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CLINICAL ARTICLE

Efficacy of misoprostol in relation to uterine position in the treatment of early pregnancy failure



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ABSTRACT

Objective: To evaluate the efficacy of misoprostol in the treatment of missed or incomplete abortion in relation to uterine position. **Methods:** In a retrospective cohort study, misoprostol was evaluated as first-line treatment for missed and incomplete abortion before 13 gestational weeks. Between 2009 and 2011, women received 600 µg of sublingual misoprostol for missed abortion or 400 µg for incomplete abortion. Follow-up examinations were performed 7–10 days later, with the option of a second administration of misoprostol. Success was defined by the absence of vaginal bleeding or sonographic signs of incomplete abortion, and falling levels of β-human chorionic gonadotropin. **Results:** In total, 111 women were included in the study. A single-dose regimen was effective for 73 (65.8%) women. The overall success rate, including repeat doses, was 73.0% (81/111). There were no significant differences in treatment success between women with missed abortion and those with incomplete abortion (56/89 [62.9%] vs 18/22 [81.8%]; $P=0.152$). Anteverted uterine position was associated with significantly higher success rates compared with diverging position (62/86 [72.1%] vs 4/18 [22.2%]; $P=0.001$). **Conclusion:** Misoprostol is an effective treatment for early pregnancy failure. Uterine position might impact the success of medical treatment for missed abortion.

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1. Introduction

Pregnancy loss without complete spontaneous expulsion in the first trimester of gestation affects up to 15% of confirmed pregnancies [1–3]. Missed abortion is defined as an arrest of embryonic development, an empty gestational sac, or an embryo without heartbeat with closed cervix and no/only slight bleeding. In the case of incomplete abortion, the cervix is opened, with vaginal bleeding and sonographic signs of retained products in the uterus.

For both conditions, manual dilation and curettage of the cervix has been the treatment of choice since the 1960s. In the late 1980s, vacuum aspiration became the standard and is now used in different modifications [4,5]. In recent years, medical treatment with misoprostol has been increasingly used as a low-cost, easy-to-use, and safe alternative to surgical management—with comparable results [6–13]—but research on timing and combination of medication is still ongoing [14]. Medical treatment is associated with high success rates compared with expectant management (88.5% vs 44.2%) [15]. Success rates for misoprostol treatment in cases of missed and incomplete abortion vary from 62% [16] to 90.7% [7], indicating that there might be additional factors affecting outcome. We hypothesized that uterine position has a

role. Uterine retroversion in non-pregnant women is a normal variant that does not usually cause symptoms. However, there are data [16] reporting a higher incidence of bleeding and spontaneous abortion in early pregnancy among women with retroversion of the uterus.

The aim of the present study was to analyze the impact of uterine position on the success of medical treatment with misoprostol for missed and incomplete abortion.

2. Materials and methods

In a retrospective cohort study at the Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria, misoprostol was evaluated as first-line treatment for missed and incomplete abortion in singleton gestations before 13 gestational weeks. Success was defined as a lack of substantial retained products of conception within the uterus, reduction of β-human chorionic gonadotropin (hCG) levels below 6 mIU/mL, and absence of severe vaginal bleeding. The study was approved by the Ethics Committee of the Medical University of Graz (IRB00002556).

Between January 1, 2009, and November 30, 2011, women who attended the study center received 600 µg of sublingual misoprostol for missed abortion or 400 µg of sublingual misoprostol for incomplete abortion, after providing informed consent [17,18]. Additionally, all women received analgesia with oral nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment options (surgical, expectant, or medical management) were offered equally, and women who opted for medical treatment were identified for inclusion in the study via keyword search

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of the digital medical records of the department. Keywords were “missed abortion,” “abortion,” “incomplete,” “AB [abortion],” “MA [missed abortion],” “miscarriage,” “anembryonic,” “molar,” “mole,” “empty sac,” “Cyproston,” “misoprostol,” “curettage,” “cur,” “vacuum,” “expectant,” “fetal loss,” and “loss.”

Before treatment began, all women underwent clinical examination and transvaginal ultrasound, and serum β -hCG levels were determined. Examinations were performed by a limited number of examiners in the outpatient department. Exclusion criteria were allergy to misoprostol or other prostaglandins, severe vaginal bleeding, ectopic pregnancy, critical hemodynamic status or shock, pelvic infection, and sepsis.

Follow-up examinations were performed 7–10 days after treatment, including transvaginal sonography and measurement of β -hCG levels. In the absence of severe vaginal bleeding with no evidence of retained products of conception on ultrasound, and with reduced β -hCG levels, expectant management was the method of choice. If there were substantial intrauterine retained products of conception on ultrasound imaging, with rising or steady β -hCG levels, repeat treatment with misoprostol (same dosage as that used for primary treatment) or curettage was offered [17,18]. If ultrasound revealed significant intrauterine residua, with decreasing β -hCG levels and no heavy bleeding, expectant management after waiting 1 week was the first-choice treatment. If further follow-up was necessary, a 7-day interval was common. Women were told to return earlier in cases of heavy vaginal bleeding, fever above 38.0°, or unbearable pain despite taking NSAIDs. After brief follow-up counseling, all women were discharged.

