



## A Comparative Study of Vaginal Misoprostol Moistened with Acetic Acid and Normal Saline in Second-trimester Pregnancy Termination: A Randomized Clinical Trial

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### ABSTRACT

**Introduction:** Second-trimester pregnancy termination with live fetuses is an important issue in obstetric practice since it is more challenging than first- and third-trimester pregnancy termination. The present study aimed to compare the effectiveness of vaginal misoprostol moistened with normal saline and acetic acid in second-trimester pregnancy termination.

**Methods:** This clinical trial was conducted on 95 pregnant women with the gestational age of 14-26 weeks admitted for medical induced abortion. The subjects were randomly divided into two groups. The first group was administered with vaginal misoprostol moistened with acetic acid (n=47), and the second group received vaginal misoprostol moistened with normal saline (n=48). The abortion rate within the first 24 hours, induced abortion interval, length of hospital stay, and curettage and its complications were assessed in the study groups using statistical methods, and the P-value of less than 0.05 was considered significant.

**Results:** Abortion within the first 24 hours occurred in 100% of the patients in the acetic acid group and 75% of the subjects in the normal saline group, and the difference was considered statistically significant (P<0.001). The mean time for fetal delivery was significantly lower in the acetic acid group (12.3±4.8) compared to the normal saline group (17.5±6.6) (P<0.001). In addition, the length of hospital stay was significantly lower in the acetic acid group compared to the normal saline group (P=0.008). The rate of abortion following the second dose of misoprostol was 46.8% in the acetic acid group and 20.8% in the normal saline group. However, no significant differences were observed in curettage and its complications between the groups.

**Conclusion:** According to the results, high vaginal acidity was associated with the increased effectiveness of misoprostol in second-trimester pregnancy termination.

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### Introduction

Termination of second-trimester pregnancy with live fetuses is an important issue in obstetric

practice since it is considerably more complicated than first- and third-trimester pregnancy termina-

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tion. The rate of second-trimester pregnancy termination is approximately 10-15%, which occurs in 42 million cases per year across the world (1).

The complications of abortion have been on the rise due to increased gestational age. Induced abortion after week 14 of pregnancy is associated with a marked increase in the rate of complications and medical costs (2). Several methods have been proposed in this regard, and there is a worldwide tendency toward terminating the second trimester of pregnancy by non-surgical methods rather than surgery (3).

Misoprostol is a synthetic analogue of prostaglandin E1, which causes effacement and uterine contractions in all gestational ages during pregnancy. This agent could be stored at room temperature, while it is relatively cost-efficient, associated with fewer side-effects, available, and easily applied (4,5). Misoprostol could be absorbed through the mucous membranes and administered via oral, vaginal, rectal, sublingual, and buccal routes. The most common route of misoprostol administration is intravaginal (3). However, misoprostol cannot be completely dissolved in the vagina, which is considered to be a significant concern.

Some studies have indicated that decreased pH may enhance the absorption and effects of misoprostol (6). Therefore, some researchers have recommended that misoprostol be moistened with acetic acid and placed in the vaginal canal. Variable findings have been reported in this regard, with some studies denoting no significant differences (7), and others demonstrating that vaginal misoprostol may be more effective if dissolved in an acidic medium (8).

The present study aimed to compare the effectiveness of vaginal misoprostol when used in an acidic vaginal environment using 3% acetic acid solution with a control group (acetic acid group), in which misoprostol was moistened in normal saline prior to vaginal insertion for second-trimester pregnancy termination in a homogenous Iranian population.

## Methods

### Study Design

This randomized clinical trial was conducted at three hospitals affiliated to Mashhad University of Medical Sciences, Iran during 2016-2017. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (code: 1394/255, registration code: IRCT2017082635898N1). Sample population consisted of the patients admitted for pregnancy termination in weeks 14-26 of pregnancy. The objectives of the research were explained to the

participants, and written informed consent was obtained prior to enrollment.

### Inclusion and Exclusion Criteria

The inclusion criteria of the study were as follows: 1) gestational age of 14-26 weeks with live fetuses; 2) admission for induced abortion; 3) pregnancy termination due to the ultrasound diagnosis of fetal structural abnormalities, detection of chromosomal abnormalities, and maternal diseases; 4) counseling with a perinatologist or a genetic counselor and 5) legal permit or letter of satisfaction from the court of justice.

