

Outcome of Single-dose Vaginal Misoprostol in Early Missed Miscarriage

MC CHAN MBBS, MRCOG (UK)

WK SIN MBBS, MRCOG (UK), FHKAM (O&G)

HC LEE MBBS, FRCOG (UK), FHKAM (O&G)

KC AU YEUNG MBBS, MRCOG (UK), FHKAM (O&G)

Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, Hong Kong

Objective: To evaluate the outcome of single vaginal dose of misoprostol treatment for first trimester–missed miscarriage.

Methods: This was a retrospective study on the use of misoprostol treatment for first trimester–missed miscarriage. During the period from 1 January 2009 to 31 December 2009, misoprostol (800 µg vaginally) was given as primary treatment to 198 cases in Tuen Mun Hospital, Hong Kong. Of these, 13 patients were excluded because they defaulted follow-up or were twin pregnancy miscarriages. Thus, outcomes of the remaining 185 cases were analysed.

Results: In 2009, of the patients diagnosed with first trimester–missed miscarriage in Tuen Mun Hospital, 65% (n=198) received vaginal misoprostol as the principal treatment, of whom 13 were excluded; 70% (n=129) of the remaining 185 patients achieved complete evacuation after an 800-µg single vaginal dose of misoprostol, while another 3% (n=5) achieved complete evacuation after a repeated dose (600 µg orally). In total, 72% (n=134) had successful medical treatment. Having a previous miscarriage (odds ratio=0.64, p=0.001) was the only factor having a significant negative influence on the success of the vaginal misoprostol treatment. The miscarriage status (embryonic miscarriage instead of fetal demise) and a report of tissue mass passage within 24 hours increased the chance of successful medical evacuation (odds ratio=1.24, p=0.584 and odds ratio=1.44, p=0.292, respectively), although the results were not significant. Approximately 4% (n=7) received antibiotic treatment for suspected infection, while 2% (n=4) had positive culture results confirming infection. No patient suffered any major consequence. The infection rate was comparable to reports from other studies on medical treatment of early miscarriages.

Conclusion: Our data support the use of 800-µg misoprostol (via the vaginal route) as effective management for first trimester–missed miscarriage. Further evaluation of this approach is needed to assess patient acceptability, and use of repeated doses to achieve more effective results. The complication rate (localised infection, systemic sepsis, significant haemorrhage treated by emergency uterine curettage or blood transfusion) was low.

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Introduction

From early studies, one in four women are expected to experience a miscarriage in their reproductive life¹. It has been estimated that over 10 to 20% of pregnancies result in miscarriages, and that the majority occur in the first trimester². In the past, surgical evacuation was the standard management of early pregnancy failure due to the low efficacy of expectant management (47%) compared to surgical evacuation (95%)³. In the last 20 years, there has been increasing evidence on the effectiveness of medical management using different regimens of misoprostol sometimes in combination with mifepristone⁴⁻⁸. Some local studies⁹⁻¹¹ also support the use of medical management of early pregnancy failure. A meta-analysis reported the success rate of medical management in early miscarriage was about 62%¹¹.

medical and expectant management with surgical management of first-trimester miscarriage (the MIST trial) showed that the likelihood of gynaecological infection after medical management of first-trimester miscarriage was low (2-3%)¹², and comparable to surgical treatment. With more emerging evidence of its safety and effectiveness in early pregnancy failure, in 2008 our department introduced medical treatment for missed miscarriages (using 800-µg misoprostol as a single dose via the vaginal route).

