



# Intravaginal Isoniazid (INH) and Sublingual Misoprostol Versus Sublingual Misoprostol Alone for First-Trimester Induced Abortion: A Randomized Controlled Trial

Ladan Haghighi<sup>1</sup>, Maryam Rahimi<sup>2</sup>, Behnaz Mohabbatian<sup>2</sup>, Zahra Rampisheh<sup>2</sup>, Mahshid Shirvani<sup>2\*</sup>, Samaneh Saghafian Larijani<sup>2\*</sup>

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## Abstract

**Background:** This study aimed to compare sublingual misoprostol alone or combined with vaginal Isoniazid (INH) for first-trimester abortion.

**Methods:** In this randomized controlled trial, 80 pregnant women with missed abortion candidates for first-trimester abortion were randomly assigned to two groups. The first group received 800 µg sublingual misoprostol every three hours maximum for three doses and the second group received 1500 mg vaginal INH followed by the same dose of misoprostol. Vaginal sonography was performed after 24 hours on both groups to observe any retained product of conception. In case of no response or incomplete abortion, the second course of misoprostol (with the same dose) was administered. The abortion (complete or incomplete) rate was reported within 48 hours after the first dose of misoprostol.

**Results:** The rate of successful intervention (either complete or incomplete) abortion within 48 hours of misoprostol administration was 75% in both groups and was not significantly different ( $P$  value = 1). Also, hospitalization duration, abortion time, total misoprostol dosage, and the rate of side effects were similar in the two groups. Five patients in the misoprostol group and three in the misoprostol plus isoniazid group underwent emergent D&C because of heavy bleeding.

**Conclusion:** A combined regimen of sublingual Misoprostol plus vaginal Isoniazid with the prescribed dosage has similar efficacy to sublingual misoprostol alone in first-trimester abortion.

**Keywords:** Abortion, First-trimester, Misoprostol, Isoniazid

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## Introduction

Induced abortion is the termination of pregnancy before 20 weeks of gestation or with a fetus weighing less than 500 g. Maternal indications include severe heart diseases, advanced vascular diseases, and invasive cervical cancer, while fetal indication can involve congenital anomalies.

Medical and surgical methods are mainly used for first-trimester abortion. Prostaglandins such as misoprostol and anti-progesterone drugs such as mifepristone are used in the medical method (1). Misoprostol works by activating collagenase, remodeling the extracellular matrix, and

**Corresponding author:** Dr Mahshid Shirvani, [shirvani.mahshid777@gmail.com](mailto:shirvani.mahshid777@gmail.com)  
Dr Samaneh Saghafian Larijani, [Saghafian.s@iums.ac.ir](mailto:Saghafian.s@iums.ac.ir)

<sup>1</sup> Endometriosis Research Center, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Obstetrics and Gynecology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

### ↑What is “already known” in this topic:

The effects of isoniazid on the cervix as a ripening agent have been considered in previous studies in term pregnancy and before hysteroscopy. Results showed that Isoniazid is more effective than Misoprostol for cervical ripening in term pregnancy and before hysteroscopy.

### →What this article adds:

We compared a combined regimen of sublingual misoprostol plus vaginal Isoniazid with misoprostol alone in first-trimester abortion and showed that the two regimens have similar efficacy.

stimulating uterine contraction (2). Mifepristone reduces stromal edema, increases the diameter of vessels, and causes erythrocyte and leukocyte diapedesis, focal hemorrhage, and disruption of the stromal extracellular matrix in the human luteal phase endometrium. These effects eventually initiate the degeneration of the endometrium, leading to impaired implantation and abortion (3). The surgical method includes suction dilation and curettage, done as Electrical Vacuum Aspiration (EVA) or Manual Vacuum Aspiration (MVA). Sharp dilation and curettages are not recommended due to increased complications (1).

Medical abortion is an effective and acceptable method for inducing abortion in the first trimester (4-6). This approach prefers drugs with the minimum dose and side effects and is utilized widely, especially in the United States (7, 8). Nevertheless, secondary invasive interventions will be required sometimes, which may endanger the health of women (9, 10). Therefore, safe and more effective medical methods are essential to reducing the need for invasive ones. Currently, different regimens involving combinations of misoprostol and mifepristone are suggested for medical abortion.

