Original Article

Effects of Using Misoprostol for Cervical Ripening in Molar Pregnancy: A Double-blinded, Randomized Controlled Trial Study

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Received: 10 July, 2025; Accepted: 25 October, 2025

DOI: 10.22037/nbm.v14i1.48925

Abstract

Background: Molar pregnancy is a rare and benign disease. If a molar pregnancy is diagnosed, treatment should be given immediately. Misoprostol is a synthetic prostaglandin analog commonly used for cervical ripening. This study was performed to determine the effects of misoprostol on cervical ripening in molar pregnancy.

Materials and Methods: This double-blind, randomized clinical trial was performed on 150 pregnant women candidates for the termination of a molar pregnancy. Patients were divided into two intervention groups, receiving vaginal misoprostol at a dose of 400 µg four hours before suction-curettage, and the control group, treated by suction-curettage and using a vaginal placebo. Information, including age, education, history of abortion, curettage, molar pregnancy, time of last menstruation, gestational age, and consequences of misoprostol use, and bleeding during and after curettage, was included in a questionnaire. Data were analyzed using Stata ver 13MP using descriptive statistics, t-tests, chi-square tests, and Bonferroni post hoc tests. A P value < 0.05 was considered significant.

Results: The study included 150 patients with an average age of 28 years. There was a significant association between the misoprostol group as an intervention and variables including age (p=0.003), gravidity (p<0.001), parity (p=0.011), delivery type (p=0.021), dilators (p<0.001), duration of surgery (p<0.001), and decreases in hemoglobin after curettage (p<0.001).

Conclusion: Our study indicated that vaginal administration of misoprostol was a simple and effective treatment for terminating molar pregnancy and seemed to have significant advantages over the current methods.

Keywords: Molar pregnancy, Misoprostol, Cervix, Clinical trial

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Please cite this article as: Mirzamoradi M, Ashrafganjoei T, Heidar Z, Parsa T, Bakhtiyari M, Parsa Y. Effects of Using Misoprostol for Cervical Ripening in Molar Pregnancy: A Double-blinded, Randomized Controlled Trial Study. Novel Biomed. 2026;14(1):13-20.

Introduction

Hydatidiform moles (HM) are benign trophoblastic tumors that account for nearly 80% of gestational trophoblastic diseases (GTDs)[1]. The exact prevalence of HM is unclear; however, many studies have shown that partial moles are more common than complete moles[2]. The incidence of complete and partial molar

pregnancies in developed countries is approximately 1.3 and 3 cases per 1000 pregnancies, respectively. The rate is markedly higher in developing countries; for example, in some Asian or African countries, it is ten times higher than in developed countries[3-5].

Currently, suction-curettage is often the treatment of choice in molar pregnancy cases, regardless of the uterus size[6]. Cervical ripening before surgery, such as curettage, reduces the risk of cervical injury and uterine perforation[7, 8]. Studies have demonstrated that misoprostol, like other drugs used, including dinoprostone and mifepristone, has a beneficial effect on cervical ripening[9, 10]. Termination of pregnancy using misoprostol is believed to be a viable alternative to surgical procedures[11, 12]. Crane et al. reported that misoprostol was effective for cervical ripening in patients undergoing dilatation and curettage (D&C)[13]. Prostaglandins are used because of their contractile effect on the myometrium and the dilating effect on the cervix. Previous studies have claimed that the use of pre-suction-curettage uterine contractions in molar pregnancies not only increases the risk of trophoblastic pulmonary embolism or metastatic disease but also increases the risk of developing malignant gestational chorionic tumor (GTN)[14-16]; nevertheless, few studies have suggested that misoprostol can be used for cervical preparation before curettage to treat pregnancy, the efficacy and safety of this method are still controversial[17].

In light of recent studies on the role of misoprostol in preparing the cervix before curettage, this study was conducted to determine the effect of misoprostol on cervical ripening in molar pregnancies and its side effects in molar cases.

Methods

Structure: This double-blind, randomized clinical trial study was conducted on 150 women with molar pregnancies who were candidates for pregnancy termination referred to Mahdiyeh and Imam Hossein hospitals in Tehran, Iran, between 2020 and 2021. The study groups included the intervention group, which received misoprostol 400 µg in vaginal form 4 hours before suction-curettage, and the control group, which received a placebo in vaginal form 4 hours before suction-curettage.