Various medical methods have been studied for using prostaglandin analogues with or without antiprogestone priming. The efficacy rate ranged from 13 to 96%, and was influenced by various factors. Among those receiving high-dose misoprostol (1200-1400 µg),

In 2006, a randomised controlled trial comparing

Correspondence to: Dr. MC Chan

Email: dr.mcchan@hotmail.com.hk

prostaglandins administered vaginally and clinical follow-up without routine ultrasound were important attributes leading to high success rates (70-96%)¹³. Misoprostol has been used for a long time in obstetrics and gynaecology. There are studies of the pharmacokinetics of misoprostol given by different routes and its effects on the uterus¹⁴⁻¹⁶, and there are suggestions on its use for different indications (e.g. induction of labour in a live pregnancy or treatment of postpartum haemorrhage). Local authors have also summarised the success rates of commonly used vaginal misoprostol regimens in missed miscarriage, although there is still no standard regimen, not even from the World Health Organization¹⁷. In a review article published in 2009 in the *British Journal of Obstetrics and Gynaecology*¹⁸, the author recommended a regimen for early fetal demise using 800- μ g vaginal misoprostol every 3 hours (maximum of 2 doses), or 600 μ g sublingually every 3 hours (maximum of 2 doses).

After a literature research, in 2008 our hospital conducted a study using a single dose of vaginal misoprostol at 800 μ g. This regimen was adopted based on a review article¹⁹ published in the *International Journal of Gynecology and Obstetrics* (IJGO) which pointed out that after both sublingual and vaginal administration, serum levels of misoprostol were higher than after rectal or oral dosing. In another study analysing mean plasma concentrations of misoprostol against time, the 'area under the curve' values were higher after vaginal and sublingual administration than other routes¹⁵. Compared to sublingual dosing, the vaginal route drug concentrations were sustained at a low level for a longer period of time. Hence a single-dose vaginal regimen of misoprostol was expected to last considerably longer. Another review article in the same edition of the IJGO suggested that a single vaginal dose of misoprostol 800 μ g might be an effective and safe alternative to traditional surgical treatment of first-trimester miscarriage²⁰.

The aim of our study was to evaluate the efficacy of a single dose of vaginal misoprostol (800 μ g) in the management of early missed miscarriage.

Methods

A retrospective study was conducted by reviewing the 2009 data of patients who received medical evacuation for missed miscarriage at or before 13 weeks of gestation.

We defined early embryonic demise as an intact gestation sac of greater than 20 mm mean diameter with no other internal structures, or a gestational sac with diameters of less than 20 mm with no interval growth in 7

to 10 days. Early fetal demise was defined as a fetal pole with a crown-rump length of over 6 mm with no heart activity, or a fetus with crown rump length of less than 6 mm with no heartbeat and no growth in 7 to 10 days based on transvaginal ultrasound scanning²¹.

Exclusion criteria for the diagnosis of silent miscarriage were severe haemorrhage or pain at presentation, body temperature exceeding 37.6°C, severe asthma, twin or higher-order pregnancy, suspected ectopic pregnancy, suspected molar pregnancy or hydropic abortion and allergy to misoprostol.

Women diagnosed with a missed miscarriage at or before 13 weeks in the gynaecological ward or at the early pregnancy assessment clinic would be offered expectant, medical, or surgical treatment. Thorough counselling about these treatment modalities was offered, including their efficacy, associated risks, complication rates, and the follow-up plans. Informed consent was then obtained. For women who decided on medical treatment, four 200- μ g tablets of misoprostol were inserted into the posterior vaginal fornix, and the patient was discharged. An information sheet of the drug effects and potential side-effects, 1-week course of analgesics and a container for tissue mass passage were given at that time. The patient was advised to bring back any passed tissue mass for pathological examination. A 24-hour telephone access to the gynaecological ward (for enquiries) was provided.

Ward follow-up was arranged after about 1 week. Transvaginal ultrasound examination with digital vaginal examination was performed to determine the result of the medical treatment. On transvaginal ultrasound, endometrial thickness of 10 mm or less was regarded as complete evacuation, while any thickness of more than 10 mm was diagnosed as incomplete miscarriage. For women diagnosed as having an incomplete evacuation, the options of conservative management (wait and rescan), second dose of misoprostol (600 μ g orally), or surgical evacuation were offered. All the tissue masses passed after misoprostol treatment and those obtained at surgical evacuation were sent for pathological examination. For women complaining of abnormal vaginal discharge, or tenderness elicited during the vaginal examination, a high vaginal swab was taken and treatment with a course of antibiotics commenced. Subsequent follow-up or management was carried out according to individual circumstances.

