RESEARCH ARTICLE

Misoprostol use in medical evacuation of spontaneous miscarriage: Pilot drug use evaluation study at the Women’s Hospital in Qatar
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ABSTRACT

Background: Misoprostol is a synthetic prostaglandin E1 that induces cervical effacement and uterine contractions at all gestational ages, thus facilitating uterine evacuation and pregnancy termination. Successful medical evacuation of spontaneous miscarriage with minimal adverse effects can be performed using misoprostol–only regimen if given as indicated and if the administered dose, frequency of the dosage, and number of total doses are appropriate.

Aim: To conduct a drug use evaluation by investigating indications, appropriateness of dosing, and clinical outcome of misoprostol-only regimen when used for medical evacuation of spontaneous miscarriage at the Women’s Hospital in Doha, Qatar.

Materials and methods: A retrospective descriptive drug use evaluation was conducted on women with spontaneous miscarriage who received misoprostol for medical evacuation during August 2013. The current practice at the Women’s Hospital was compared with the recommendation from the World Health Organization (WHO). Patients were stratified into three groups based on weeks of amenorrhea.

Results: A total of 107 patients received misoprostol during August 2013, of which 33 (31%) were included in the study. In these patients, the main indication for misoprostol use was missed miscarriage (54.5%). In the group of patients at ≥9 weeks of gestation, 80% received an initial dose of 800 µg, 80% received frequency within the WHO recommendation, and the majority had surgical evacuation (80%). In the group of patients at 10–12 weeks of gestation, more than 80% received an initial dose of 800 µg, 6% received frequency within the WHO recommendation, and more than 75% had successful evacuation.

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Misoprostol use in medical evacuation of spontaneous miscarriage

ElSalem et al.

INTRODUCTION

Miscarriage is termination of pregnancy before 20 weeks of gestation with a fetus/embryo weighing ≤ 500 g.1–4 Pregnancy termination can be either spontaneous or induced.1,2 Spontaneous miscarriages are categorized as threatened miscarriage, inevitable miscarriage, incomplete miscarriage, missed miscarriage, septic miscarriage, and complete miscarriage.2 Medical evacuation of spontaneous miscarriage has expanded over the past two decades as a safe, effective, and feasible alternative to surgical uterine evacuation.2,3

Medical options include combination of methotrexate and misoprostol, combination of mifepristone and misoprostol, and misoprostol-only regimen.2 In the Women's Hospital (WH) in Doha, Qatar, misoprostol-only regimen is widely used in the first- and second-trimester for medical evacuation of spontaneous miscarriage. The sale of misoprostol increased between 2002 and 2007 in the Middle East region, with an increase of retail pharmacy sales by 1022%.5 The use of misoprostol-only regimen neither in the Middle East nor in Qatar has previously been reported in the literature.

Misoprostol is a synthetic prostaglandin E1 that induces cervical effacement and uterine contractions at all gestational ages, thus facilitating uterine evacuation and pregnancy termination.2,4,6 The World Health Organization (WHO) approved the regimen of misoprostol that differs according to the gestational age based on the weeks of amenorrhea or last menstrual period (LMP).2,7–10 For women at ≤ 9 weeks of gestation, misoprostol is given as 800 μg per vaginal (PV) every 3 to 12 hours with a total of two doses and a third dose can be given only if miscarriage is not complete after 48 hours of the second dose.7,8,10 For women at 10 – 12 weeks of gestation, misoprostol is given as 800 μg PV every 12 hours with a maximum of three doses.7,9–11 For women at 13 – 22 weeks of gestation, misoprostol is given as 400 μg PV every 3 – 6 hours with a maximum of five doses or as 600 μg PV every 12 hours, and both of these different protocols can be repeated after 24 hours if miscarriage is not complete.8–11 For women at ≥ 23 weeks of gestation, there is no well-established regimen; however, it may be wise to use a decreased dose due to increased uterine sensitivity to prostaglandins with increasing gestational age.8–11 Therefore, one option is to give misoprostol as 400 μg PV every six hours.2,8,10,11 The success rate of pregnancy termination does not increase with intake of any additional dose more than the recommended maximum number of doses, but rather the success rate will be static with increased incidence of adverse effects.2–4,8,10,11

