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The Effect of Vaginal pH on the Efficacy of Vaginal Misoprostol for the Induction of Midtrimester Pregnancy Termination

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Abstract

Background: Vaginal misoprostol is said to dissolve better in an acidic environment, thus, in this study we aimed to evaluate the influence of increasing vaginal acidity on the effectiveness of vaginal misoprostol for the induction of midtrimester pregnancy using acidic environment.

Methods: A total of 40 women requiring second trimester pregnancy termination were randomly assigned to one of two treatment groups: (A) in the saline group, 400 μg of intra-vaginal misoprostol was moistened in normal saline before the vaginal insertion as controls (n = 20); and (B) in the acetic acid group, the acidity of the vagina was increased with 3% of acetic acid, (4 mL of 3% acetic acid was delivered into the vagina every 6 hours) before the insertion of an initial dose of 400 μg misoprostol (n = 20). Then 200 μg dosage was repeated every 4 hours for a maximum of 5 doses within 24 hours. If the patient did not have adequate uterine contractions, the same regimen was repeated over the following 24 hours and if no response was achieved, this was considered a failure of therapy.

Results: There was no significant difference in the vaginal pH between the control and intervention groups before the vaginal application of acetic acid (5.80 $\pm$ 0.62 versus 5.89 $\pm$ 0.49, P = 0.622,). The vaginal pH was significantly lower in the acetic acid group after the vaginal application of acetic acid compared to the control group (5.11 $\pm$ 0.56 versus 5.80 $\pm$ 0.62, P = 0.001). Overall, 95% of pregnancies were successfully terminated in the acetic acid group compared to 85% in the control group. These differences were not statistically significant (P =0.241). The success rate within 24 hours and 48 hours, the adverse effects, mean termination time, total misoprostol administered, and the number of curettage were, also, comparable between the two groups.

Conclusions: Findings from this study shows that increasing Vaginal acidity does not improve the efficacy of misoprostol administered intra-vaginally for the second trimester pregnancy termination.

Keywords: Vaginal pH, Misoprostol, Second Trimester of Pregnancy, Termination of Pregnancy

1. Background

Surgical uterine evacuation remains the standard method for the termination of pregnancy after 14 weeks of gestation in many countries; however, this is associated with complications such as cervical laceration, uterine perforation, increased risk of bleeding and infection, and cervical incompetence from forceful dilation of the cervix. Non-surgical methods for pregnancy termination after 14 weeks of gestation which are equally effective avoid these complications. Non-surgical methods include expectant management, the use of vaginal prostaglandins, intravenous oxytocin infusion, and intra-amniotic hypertonic saline injection.

Expectant management often results in patient anxiety and, rarely, coagulopathy. Vaginal prostaglandin is relatively expensive particularly in low income countries, while intra-amniotic hypertonic saline is an invasive procedure with increased risk of chorio-amnionitis. Although intravenous oxytocin infusion is less costly and easy to administer, it is often less effective because of the relative insensitivity of the uterus to oxytocin in the second trimester of pregnancy (1-4).

Misoprostol is now commonly used for the medical termination of pregnancy during the second trimester and for the management of intrauterine fetal death (2). It provides a safe and effective treatment and is particularly useful in low income countries because it is easy to store and use, it is less expensive and has relatively few side effects.

Misoprostol dissolves much more easily in acidic environment and, therefore, it is possible vaginal pH may affect its absorption. There are conflicting reports in the literature on whether its effectiveness is altered when it is moistened in normal saline or acetic acid before vaginal application. Thus, the effect of vaginal pH on the efficacy of misoprostol when used for medical termination of mid-trimester pregnancy remains uncertain. The aim

of this study is to investigate whether increased acidity of the vagina affects the pharmacokinetics of the misoprostol and, therefore, its efficacy.

In this study, we have compared the effectiveness of vaginal misoprostol when used in acidic vaginal environment using 3% acetic acid solution (acetic acid group) and a control group in which the misoprostol was moistened in normal saline (saline group) prior to vaginal insertion for the second trimester pregnancy termination in a homogenous Iranian population.

2. Materials and Methods

This study was a randomized triple-blind control trial in which 40 women who referred for the second trimester medical pregnancy termination with vaginal misoprostol in Firouzgar and Shahid Akbarabadi hospitals were randomized into two groups by Random block sampling method.