The exclusion criteria were as follows: 1) presence of allergies or increased sensitivity to prostaglandins and intrauterine device; 2) increased risk of uterine rupture (e.g., history of uterine rupture, classic uterine incision or myomectomy) and coagulopathy; 3) hemodynamic instability and 4) contraindication for medical termination (e.g., previa, uterine contractions or rupture of membranes) before the intervention.

Prior to the treatment, blood samples were collected from the patients in order to determine the complete blood count and BG-Rh and perform coagulative, renal, and hepatic tests. Afterwards, the vaginal pH was measured using a pH meter paper, which was attached to the upper vaginal wall.

In the acetic acid group, misoprostol (400 µg) was moistened in three cc of 3% acetic acid, and in the normal saline group, misoprostol (400 µg) was moistened in three cc of normal saline. Afterwards, misoprostol was inserted into the posterior fornix of the vagina, and the process was repeated every four hours if abortion did not occur or adequate uterine contraction was not achieved.

After abortion, 20 miliunits of oxytocin was infused in one liter normal saline. The patients were randomly assigned to two groups based on random access generated computer. This was a double-blind study, in which the patients were blinded to grouping (acetic acid or normal saline). Misoprostol was placed by a resident, and the assessment of the data and outcomes was performed by an obstetrician who was also blinded to the grouping of the patients. The number of misoprostol doses, time of fetus delivery, and time of placenta delivery were also determined. Curettage was carried out if necessary, and the side-effects of misoprostol (e.g., nausea and vomiting, diarrhea, and chills and fever) were recorded.

The primary outcome of the study was the comparison of the frequency of abortion within the first 24 hours between the groups. The secondary outcomes were abortion following the use of the first and second dose of misoprostol, induced abortion interval, length of hospital stay, frequen-

cy of complications (nausea and vomiting, chills and fever, and diarrhea), frequency of curettage, and frequency of the other methods used for the termination of pregnancy in the groups.

### Sample Size and Statistical Analysis

The sample size was calculated based on the initial outcome of the study (i.e., frequency of abortion within the first 24 hours). The sample size values were extracted from the study by Bulent Yilmaz et al. (3), and the frequency of abortion within the first 24 hours in the acetic acid and control groups was estimated at 96.7% and 78.7%, respectively. Considering  $\alpha=0.05$  and  $\beta=0.2$ , the sample size of the study was calculated to be 84 for each group using the PASS software. Finally, 95 patients were enrolled in the study considering 10% sample loss.

Data analysis was performed using various statistical methods, and a P-value of less than 0.05 was considered significant.

### Results

In total, 95 patients were enrolled in the study, including 47 patients in the acetic acid group and 48 patients in the normal saline group, with no sample loss. The median age of the subjects was  $28.96\pm 6.471$  years in the acetic acid group and  $28.10\pm 6.953$  in the normal saline group, and no significant difference was observed between the groups in this regard ( $P=0.538$ ). The median gestational age was 18 weeks (minimum: 15, maximum: 20) ( $P=0.961$ ), and the median vaginal pH before misoprostol administration was 6 (5-7) in the acetic acid group and 5.5 (5-7) in the normal saline group. No significant difference was observed between the groups in this regard.

Demographic characteristics of the patients in the two groups are presented in Table 1. Within the first 24 hours, abortion occurred in 100% of the patients in the acetic acid group, as well as 75% of the patients ( $n=36$ ) in the normal saline group, which was considered statistically significant ( $P<0.001$ ). However, no significant difference was observed between the groups in terms of receiving the first and second dose of misoprostol ( $P>0.05$ ). In the acetic acid group, the number of the patients who received the third, fourth, fifth, and sixth dose of misoprostol was significantly lower compared to the normal saline group, which was considered statistically significant ( $P<0.05$ ).