The WHO defines drug use evaluation (DUE) as “a system of continuous, systematic, criteria-based drug evaluation that ensures the appropriate use of drugs. It is a method of obtaining information to identify problems related to drug use and if properly developed, it also provides a means of correcting the problem and thereby contributes to rational drug therapy”.12 Furthermore, DUE can evaluate the administration/dispensing process of a medication,12 which includes assessment of appropriate indications, dose, route of administration, and duration of therapy.12 Moreover, DUE can be used to evaluate the outcomes of therapy used.12 Misoprostol-only regimen can be used for medical evacuation of spontaneous miscarriage successfully with minimal adverse effects if given as indicated and if the administered dose, frequency of the dosage, and number of total doses are appropriate.13 Accordingly, the aim of this study was to perform a DUE by investigating the appropriateness of dosing, dosing frequency, the number of administered doses of misoprostol, and the clinical outcome in patients with spontaneous miscarriage who aim for complete evacuation of spontaneous miscarriage at WH, Doha, Qatar. In addition, the current practices at WH were compared with the WHO recommendations.
MATERIALS AND METHODS

Study design
This study was a retrospective, descriptive, observational, single-centered, pilot drug use evaluation study. It was conducted at the Medical Records Department of the Women’s Hospital, Doha, Qatar. The hospital has 334 beds for antenatal, postnatal, and gynecology cases and 80 beds for neonatal intensive care units (NICU).

Patients
The study included women with spontaneous miscarriage who received misoprostol-only regimen as a medical evacuation therapy during August 2013. Alternatively, women who received misoprostol for indications other than spontaneous miscarriage and women who received misoprostol in combination with mifepristone were excluded from the study. Patients were stratified into the following three groups based on weeks of amenorrhea: patients at ≤9 weeks of gestation, patients at 10–12 weeks of gestation, and patients at 13–22 weeks of gestation.

Data collection
All misoprostol prescriptions during the month of August 2013 were collected from the narcotics room in the WH Pharmacy Department. Medical records were contacted to retrieve the patients' data using a pre-prepared data collection sheet. Patients’ eligibility screening was performed during the data collection process. The following data were collected: 1) demographics; 2) past medical and obstetric/gynecological history; 3) gestational age by last menstrual period; 4) indications for using misoprostol-only regimen; 5) details of misoprostol-only regimen dosing; 6) clinical outcome; and 7) waiting time between the medical and surgical evacuation. The current practice at WH was compared with the WHO recommendation.

Ethical considerations
Ethics approval was obtained from the Hamad Medical Research Center, Institutional Review Board (IRB), and a waiver of signed informed consent was obtained.

Measured outcomes
The outcomes measured in this study were as follows:
1. Indications for using misoprostol-only regimen.
2. Appropriateness of the dosing, dosing frequency, and the number of administered doses of misoprostol.
3. Clinical outcome of using misoprostol-only regimen: successful medical evacuation of spontaneous miscarriage versus unsuccessful evacuation and the need for surgical uterine evacuation.
4. Reasons for surgical uterine evacuation after the use of misoprostol-only regimen.
5. Waiting time between the use of misoprostol-only regimen and the need for surgical uterine evacuation.
6. Comparison of the current practice at WH with the WHO recommendation.

Statistical analysis
Data were analyzed using descriptive analysis. All data are presented as frequencies and percentages, unless otherwise stated. Comparisons were done using Student’s t test and Pearson’s correlations in Microsoft Excel 2010.

RESULTS
A total of 107 patients had at least one prescription of misoprostol during August 2013. Of these, 33 (31%) met the study inclusion criteria and were included in the analysis. The patients' demographics are summarized in Table 1. The majority of the patients were older than 30 years of age (69.7%) and most of the patients were of Arab origin (63.7%). Most of the women (58%) were multiparous. Approximately 24% of the patients had a history of miscarriage and 18% had a history of lower segment cesarean section delivery (Table 2). The main indication for using misoprostol-only regimen was missed miscarriage (54.5%), followed by incomplete

| Table 1. Demographics of the patients. |
| --- |
| Age |
| n (%) |
| <20 years | 1 (3) |
| 21–30 years | 9 (27.3) |
| 31–40 years | 18 (54.5) |
| >40 years | 5 (15.2) |
| Nationality |
| n (%) |
| Qatari | 15 (45.5) |
| Indian | 5 (15.2) |
| Sudanese | 3 (9.1) |
| Pakistani | 4 (12) |
| Other Arab nationalities | 3 (9.1) |
| Other non-Arab nationalities | 3 (9.1) |
miscarriage (33.3%), septic miscarriage (6.1%), and abnormal baby (6.1%). Appropriateness of misoprostol-only regimen dosing was assessed in the patients included in the study. The patients’ data were divided into three groups based on their gestational age: patients at ≤9 weeks of gestation (15.2%), patients at 10–12 weeks of gestation (51.5%), and patients at 13–22 weeks of gestation (33.3%).