Since the study was a clinical trial and considering the limited number of patients who had the criteria for inclusion and the limitation of residency, after consultation with the supervisor of the statistics and ethics committee in the medical research center of Iran University of Medical Sciences, a sample size of 20 patients in each group was determined.

In the saline group, the misoprostol was moistened in normal saline before vaginal insertion as controls, while in the acetic acid group, the acidity of the vagina was increased with acetic acid 3% before the insertion of the misoprostol.

All the women carried singleton pregnancies and were between 14 and 26 weeks of gestational ages with no cervical effacement or dilatation prior to the termination process. The exclusion criteria were intrauterine death (IUD), multiple pregnancy, history of cervical surgery (cerclage, cauterization, treatment of ectropion, and conization), structural anomalies of the uterus, previous cesarean section or previous surgery of the uterus, previous attempt at termination of pregnancy, placenta previa, history of asthma, glaucoma, cardiovascular disease, and metabolic acidosis. Other exclusion criteria were parity greater than 6, the presence of spontaneous contraction with or without cervical changes, vaginal bleeding or drug allergy.

A full explanation was given to the participants about the aim of the study, the drug being used in the study including possible side effects. A written informed consent was then obtained from all the participants. The study was approved by the medical research committee of Iran University of Medical Sciences (code: 94/d/105/533 94/02/07).

Prior to intervention, a speculum examination was performed to measure the vaginal pH with a pH paper meter which had an accuracy of 0.5%

A vaginal examination was, then, performed by the only investigator on all the participants, once before the application of acetic acid and again before the insertion of the misoprostol to measure dilation, effacement, and the softness or stiffness of the cervix. After the application of 3% acetic acid, the medical treatment of the termination of pregnancy was performed with misoprostol for 48 hours.

In group one (saline group), the misoprostol was soaked in normal saline prior to the insertion into the vagina. The misoprostol was, then, inserted into the posterior fornix of the vagina. In the acetic acid group, 4 mL of 3% acetic acid (Razi pharmaceutical company, Tehran, Iran) was delivered into the vagina every 6 hours using a 5 mL syringe for 24 hours.

In both groups of women, an initial dose of 400 micrograms of misoprostol (Samisaz pharmaceutical company, Mashhad, Iran) moistened with normal saline was placed in the posterior fornix. If no response occurred, the misoprostol was then repeated every 4 hours with 200 mcg up to a maximum of 5 doses of repetition in the 24 hours. If no response occurred in 24 hours, the misoprostol was continued for up to 48 hours. The dose of the misoprostol used was based on the previous studies and after the approval of the ethics committee. The treatment was considered successful if the complete or incomplete evacuation of the uterus occurred within 48 hours after the first dose of vaginal misoprostol. If the delivery of the fetus and or the placenta did not occur after 48 hours, this was considered as a treatment failure and alternative management was, then, considered based on clinical judgment. Clinical observations were recorded by the investigator.

The vital signs and the adverse effects of the treatments were recorded since the start of the termination process (the time of the insertion of the first dose of the vaginal misoprostol) until one hour after the expulsion of the fetus and the placenta. The outcome measures recorded were the effectiveness of the two techniques studied for the termination of pregnancy, maternal complications, length of hospital stay, and the need for curettage.

At first, the normality of the data was tested by Kolmogorov-Smirnov test. The data were expressed as mean $\pm$ standard deviation, and comparison between the groups was carried out with the use of independent t-test. P value of < 0.05 was considered significant. Statistical analysis was performed using SPSS software, version 22 (IBM, Armonk, NY, USA).

3. Results

The demographic characteristics of the two groups are summarized in

Table 1. Characteristics of Patient Group [a]

Characteristics	Controls	Acetic	P-value
Age, y	27.75 ± 7.20	28.60 ± 5.53	0.678
BMI	21.75 ± 2.16	21.69 ± 2.53	0.600
Parity, N%			
Nullipara	11. 55	9.45	0.539
Multipara	9.45	11.55	
Gravid, N%			
First delivery	9.45	9.45	1.000
Second and higher delivery	11. 55	11.55	
Gestational age, day/week	16.23 ± 2.57	17.11 ± 2.10	0.240

[a] N = number.

There was no significant difference in vaginal pH between the control and intervention groups before the vaginal application of acetic acid (5.80 ± 0.62 versus 5.89 ± 0.49, P = 0.622, for control and acetic acid groups, respectively). The vaginal pH was significantly lower in the acetic acid group after the vaginal application of acetic acid compared to the control group (5.11 ± 0.56 versus 5.80 ± 0.62, P = 0.001 for the intervention and the control groups, respectively), (Table 2 and Figures 1 and 2).