In the control group, a placebo tablet identical in appearance, shape, and color to the misoprostol tablet (manufactured by Darou Pakhsh Pharmaceutical Co., Tehran, Iran) was prepared and used. The placebo contained inert ingredients, with no active pharmaceutical ingredient.

Randomization: In this study, individuals were randomly assigned to two intervention groups and to the current treatment using the balanced block randomization technique. The blocks considered in this study were four blocks. Random strings 1-6 were generated using Stata software to achieve the required sample size. A random assignment sequence was prepared and placed in a sealed numbered envelope with a 5-digit serial number by a third party who was not involved in the study's design. All 150 envelopes contained basic information and a random 5-digit serial number, which was opened shortly after the test was completed and assigned to the intervention group (misoprostol) or the control group. Also, neither the patient nor the surgeon is aware of the assignment. Inclusion criteria were women diagnosed with molar pregnancy confirmed by ultrasound and β-hCG measurement who were candidates for uterine evacuation. Exclusion criteria included a history of previous gestational trophoblastic neoplasia (GTN), uterine anomalies, contraindications to prostaglandin use, severe medical illness, or refusal to provide informed consent.

Data collection: The survey data were collected by filling out a two-part questionnaire. This information included age, education level, miscarriage history, curettage, molar pregnancy, last menstrual period, gestational age, outcomes of misoprostol use, and curettage and bleeding during and after curettage. In addition, written consent was obtained from all participants prior to their participation in the study. In addition, this study was registered in the Iranian Registry of Clinical Trials (RCT code No: IRCT20200216046519N1).

The primary outcomes were the need for mechanical dilators, duration of surgery, and decrease in hemoglobin after curettage. Secondary outcomes included β-hCG level after surgery and postoperative complications.

Statistical analyses: Data were analyzed by Stata ver. 13MP using descriptive statistics (mean and standard

deviation), t-test, chi-square, and Bonferroni post hoc test. A descriptive study was presented as median (IQR) and frequency (percentage) for continuous and categorical data, respectively. The association between the intervention and categorical variables was evaluated using the Pearson Chi-square test or the Fisher's exact test. The relationship between the continuous variables and the intervention was assessed using the median test with Yates' correction for continuity. The difference in column proportions between rows was evaluated using the Bonferroni correction. The univariate effects of variables on the outcomes were assessed using logistic and linear regression. The intervention's adjusted impact on the outcomes was also analyzed, controlling for other variables. Log transformation was used to normalize skewed results. A P-value of less than 0.05 was considered as statistically significant.

All methods used in the present study are based on the principles of the Declaration of Helsinki. Patient information will be kept confidential throughout the study and after the study. The study's methodology was approved by the ethics committee of Shahid Beheshti University of Medical Sciences under ethics code IR.SBMU.MSP.REC.1398.530. Also, this study was registered in the Iranian Registry of Clinical Trials (RCT code: IRCT20200216046519N1).

Results

The study included 150 patients with an average age of 28 years. The control and intervention groups were evenly divided, with median ages of 30 and 26 years, respectively. There was a statistically significant age difference between control and intervention (p=0.003). Detailed descriptive statistics for the variables and their relation to the intervention are presented in Table 1. Therefore, there was a significant association between the misoprostol group as an intervention and variables including age (p=0.003), gravidity (p<0.001), parity (p=0.011), delivery type (p=0.021), dilators (p<0.001), duration of surgery (p<0.001), and decreases in hemoglobin after curettage (p<0.001). As depicted in Figure 1, younger patients were observed in the intervention compared to controls. Additionally, the intervention group had shorter post-curettage surgery time and lower hemoglobin levels than the control group.

