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Optimal timing of misoprostol administration in nulliparous women undergoing office hysteroscopy: a randomized double-blind placebo-controlled study

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Objective: To determine the optimal timing of vaginal misoprostol administration in nulliparous women undergoing office hysteroscopy.
Design: Randomized double-blind placebo-controlled study.
Setting: University teaching hospital.
Patient(s): One hundred twenty nulliparous patients were randomly allocated in a 1:1 ratio to the long-interval misoprostol group or the short-interval misoprostol group.
Intervention(s): In the long-interval misoprostol group, two misoprostol tablets (400 μg) and two placebo tablets were administered vaginally at 12 and 3 hours, respectively, before office hysteroscopy. In the short-interval misoprostol group, two placebo tablets and two misoprostol tablets (400 μg) were administered vaginally 12 and 3 hours, respectively, before office hysteroscopy.
Main Outcome Measure(s): The severity of pain was assessed by the patients with the use of a 100-mm visual analog scale (VAS). The operators assessed the ease of the passage of the hysteroscope through the cervical canal with the use of a 100-mm VAS as well.
Result(s): Pain scores during the procedure were significantly lower in the long-interval misoprostol group (37.98 $\pm$ 13.13 vs. 51.98 $\pm$ 20.68). In contrast, the pain scores 30 minutes after the procedure were similar between the two groups (11.92 $\pm$ 7.22 vs. 13.3 $\pm$ 6.73). Moreover, the passage of the hysteroscope through the cervical canal was easier in the long-interval misoprostol group (48.9 $\pm$ 17.79 vs. 58.28 $\pm$ 21.85).
Conclusion(s): Vaginal misoprostol administration 12 hours before office hysteroscopy was more effective than vaginal misoprostol administration 3 hours before office hysteroscopy in relieving pain experienced by nulliparous patients undergoing office hysteroscopy.
Clinical Trial Registration Number: NCT02316301. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Pain, office hysteroscopy, misoprostol

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Office hysteroscopy has become the method of choice for evaluation of the cervical canal and uterine cavity. Because of the miniaturization of scopes and instruments, hysteroscopy can be performed in an outpatient setting without the need for general or regional anesthesia or operation theatre facilities. Consequently, office hysteroscopy is more time saving, cost effective and preferable to patients compared with inpatient hysteroscopy (1, 2).

Office hysteroscopy performed by an experienced hysteroscopist with the use of the vaginoscopic approach (without tenaculum and speculum) is usually associated with mild pain and discomfort (3). Sometimes, the introduction of the hysteroscope into the uterine cavity is difficult and associated with severe pain and vasovagal reaction. Several studies revealed that the subgroups of patients with a narrow cervical canal (nulliparous and

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menopausal patients) are at high risk for experiencing severe pain during office hysteroscopy (4, 5).

Several pharmacologic agents have been used to suppress pain associated with office hysteroscopy: opioid and nonopioid analgesics, paracervical block, intracervical instillation of anesthetics, and intrauterine injection of anesthetics. Moreover, easier and less painful passage of the hysteroscope through the cervical canal can be achieved with the use of prostaglandins and osmotic dilators, which soften the cervix and increase the cervical canal width (6). However, studies evaluating the effectiveness of various pharmacologic agents in relieving pain during office hysteroscopy have produced conflicting results. Consequently, there is no consensus regarding the safest and most effective method for pain relief during office hysteroscopy (1).

Few studies have examined the effectiveness of misoprostol (a methyl analogue of natural prostaglandins) in reducing pain experienced during office hysteroscopy. However, the studies varied in dose, route, and timing of misoprostol administration. Moreover, the studied populations were diverse and sample sizes were small (7–11). Consequently, there are no solid guidelines regarding the efficacy, dose, timing, and route of misoprostol administration before office hysteroscopy.

