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CLINICAL ARTICLE

Vaginal acidity enhancement with a 3% acetic acid gel prior to misoprostol treatment for pregnancy termination in the midtrimester

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ABSTRACT

Objective: To investigate whether enhancing vaginal acidity improves the success of medical abortions in the midtrimester. *Methods:* A double-blind, randomized, placebo-controlled trial was conducted with 48 women with missed midtrimester abortions. Twice daily, the study participants (n = 24) were treated with a 3% acetic acid gel and the controls (n = 24) with a placebo gel, starting 2 days prior to initiating the misoprostol treatment. The primary outcome measures were the rates of successful abortion within 24 and 48 hours. Secondary measures included gel tolerability and adverse effects of the misoprostol treatment. *Results:* The success rates were higher in the study group, within both 24 hours (11/23 vs 3/24; $P = 0.011$) and 48 hours (18/23 vs 6/24; $P < 0.001$). Among the women with a vaginal pH of 5 or higher at baseline, acidic gel was also associated with higher success rates within 24 hours (8/13 vs 2/15; $P < 0.01$) and 48 hours (13/13 vs 3/15; $P < 0{,}001$). The vaginal gels were well tolerated and the misoprostol treatment produced no serious adverse effects. *Conclusion:* A 3% acetic acid gel appears to be an effective and safe preparatory adjuvant to vaginal misoprostol treatment for midtrimester medical abortions, especially in women with a vaginal pH of 5 or higher.
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1. Introduction

A lower initial vaginal pH has been shown to highly increase the rate of success of vaginally applied misoprostol for midtrimester abortion [1] and labor induction [2]. Misoprostol tablets sometimes dissolve incompletely in the vagina [3], which led to the suggestion of moistening them with water or a saline solution [4,5]. Yet, a recent randomized trial did not show improved efficacy in terminating second-trimester pregnancies [6]. Although misoprostol tablets are known to liquefy more easily in an acidic medium [7], there are conflicting reports on the value of the use of acetic acid to dissolve them for vaginal application [8,9]. A study of the effects of vaginal misoprostol in the second trimester was recently carried out with women with missed abortions [1]. Even though all participants received misoprostol tablets premoistened with an acidifying agent, the study reported a positive correlation between vaginal pH at baseline and time to expulsion of the fetus—a finding suggesting that the effect of vaginal pH might extend beyond the pharmacokinetics of the drug.

The present study was carried out to test the hypothesis that enhancing vaginal acidity will induce cervical changes facilitating the success of medical termination of pregnancy (MTOP) with misoprostol. It evaluates the efficacy and safety of lowering vaginal pH using a 3% acetic acid gel in women undergoing MTOP with misoprostol following a missed abortion in the midtrimester.

2. Materials and methods

A double-blind, randomized, placebo-controlled clinical trial was carried out from October 30, 2010, to March 28, 2011, at Ain Shams University Maternity Hospital after approval from the ethics and research committee of the University's Obstetrics and Gynecology Department. The participants were 48 women undergoing MTOP with misoprostol following a missed midtrimester abortion. The inclusion criteria were age between 18 and 40 years, singleton pregnancy of 14–26 weeks, normal uterus and cervix on clinical examination, no cervical dilatation or effacement of the cervix, and absence of uterine activity. The exclusion criteria were parity of 6 or higher; spontaneous onset of abortion, defined as uterine contractions with or without cervical changes; vaginal bleeding; ruptured membranes or suspicion of septic abortion, as evidenced by a body temperature of 38 °C or higher; uterine tenderness or a foul-smelling vaginal discharge; intrauterine contraceptive device in situ; multifetal pregnancy or polyhydramnios; history of cervical surgery, including cervical cerclage during the current or a previous pregnancy, cauterization of a cervical erosion, and cervical dilatation or other intervention that resulted in cervical tears or lacerations; uterine anomalies; 2 or more cesarean deliveries; previous uterine surgery or trauma, such as myomectomy or uterine perforation;

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previous attempt at inducing abortion or use of a preinduction agent during the current pregnancy; a contraindication (such as placenta previa) to medical abortion; a contraindication to the administration of prostaglandin analogues, such as a known hypersensitivity to the medications, a history of asthma, the presence of glaucoma, and the presence of cardiac or cardiovascular disease; metabolic acidosis resulting from a medical disorder or associated with a collagen or autoimmune disorder; a history of adverse reactions to vaginally administered medications; the likelihood that treatment with drugs not permitted by the study protocol, including all vaginal forms of medications, would be required during the study period; and a mental condition preventing the patient from understanding the nature, scope, and possible consequences of the study.

The object of the study was explained to the successive eligible patients who all signed written informed consent. Each new participant was allocated the next available number in the concealed computer-generated randomized sequence, and thus was assigned to 1 of 2 groups. Before misoprostol administration, those in the study group (group 1, n = 24) were treated with an acidifying gel containing 3% acetic acid and those in the control group (group 2, n = 24) received the same gel without the active agent (both versions of the gel were manufactured specifically for the trial by Wyth Co., Cairo, Egypt). Five milliliters of the assigned gel was applied vaginally every 12 hours, starting 2 days ahead of the planned MTOP. The packaging of the vaginal gel was identical in the 2 groups, allowing the blinding of both participants and attending staff.