The data were analysed using the Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc,

US). The Hosmer and Lemeshow test was used to assess the goodness-to-fit for categorical variables. Multiple binary regression was performed to analyse the influence of different factors on the success of misoprostol evacuation. A p value of less than 0.05 was considered statistically significant.

Results

Demographics

In 2009 (the period studied), there were 307 patients diagnosed with missed miscarriages in Tuen Mun Hospital; 109 patients opted for surgical evacuation as primary management while 198 decided on medical evacuation. More women preferred medical than surgical evacuations (64% vs 36%), and none chose conservative management. Among the 198 patients, five defaulted their first follow-up; and another five patients were early twin pregnancy failures. These 10 patients were excluded from the study. The three others who defaulted subsequent follow-up were also excluded from the analysis. Thus, the results of 185 cases were analysed.

Among the 185 patients, 179 (97%) were Chinese, 4 (2%) were Nepalese and 2 (1%) were Caucasian (Table 1). Since there were only a few non-Chinese, racial factors were not subjected to analysis.

The patients were aged 17 to 46 (median, 32) years. A large proportion of them were either nulliparous (43%) or primiparous (39%). The mean parity was 0.8. Concerning their previous delivery experience, 38% (n=70) of the study group had had previous vaginal deliveries only, 17% (n=31) had had a Caesarean section only, while 2% (n=4) had experienced both. Moreover, 54% (n=99) had a history of one or more miscarriages/abortions.

A majority of the patients (68%; n=126) who received medical evacuation in this study had a fetal demise. The anembryonic group consisted of 32% (empty sac 22% and in-utero sac yolk sac 10%). The mean sac diameter ranged from 6 to 33 mm with a mean of 19 mm.

Clinical Response and Management

The majority of the first follow-up sessions were scheduled after about 1 week (mean 8, range 6-13) days. The timing of the follow-up varied depending on availability of vacancies in the follow-up sessions (e.g. public holiday) and patient preference.

Among the 185 patients receiving misoprostol treatment that were analysed, 88% (n=162) reported the

passage of tissue mass, of whom 152 reported the time or date of such passage, of which the majority (64%; n=97/152) occurred on the same day as misoprostol treatment. Moreover, 75% (n=121/162) of the patients reporting passage of tissue mass achieved complete medical evacuation (Table 2).

The reported time of tissue mass passage ranged from day 0 (within 24 hours) to day 5; in one case, tissue mass was removed during gynaecological examination at the first follow-up (day 8). The median time of tissue mass passage was day 0 (Table 2).

The distribution of the patients receiving vaginal misoprostol and its success rate is shown in Table 3. More

Table 1. Patient demographics

Demographics	No. (%) or median (range)
Race	
Chinese	179 (97%)
Non-Chinese	6 (3%)
Age (years)	
<20	5 (3%)
20-24	21 (11%)
25-29	26 (14%)
30-34	65 (35%)
≥35	68 (37%)
Median (range)	32 (17-46)
Previous miscarriages / abortions	99 (54%)
Spontaneous complete miscarriage	15 (8%)
Previous dilation and curettage	82 (44%)
Previous medical abortion	16 (9%)
No. of previous delivery	
0	80 (43%)
1	73 (39%)
2	28 (15%)
3	4 (2%)
Median	1
Previous delivery experience	
Never	80 (43%)
Vaginal deliveries only	70 (38%)
Caesarean deliveries only	31 (17%)
Both	4 (2%)
Status of the index miscarriage	
Empty in-utero sac	40 (22%)
In-utero sac with yolk sac seen	19 (10%)
Fetal pole without pulsation	126 (68%)

Table 2. The relationship between the response and the success rate at the first follow-up

	Complete miscarriage	Incomplete miscarriage	Total
Report of tissue mass passage	121	41	162
Reporting of tissue mass passage with time	114	38	152
Day 0	74	23	97
Day 1	23	9	32
Day 2	6	2	8
Day 3	4	1	5
Day 4	2	1	3
Day 5	4	1	5
Day 6	0	0	0
Day 7	0	0	0
Day 8	1	1	2
Reporting of tissue mass passage without time	7	3	10
No tissue mass passage reported	13	10	23
Total	134	51	185