Studies evaluating the use of misoprostol before inpatient hysteroscopy revealed that the efficacy of misoprostol in cervical ripening was time dependent. Fernandez et al. reported that the administration of misoprostol via the vaginal route 4 hours before operative hysteroscopy was not effective in facilitating cervical dilation (12). However, other studies found that the administration of misoprostol 8–12 hours before operative hysteroscopy led to a significantly greater cervical width compared with placebo (13–15). Based on these studies, we think that it is better to wait for 8–12 hours after intravaginal misoprostol administration before performing office hysteroscopy.

The aim of the present study was to determine the optimal timing of vaginal misoprostol administration in nulliparous women undergoing office hysteroscopy.

MATERIALS AND METHODS

From February 2015 to December 2015, this double-blind, placebo-controlled, randomized, controlled study was conducted at the Obstetrics and Gynecology Department of Cairo University, Egypt. The study protocol was approved by the institutional Ethics Committee (ref. no. N–7–2015), and all of the patients gave informed consent before randomization.

Nulliparous women of reproductive age with an indication for office hysteroscopy were recruited for the study. The exclusion criteria included contraindication to misoprostol (asthma, glaucoma, renal failure, hypertension, and severe heart disease), allergy to misoprostol, severe vaginal bleeding, pelvic inflammatory disease, history of cervical operation, pregnancy, lesions of the endocervical canal, and treatment with GnRH agonists.

A total of 120 patients were randomly allocated to either the long-interval misoprostol group (n = 60) or the short-interval misoprostol group (n = 60) with the use of a computer-generated randomization list and sequentially numbered sealed envelopes. The randomization list and sealed envelopes were prepared by a college not directly involved in the study. Each sequentially numbered sealed envelope contained two labeled plastic bags (A and B), and each bag contained either two misoprostol tablets (each tablet 200 μg; Cytotec; Pfizer) or two placebo tablets of identical appearance. In the long-interval misoprostol group, bag A contained misoprostol tablets and bag B contained placebo tablets. In the short-interval misoprostol group, bag A contained placebo tablets and bag B contained misoprostol tablets. After informed consents were signed, the sealed envelopes were opened sequentially by the study nurse. Patients were instructed to insert the tablets in the bags A and B as deeply as possible inside the vagina. Tablets in bag A were inserted 12 hours before the scheduled office hysteroscopy, and tablets in bag B were inserted 3 hours before the scheduled office hysteroscopy. The doctors and patients were blinded to the treatment received.

On the day of scheduled office hysteroscopy, the Arabic version of State-Trait Anxiety Inventory (form Y) was used to assess the state of anxiety and the trait of anxiety. The vagina was washed with saline solution, and any remaining fragments of placebo or misoprostol tablets were removed by the study nurse. The time interval between the arrival of the patients at the clinic and the performance of office hysteroscopy (waiting time) was measured.