Misoprostol, a synthetic analog of prostaglandin E1, has been approved by FDA for preventing and treating NSAID-induced peptic ulcers. However, as mentioned earlier, it is also used as a combination therapy with mifepristone (11) for inducing abortion in the first or second trimesters. Misoprostol affects the contractility of the uterus. Therefore, it is used for various indications in obstetrics and gynecology, including medical abortion, labor induction, cervical ripening prior to surgery, and postpartum hemorrhage management (12).

Misoprostol is used in sublingual, buccal, vaginal, and oral forms. The side effects are usually rare and subtle. They include diarrhea, chills, nausea, vomiting, pain, hyperthermia, constipation, dyspepsia, headache, bleeding, and sometimes irregular bowel movements. The sublingual form of misoprostol has a faster onset of action than the vaginal form; however, it is associated with a higher rate of side effects (13).

Currently, the recommended regimen for first-trimester medical abortion is the combination of 200-600 mg oral mifepristone, followed by misoprostol, 200-600  $\mu\text{g}$  orally or 400-800  $\mu\text{g}$  vaginally, buccally, or sublingually. Furthermore, for pregnancies with a gestational age of <63 days, the American College of Obstetricians and Gynecologists suggested 200 mg oral mifepristone, followed by 800  $\mu\text{g}$  misoprostol in vaginal, buccal, or sublingual forms for 24-48 hours. Also, misoprostol alone has been used for first-trimester abortion with a dose of 800  $\mu\text{g}$  vaginally or sublingually every three hours for three doses (14).

Studies have shown that the extent of cervical tissue integrity during pregnancy depends on the collagen network, which is the main content of cervical tissue. Destruction or disintegration of collagen fibers reduces the strength of the cervix tissue, leading to its loosening and dilation (15). Some studies showed that certain drugs, such as isoniazid, have an effect similar to misoprostol on collagen tissue (16, 17). Isoniazid is known as an anti-tuberculosis agent. This drug inactivates the lysyl oxidase

enzyme, the main enzyme involved in collagen production. In fact, with the inhibition of this enzyme, isoniazid increases the solubility of collagen, leading to the loosening of fiber arrangement (18, 19). Accordingly, it is believed that isoniazid may play an essential role in cervical softening. Therefore, this study aimed to assess the effect of isoniazid on the cervix and compare the efficacy of misoprostol alone with the combination of misoprostol and isoniazid in first-trimester-induced abortion.

## Methods

The present randomized-controlled trial (RCT) was conducted on 80 pregnant women from 2017 to 2020 at Akbarabadi Hospital, affiliated with Iran University of Medical Sciences. This study was designed to compare the efficacy of sublingual misoprostol alone with the combination of sublingual misoprostol and vaginal isoniazid for first-trimester-induced abortion. With the registration number IRCT20190819044561N1, this RCT was approved by the Scientific and Ethics Committee of Iran University of Medical Sciences (reference number IR.IUMS.FMD.REC.1396.9511290012).

All primigravida women with a gestational age of  $\leq 91$  days (based on LMP and sonography), closed cervix, and with a diagnosis of missed abortion in sonography were included in this study. We excluded those with a history of classic or T shape incision on the uterus or myomectomy, allergy to prostaglandins, vaginal bleeding, severe anemia ( $\text{Hb} < 7$ ), coagulopathy, active liver diseases, cardiovascular diseases, renal failure, chronic adrenal insufficiency, disturbances requiring glucocorticoid, membrane rupture, vaginitis, and those who preferred to be managed as an outpatient. All patients signed informed consent.

The sample size was calculated according to one study that compared the abortion rate between two regimens: misoprostol alone and mifepristone, followed by misoprostol (20). To detect an effect size of 3.95 with 80% power, a sample size of 80 patients (40 in each group) was necessary. Initially, 97 women were selected for this study, but 17 were excluded because of spotting. Eighty patients were randomly assigned to two groups by means of computer-generated randomization, and sealed opaque medication packets were used consecutively. The research coordinator took the information of patients and assigned them to two groups based on a sequence of numbers generated by a statistician prior to the study.