Timeline observations were performed to evaluate whether the time between primary treatment and return for first follow-up examination could have confounded treatment decision and type of further treatment. Information regarding uterine position was retrieved from ultrasound records or, if not documented, from digitally stored ultrasound images of the initial examination, and from surgery records when appropriate. Previous studies [16,19,20] of uterine position discussed mainly retroversion as a factor affecting adverse pregnancy outcome. Therefore, uterine position was categorized in the present study as anteverted (anteverted fundal position) or diverging (retroverted and axial fundal position). Cervicouterine axis (flexion) was not used for group classification.

Demographic and clinical data were extracted from the local medical documentation systems (ViewPoint [GE Healthcare, Chalfont St Giles, UK] and openMEDOCS [SAP Austria, Vienna, Austria]).

SPSS version 18.0 (IBM, Armonk, NY, USA) was used for data analysis. Group comparisons were conducted via *t* test for independent groups and Mann–Whitney *U* test. The normality of data distribution was tested via Kolmogorov–Smirnov test, Q–Q plot, and analysis of variance. Categorical variables were compared with Pearson χ^2 test (using the exact option in SPSS) or Fisher exact test for expectation values below 5. For all tests, a significance level of 0.05 was used.

3. Results

In total, 111 women (89 [80.2%] with missed abortion and 22 [19.8%] with incomplete abortion) were included in the study. Successful treatment with a single dose of misoprostol was achieved in 73 (65.8%) cases. The overall success rate of medical treatment (including the 8 women treated successfully with a repeat dose of misoprostol) was 73.0% (81/111). Curettage was required in 25 (22.5%) cases after failure of medical treatment, and in 5 (4.5%) cases after 2 failed applications of misoprostol.

There were no significant differences in success between cases of missed abortion treated with a single dose of misoprostol and cases of incomplete abortion treated with a single dose of misoprostol (56/89 [62.9%] vs 18/22 [81.8%]; $P=0.152$). Repeat dosage of misoprostol was administered in 12 (13.5%) cases of missed abortion, with a success rate of 58.3% ($n=7$). In 5/12 (41.7%) cases of missed abortion, curettage was required after repeat use of misoprostol.

Table 1
Characteristics according to type of spontaneous abortion ($n=111$).

	Missed abortion	Incomplete abortion	<i>P</i> value
Gestational age at primary treatment, wk	8.49 \pm 2.64	8.44 \pm 1.73	0.911
Gravidity	2.02 \pm 1.12	2.27 \pm 1.45	0.458
Parity	0.64 \pm 0.82	0.95 \pm 1.36	0.304
Maternal age, y	32.80 \pm 6.74	32.40 \pm 6.61	0.817

There was no significant difference between the number of women with missed abortion and the number of women with incomplete abortion who underwent curettage after treatment with a single dose of misoprostol (21/89 [23.6%] vs 4/22 [18.2%]; $P=0.984$). Table 1 shows patient characteristics according to type of abortion.

In 7 cases, uterine position was not documented, leaving a total of 104 cases for subgroup analysis. Anteverted uterine position was detected in 86 cases (82.7%); diverging uterine position was recorded in 18 cases (17.3%), including retroverted ($n=14$) and axial ($n=4$) positioning. Table 2 shows patient characteristics according to uterine position.

There was a significantly higher rate of successful treatment after single-dose misoprostol among women with an anteverted uterus than among those with diverging uterine position (62/86 [72.1%] vs 4/18 [22.2%]; $P=0.001$). In 5/86 (5.8%) cases involving anteverted uterus and in 2/18 (11.1%) cases involving diverging uterine position, repeat misoprostol dosage led to success ($P=0.447$). Thus, the overall success rate of medical treatment was significantly different ($P=0.002$) between women with anteverted uterine position (67/86 [77.9%]) and those with diverging position (6/18 [33.3%]). Need for curettage after single use of misoprostol was significantly lower among women with anteverted uterine position than among those with diverging position (16/86 [18.6%] vs 10/18 [55.6%]; $P=0.003$). In 3/86 (3.5%) women with anteverted and in 2/18 (11.1%) women with diverging uterine position, curettage was necessary after repeat application of misoprostol ($P=0.283$).

Subgroup analysis evaluated the success rates of treatments for missed abortion and incomplete abortion with regard to uterine position (Table 3). However, because there was only 1 case of incomplete abortion and diverging uterine position in the study population, analysis of the incomplete abortion group did not reveal significant results.

Reasons for repeat misoprostol application or curettage were categorized as persistence of the amniotic cavity, retained intrauterine products of conception with steady or increasing β -hCG levels, and severe vaginal bleeding, which occurred in 7, 3, and 6 cases of anteverted uterine position, respectively, and in 4, 7, and 2 cases of diverging position, respectively ($P=0.729$). Severe vaginal bleeding requiring immediate curettage was documented in 1 case involving anteverted and 1 case involving diverging position. In 1 case involving diverging position, a septic incomplete abortion required curettage 2 days after misoprostol treatment.

The mean time interval between treatment and follow-up examination was 7.1 \pm 3.8 days. There were no significant differences in any of the subgroups ($P=0.182$; Table 4). Mean time to repeat application of misoprostol was 4.88 \pm 2.03 days. There was no significant difference

Table 2
Characteristics according to uterine position ($n=104$).

	Anteverted group	Diverging group	<i>P</i> value
Gestational age at primary treatment, wk	8.58 \pm 2.33	7.46 \pm 3.10	0.542
Gravidity	2.10 \pm 1.24	2.07 \pm 1.20	0.491
Parity	0.73 \pm 0.98	0.56 \pm 0.78	0.472
Maternal age, y	32.91 \pm 7.04	30.78 \pm 4.28	0.220

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