The first group included patients at ≤9 weeks of gestation, of which more than 80% received an initial dose of 800 μg misoprostol and approximately 70% continued the regimen with 400 μg dose. Only 6% received frequency within the WHO recommendation, and more than 60% received ≤3 total doses of misoprostol. Most of the patients (76.5%) had successful medical evacuation as a clinical outcome. The waiting time between the use of misoprostol-only regimen and surgical evacuation was within 24 hours for 75% of patients (Table 4).

The second group included patients at 10–12 weeks of gestation, of which more than 80% received an initial dose of 800 μg misoprostol and approximately 70% continued the regimen with 400 μg dose. Only 6% received frequency within the WHO recommendation, and more than 60% received ≤3 total doses of misoprostol. Most of the patients (76.5%) had successful medical evacuation as a clinical outcome. The waiting time between the use of misoprostol-only regimen and surgical evacuation was within 24 hours for 75% of patients (Table 4).

Table 2. Past medical and gynecological history.

| Drug allergy                      | n (%)   |
|-----------------------------------|---------|
| No known drug allergy             | 30 (90.9) |
| Others, e.g. penicillin, ibuprofen, paracetamol | 3 (9.1) |

| Medical history                   |         |
|-----------------------------------|---------|
| None                              | 24 (72.9) |
| Hypothyroidism                    | 6 (18) |
| Hypertension                      | 2 (6.1) |
| Asthma                            | 1 (3) |

| Surgical history                  |         |
|-----------------------------------|---------|
| None                              | 24 (73) |
| Lower segment cesarean section    | 6 (18) |
| Evacuation                        | 1 (3) |
| Appendectomy                      | 2 (6) |

| Gestational age by LMP            |         |
|-----------------------------------|---------|
| ≤9 weeks                          | 5 (15.2) |
| 10–12 weeks                       | 17 (51.5) |
| 13–22 weeks                       | 11 (33.3) |
| ≥23 weeks                         | 0 |

| Parity                            |         |
|-----------------------------------|---------|
| P0                                | 7 (21) |
| P1                                | 7 (21) |

| Multiparous (≥P2)                 | 19 (58) |

| Gynecological history             |         |
|-----------------------------------|---------|
| None                              | 25 (75.8) |
| Miscarriage                       | 8 (24.2) |

Table 3. Appropriateness of misoprostol-only regimen dosing for patients at ≤9 weeks of gestation.

| Characteristics | n (%)   |
|-----------------|---------|
| Initial dose    |         |
| Appropriate 800 μg | 4 (80) |
| Inappropriate 400 μg | 1 (20) |

| Next doses | n (%)   |
|------------|---------|
| Appropriate 800 μg | 0 |
| Inappropriate 400 μg | 5 (100) |
| Inappropriate 200 μg | 0 |

| Route | n (%)   |
|-------|---------|
| PF    | 5 (100) |

| Frequency | n (%)   |
|-----------|---------|
| Average and range of administered frequency in hours | 5.8 (4–13) |

| Number of patients received frequency within the WHO recommendation (every 3–12 h) | 4 (80) |
| Number of patients received frequency as prescribed by the physician (every 4 h) | 2 (20) |

| Number of doses | n (%)   |
|-----------------|---------|
| 1 dose          | 0 |
| 2 doses         | 1 (20) |
| 3 doses         | 2 (40) |
| ≥4 doses        | 2 (40) |

| Clinical outcome | n (%)   |
|------------------|---------|
| Successful medical termination | 1 (20) |
| Surgical termination/reasons | 4 (80) |

| Waiting time between the use of misoprostol-only regimen and surgical evacuation | n (%)   |
|---------------------------------------------------------------------------------|---------|
| Within 24 h                        | 4 (100) |
| Within 48 h                        | 0 |
| ≥72 h                              | 0 |
The third group included patients at 13–22 weeks of gestation, of which more than 80% received an initial dose of 400 mg misoprostol and more than 70% continued the regimen with 400 mg dose. More than 80% of patients received frequency within the WHO recommendation and more than 70% received ≥2 total doses of misoprostol. More than 50% had successful medical evacuation as a clinical outcome. The waiting time between the use of misoprostol–only regimen and surgical evacuation was within 24 hours for 60% of patients (Table 5). Among all the patient groups, 20 patients (61%) had successful medical evacuation as a clinical outcome.