In the case group, a physician blinded for intervention inserted 1,500 mg isoniazid (5 $\times$ 300 mg tablets; Darupakhsh Co., Iran) vaginally as moisturized tablets. The subjects were requested to lie down for one hour. After 12 hours, they received 800  $\mu\text{g}$  of sublingual misoprostol (4 $\times$ 200  $\mu\text{g}$  tablets, Samisaz Co., Iran) every three hours maximum for three doses. The isoniazid dosage was chosen empirically because no information is currently available on the mechanism of this drug. Subjects in the control group received only misoprostol with the same regimen in the case group. Cervical examinations were performed with the onset of vaginal bleeding by another specialist, who was also unaware of the interventions. The intervention was considered successful if there was the

expulsion of conception products within 48 hours after the first dose of misoprostol. If the patient did not tolerate pain, the analgesic (mefenamic acid, 250 mg capsules, Alborz Daru, Iran) was given. Vaginal sonography was performed by a radiology specialist, blinded to the intervention, 24 hours after the first dose of misoprostol to observe any retained product of conception.

During sonography, if the uterine cavity was empty, complete abortion was reported and if retained tissue was seen, incomplete abortion was reported. With the observation of the gestational sac in the uterus, the intervention was considered unsuccessful and reported as "no response." In the presence of no response or incomplete abortion (retained tissue >3 cm in sonography) (21), the second course of misoprostol (800 µg every three hours, three doses at maximum) was administered. Similarly, vaginal ultrasound was performed 24 hours after the first dose of misoprostol in the second cycle. In the case of heavy bleeding, the passage of large blood clots (larger than a plum or fist) or bleeding that saturates a standard sanitary pad in one hour, syncope or orthostatic hypotension (22), emergency suction curettage was performed. Finally, D&C was performed 48 hours after receiving the first dose of misoprostol if any tissue greater than 3 cm was seen in ultrasound, the gestational sac was seen on the sonogram, or the patient was reluctant to continue the study.

Secondary outcomes included side effects of drug regimens such as fever (oral temperatures of 38°C or above), chills, nausea, vomiting, and diarrhea, the need for analgesia (from the first dose of misoprostol to the expulsion of product of conception), hospitalization duration, and the total dose of received misoprostol.

### Statistical analysis

Normally and abnormally distributed data were analyzed by the independent t-test and the Mann-Whitney U test, respectively. The Chi-square test was used for the analysis of qualitative variables. A multivariate logistic regression test determined the differences in outcomes between the two groups. Statistical analysis was performed using SPSS version 16 software.

### Results

Among 80 pregnant women who participated in the study, eight (five in the misoprostol group and three in the misoprostol + isoniazid group) underwent D&C because of heavy bleeding. A total of 72 pregnant women completed the study. Thirty-five cases were treated with sublingual misoprostol alone, and 37 received sublingual misoprostol combined with vaginal isoniazid. As shown in Table 1, there were no statistically significant differences between the two groups in terms of BMI, gestational age, and maternal age. Our findings did not show any significant differences between the two groups regarding "no response" results ( $P = 0.498$ ) and the rate of complete ( $P = 0.152$ ) and incomplete ( $P = 0.178$ ) abortion.

Intravaginal tablets were not palpable in any cervical examinations, implying that INH tablets were dissolved in vaginal secretion during the first 12 hours after insertion.

There were no significant differences between the study groups in terms of hospitalization duration ( $P = 0.113$ ), the time from misoprostol initiation to abortion (abortion time) ( $P = 0.792$ ), and total misoprostol dosage ( $P = 0.98$ ). Furthermore, the rate of side effects, including diarrhea, nausea, vomiting, chills, fever, and pain, were similar in the two groups. According to Table 2, abortion time was similar in pregnancies with a gestational age of < 9 weeks

Table 1. Baseline characteristics in study groups

Baseline Characteristic	Misoprostol (n=40)	Isoniazid + Misoprostol (n=40)	P Value
Age (year) (mean±SD)	30.98 ± 6.78	33.25 ± 5.10	0.094
BMI (kg/m <sup>2</sup> ) (mean±SD)	26.33 ± 5.53	25.1 ± 5.36	0.316
Gestational Age (day) (mean±SD)	60.2 ± 14.14	56.7 ± 13.51	0.261