Table 3. The success rate of medical evacuation after missed miscarriage at different gestational ages

Maturity (in completed weeks)	Successful cases (n = 134)	Failed cases (n = 51)	Total No. of cases (n = 185)
<7	50 (75%)	17 (25%)	67
7	25 (93%)	2 (7%)	27
8	28 (60%)	19 (40%)	47
9	12 (67%)	6 (33%)	18
10	8 (67%)	4 (33%)	12
11	8 (80%)	2 (20%)	10
12	2 (100%)	0	2
13	1 (50%)	1 (50%)	2

patients obtained successful medical evacuation at or less than 7 weeks' gestations and between 11 and 12 weeks' gestation.

The success rate of misoprostol evacuation of the uterus was 73% (n=134). Among the successful cases, 86% (n=115/134; Figure) had achieved complete evacuation by the first follow-up, whereas 12% (n=16) and 2% (n=3) of the successful cases were noted to have achieved complete evacuation only at the second and third follow-up, respectively.

At the first follow-up, 70 patients were found to have incomplete miscarriage, of whom 30 proceeded to surgical evacuation after counselling, but 31 of them opted for conservative management (second follow-up without additional treatment). The remaining 9 opted to take a second dose of misoprostol (600 µg orally) and were followed up.

At the second follow-up, 40 patients were assessed. Of whom 16 achieved complete miscarriage (including 2 who received a second dose of misoprostol). Among the 24 cases of incomplete miscarriage, 18 had surgical evacuation (1 of whom had signs of infection at the second follow-up), and 1 opted for a third dose of misoprostol (600 µg), and 1 opted for her first repeated misoprostol (conservative management in the first ward follow-up but 600 µg orally was prescribed at the second follow-up). Four patients preferred continuing with conservative management (Figure).

At the third follow-up, three of six patients achieved complete evacuation (1 had had a repeated misoprostol dose at first follow-up but conservative management at the second, 1 had a repeated misoprostol dose only at the second follow-up, 1 was given two oral doses of misoprostol). The remaining three patients were diagnosed to have persistently incomplete evacuation and received