Demographic information collected included age, duration of marriage, weight, height, gravidity, parity, gestational age, and detailed medical history. A speculum examination was performed and vaginal pH measured using indicator paper (Merck KGbA, Darmstadt, Germany). A digital vaginal examination was then performed twice by a single investigator (I.G-E-D), prior to the first gel application and prior to initiating the misoprostol treatment, to assess cervical dilatation, length, and whether the cervix was firm or soft. After pretreatment with the vaginal gel for 2 days, MTOP was initiated, usually starting at 8:00 AM. All participants received misoprostol (Misotac; Sigma Co., Cairo, Egypt) vaginally as follows: a first dose of 800 μg (four 200-μg tablets), followed by 400 μg 4-hourly, to a maximum of 5 doses in the first 24 hours [10]. The misoprostol was moistened with a 7% solution of acetic acid prior to its insertion into the posterior vaginal fornix to ensure its complete dissolution. If a participant did not have adequate uterine contractions within 8 hours of the fifth dose of misoprostol, the same regimen was repeated over the following 24 hours. No uterine response within 48 hours of treatment initiation was considered treatment failure. Alternative interventions were then carried out according to the judgment of the treating clinicians.

The primary outcome measure was the rate of successful abortion (defined as expulsion of the fetus) within 24 and 48 hours of treatment initiation (defined as the time when the first misoprostol tablet was inserted). Secondary outcomes included gel tolerability, blood loss (by visual estimation of the attending obstetrician), rate of incomplete abortion, need for surgical evacuation of the uterus, occurrence of marked abdominal pain, need for analgesia, total dose of analgesia used, and occurrence of adverse effects of misoprostol, including vomiting, diarrhea, and fever (defined as a single temperature reading exceeding 38 °C).

In a previous study of missed midtrimester abortion, the rate of successful abortion within 24 hours of initiating misoprostol treatment was 100% when the baseline vaginal pH was less than 5 and 63.8% when it was 5 or higher [1]. When the sample size was calculated for the present study, the chosen primary outcome was abortion rate within 24 hours. In light of the previous findings, for 2-tailed P values, a significance level of 0.05, and 0.80 power, the sample size needed was 40 participants. However, assuming that 20% of the participants may be eventually excluded from analysis, particularly for spontaneous onset of abortion during pretreatment with the vaginal gel, the total study population was adjusted to 48 participants.

Statistical analysis was performed using Statistica 5.0 (StatSoft, Tulsa, OK, USA). The Mann–Whitney U test (for independent parameters) and the rank-sign test (for dependent parameters) were used for continuous variables whereas the Pearson χ^2 test and the Fisher exact test, as appropriate, were used for categorical variables. $P<0.05$ was considered significant.

3. Results

Sixty-five women with missed midtrimester abortion were evaluated for entry into the study and 48 met the inclusion criteria (Fig. 1). There were no statistically significant differences between the 2 groups regarding demographic and clinical data (Table 1). One patient in group 1 had spontaneous onset of abortion after receiving 2 doses of vaginal gel and was excluded from analysis.

Abortion occurred within 24 hours in 14 (29.8%) of the 47 participants, with a mean treatment initiation to abortion interval of 16.8 ± 3.9 hours, and it occurred within 48 hours in 24 (51.1%) of the participants, with a mean treatment initiation to abortion interval of 24.4 ± 10 hours. The rates of abortion were significantly higher within 24 hours (11/23 [47.8%] vs 3/24 [12.5%]; $P = 0.01$) and 48 hours (18/23 [78.3%] vs 6/24 [25.0%]; $P<0.001$) in group 1 than in group 2. However, the treatment initiation to abortion interval, the treatment initiation to hospital discharge interval, and the total dose of misoprostol used in the participants in whom abortion occurred within 48 hours were not statistically different (Table 2). The cervix was closed in all participants before pretreatment with the gel and was still closed just before initiating the misoprostol treatment. Moreover, there were no differences between the 2 groups in cervical length or consistency before pretreatment with the gel. After the gel applications, the cervix was significantly shorter in both groups but the number of participants with a soft cervix was significantly increased only in group 1. Furthermore, the differences between the 2 groups in cervical length and number of participants with a soft cervix were both significant (Table 2).

A subgroup analysis showed that a significant shortening of the cervix was associated with a vaginal pH of 5 or higher in both groups after the gel application, but that only group 1 had a significantly greater number of participants with a soft cervix than at baseline. After the gel application in the subgroup of group 1 participants with a vaginal pH of 5 or higher, cervical length and number of participants with a soft cervix were significantly different from what they were in the other 3 subgroups (Table 3). The incidence of abortion in this subgroup exceeded 60% within 24 hours and reached 100% within 48 hours, and the differences with the other 3 subgroups were significant (Table 3).

Both vaginal gels were well tolerated, as no participant reported any vaginal irritation or itching. There was no difference between the 2 main groups in incidence of surgical interventions following expulsion of the fetus or in adverse effects of misoprostol apart from a significantly higher incidence of mild diarrhea in group 1 (Table 4).

4. Discussion

The present randomized, placebo-controlled study may be the first to evaluate the efficacy of vaginal acidity enhancement as a preparatory step to misoprostol application in women undergoing a MTOP following a missed second-trimester abortion. Its main result was that, compared with a placebo application, enhancing vaginal acidity with a 3% acetic gel significantly increased the rates of successful abortion within 24 and 48 hours.

The reports on the effect of moistening misoprostol tablets with acetic acid before vaginal insertion have been contradictory [8,9,11]. The findings of the present study could not be explained by