Table 2. Outcomes in study groups

Main Outcome	Misoprostol (n=40)	Isoniazid + Misoprostol (n=40)	P Value
Unsuccessful			
No Response	4 (10%)	6 (15%)	0.498
Need for D&C due to Heavy bleeding	5 (12.5%)	3 (7.5%)	0.456
Successful			
Complete abortion	16 (40%)	10 (25%)	0.152
Incomplete abortion	15 (37.5%)	21 (52.5%)	0.178
Secondary outcomes			
Duration of Hospitalization (day) (mean±SD)	2.48 ± 0.67	2.77 ± 0.93	0.113
Abortion Time (min) (mean±SD)	521.25 ± 243.11	506.129 ± 269.06	0.792
Misoprostol Dose (µg) (mean±SD)	2365 ± 1098.9	2370 ± 955.6	0.982
Side Effects			
Diarrhea	12 (30%)	11 (27.5%)	0.804
Vomiting	12 (30%)	9 (22.5%)	0.446
Nausea	21 (52.5%)	18 (45%)	0.502
Chills	7 (17.5%)	8 (20%)	0.766
Fever	3 (7.5%)	3 (7.5%)	1.000
Pain (VAS* ≥ 7)	9 (22.5%)	6 (15%)	0.390

\*VAS=Visual analogue scale, GA=gestational age

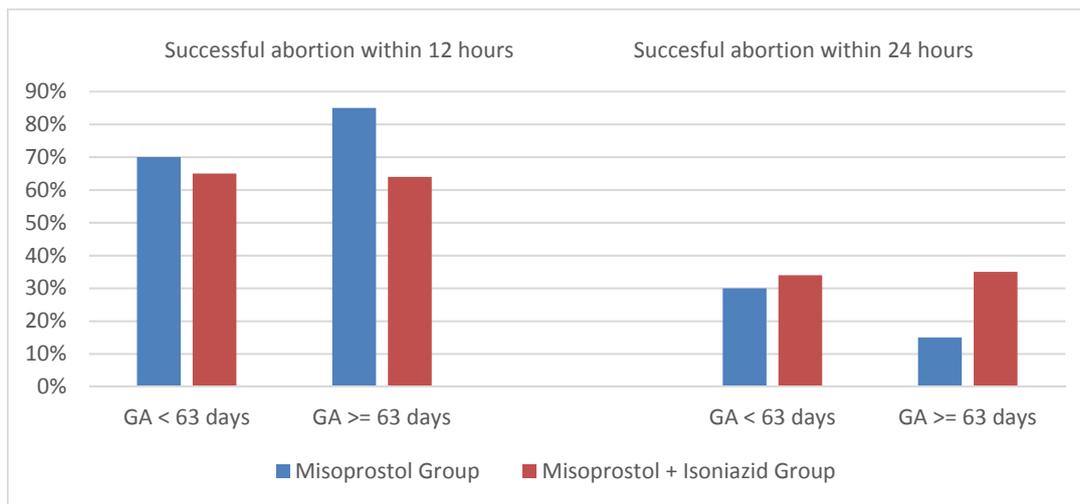


Figure 1. Abortion time in both groups regarding gestational age

Table 3. Rate of abortion in relation to gestational age in study groups

GA < 9 weeks	Outcome	Misoprostol	Misoprostol + Isoniazid	
Successful	Complete	10 (43%)	7 (29%)	
	Incomplete	7 (31%)	13 (54%)	
	Total	17 (74%)	20 (83%)	
	Unsuccessful	No Response	3 (13%)	3 (13%)
		D&C due to heavy bleeding	3 (13%)	1 (4%)
Total	6 (26)	4 (17%)		
P Value		0.430		
GA ≥ 9 weeks	Complete	6 (35%)	3 (19%)	
	Incomplete	8 (47%)	8 (50%)	
	Total	14 (82%)	11 (69%)	
	Unsuccessful	No Response	1 (6%)	3 (19%)
		D&C due to heavy bleeding	2 (12%)	2 (12%)
Total	3 (18%)	5 (31%)		
P value		0.362		

and those with a gestational age of ≥ 9 weeks. 62 (77.5%) patients aborted in the first 24 hours (26 complete and 36 incomplete abortions). No abortion occurred in the second 24 hours.

As shown in Figure 1, the abortion rate within 12 hours and 24 hours was similar in patients with a gestational age of < 9 weeks, as well as in those with a gestational age of ≥ 9 weeks. Moreover, 10% of cases in the misoprostol group and 15% of cases in the INH + misoprostol group did not abort within 48 hours.

