



# Vaginal versus intrauterine extra-amniotic administration of misoprostol for second-trimester pregnancy termination; a randomized clinical trial

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## Abstract

**Introduction:** Misoprostol is a widely used prostaglandin to terminate pregnancy in the second trimester. The route of drug administration has a significant effect on the quality of treatment.

**Objectives:** In this study, we aimed to compare efficacy and adverse effects of vaginal and intrauterine extra-amniotic administration of misoprostol in second-trimester termination.

**Patients and Methods:** In a randomized clinical trial, 112 women with an intrauterine fetal death between 13–24 weeks of gestation attended Akbarabadi hospital were enrolled during 2018-2019. Patients were randomly divided into two groups. In group A, 200 µg misoprostol was diluted in 10ml of normal saline and administered extra-amniotic every 4 hours. Group B received vaginal tablets (200 µg in each) according to FIGO protocol. The primary outcomes were the time needed to expel gestational products and hemoglobin level changes.

**Results:** In group A, conception product expulsion occurred within an average of  $7.52 \pm 0.29$  hours, significantly faster than group B ( $12.02 \pm 0.42$  hours;  $P < 0.05$ ). In group A, the Hemoglobin level decreased after intervention ( $-1.23 \pm 1.20$  g/dL), and the changes were more prominent than group B ( $-0.15 \pm 0.51$  g/dL;  $P < 0.05$ ).

**Conclusion:** For pregnancy termination, intrauterine extra-amniotic administration of misoprostol is a more effective method than the vaginal route in the second trimester. However, regarding further hemoglobin decrease in this method, its safety is still unclear and needs to be approved by further clinical trials with a larger sample size.

**Trial Registration:** The trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT20190606043830N1; <https://en.irct.ir/trial/40184>, ethical code: IR.IUMS.FMD.REC1396.941129004).

## Citation:

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## Introduction

Current advances in diagnosing fetal anomalies and life-threatening maternal diseases have increased the number of pregnancy termination cases (1). Abortion is usually required in the following cases: intrauterine fetal death, fetal anomalies, maternal etiologies, especially cardiac problems, severe persistent loss of amniotic fluid, and premature rupture of membranes (2). There are multiple medical and surgical approaches for termination of pregnancy, that each one would have advantages and disadvantages (3,4). Miscarriage access and safety is improved by medical termination due to its simplicity compared to surgical termination (5). Prostaglandins are molecules of lipid that have different hormone-like effects. In uterine, they have a major effect on myometrial contractility, relaxation, and

## Key point

Intrauterine extra-amniotic administration of misoprostol is more effective than vaginal route for expulsion of products of pregnancy. However, there are safety issues that have to be more investigated.

inflammation (1). Prostaglandins promote cervical ripening for labor induction. Prostaglandins possibly change extracellular matrix structure that helps to ripening of the cervix. Among the prostaglandins, misoprostol as a synthetic prostaglandin E1 analog, causes strong myometrial contractions by binding to myometrial cells leading to the expulsion of products of conception. This agent also causes cervical ripening with softening and dilation of the cervix (1). Misoprostol is a safe medication with more potent uterine contractures that is



inexpensive. However, it is not FDA-approved for obstetric purposes due to possible teratogenic effects though extensively used worldwide (6,7). Based on the results of previous trials, misoprostol was more effective against oxytocin in inducing labor (8). The most common adverse effects include nausea, vomiting, diarrhea, fever, and chills, especially in the first 24 hours after drug administration (2). Intrauterine extra-amniotic (IUEA) misoprostol administration is a rarely studied method for pregnancy termination. Abbas Mitwaly et al found this method safe and more efficient than vaginal misoprostol (9).

## Objectives

The main aim of this study was to compare IUEA Administration of misoprostol with the vaginal route for inducing abortion in the second trimester.

## Patients and Methods

### Study design

In this randomized clinical trial, 112 consecutive women at 13 to 24 weeks of gestational age with fetal death were enrolled. The study was conducted in Akbarabadi hospital during 2018-2019. Two separate ultrasound assessments were needed to confirm the loss of fetal heart rate. Exclusion criteria were previous cesarean section, history of hypersensitivity to misoprostol, asthma, adrenal disease, amniotic membrane rupture, and placenta previa.

Patients were randomly assigned into two groups of 56 (Figure 1). In group A, misoprostol tablet solution (200 µg/10 mL of normal saline) was infused into IUEA

space by a Foley catheter at 4-hour intervals. In group B, placement of a misoprostol tablet (200 µg) in the posterior fornix of the vagina was performed.