Table 2. Vaginal pH Distribution Between the Two Groups of Study Subjects

Groups of Study	Vaginal pH		
	Mean ± SD	Minimum	Maximum
Control group	5.80 ± 0.62	4.75	7.00
Intervention group before using acid	5.89 ± 0.49	5.00	6.50
Intervention group after using acid	5.11 ± 0.56	4.00	6.00

The control group had 65% (13 cases) termination of pregnancy in the first 24 hours, 20% (4 patients) termination within 48 hours, and 15% (3 cases) of failure. The acetic acid group had 80% (16 patients) termination of pregnancy in the first 24 hours, 15% (3 patients) termination within 48 hours, and 5% (1 cases) of failure, however there was not any statistically significant difference between the two groups, (P = 0.241) (Figure 3).

Overall, 95% of pregnancies were successfully terminated in the acetic acid group compared with 85% in the control group and this was not statistically significant (P = 0.241).

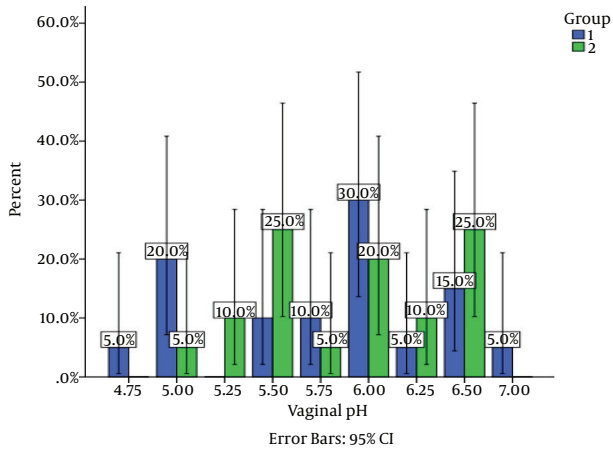

Figure 1. The Distribution of the Vaginal pH Between the Control Group and the Intervention Group Before Using Acid (P = 0.622)

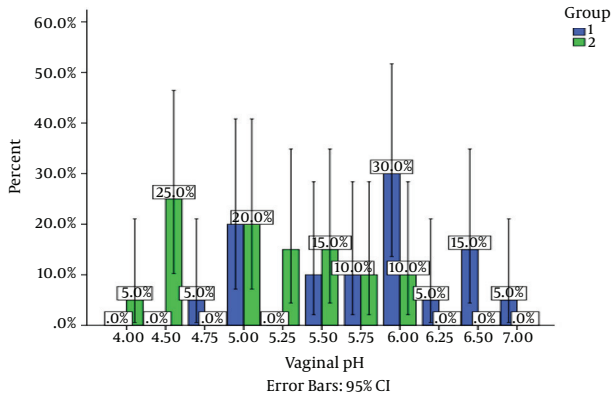

Figure 2. The Distribution of Vaginal pH Between Control Group and the Intervention Group After Using Acid (P = 0.001)

The time taken for the termination during the 24 hours (14.77 ± 6.81 versus 12.25 ± 4.95 hours, P = 0.259 for controls and intervention) and 48 hours (24 ± 14.80 versus 17 ± 11.23 hours, P = 0.10, for control and intervention groups, respectively) were shorter in the acetic acid group compared to the controls, however the differences were not statistically significant.

Side effects were few and not significantly different between the groups. There was one case of pyrexia (5%) in the control group (known adverse reaction to misoprostol), but none in the acetic acid group. Nausea and vomiting occurred in 10% of cases in the acetic acid group and 15% in the control group (P = 0.643). Abdominal pain occurred in 15% cases in the acetic acid group and 20% in the control group (P = 0.687). An amount of 25% (5 cases) in each

Table 3. The Distribution of Misoprostol Consumption in the Two Groups of Subjects During 24 Hours and 48 Hours

Total Misoprostol Administered	Groups	Mean ± SD, μg	Minimum, μg	Maximum, μg	P-value
Total Misoprostol administered in 24 hrs	Control groups	1100 ± 350	400	1400	0.144
	Acetic acid group	940 ± 325	400	1400	
Total Misoprostol administered in48 hrs	Control groups	1400 ± 740	400	2600	0.109
	Acetic acid group	1060 ± 560	400	2600	