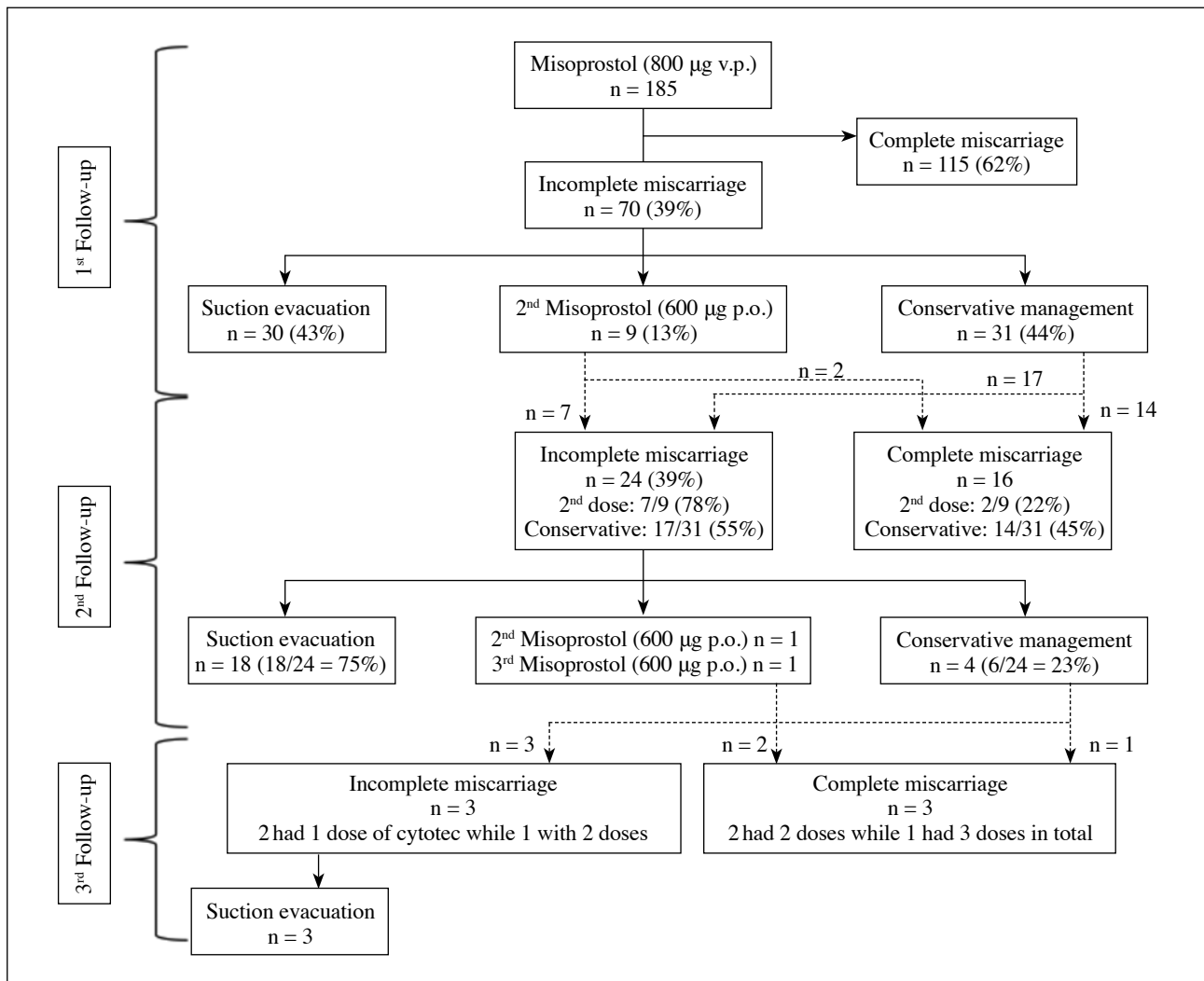


Figure. Flowchart of treatment

evacuation of the uterus by suction (2 of whom had one dose of misoprostol while the third patient had tried two doses of misoprostol).

Among the 188 patients who received medical treatment, 67% (n=125) called back for enquiries. The majority did so for the advice after tissue mass passage, while one called back for general enquiries.

Predictive Factors of Successful Medical Evacuation

All the 185 cases were analysed by multiple regression using SPSS. The more the number of previous episodes of miscarriages/abortions, the less the likelihood of success with misoprostol treatment (odds ratio [OR]=0.64, $p=0.001$). Our data also found that the reporting of mass passage within 24 hours and the anembryonic status of the index miscarriage were more likely to be associated with complete medical evacuation, although the results were not statistically significant (OR=1.44, $p=0.292$ and OR=1.24, $p=0.584$, respectively). The age and number of previous

deliveries were not useful predictors of success of the misoprostol treatment (Table 4).

Adverse and Unpredicted Events

For those who had infections and emergency admissions, the overall complication rate was 5%.

Infection

There were four (2%) cases complicated by infection in this series, all of whom had incomplete miscarriages at the first follow-up; three suffered from localised infections and one had a positive blood culture.

The woman with a positive blood culture had signs of infection during gynaecological examination in the first follow-up. Intravenous antibiotics were started prior to the surgical evacuation, but she developed a high fever after the operation. High vaginal and endocervical swab cultures were negative, but the blood culture yielded *Dialister* species and *Eubacterium aerofaciens*.

Table 4. Predictive value of factors predisposing to successful misoprostol treatment

	Odds ratio (95% confidence interval)	p Value
Age	0.99 (0.93-1.05)	0.752
No. of previous deliveries	1.02 (0.63-1.67)	0.930
No. of previous miscarriages / abortions	0.64 (0.49-0.83)	0.001
Status (0 = single dead fetus, 1 = anembryonic)	1.24 (0.58-2.63)	0.584
Reported time of tissue mass passage (0 = no such report or >24 hours, 1 = <24 hours)	1.44 (0.73-2.86)	0.292

One of the three localised infections was detected in the first follow-up, surgical evacuation was performed and the operation was uneventful. Group B streptococcus was cultured in high vaginal swab. The other two localised infection cases were detected at the second follow-up, and were associated with incomplete miscarriage after a single dose of misoprostol. They received conservative management after counselling, but as the infections persisted at the second follow-up, surgical evacuation was performed. Endocervical swabs from both cases yielded enterococci.