The rate of abortion following the first dose of misoprostol was 6.4% ( $n=3$ ) in the acetic acid group. In the normal saline group, no cases of abortion were reported following the first dose of misoprostol, which was not considered statistically significant ( $P>0.05$ ). The rate of abortion fol-

lowing the second dose of misoprostol was 46.8% ( $n=22$ ) in the acetic acid group and 20.8% ( $n=10$ ) in the normal saline group, which was considered statistically significant ( $P=0.009$ ) (Table 2).

**Table 1.** Demographic Characteristics of Acetic Acid and Normal Saline Groups.

Groups Variables	Acetic Acid	Normal Saline	***P-value
Age (year)*	28.96±6.471	28.10±6.953	0.538****
Gestational Age (week)**	18 (15-20)	18 (15-20)	0.961
Parity**	1 (0-5)	1 (0-3)	0.425
Abortion**	0 (0-2)	0 (0-2)	0.304
Dilatation**	0 (0-2)	0 (0-2)	0.563
Vaginal pH**	6 (5-7)	5.5 (5-7)	0.725

\*median±SD; \*\*mean (minimum-maximum); \*\*\*Mann-Whitney U test; \*\*\*\*t-test

**Table 2.** Comparison of Vaginal Misoprostol Moistened with Acetic Acid and Normal Saline in Second-trimester Pregnancy Termination.

Groups Outcomes	Acetic Acid	Normal Saline	***P-value		
Abortion Following First Dose*	3 (6.4)*	0	0.117		
Abortion Following Second Dose*	22 (46.8)	10 (20.8)	0.009		
Time of Fetus Delivery (hour)**	12.3±4.8	17.5±6.6	<0.001		
Time of Placental Delivery (hour)**	12.6±4.8	17.9±6.6	<0.001		
Abortion within First 24 Hours*	100	36 (75)	<0.001****		
Length of Hospital Stay (day)*	1	11 (23.4)	6 (12.5)	0.008	
	2	34 (72.3)			30 (62.5)
	3	2 (4.3)			12 (25)
Curettage*	24 (51.1)	17 (35.4)	0.149		

\*Frequency and percentage; \*\*Median±SD; \*\*\*t-test; \*\*\*\*Mann-Whitney U test

The mean time of fetal delivery in the acetic acid group ( $12.3\pm 4.8$ ) was significantly lower compared to the normal saline group ( $17.5\pm 6.6$ ), which was considered statistically significant ( $P<0.001$ ). In addition, the length of hospital stay was significantly lower in the acetic acid group ( $P=0.008$ ) (Table 2). However, no significant difference was observed in the incidence of curettage and its complications, as well as the need for other methods ( $P>0.05$ ) (Tables 2 & 3).

**Table 3.** Comparison of Side-effects of Vaginal Misoprostol Moistened with Acetic Acid and Normal Saline in Second-trimester Pregnancy Termination.

Groups Side-effects	Acetic Acid N (%)	Normal Saline N (%)	P-value
Fever (temperature≥38°C)	5 (10.6)	3 (6.2)	0.486
Chills	9 (19.1)	13 (27.1)	0.467
Nausea	9 (19.1)	12 (25)	0.622
Vomiting	1 (2.1)	1 (2.1)	>0.99
Diarrhea	1 (2.1)	7 (14.6)	0.059

## Discussion

According to the results of the present study, high vaginal acidity increased the effectiveness of misoprostol in second-trimester pregnancy termination. The study groups were homogenous in terms of the demographic characteristics. The rate of abortion within the first 24 hours was also higher in the acetic acid group compared to the normal saline group. In addition, the rate of abortion following the administration of the first and second dose of misoprostol was higher in the acetic acid group compared to the normal saline group. On the other hand, induced abortion interval and length of hospital stay were lower in the acetic acid group compared to the normal saline group. However, no significant differences were observed between the groups in terms of curettage and its complications, as well as the use of other methods.

The results of the present study were consistent with the findings of Tayba Jahed et al. (2014) (7), Abd-EI (2012), Maboud K. H. et al. (2008) (9,10), Yilmaz et al. (2005) (3), which denoted no significant differences in the side-effects of misoprostol between the groups. With the exception of the studies by Abd-EI and Maboud K. H. et al. (2008), the rate of complications has been reported to be lower in the acetic acid group due to the lower dosage of misoprostol (9). Tayebah Jahed et al. (2014) and Yilmaz et al. (2005) investigated the need for curettage, reporting no significant difference between the groups, which is in line with the current research (3,7).