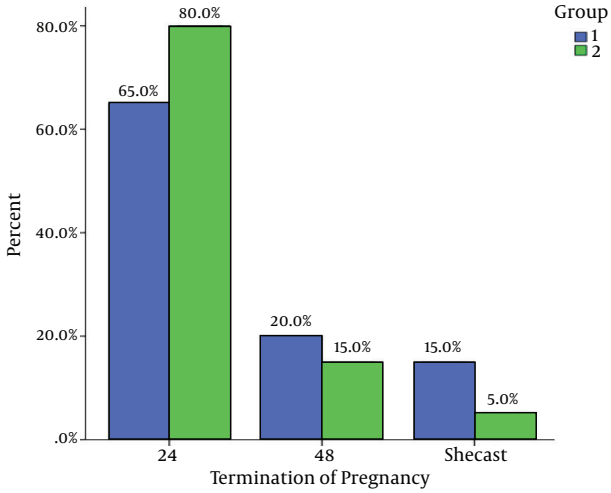

Figure 3. The Distribution of Termination of Pregnancy in the Two Groups of Subjects (P = 0.241)

group required surgical evacuation of the retained products of conception (P = 1.000).

4. Discussion

This study sought to establish whether the efficiency of the misoprostol for the second trimester pregnancy termination is enhanced by increased vaginal acidity. The study shows that decreased vaginal pH does not influence the effectiveness of the vaginal misoprostol for the pregnancy termination. Our data is similar to other reports (5-10) which showed that lowering the vaginal pH does not make a difference. Thus, this study supports these reports because we only studied homogenous Iranian women. However, our observations are in contrast with those by Abd-El-Maeboud et al. (11) and Yilmaz et al. (12). In a study in Cairo, Abd-El-Maeboud et al. reported that 3% acetic acid gel as adjuvant to misoprostol was more effective for mid-trimester termination especially at vaginal pH values less than 5. Similarly, the study by Yilmaz et al. (12) showed Misoprostol moistened in acetic acid when given vaginal 3 hourly, 6 hourly, and 12 hourly was more effective for the second trimester termination. It is possible the different observations by these two groups are due to the heterogeneous populations the studies compared to the homogenous Iranian women in this study, as the pH values reported in the two studies are similar to ours.

There was no statistical difference between the vaginal pH in both groups before the intervention. However, after the intervention, the average pH of the vagina in the acetic acid group was statistically lower compared to the control group. This shows the acetic acid 3% was effective in lowering the vaginal pH, in spite of the lack of enhanced effect on misoprostol.

The two groups of women in this study were similar in age, height, weight, and parity. Therefore, it is unlikely these demographic factors had confounding effects on our observations.

The average time from the start of the Induction to the expulsion of the fetus was not significantly different between the both groups at 24 hours and 48 hours. This is consistent with other studies that used vaginal misoprostol for the induction of labour (8, 10). There was, also, no correlation between the vaginal pH and the duration and outcome with the induction of labour in these studies. There was no statistically significant difference in the total dose of misoprostol and duration and the number of the termination of pregnancy at 24 and 48 hours. Other studies have previously reported the use of different doses of misoprostol (5). In spite of the similar total doses of misoprostol in the two groups in this study, there was no difference in the percentage of women requiring surgical uterine curettage between the two groups. There was no significant difference in the incidence's adverse effects of misoprostol between the groups.

There was one case of pyrexia in the both group (2.5%), but this is significantly lower compared with the 4% to 8% reported by Herabutya et al. (13) and Srisomboon et al. (14). The incidence of nausea, vomiting, and abdominal pain in both groups were, also, lower compared to that reported by Srisomboon et al. and Herabutya et al. who reported 20% nausea and vomiting and abdominal pain 62%. It possible the differences in the adverse effect to misoprostol is

due to racial differences and the higher dose of misoprostol consumption (400 - 600 mcg/dose) in the other studies (13, 14).

4.1. Conclusion

We accept that the number of cases in this group is small. However, it likely our observations represent the true effect of low vaginal pH on the effect of vaginal misoprostol and provides a more accurate observation compared to other reports because of the homogenous population studied. A larger and multicenter study is required involving homogenous populations to confirm our observations.

In summary, we have shown that increasing vaginal acidity does not increase the efficiency of vaginal misoprostol for the second trimester pregnancy termination.

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