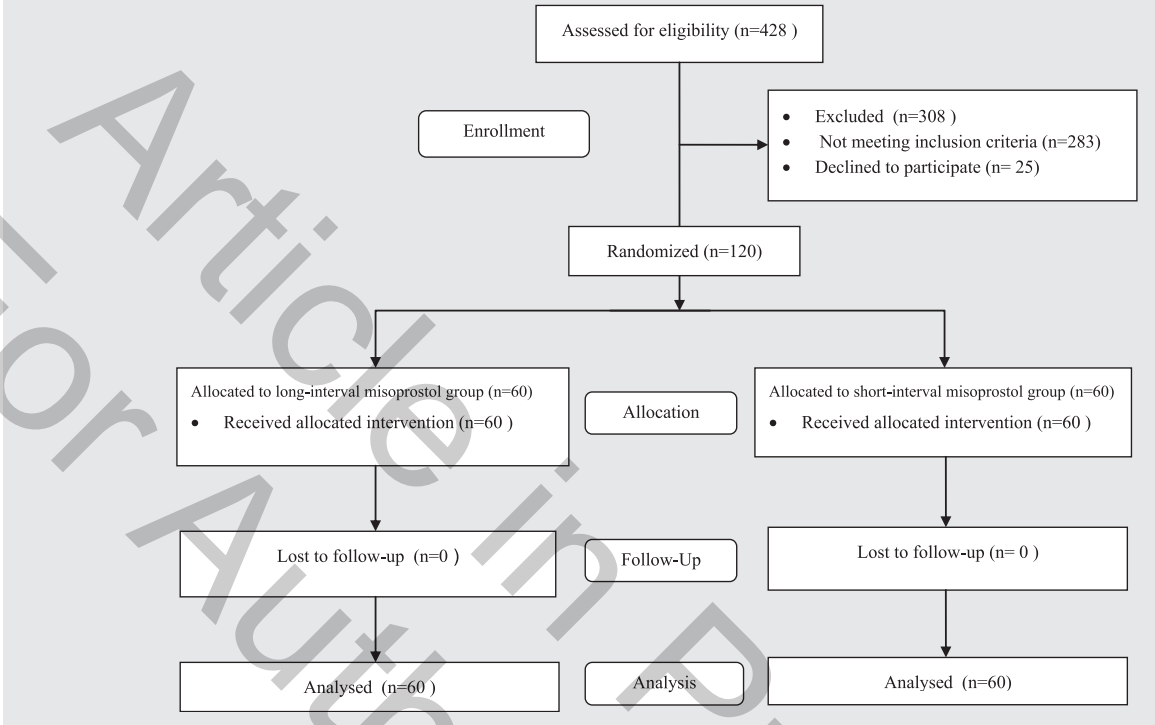
All of the procedures were performed during the proliferative phase of the menstrual cycle by three experienced operators. We used a rigid 2.9-mm hysteroscope with a 30° forward oblique lens and an outer sheath diameter of 5 mm in this study. Normal saline solution was used to distend the uterine cavity. The pressure of the distension media was maintained between 60 and 100 mm Hg. Hysteroscopy was performed with the use of the nontouch technique (vaginoscopic approach) as described by Bettocchi and Selvaggi (16). All of the procedures were diagnostic.

Procedure duration (from the introduction of hysteroscope into the vagina until completing hysteroscopy examination) was measured. The intensity of pain was assessed with the use of a 100-mm visual analog scale (VAS; 0 = the absence of pain; 100 = the worst experienced pain). The patients were asked to record the intensity of pain during and 30 minutes after the procedure.

After the end of the procedure, the operators assessed the ease of the passage of the hysteroscope through the cervical canal with the use of a 100-mm VAS (0 = the easiest insertion of the hysteroscope into the uterine cavity; 100 = the most difficult insertion of the hysteroscope into the uterine cavity). Any operative complications, such as uterine perforation, creation of false tract, and cervical lacerations, were recorded. Patients were contacted by telephone 24 hours after the office hysteroscopy to detect occurrences of the adverse effects of misoprostol, such as nausea, vomiting, fever (temperature >37.8°C), shivering, abdominal cramps, and diarrhea.

The primary outcome was the intensity of pain during the procedure, and secondary outcomes included the intensity of pain 30 minutes after the procedure, the ease of passing the hysteroscope through the cervical canal, surgical complications and adverse drug effects.

FIGURE 1



The flow of the patients in the study.

Fouda. Misoprostol before office hysteroscopy. Fertil Steril 2016.

Sample Size Calculation

A randomized controlled study revealed that the VAS pain score of patients who received 400 μg misoprostol 3 hours before office hysteroscopy was 34.5 ± 13.72 mm (17). We considered a 10-mm difference (~30% difference) in mean VAS pain score between both groups a clinically significant difference. Power calculation indicated that a sample size of 49 patients would be needed in each group to detect a >10-mm difference in VAS pain score between both groups with an alpha error level of 5% and a beta error of 5% (study power 95%) (calculated at https://www.sealedenvelope.com/power/continuous-superiority). We recruited 60 patients to each arm of the study because we expected the drop-out incidence to be 20%.

Statistical Analysis

Statistical analysis was performed with the use of Student's *t* test or χ^2 test as appropriate. A Fisher exact test was used when the expected frequency was less than five. *P* value <.05 was considered to be statistically significant. All statistical calculations were performed with the use of Excel version 7 (Microsoft) and SPSS.