The study by Tayebah Jahed et al. (2014) was conducted on 91 patients using a similar method to the present study. In the mentioned study, induced abortion interval in the normal saline and acetic acid groups was 26.5 and 15.7 hours, respectively. The mean dose of misoprostol in the normal saline and acetic acid groups was 1,115 and 775 micrograms, respectively, which was

considered significant. Furthermore, the drug side-effects were similar in the groups, which is also in congruence with the present study. In the mentioned research, placental retention was also similar in the groups. In the current research, the number of the patients requiring curettage was higher in the acetic acid groups compared to the normal saline group, while the difference was not considered significant. The results of the mentioned study are consistent with the current research, which could be attributed to the similar methodology and sample size (7).

Another study in this regard was conducted by Mansoureh Zanjani et al. (2017) on 40 pregnant women, with 20 patients in each group. According to the findings, vaginal acidity increased after using four cc of 3% acetic acid, which was inserted into the vagina every six hours in the acetic acid group. In addition, the induced abortion interval was shorter in the acetic acid group, while the difference was not considered significant. Few complications were reported, with no significant differences between the groups in this regard. In the mentioned research, no significant difference was observed in the vaginal pH between the groups before the administration of acetic acid (5.80 versus 5.89). After the administration of acetic acid, the vaginal pH was lower in the acetic acid group (5.80 versus 5.11). This discrepancy could be due to the different methodologies and lower sample size. The difference in the vaginal pH before and after the administration of acetic acid in the mentioned study confirmed the effects of acetic acid on the lowering of pH and increasing of acidity (8).

Similar results have been reported in the study by Abd-EI et al. (2012) despite the difference in methodology. The researchers assigned 48 women with missed second-trimester abortion into two randomized groups. In 24 patients, 3% acetic acid gel was administered, and the other subjects received placebo gels. Those administered with acid gels showed better outcomes within 24 and 48 hours. Despite the smaller sample size of the mentioned research, the results are consistent with the present study, which could be due to the similar procedure (10).

Another research in this regard was performed by Bhattacharjee N. (2012) on 322 pregnant women with the gestational age of 13-20 weeks, while Saipin Pongsatha et al. (2011) examined 179 pregnant women with the gestational age of 14-28 weeks. The results of the mentioned studies were inconsistent with the current research as the researchers concluded that the misoprostol tablets moistened with acetic acid or normal saline or used as dry tablets had no significant difference in terms of the outcomes. Despite the



completely similar methodology to the present study, the discrepancy in the results could be attributed to the larger sample size compared to the present study (11,12).

In the study by Abd-El and Maboud K. H. et al. (2008), the methodology differed from the current research. The mentioned study was conducted on 110 women with the gestational age of 26-14 weeks, who were candidates for induced abortion. The patients were divided into two groups of A (pH<5; n=63) and B (pH≥5; n=47) and received 200 micrograms of vaginal misoprostol moistened with acetic acid every four hours. The findings indicated a significant association between the vaginal pH and interval of misoprostol administration for abortion, which was significantly lower in group A compared to group B. Moreover, the rate of successful abortion in group A was 100%, while it was 63.8% in group B. The results of the mentioned study are consistent with our research, which could be attributed to the similar sample sizes since the patients in the mentioned research were not homogeneous (initially divided into different groups based on vaginal pH), indicating that there was no randomization, which is a research limitation. Due to the lower administered dose of misoprostol in group A, the incidence of complications was lower in this group. It is notable that this was the only study in which the complications had no differences in the groups, and this may justify the effects of the initial pH on the rapid termination of pregnancy (9).

The study by Yilmaz et al. (2005) was conducted on 66 pregnant women, who were candidates for second-trimester pregnancy termination. The methodology of the mentioned research was similar to the present study. According to the findings, the time of pregnancy termination was significantly lower in the acetic acid group compared to the second group. In addition, the rate of abortion following the first dose of misoprostol was significantly higher in the acetic acid group. However, no significant differences were observed between the groups in terms of complications and placental retention. These findings are in line with the results of the present study, which could be attributed to the similar methodology despite the smaller sample size (3).