None of the four patients endured major consequences after completing their antibiotic treatment and surgical evacuations. Our experience highlights the possibility of infection after missed miscarriages, especially after failed treatment. As long as medical evacuation is incomplete, the patients should be advised to watch out for any symptoms of infection and seek medical advice accordingly.

Emergency Admission

Six patients (3%) had unscheduled emergency admissions to the gynaecological ward, all within the first 2 days of misoprostol treatment and were associated with vaginal bleeding with tissue mass passage; three had complete and three had incomplete miscarriages. The latter three patients refused conservative management or further misoprostol therapy and had surgical evacuations. None of them were anaemic and none received blood transfusions.

Partial Molar Pregnancy

In our study of almost 200 patients using misoprostol treatment, there was one partial molar pregnancy. The patient was diagnosed to have a failed pregnancy at 10 weeks of gestation based on the last menstrual period. Transvaginal ultrasound showed an intrauterine sac with yolk sac only, no features of molar changes were apparent. The products of gestation passed out on the day she took misoprostol. Incomplete evacuation was detected at the

first follow-up and hence suction evacuation was arranged. Just before the operation, the pathology of the tissue mass was reported as partial hydatidiform mole. Chest X-ray and serum beta-human chorionic gonadotropin (β -HCG) were checked before the operation; the β -HCG level was 521.7 IU/L. One week after the surgical evacuation, the level dropped to 56.3 U/L, and was normal 8 weeks later. After 1-year follow-up at our mole specialist clinic, there was no biochemical or clinical evidence of recurrence of gestational trophoblastic disease.

Discussion

Medical Evacuation of Early Missed Miscarriage by Misoprostol

In our study, after excluding the 10 patients who had repeated doses of misoprostol, the success rate of single-dose vaginal misoprostol treatment was 70% (n=129/185). This rate was lower than that in another study using repeated doses of vaginal misoprostol⁹, which achieved a success rate of 83%. The acceptability of such an intensive regimen (drug given on days 1, 3, and 5) may need further evaluation. Another local study compared surgical evacuation and vaginal misoprostol (using the day 1, 3, 5 misoprostol with or without water) in first-trimester termination of pregnancy²². This investigation reported low acceptability of the misoprostol regimen; 40% of women would not choose the medical treatment again, as it was inconvenient and required repeated visits.

Compared with an overseas study²³ using a similar regimen (single dose of 800- μ g vaginal misoprostol, repeated dose on day 3 in selected cases), our success rate was similar. In that report, patients with a persistent in-utero gestational sac (for both anembryonic and fetal demise cases) on day-3 follow-up had a repeated dose of misoprostol. The quoted success rates were 71% and 84%, respectively in the single-dose and repeated-dose cases.

The pharmacokinetic / pharmacodynamic profile of misoprostol has been reviewed by local authors¹⁹. The onset of action through the vaginal route took 20 minutes

and its duration of action was about 4 hours. In our study, 162 women reported tissue mass passage after misoprostol and 129 (80%) of them reported that the time to passage of tissue mass was within 2 days (i.e. day 0 and day 1 after taking misoprostol; Table 2). Among them, 75% (97/129) had a successful medical evacuation, although its timing was not a significant factor in the analysis as stated above. Another 17 patients reported later passage of tissue mass (days 2 to 8) but also achieved successful medical treatment. It appeared that the follow-up time at 1 week, rather than the shorter 3-day interval in other studies might be more appropriate, as 17/134 (13%) achieved complete miscarriage later. On the other hand, 31 patients who had incomplete miscarriage at the first follow-up chose conservative treatment (i.e. no more misoprostol dosing), 14 nevertheless achieved complete evacuation. Obviously, despite the pharmacodynamics of misoprostol, waiting for a longer period increases the success rate.