RESULTS

From February 2015 to December 2015, 120 nulliparous patients were recruited to the study. Patients were randomly assigned to either the long-interval misoprostol group (n = 60) or the short- interval misoprostol group (n = 60). The flow of patients through the study is shown in Figure 1.

The two groups were similar regarding age, body mass index, gravidity, parity, indications for hysteroscopy, history of previous cervical dilatation, state-anxiety score, and trait-anxiety score (Table 1). The waiting times in the long-interval misoprostol group and the short-interval misoprostol group were 51.27 ± 16.03 and 46.98 ± 17.71 minutes, respectively (*P*=.167).

TABLE 1

Characteristics of the participants.

Characteristic	Long-interval misoprostol group	Short-interval misoprostol group	*P* value
Number	60	60	
Age (y)	29.8 ± 6.95	28.72 ± 6.24	.371
Body mass index (kg/m^2)	27.72 ± 6.36	29.25 ± 6.02	.177
Gravidity	0.38 ± 0.94	0.28 ± 0.80	.533
Previous cervical dilatation	8 (13.33%)	6 (10%)	.57
State-anxiety score	45.72 ± 10.48	43.33 ± 10.59	.218
Trait-anxiety score	38.83 ± 10.07	41.25 ± 7.97	.148
Indications of examination			
Infertility	45 (75%)	47 (78.33%)	.666
Recurrent abortion	9 (15%)	7 (11.67%)	.591
Other	6 (10%)	6 (10%)	>.999

Note: Values are presented as mean ± SD or n (%).

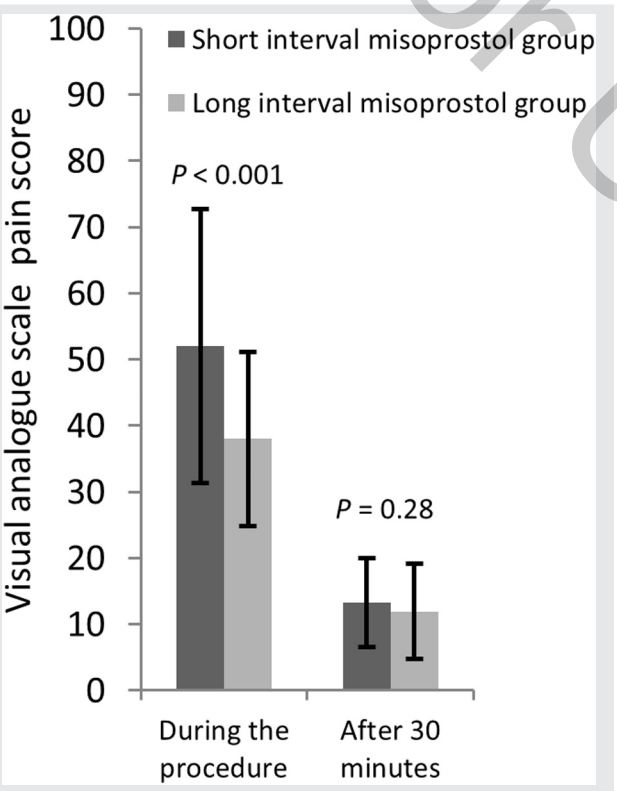
Fouda. Misoprostol before office hysteroscopy. Fertil Steril 2016.

The operators were evenly distributed to each group of the study. Patients in the short-interval misoprostol group experienced more pain during office hysteroscopy (51.98 ± 20.68 vs. 37.98 ± 13.13; $P<.001$). In contrast, the pain scores 30 minutes after the procedure were similar between groups (13.3 ± 6.73 vs. 11.92 ± 7.22; $P=.28$) (Fig. 2).The passage of the hysteroscope through the cervical canal was easier in the long-interval misoprostol group (48.9 ± 17.79 vs. 58.28 ± 21.85; $P=.011$). The procedure duration and side effects of misoprostol administration were similar between the groups (Table 2). There were no operative complications in either group.