### **The Strengths and Limitations of the Study**

One of the strengths of the present study was the homogeneity of the groups in terms of the demographic characteristics, pH factors, and primary dilatation. However, the induced abortions of live fetuses (causes of pregnancy termination: rupture of membranes or IUFD, requiring a lower dose of misoprostol for termination) was not tak-

en into account. The main strength of the research was the double-blind design, while it was not possible to blind the analyzer of the results.

### **Recommendations**

Since some of the previous studies with larger sample sizes have reported different results, it is recommended that similar investigations be conducted on larger sample sizes. Furthermore, it is suggested that the pH of patients be evaluated after the administration of misoprostol in order to measure acetic acid and normal saline in anesthetized patients and compare the values with the primary pH.

### **Conclusion**

According to the results, high vaginal acidity increases the effectiveness of misoprostol in second-trimester pregnancy termination. In addition, the rate of abortion within the first 24 hours and with the lower doses of misoprostol was higher after increasing the vaginal acidity, while the length of hospital stay and induced abortion interval decreased. However, no significant differences were observed in the associated complications, requiring curettage and other methods of pregnancy termination.

Considering the convenience, no need for training, and no differences in complications, misoprostol moistened with acetic acid could be used in the patients who are admitted for medical abortion in order to decrease the time of abortion and length of hospital stay, while accelerating the abortion process with lower doses of misoprostol.

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### **Conflict of Interest**

The authors declare no conflict of interest.

### **References**

1. ACOG Practice Bulletin No. 135: Second-trimester abortion. *Obstet Gynecol.* 2013;121:1394-1406.
2. Jatlaoui TC, Ewing A, Mandel MG, et al. Abortion Surveillance - United States, 2013. *MMWR Surveill Summ.* 2016;65:1-44.
3. Yilmaz B, Kelekci S, Ertas IE, et al. Misoprostol moistened with acetic acid or saline for second trimester pregnancy termination. *Hum Reprod.* 2005;20:3067-3071.
4. Cassing H. second trimester pregnancy termination induction medication termination. Available at: [www.uptodate.com](http://www.uptodate.com): Updated in.May 24,2017.
5. Tang OS, Gemzell-Danielsson K, Ho PC. pharmacokinetic profiles, effects on the uterus and side effects. *Int J Gynaecol Obstet.* 2007;99:S160-167.

6. Najafian A, Rajaei M, Beheshti S. Efficacy of vaginal misoprostol and vaginal washing with 3% acetic acid for first trimester pregnancy termination: A randomized single blind clinical trial. *Hormozgan Med J.* 2017;20:301-306.
7. Jahed Bozorgan T, Rahmati Jafarabadi N, Zonoubi Z. Comparison of therapeutic and side effects of misoprostol moistened with normal saline and acetic acid in induced abortion. *JQUMS.* 2014;18:22-27.
8. Zanjani M, Kohpayeh J, Karimi Zh. The Effect of Vaginal pH on the Efficacy of Vaginal Misoprostol for the Induction of Midtrimester Pregnancy Termination. *Obstet Gynecol Cancer Res.* 2017;2:e8953.
9. Abd-El-Maeboud KH, Ghazy AA, Nadeem AA, et al. Effect of vaginal pH on the efficacy of vaginal misoprostol for induction of midtrimester abortion. *J Obstet Gynaecol Res.* 2008;34:78-84.
10. Abd-El-Maeboud KH, Ghazy A, Ibrahim A, et al. Vaginal acidity enhancement with a 3% acetic acid gel prior to misoprostol treatment for pregnancy termination in the midtrimester. *Int J Gynecol Obstet.* 2012;119:248-252.
11. Bhattacharjee N, Saha SP, Ganguly RP, et al. A randomized comparative study on vaginal administration of acetic acid-moistened versus dry misoprostol for mid-trimester pregnancy termination. *Arch Gynecol Obstet.* 2012;285:311-316.
12. Pongsatha S, Tongsong T. Randomized controlled study comparing misoprostol moistened with normal saline and with acetic acid for second-trimester pregnancy termination. Is it different?. *J Obstet Gynaecol Res.* 2011; 37:882-886.