Ten patients had received repeated dose (600- μ g oral misoprostol) during subsequent follow-up, and in them the success rate was only 50% (n=5). Since only a small number of women received repeated dose in our study, we could not conclude whether there might be any significant difference in the success rate after repeated doses.

Predictors of Successful Medical Evacuation by Misoprostol

In two overseas studies^{23,24}, the authors demonstrated significant predictors of success after repeated dose of misoprostol treatment, namely nulliparity or one previous delivery, vaginal bleeding within 24 hours, and an opened os on day 3 of misoprostol treatment. Since the amount of vaginal bleeding was only 'subjectively' assessed, blood loss was not included in our analysis. However, we did find nulliparity (79%) a primiparity (67%) having a high success rate, though the number of previous deliveries per se did not yield a statistically significant correlation (OR=1.02, p=0.930). Instead, number of previous miscarriages / abortions (despite the management) showed a significant negative effect on the success of misoprostol treatment (OR=0.64, p=0.001) [Table 4]. Further studies are needed to evaluate the efficacy of different misoprostol regimens among patients with different parities.

Adverse Outcomes of Medical Evacuation by Misoprostol

Medical evacuation has been documented to increase the risk of chemotherapy in gestational trophoblastic disease²³. The use of medical evacuation as primary treatment in early miscarriages therefore imposes potential harm on these patients, as some molar pregnancies

in early gestation may mimic the picture of anembryonic miscarriage. Notably, in partial molar pregnancies, a fetal component may be detected on ultrasound. Furthermore, the prevalence of gestational trophoblastic disease is higher in Asians, and is reported 1 in 387 live births versus 1 in 714 in non-Asians²⁵. The prevalence of gestational trophoblastic disease in Hong Kong was quoted to be 4.1 per 1000 deliveries²⁶. It is therefore important to undertake pathological examination of the products of gestation for all women who receive medical evacuation of the uterus for early miscarriage.

There were six cases of unplanned emergency admissions in our study, all due to 'subjective' heavy bleeding and passage of products of gestation. Although clinical assessment did not reveal significant bleeding, three of them had emergency surgical evacuations due to incomplete medical evacuations. The remaining three actually had complete abortions and were discharged from hospital. In our study, strategies for risk management were applied to reduce emergency admissions. These included a 24-hour phone line for enquiries, and an information leaflet about the potential side-effects of the medical treatment. Nevertheless, access to emergency admission should still be provided in units conducting medical evacuation of the uterus.

There were four cases complicated by infection, all of whom had incomplete miscarriages at the first follow-up. Infection was diagnosed in the first follow-up in two of them and at the second follow-up in the other two. None had major consequences after completing their antibiotic courses and surgical evacuation. Our experience highlights the importance of considering possible infection in those with missed / incomplete miscarriages after being offered medical evacuation, and patients should be duly advised to watch out for any symptoms of infection and seek medical advice accordingly. Prophylactic antibiotics for all women receiving medical evacuation may reduce the infection risk. The potential for allergic reactions and inducing antibiotic-resistant bacteria could be reasons for resisting such a strategy. In our study, all the infections were in patients with failed medical evacuations. Undertaking vaginal swabs at the first follow-up for all asymptomatic patients with failed medical evacuations may be appropriate, as half of the patients developing the infections were detected at the second follow-up.

Conclusion

A single dose of 800 μ g of vaginal misoprostol is an effective treatment for early pregnancy failure. Follow-

up in 1 week's time is appropriate to review the response. Most of the responses occurred within 48 hours, but some patients did so later. Repeated doses of misoprostol may increase the success rate, but may not be acceptable to women, though persistent incomplete miscarriage (and infections) would still need to be considered. The products of gestation should always be examined histologically, in view of the high prevalence of gestational trophoblastic disease in our locality. Further studies on different

regimens, including the timing and doses of repeated treatment, and their acceptability are necessary, and may help us to provide more effective and acceptable treatment for early pregnancy failure.

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