DISCUSSION

The data presented in this study reveal that the efficacy of vaginal misoprostol in relieving pain experienced by nulliparous patients undergoing office hysteroscopy is time dependent. Patients who received misoprostol 12 hours before office hysteroscopy experienced less pain during office hysteroscopy compared with patients who received misoprostol 3 hours before office hysteroscopy. To our knowledge, this is the first study that investigated the optimal timing of misoprostol administration in nulliparous women undergoing office hysteroscopy.

FIGURE 2



Visual analog scale pain score (mean ± SD) during the procedure and 30 minutes after the procedure.

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TABLE 2

Details of the procedure.

Variable	Long-interval misoprostol group	Short-interval misoprostol group	*P* value
Number	60	60	
Procedure time (s)	224.23 ± 52.75	216.63 ± 51.28	.425
Operator			.705
First operator	17 (28.33%)	21 (35%)	
Second operator	24 (40%)	23 (38.33%)	
Third operator	19 (31.67%)	16 (26.67%)	
Pain scores[a]			
During the procedure	37.98 ± 13.13	51.98 ± 20.68	<.001
30 min after the procedure	11.92 ± 7.22	13.3 ± 6.73	.28
Ease of hysteroscope insertion[b]	48.9 ± 17.79	58.28 ± 21.85	.011
Adverse effects of misoprostol			
Abdominal cramps	12 (20%)	10 (16.67%)	.637
Nausea	9 (15%)	8 (13.33%)	.794
Diarrhea	4 (6.67%)	3 (5%)	>.999
Vaginal bleeding	9 (15%)	11 (18.33%)	.624
Fever	3 (5%)	2 (3.33%)	>.999

Note: Values are presented as mean ± SD or n (%).

[a] Assessed by the patients with the use of a 100-mm visual analog scale (0 = no pain; 100 = the worst experienced pain).

[b] Assessed by the operators with the use of a 100-mm visual analog scale (0 = the easiest insertion of the hysteroscope into the uterine cavity; 100 = the most difficult insertion of the hysteroscope into the uterine cavity).

Fouda. Misoprostol before office hysteroscopy. Fertil Steril 2016.

In previous studies, time interval from administration of misoprostol and office hysteroscopy ranged from 2 to 24 hours (7–11). Two randomized controlled trial revealed that 400 μg misoprostol administered vaginally 12–24 hours before office hysteroscopy considerably reduced the pain experienced during office hysteroscopy (11, 18). In a randomized controlled trial, 200 μg misoprostol administered sublingually 2 hours before office hysteroscopy was more effective than lidocaine spray in minimizing pain experienced during office hysteroscopy (10). In contrast, a randomized controlled study revealed that 400 μg misoprostol administered vaginally 6 hours before office hysteroscopy was not effective in reducing pain experienced during office hysteroscopy (7).

Misoprostol is used before inpatient and office hysteroscopy to soften the cervix and to dilate the cervical canal. Misoprostol increases the influx of leucocytes to cervical stroma, stimulates matrix metalloproteinases activity (which degrades connective tissue matrix), increases hyaluronic acid and water content in the cervical stroma, thereby leads to cervical softening and dilation (19). Moreover, misoprostol stimulates uterine contractions, which increase the dilation of the softened cervix (20).

Misoprostol can be administered orally, vaginally, or sublingually. Misoprostol is rapidly absorbed after administration via oral or sublingual routes. The plasma level of its active metabolite (misoprostol acid) peaks within 30 minutes, and then the plasma level of misoprostol acid rapidly declines within 2 hours. After vaginal administration, the plasma level of misoprostol acid peaks within 70–80 minutes, and then the plasma level of misoprostol acid declines gradually, reaching

60% of the peak level 6 hours after misoprostol administration. The plasma levels of misoprostol acid remain elevated for a longer period after misoprostol administration via the vaginal route compared with the oral and sublingual routes (21, 22).