The time interval between the first administration of misoprostol and expulsion of conception products was recorded and compared between the groups. A 16 French Foley catheter was placed by a ring forceps into the cervical canal under direct observation. Its balloon was inflated immediately after passage from internal ostium with 30ml of sterile distilled water. In group A, the Foley catheter was fixed in the cervix, and then the misoprostol solution was infused through the catheter (1 mL/min; every 4 hours up to 4 times). In group B, the misoprostol tablet was administered vaginally every 4 hours up to 4 times according to FIGO protocol. Patients without any expulsion of gestational products within the first 24 hours of treatment were considered as non-responders. After any expulsion of pregnancy products, 30 units of oxytocin in 500 mL of ringer serum was infused intravenously. All patients who underwent treatment received 500 mg of intravenous cefazolin despite their response.

Vital signs were assessed every hour, and all the patients were observed for any adverse effects, including headache, nausea, vomiting, and diarrhea. Surgical intervention was performed in cases with massive vaginal bleeding or hemodynamic instability. Twenty-four hours after expulsion, an expert radiologist searched for retained products of conception in the uterus and measured their size, if any. Acetaminophen (500 mg tablet) was prescribed for postoperative pain management as needed. Complete

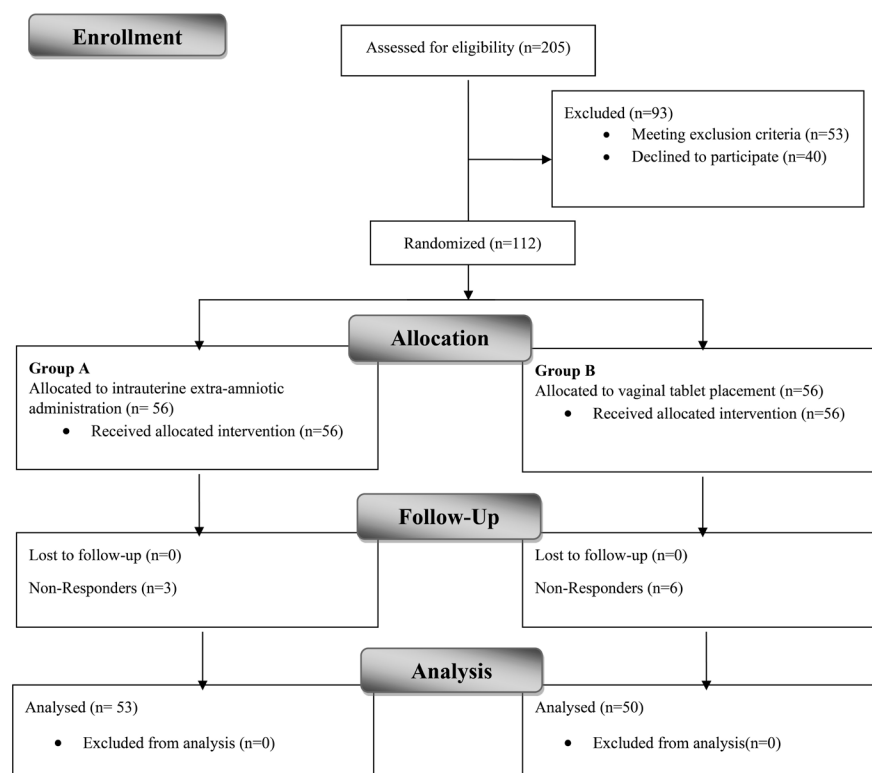


Figure 1. CONSORT diagram of the study.

blood counts were examined at the time of hospitalization and six hours after expulsion. The study method was clearly explained to each patient and informed written consent was received from all incorporated patients.

### Statistical analysis

Data analysis was performed by STATA (version 15.0) software. The normality of the data was analyzed by Kolmogorov-Smirnov test. Comparisons between groups were performed using the independent-samples *t* test for continuous data, chi-square for categorical data. The effect size was calculated (Cohen's *d*), and the *P* value less than 0.05 was considered statistically significant.

### Results

As shown in Table 1, all other background variables were alike across the groups except for the age ( $P > 0.05$ ). The time required for pregnancy product expulsion in group A ( $7.52 \pm 0.29$  hours) was significantly lower than group B ( $12.02 \pm 0.42$  hours;  $P < 0.05$ ). The mean difference was calculated  $-4.49 \pm 0.50$  hours with Cohen's *D* of  $-12.468$  and effect size of  $-0.987$ . As demonstrated in Table 2, hemoglobin concentration reduction in group A ( $1.23 \pm 1.20$  g/dL) was significantly more than in group B ( $0.15 \pm 0.51$  g/dL;  $P < 0.05$ ).

The mean size of retained conception products was  $16.31 \pm 2.34$  mm in group A,  $17.30 \pm 1.64$  mm in group B, and no significant difference was observed between groups. Treatment-related side effects were followed in all cases. There were cases of nausea and vomiting (12.5% in both groups), diarrhea (10.7% in both groups), fever, and chills (28.5% in group A, 25% in group B). However, in each case, the differences between the two groups were not

significant ( $P > 0.05$ ). Emergency surgery was needed for 21.4% of cases in group A and 10.7% in group B ( $P > 0.05$ ). There were 5.3% (3 cases) and 10.7% (6 cases) non-responders in the A and B groups, respectively, without significant difference ( $P > 0.05$ ).