In the misoprostol group, 17 out of 23 (74%) patients with gestational age < 9 weeks and 14 out of 17 (82%) patients with gestational age ≥ 9 weeks had successful abortions and the success rate was not significantly different between the two groups ( $P = 0.430$ ). Similarly, in the isoniazid + misoprostol group, 20 out of 24 (83%) patients with gestational age < 9 weeks and 11 out of 16 (69%) patients with gestational age ≥ 9 weeks had successful abortions, indicating no significant difference ( $P = 0.281$ ). Furthermore, the rate of successful abortion was similar with either misoprostol alone or combined with isoniazid at gestational age of < 9 weeks ( $P = 0.43$ ) and also at gestational age ≥ 9 weeks ( $P = 0.362$ ) (Table 3). Regardless of the type of regimen, 37 out of 47 (79%) patients with gestational age < 9 weeks and 25 out of 33 (76%) patients with gestational age ≥ 9 weeks had successful abortions. Thus, concerning gestational age, there was no statistically

significant difference in the success rate between the two groups.

### Discussion

This study aimed to compare sublingual misoprostol alone with sublingual misoprostol plus vaginal isoniazid for inducing first-trimester abortion. The primary outcome was the abortion rate, and the secondary outcomes were the prescribed dose of misoprostol, hospitalization duration, and the time from drug administration to abortion.

Misoprostol alone or combined with mifepristone is the standard regimen for medically induced abortion in the first trimester of pregnancy. However, due to several undesirable side effects, ongoing studies are trying to find new drug therapies. Recently, isoniazid has been introduced for the ripening of the cervix without any adverse effects. Haghghi and Mohabatian (16) compared the efficacy and safety of vaginal isoniazid with those of misoprostol in cervical ripening in 150-term pregnancies and concluded that isoniazid was more effective than misoprostol. In another study, Haghghi et al. (17) compared the effect of isoniazid and misoprostol in 183 women who underwent cervical ripening before hysteroscopy. It also showed that vaginal isoniazid was more effective than misoprostol for cervical ripening before hysteroscopic surgery.

This is the first study evaluating the efficacy of miso-

prostaglandin combined with isoniazid for inducing abortion in the first trimester of pregnancy. However, several studies have compared the efficacy of misoprostol alone or combined with mifepristone. In a systematic review conducted by Raymond et al. (23), the misoprostol dose and administration route affected the rate of induced abortion. In a study by Chen et al. (24), the combination of misoprostol and mifepristone was more effective in inducing abortion than misoprostol alone, although this effect was found to be highly dose-dependent. In another study by Wu et al. (25), the effect of misoprostol alone on abortion induction was analyzed, concluding that its effect depended on the dose and method of application, and these two factors determined the rate of induced abortions and side effects.

In our study, with the regression model, demographic factors, including patients' age, BMI, and gestational age, did not affect the success rate of abortion. However, some studies reported gestational age as an essential factor influencing the success rate of induced abortion. In a study by Raymond et al. (9), the highest rate of failure in induced abortion was seen in women with a gestational age > 8 weeks, a time interval of < 24 hours between misoprostol and mifepristone administrations, and misoprostol dose < 400 µg, or oral administration of misoprostol. On the other hand, Chen et al. (24) showed that a longer prescribing interval between mifepristone and misoprostol decreased the complete abortion rate at the gestational age of 8-10 weeks, but in higher gestational ages, prescribing intervals had no effect on efficacy. In the study by Ashok et al. (26), previous abortion was a risk factor for medical abortion failure and caused the need for surgical treatment. Also, women with previous pregnancies were older than those without previous pregnancies. However, in our study, the age of participants did not affect the outcomes.

In our study, the rate of successful abortion in women with gestational age ≥ 9 weeks was 82% in the misoprostol group and 69% in the Misoprostol + Isoniazid group, and there was no statistically significant difference between the two groups. Kapp et al. (27) estimated the rate of complete abortion in the late first trimester from 78.6% to 94.6% which is similar to the successful abortion rate in our study.

In the present study, adding isoniazid to misoprostol for inducing abortion, with the given dose and treatment protocol, had no significant effect on the efficacy of misoprostol. The lack of significant difference between the two groups implies that larger sample sizes, various doses of isoniazid, and longer intervals between isoniazid and misoprostol administrations can be assessed in future studies.

### Ethics Approval

The Scientific and Ethics Committee of the Iran University of Medical Sciences approved this study with the reference number IR.IUMS.FMD.REC.1396.9511290012. The patients' names were not pointed out in the paper, and the subject's right was protected to keep ethical principles.

### Informed Consent

Written informed consent was obtained from the patients for the publication of this article and any accompa-

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### Conflict of Interests

The authors declare that they have no competing interests.

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