Cervical dilation induced by misoprostol administration is the result of remodeling of the cervical tissues and uterine contractions. Several studies revealed that the uterotonic effect of misoprostol is influenced by the route of misoprostol administration. Regular uterine contractions begin 1–2 hours after administration of a single dose of misoprostol via vaginal or sublingual routes. In contrast, uterine contractions start after administration of repeated doses of misoprostol via the oral route. Uterine contractions persist for longer periods after misoprostol administration via the vaginal route compared with the sublingual route because the plasma levels of misoprostol acid remain elevated for a longer period after misoprostol administration via the vaginal route compared with the sublingual route (20, 23).

We think that the ideal route for misoprostol administration before inpatient or office hysteroscopy is the vaginal route. In contrast to oral and sublingual routes, vaginal misoprostol induces more powerful uterine contractions that persist for a longer period and therefore could be more effective in dilating the cervix (20, 23). Regular uterine contractions persist for >6 hours after vaginal misoprostol administration; therefore, we think it is necessary to wait for >6 hours after vaginal misoprostol administration to obtain the maximal cervical dilation.

Several studies revealed that vaginal misoprostol (400 μg) administered 3 hours before suction evacuation was the optimal dose and timing of vaginal misoprostol for cervical priming before first-trimester termination of pregnancy by means of vacuum aspiration (24, 25). Singh et al. (25) reported that misoprostol (400 μg) administered vaginally 3 hours before suction evacuation was more effective in achieving preoperative cervical dilation ($\geq$8 mm) than misoprostol (600 μg) administered vaginally 2 hours before suction evacuation (93.3% vs. 16.7%; $P<.001$). In contrast, a randomized controlled trial revealed that misoprostol administration 4 hours before operative hysteroscopy was not effective in increasing cervical width (12). Other studies reported that misoprostol administration 8–12 hours before operative hysteroscopy was effective in facilitating cervical dilation (13–15).

Several authors have suggested that the priming effect of misoprostol is influenced by the level of circulating estrogens. Cervical ripening does not occur in pregnant women with low circulating estrogens, owing to placental sulfatase deficiency, and misoprostol is less effective in softening the cervix in menopausal patients than it is in patients of reproductive age (1, 26). Stygar et al. (27) detected the presence of estrogen receptor beta in cervical leukocytes. They suggested that estrogen regulates the function of the leukocytes of the cervix. Based on these findings, we think that misoprostol has a weaker cervical priming effect in nonpregnant women than in pregnant women.

Histologic and immunohistochemical studies revealed the presence of dense collagen fibers in the cervical tissues of nonpregnant women. In early pregnancy, the collagen fibers become slightly sparse. In late pregnancy, collagen fibers become widely dissociated, separated by clear spaces (edema) and infiltrated with inflammatory cells (19, 28). The concentration of collagen in the cervix at 10 weeks of gestation and at full term are, respectively, 70% and 30% of the concentration of collagen in nonpregnant cervix (29). Previous studies revealed that larger doses of misoprostol and longer duration of misoprostol administration are needed to ripen the cervix in early pregnancy than in late pregnancy (30). This might indicate that the more dense the collagen fibers in cervical tissues, the less the sensitivity of the cervix to ripening with misoprostol and the more dose and duration of misoprostol administration required to ripen the cervix.

We think it is necessary to wait for 8–12 hours after vaginal misoprostol administration before performing office hysteroscopy in nonpregnant women (especially the subgroups of patients with a narrow cervical canal, such as nulliparous and menopausal patients). If the time interval between misoprostol administration and office hysteroscopy is short, misoprostol will be less effective in ripening the cervix and dilating the cervical canal and, therefore, the passage of the hysteroscope through the cervical canal will be more difficult and associated with more pain and discomfort.

In conclusion, vaginal misoprostol administration 12 hours before office hysteroscopy is more effective than vaginal misoprostol administration 3 hours before office hysteroscopy in relieving pain experienced by nulliparous patients undergoing office hysteroscopy.

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