### Discussion

Finding a safe and effective technique to terminate pregnancy in the second trimester is one of the priorities of gynecologists. This study compared two methods of misoprostol administration, including vaginal and IUEA routes. The time required for expulsion was significantly shorter in group A than in group B, indicating that the IUEA administration technique was more efficient than the vaginal route. Previous studies have confirmed the high rate of abortion intrauterine administration and supported the method's safety, which seems to require more extensive studies (9). We found a risk for a high bleeding rate in the latter method, and the patients showed significantly lower hemoglobin levels than the vaginal administration group. Based on these results, it is not possible to conclude that this method is safe.

There was no significant difference between the sizes of retained products of conception in the two groups. None of the adverse therapeutic effects, including nausea and vomiting, headache, diarrhea, fever, and chills, differed across the groups. Previous studies reported uterine rupture as an important cause of urgent surgery (10). In this study, no case developed this complication, and there was no requirement for laparotomy. The only reason for surgical intervention was vaginal bleeding which was controlled by suction and curettage.

**Table 1.** Clinical and demographic baseline variables across the groups

	Group A (n=50)	Group B (n=53)	Mean difference	95% Confidence interval	<i>P</i> value
Age (y)	31.92 ± 0.79	29.75 ± 0.75	2.17 ± 1.09	0.002 ± 4.35	0.028
Gestational age (wk)	14.25 ± 0.39	14.44 ± 0.56	- 0.19 ± 0.68	- 1.55 ± 1.16	0.612
Parity	1.70 ± 0.14	1.55 ± 0.11	0.15 ± 0.18	- 0.532 ± 0.216	0.203
Gravidity	2.69 ± 0.19	2.48 ± 0.16	0.21 ± 0.25	0.282 ± 0.711	0.197
Live birth	1.66 ± 0.13	1.53 ± 0.11	0.12 ± 0.17	- 0.220 ± 0.476	0.233
Abortions	1.33 ± 0.15	1.28 ± 0.12	0.04 ± 0.22	- 0.401 ± 0.496	0.415
Weight (kg)	66.45 ± 1.41	67.94 ± 1.55	- 1.48 ± 2.10	- 5.65 ± 2.67	0.760
Height (cm)	160.50 ± 5.44	160.7 ± 0.76	- 0.24 ± 1.7	- 2.36 ± 1.88	0.588
Body mass index (kg/m <sup>2</sup> )	25.68 ± 0.52	26.43 ± 0.52	- 0.74 ± 0.74	- 2.21 ± 0.073	0.839

Data shown as mean ± standard deviation.

**Table 2.** The mean baseline and final hemoglobin and alteration across groups

Hemoglobin (g/dL)	Group A (n=50)	Group B (n=53)	Cohen's <i>d</i>	Effect size ( <i>r</i> )	95% Confidence interval	<i>P</i> value
Baseline	12.76 ± 1.09	12/56 ± 1.40	0.930	0.421	-0.31 ± 0.62	0.254
After intervention	11.53 ± 1.44	12.17 ± 1.16	0.861	0.395	- 2.30 ± 4.27	0.277
Decrease	- 1.23 ± 1.2	- 0.15 ± 0.51	0.213	0.454	1.0 ± 1.67	0.0001

## Conclusion

We found the IUEA technique more effective than the vaginal method, but its safety is still debatable, and many clinicians prefer the latter (11-13). Undoubtedly, the technique needs to be improved, and studies with a larger sample size permit more accurate comparisons between safety factors.

## Limitations of the study

Our limitations were long-time interval for data collection and some cases with exclusion criteria that led to lower accessible sample population. Lack of significant difference between groups from point of adverse effects may be due to small sample size and power of the study.

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## Authors' contribution

NBM as the head of the study team, performed the drug administration, and drafted the manuscript. SH helped in data collection during the study. RS was the radiologist and performed sonographic evaluations. MBM and SM had a major contribution to the literature search and drafting of the discussion. ZR provided administrative, technical, and material support. HG edited the final draft. All authors contributed to editing the final draft and approval of the manuscript.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Iran University of Medical Sciences approved this study. The institutional ethical committee at Iran University of Medical Sciences accepted all study protocols (#IR.IUMS.FMD.REC1396.941129004). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of obstetrics and gynecology residency thesis of Niloufar Beheshti Monfared at this university (Thesis#5017). The trial protocol was also approved by the Iranian Registry of Clinical Trials (identifier: IRCT20190606043830N1; <https://en.irct.ir/trial/40184>). Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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