In the next step, univariate analysis was used to assess the single impact of variables on the outcome, including dilators, duration of surgery, logarithmic transformation of hemoglobin reduction after curettage, and logarithmic transformation of beta-hCG after surgery. As shown in Table 2, misoprostol was 86% less likely to cause dilation than the control group (OR=0.14, p<.0.001). The duration of surgery, as an outcome, was significantly affected by gravidity, preoperative beta-hCG, and intervention. Based on these results, higher gravidity was associated with shorter surgery times (β = -1.42, p = 0.042). The mean surgery duration was significantly longer in patients with beta-hCG levels above 100,000 than in those with lower levels (beta=5.57, p=0.042). Moreover, the mean sugary duration in the intervention group was 19 units shorter than in the control group, and this difference was statistically significant (beta = -19.0, p < 0.001). Only misoprostol showed a significant effect among the variables that affect the logarithm of hemoglobin reduction after curettage. The mean decrease in hemoglobin after curettage in the intervention group was 0.72 units lower than in the control group (beta = -0.72, p < 0.001). Outcomes of Postoperative Logarithm beta-hCG logarithm were affected by gravity (beta=-0.24, p=0.011), curettage (beta=-1.28, p=0.014), and Bhcg before surgery (beta=2.17, p<0.001). The intervention did not significantly impact this outcome.

Table 3 demonstrates the adjusted effect of misoprostol on the results. In the misoprostol group, the odds of dilators were 92% lower than the control group (OR=0.08; 95% CI: 0.02, 0.35; p=0.001). Compared with the control group, the mean surgical duration was 17.75 units shorter in the misoprostol group (β = -17.75; 95% CI: -23.73, -11.78; p < 0.001). The average decrease in hemoglobin after curettage (log) was 0.84 units less in misoprostol than in the control group (beta=-0.84; 95% CI: -1.17, -0.52; p<0.001). Beta-hCG levels (log) in misoprostol were 0.39 higher than those of the control group (beta=0.39; 95%CI: -0.28, 1.05; p=0.253).

Discussion

Prostaglandins have been used to terminate second-trimester pregnancies since the mid-1970s. Since the

introduction of transvaginally administrable

Table 1. Descriptive statistics of variables by misoprostol

Variables	Levels	Total (n=150)	Misoprostol		P-value
			No (n=75)	Yes (n=75)	
Age	----	28 (23, 33)	30 (25, 35)	26 (22, 32)	0.003
Gestational age week					0.077
	0	1 (0.67)	0 (0)	1 (1.33)	
	5	2 (1.33)	1 (1.33)	1 (1.33)	
	6	6 (4)	3 (4)	3 (4)	
	7	18 (12)	6 (8)	12 (16)	
	8	39 (26)	22 (29.33)	17 (22.67)	
	9	15 (10)	7 (9.33)	8 (10.67)	
	10	23 (15.33)	12 (16)	11 (14.67)	
	11	11 (7.33)	8 (10.67)	3 (4)	
	12	14 (9.33)	4 (5.33)	10 (13.33)	
	13	6 (4)	5 (6.67)	1 (1.33)	
	14	3 (2)	2 (2.67)	1 (1.33)	
	15	4 (2.67)	0 (0)	4 (5.33)	
	16	3 (2)	3 (4)	0 (0)	
	17	3 (2)	2 (2.67)	1 (1.33)	
	23	2 (1.33)	0 (0)	2 (2.67)	
	Median	9 (8, 11)	9 (8, 11)	9 (8, 12)	0.743
Gravidity					<0.001
	1	42 (28)	10 (13.33)*	32 (42.67)	
	2	40 (26.67)	23 (30.67)	17 (22.67)	
	3	39 (26)	20 (26.67)	19 (25.33)	
	4	16 (10.67)	13 (17.33)*	3 (4)	
	5	4 (2.67)	2 (2.67)	2 (2.67)	
	6	2 (1.33)	2 (2.67)	0 (0)	
	7	2 (1.33)	2 (2.67)	0 (0)	
	8	5 (3.33)	3 (4)	2 (2.67)	
	Median	2 (1, 3)	3 (2, 4)	2 (1, 3)	0.014
Parity					0.011
	0	54 (36)	19 (25.33)*	35 (46.67)	
	1	40 (26.67)	20 (26.67)	20 (26.67)	
	2	32 (21.33)	18 (24)	14 (18.67)	
	3	13 (8.67)	10 (13.33)*	3 (4)	
	4	4 (2.67)	4 (5.33)*	0 (0)	
	5	1 (0.67)	1 (1.33)	0 (0)	
	6	1 (0.67)	1 (1.33)	0 (0)	
	7	3 (2)	2 (2.67)	1 (1.33)	
	8	2 (1.33)	0 (0)	2 (2.67)	
	Median	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.011
Abortion history					0.056