**DISCUSSION**

Misoprostol is a synthetic prostaglandin E1 that induces cervical effacement and uterine contractions at all gestational ages, thus facilitating uterine evacuation and pregnancy termination.2,4,6

Table 4. Appropriateness of misoprostol-only regimen dosing for patients at 10–12 weeks of gestation.

| Characteristics                       | n (%)   |
|---------------------------------------|---------|
| **Initial dose**                      |         |
| Appropriate 800 µg                   | 14 (82.4)|
| Inappropriate 400 µg                 | 3 (17.6)|
| **Next doses**                        |         |
| Appropriate 800 µg                   | 12 (70.5)|
| Inappropriate 400 µg                 | 1 (6)   |
| **Route**                             |         |
| PF                                    | 17 (100)|
| **Frequency**                         |         |
| Average and range of administered frequency in hours | 6.4 (2.5–19) |
| Number of patients received frequency within the WHO recommendation (every 12 h) | 1 (6) |
| Number of patients received frequency as prescribed by the physician (every 4 h) | 8 (47) |
| **Number of doses**                   |         |
| 1 dose                                | 4 (23.5) |
| 2 doses                               | 3 (17.6) |
| 3 doses                               | 4 (23.5) |
| ≥4 doses                              | 6 (35.4) |
| **Clinical outcome**                  |         |
| Successful medical termination        | 13 (76.5)|
| Surgical termination/reasons          | 4 (23.5) |
| **Waiting time between the use of misoprostol-only regimen and surgical evacuation** |         |
| Within 24 h                           | 3 (75)  |
| Within 48 h                           | 1 (25)  |
| ≥72 h                                 | 0       |

Table 5. Appropriateness of misoprostol-only regimen dosing for patients at 13–22 weeks of gestation.

| Characteristics                       | n (%)   |
|---------------------------------------|---------|
| **Initial dose**                      |         |
| Appropriate 400 µg                   | 2 (18.2) |
| Inappropriate 800 µg                 | 9 (81.8) |
| **Next doses**                        |         |
| Appropriate 400 µg                   | 8 (73)  |
| Inappropriate 200 µg                 | 1 (9)   |
| **Route**                             |         |
| PF                                    | 11 (100) |
| **Frequency**                         |         |
| Average and range of administered frequency in hours | 5.3 (4–13) |
| Number of patients received frequency within the WHO recommendation (every 3–6 h) | 9 (81.8) |
| Number of patients received frequency as prescribed by the physician (every 4 h) | 10 (91) |
| **Number of doses**                   |         |
| 1 dose                                | 3 (27.3) |
| 2 doses                               | 5 (45.5) |
| 3 doses                               | 2 (18.2) |
| ≥4 doses                              | 1 (9)   |
| **Clinical outcome**                  |         |
| Successful medical termination        | 6 (54.5) |
| Surgical termination/reasons          | 5 (45.5) |
| **Waiting time between the use of misoprostol-only regimen and surgical evacuation** |         |
| Within 24 h                           | 3 (60)  |
| Within 48 h                           | 1 (20)  |
| ≥72 h                                 | 1 (20)  |
In this pilot DUE, the main indication for using misoprostol was missed miscarriage. In the group of patients at ≤ 9 weeks of gestation, most of the women received frequency within the WHO recommendation but the majority of them had surgical evacuation. In the group of patients at 10–12 weeks of gestation, most of them did not receive frequency within the WHO recommendation but the majority had successful medical evacuation. In the group of patients at 13–22 weeks of gestation, the majority received frequency within the WHO recommendation and many had successful medical evacuation. Overall, more than 60% of patients had successful medical evacuation as a clinical outcome, but the current practice at WH was not always found to be in accordance with the WHO recommendation. This can be attributable to the lack of complete knowledge of the WHO recommendation. Furthermore, misoprostol-only regimen was perceived as an effective regimen regardless of the administered dose, frequency of the dosage, and number of doses. Thus, following the guidelines was not a priority practice.

