study is the first study in Hong Kong comparing the use of misoprostol with or without mifepristone in second trimester MTOP. It can be a pilot study for future larger-scale studies and prospective studies. Patients at late second trimester (22 weeks to 23 weeks 6 days) were excluded owing to the possible confounding effect of fetocide on the time from induction to abortion[25]. Both vaginal and oral routes were used for misoprostol administration. Some studies reported the vaginal route more effective[26,27]; others reported inconclusive evidence[28,29]. A holistic approach to service delivery should be aimed at; patient satisfaction and acceptability should have been assessed in addition to objective outcome measures. Our findings are specific to a tertiary hospital in Hong Kong and may not be generalised to other settings.

## Conclusion

The mifepristone-misoprostol regimen is associated with shorter induction-to-abortion interval and reduced misoprostol dosage, while maintaining similar complications rates, analgesics requirement, length of hospital stay, and readmissions. It is effective and safe for second trimester MTOP. Optimisation of the regimen should aim at improving the complete abortion rate and reducing the length of hospital stay.

## Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Conflicts of interest

All authors have disclosed no conflicts of interest.

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## Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

## Ethics approval

The study was approved by the Kowloon Central/Kowloon East Research Ethics Committees (KC/KE-21-0193/ER-4). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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