Variables	Levels	Total (n=150)	Misoprostol		P-value
			No (n=75)	Yes (n=75)	
	No	114 (76)	52 (69.33)	62 (82.67)	
	Yes	36 (24)	23 (30.67)	13 (17.33)	
Curettage history					0.262
	No	136 (90.67)	66 (88)	70 (93.33)	
	Yes	14 (9.33)	9 (12)	5 (6.67)	
Molar history					1.000
	No	143 (95.33)	71 (94.67)	72 (96)	
	Yes	7 (4.67)	4 (5.33)	3 (4)	
Mole type					0.125
	Partial	125 (83.33)	59 (78.67)	66 (88)	
	Complete	25 (16.67)	16 (21.33)	9 (12)	
Beta-hCG before surgery					0.253
	Less than 100k	73 (48.67)	33 (44)	40 (53.33)	
	More than 100k	77 (51.33)	42 (56)	35 (46.67)	
GTN score					1.000
	Otherwise	147 (98)	73 (97.33)	74 (98.67)	
	Less than 7	3 (2)	2 (2.67)	1 (1.33)	
GTN					1.000
	No	147 (98)	73 (97.33)	74 (98.67)	
	Yes	3 (2)	2 (2.67)	1 (1.33)	
Delivery type					0.021
	Caesarean	36 (37.5)	16 (28.07)	20 (51.28)	
	Vaginal	60 (62.5)	41 (71.93)	19 (48.72)	
Dilators					<0.001
	No	115 (76.67)	46 (61.33)*	69 (92)	
	Yes	35 (23.33)	29 (38.67)*	6 (8)	
Duration surgery (min)					
	Median	30 (20, 40)	40 (30, 50)	20 (20, 30)	<0.001
Decreased hemoglobin after curettage					
	Median	0.6 (0.3, 0.925)	0.7 (0.6, 1.2)	0.3 (0.2, 0.6)	<0.001
Beta-hCG after surgery					
	Median	24420 (3800, 72660)	23084 (4187.5, 87365.5)	25837 (3530, 61995)	0.680

The association between categorical variables and misoprostol was evaluated using the Pearson Chi-square test or the Fisher's exact test. The relationship between continuous variables and misoprostol was assessed using the median test with Yates' correction for continuity. * Significant difference between column proportions using the Bonferroni method.

Table 2. The single impact of variables on the outcome including dilator, duration surgery, decreases in hemoglobin after curettage (log) and beta-hCG after surgery (log)

Explanatory variables	Outcome							
	Dilators		Duration surgery		Log of decreased hemoglobin after curettage		Log of beta-hCG after surgery	
	OR	P-value	beta	P-value	beta	P-value	beta	P-value
Age	0.96	0.206	-31.33	0.259	-1.20	0.578	-0.02	0.420
Gestational age week	0.98	0.785	5.00	0.811	0.68	0.601	-0.03	0.560
Gravidity	1.22	0.075	**-1.42**	**0.042**	0.27	0.585	**-0.24**	**0.011**
Parity	1.15	0.212	-1.16	0.276	0.24	0.698	-0.11	0.243
Abortion history; Yes vs. No	1.37	0.471	3.20	0.329	0.13	0.373	-0.50	0.168
Curettage history; Yes vs. No	0.23	0.165	1.11	0.818	0.03	0.908	**-1.28**	**0.014**
Molar history; Yes vs. No	0.53	0.568	-0.44	0.947	0.09	0.771	-0.71	0.329
Mole type, Complete vs. Partial	0.40	0.154	4.12	0.273	-0.14	0.402	0.40	0.333
Bhcg before surgery, >100k vs. <100K	1.17	0.690	**5.67**	**0.042**	0.08	0.545	**2.17**	**<0.001**
GTN score, <7 vs. Otherwise	0.00	0.991	-4.32	0.667	-0.38	0.412	-0.08	0.940
GTN; Yes vs. No	0.00	0.991	-4.32	0.667	-0.38	0.412	-0.08	0.940
Delivery type, Vaginal vs. Caesarean	0.79	0.627	0.67	0.842	0.17	0.325	0.63	0.118
Misoprostol; Yes vs. NO	**0.14**	**<0.001**	**-19.00**	**<0.001**	**-0.72**	**<0.001**	-0.04	0.891