Misoprostol-only regimen can be used for medical evacuation of spontaneous miscarriage successfully with minimal adverse effects if given as indicated and if the administered dose, frequency of the dosage, and number of total doses are appropriate. Accordingly, this study performed a DUE by investigating the appropriateness of the dosing, dosing frequency, the number of administered doses of misoprostol, and the clinical outcome in patients with spontaneous miscarriage who aim for complete evacuation of spontaneous miscarriage at WH, Doha, Qatar.

In this DUE, the use of misoprostol-only regimen was found to be effective. Furthermore, it is a cheaper alternative when compared with other conventional prostaglandins. In a study conducted by Creinin, the efficacy, acceptability, and cost of medical therapy were compared with surgical evacuation and the study concluded that surgical evacuation requires around 10 times more personnel cost than medical evacuation using misoprostol.

In this DUE study, 10 out of the 13 patients who had surgical evacuation (77%) underwent evacuation within 24 hours of using misoprostol-only regimen. It is considered safe, particularly in the first trimester, to wait for two weeks after the misoprostol-only regimen and arrange for a follow-up scan. In this DUE study, the successful medical evacuation rate might have been higher if the patients were given more waiting time before surgical evacuation. This study was the first of its kind in Qatar to evaluate the indications, appropriateness of dosing, and clinical outcome of misoprostol-only regimen when used for medical evacuation of spontaneous miscarriage. Nevertheless, the study has some limitations. The study lacks the stratification of obstetric and gynecological history, for example, lower segment cesarean section, parity, and previous miscarriage. Furthermore, the sample size of the overall study was small, which can hinder the generalization of the study results. Studying the expected effectiveness of the WHO recommendation of misoprostol-only regimen might not be fully accurate. This is mainly because of the small sample size and the fact that this is a pilot study. The current practice at WH was neither in accordance with the WHO recommendation nor following the dosing frequency as prescribed by the physician. The results of this DUE can be used to improve the current practice at WH. The study results can be used as a starting point in standardizing the practice and dosing regimen of misoprostol at WH, Doha, Qatar. Further studies are needed to overcome the limitations of this study. Moreover, future studies must evaluate in depth the use of

In a study conducted by Sirimai et al., the successful medical evacuation rate was 74.1%. They reported that the use of misoprostol-only regimen is not contraindicated in patients with a history of lower segment cesarean section. This study included 19 patients with previous lower segment cesarean section. Of 19 patients, 16 (84.2%) had successful medical evacuation within 24 hours, two (10.5%) needed more than 24 hours for complete medical evacuation, and one (5.3%) needed laparotomy due to uterine rupture with previous scar. In this DUE study, patients who had a history of lower segment cesarean section received half of the misoprostol dose that was given to unscarred uterus patients. This is because patients with scarred uterus have higher rates of uterine rupture than patients with unscarred uterus.

In this DUE study, 10 out of the 13 patients who had surgical evacuation (77%) underwent evacuation within 24 hours of using misoprostol-only regimen. It is considered safe, particularly in the first trimester, to wait for two weeks after the misoprostol-only regimen and arrange for a follow-up scan. In this DUE study, the successful medical evacuation rate might have been higher if the patients were given more waiting time before surgical evacuation. This study was the first of its kind in Qatar to evaluate the indications, appropriateness of dosing, and clinical outcome of misoprostol-only regimen when used for medical evacuation of spontaneous miscarriage. Nevertheless, the study has some limitations. The study lacks the stratification of obstetric and gynecological history, for example, lower segment cesarean section, parity, and previous miscarriage. Furthermore, the sample size of the overall study was small, which can hinder the generalization of the study results. Studying the expected effectiveness of the WHO recommendation of misoprostol-only regimen might not be fully accurate. This is mainly because of the small sample size and the fact that this is a pilot study. The current practice at WH was neither in accordance with the WHO recommendation nor following the dosing frequency as prescribed by the physician. The results of this DUE can be used to improve the current practice at WH. The study results can be used as a starting point in standardizing the practice and dosing regimen of misoprostol at WH, Doha, Qatar. Further studies are needed to overcome the limitations of this study. Moreover, future studies must evaluate in depth the use of
misoprostol-only regimen in patients with a history of lower segment cesarean section, in multiparous patients, and in patients with previous miscarriage. Evaluating the use of misoprostol-only regimen in these patients will improve our understanding of the medical evacuation success rate when compared with women with insignificant obstetric/gynecological history.

CONCLUSIONS

In summary, although the current practice at WH was not always matching the WHO recommendation, most of the patients had successful medical evacuation as a clinical outcome.

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