Table 3. The adjusted impact of misoprostol on the outcome including dilator, duration surgery, decreases in hemoglobin after curettage (log) and beta-hCG after surgery (log)

Dependent variables	Intervention	B/ OR	95% CI	P-value
Dilators	Misoprostol; Yes vs. No	0.08*	0.02, 0.35	0.001
Duration surgery min	Misoprostol; Yes vs. No	-17.75	-23.73, -11.78	<0.001
Log of decreased hemoglobin after curettage	Misoprostol; Yes vs. No	-0.84	-1.17, -0.52	<0.001
Log of beta-hCG after surgery	Misoprostol; Yes vs. No	0.39	-0.28, 1.05	0.253

* Odds ratio (OR)

prostaglandin analogs, they have been used at the end of the first trimester of pregnancy to dilate the cervix before D&C. The role of prostaglandins in the cervical preparation of molar pregnancies remains controversial. In light of new guidelines, to reduce the risk of trophoblastic cell embolization, long-term cervical ripening, especially with prostaglandins, should be avoided[18].

Our results showed statistically significant differences between the two groups in some demographic variables, including age and gravidity. These differences were adjusted for in the multivariate analysis to minimize potential confounding.

Another benefit of using misoprostol highlighted in this study is the shorter surgical time for patients taking it. Therefore, the intervention group's time was approximately half that of the control group, and the difference was statistically significant. In the control group, the duration of surgery was long, despite the high number of previous vaginal deliveries[19].

One of the most critical complications during curettage is hemorrhage. Indeed, cervical ripening could shorten

surgery time and, consequently, reduce bleeding. Besides, our results showed that hemoglobin levels in patients in the control group decreased more during curettage than in those in the intervention group[20].

GTD causes a wide range of symptoms. The most common clinical sign is unexpected vaginal bleeding. There are concerns about trophoblastic embolism and uncontrolled vaginal bleeding when using vaginal misoprostol[21]. Complications of misoprostol use, such as uncontrolled vaginal bleeding and trophoblastic embolism, have been reported by Seckl et al.[22]. However, there were no serious complications in the current study, including dyspnea and pulmonary emboli among the studied patients.

GTD could be presented with various signs and symptoms, with vaginal bleeding being the most common manifestation. Additionally, theca lutein cysts and elevated serum β-hCG levels can be detected in molar pregnancies[23]. Serum β-hCG levels were measured before the intervention in 77 patients (51.3%) and were higher than those in a normal pregnancy. In addition, in the present study, all patients had vaginal bleeding, and 4% had a theca lutein cyst.

GTN is a rare tumor reported in 50% of cases in molar pregnancies, and the treatment of choice is chemotherapy[24]. Flam et al., in their study, revealed that of the 219 patients with a molar pregnancy, there was no evidence of an increased risk associated with the need for chemotherapy and cervical preparation immediately before suction curettage[16]. Niemann et al.[17] indicated that drug therapy alone to treat molar pregnancy could increase the need for chemotherapy. However, using preoperative drug therapy for cervical ripening does not increase the risk of chemotherapy in the future.

In the present study, 2% of patients had a GTN, suggesting that misoprostol does not increase the risk of GTN or metastasis. These findings were consistent with the findings of the studies by Flam et al.[16] and Niemann et al.[17].

Conclusion

Our study showed that using misoprostol for cervical ripening in the treatment of molar pregnancy could reduce postpartum hemorrhage, the use of dilators, and the duration of surgery. Current studies have found no evidence of an increased incidence of trophoblastic disease after treatment of molar pregnancy and trophoblastic embolization in patients taking prostaglandin. Therefore, using vaginal prostaglandins before suction curettage can reduce its complications and does not increase mothers' complications. In this regard, future studies are needed to confirm the efficacy of prostaglandins in facilitating the termination of molar pregnancy.

Acknowledgment

We would like to thank all the patients who participated in the current study.

Funding

This study received no funding/support.

Conflict of interest

The authors further declare that they have no conflict of interest.

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