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# Cervical Priming Before Diagnostic Operative Hysteroscopy in Infertile Women: A Randomized, Double-Blind, Controlled Comparison of 2 Vaginal Misoprostol Doses

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**The aim of this study was to evaluate the efficacy of vaginal misoprostol for cervical priming at doses of 200 mcg and 400 mcg, 12 to 15 hours before diagnostic office hysteroscopy (OH) without anesthesia in patients with infertility. Sixty infertile patients requiring a diagnostic office hysteroscopy for investigation of infertility were included in the study. The patients were randomly allocated into 3 vaginally administered misoprostol groups: (1) control group, (2) 200-mcg dose group, and (3) 400-mcg dose group. Misoprostol significantly facilitated the procedure of OH: cervical entry was easier; procedural time was shorter; baseline cervical width was larger; and pain scoring was lower in the misoprostol groups compared with the control group. Increasing the dose of misoprostol from 200 mcg to 400 mcg did not improve the effect on cervical dilation. Misoprostol is a promising analog to use for cervical priming before OH. Since doses of 200 mcg and 400 mcg vaginal misoprostol 12 hours before the OH both have proven to be effective regimens, 200 mcg may be preferred. However, before routine clinical usage, further research is needed through large, randomized, controlled trials powered to detect a difference in complications to determine whether misoprostol reduces complications in OH.**

*Key words*: Cervical priming – Misoprostol – Office hysteroscopy

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Office hysteroscopy (OH) is a common gynecologic procedure, mainly used to detect uterine pathologies, that requires the cervix to be dilated. Complications such as uterine perforation, cervical laceration, failure to dilate, and creation of a false track can occur during cervical entry.[1] While there are several techniques, such as hysterosalpingogram (HSG), saline infusion sonogram (SIS), and transvaginal ultrasound (TVUS), to investigate uterine pathologies, OH has become the gold standard in the detection of anomalies.[2] OH is a convenient and patient-friendly technique.

Misoprostol, a synthetic prostaglandin E1 analog, has been used for cervical priming prior to its use in OH, but there is still no agreement on the recommended dose, route (oral or vaginal), or time of administration.[3–4] Misoprostol has generally shown good efficacy in achieving cervical dilation and facilitating OH. Nevertheless, earlier studies on this topic investigated the use of vaginal misoprostol before OH under anesthesia. Currently, there are only a few published studies on the effects of misoprostol at different doses and routes before OH without the use of anesthesia.

In this study, our aim was to compare the efficacy of vaginal misoprostol for cervical priming at doses of 200 mcg and 400 mcg, 12 to 15 hours before diagnostic OH without anesthesia in patients with infertility.

## Material and Methods

This double-blind randomized controlled trial (RCT) was conducted between July 2011 and February 2012 at the Infertility Clinic of Istanbul University School of Medicine. A total of 92 infertile women of reproductive age requiring a diagnostic OH for investigation of infertility were eligible for study recruitment. A sample size of "convenience" was used as the study was regarded as a feasibility pilot study. The study protocol was approved by the Ethics Committee of Istanbul University, and informed consent was obtained from each of the patients prior to the treatment.

The following are the inclusion criteria: (1) patients requiring a diagnostic hysteroscopy as part of an infertility diagnosis work-up; (2) detection of normal intrauterine cavity according to hysterosalpingography (HSG) and transvaginal ultrasound (TVUS) evaluations. The exclusion criteria included the following: (1) contraindications to OH (*i.e.*, pregnancy, cervical malignancy, pelvic inflammatory disease, etc); (2) any possible contraindications to use of prostaglandins (cardiovascular disease, hypertension, renal failure, etc); (3) previous cesarean delivery; (4) previous cervical surgery; (5) previous abortion; (6) neurologic disorders affecting the evaluation of pain.

Thirty-two women were excluded for the following reasons: inclusion criteria were not met (n = 21); OH had to be rescheduled because of administrative problems (n = 5); and no consent was given for participation in the study (n = 6). The remaining 60 patients were included in the final analyses.

The patients were randomly allocated into 3 groups by a computer-generated randomization table prepared by one of the authors (AN), who was not responsible for the follow-up of the patients: group I (control group; 20 patients), group II (200-mcg misoprostol group; 20 patients), and group III (400-mcg misoprostol group; 20 patients). This was a double-blind randomized trial because the patients, surgeons, and outcome evaluators were blinded to patient allocation. All patients underwent vaginal examination 12 to 15 hours before OH. In group I, the vaginal examination was performed without misoprostol administration; in group II, 200 mcg misoprostol (Cytotec; Pfizer, Instanbul, Turkey), moistened with saline solution, was inserted into the vagina during the examination; in group III, the same procedure as group I was repeated with 400 mcg misoprostol.

All patients underwent diagnostic OH during the proliferative phase of their menstruation cycle between days 1 and 14. OH was performed by a single gynecologist (EB) to reduce individual variability. In the office, the patient was prepared and draped in the dorsal lithotomy position with her legs in adjustable stirrups. Traditional saline hysteroscopy was chosen, which utilizes speculum and tenaculum. After a bimanual examination, speculum was used to bring the cervix into view. Then, the cervix was cleaned with povidone-iodine solution. A single-toothed tenaculum was applied to the anterior lip of the cervix. A 5-mm hysteroscope (Karl-Storz GmbH & Co KG, Tuttlingen, Germany) was introduced to the external cervical os and was advanced into the endocervical canal without anesthesia. Cervical dilatation up to 5 mm was utilized. A 0.09% NaCl solution distention media was used, while the hysteroscope was slowly slid into the uterine cavity. Patients returned to their daily activities after 1 hour of observation in the hospital. Doxycycline 100 mg was given orally twice daily for 2 days starting on the day of the procedure until the day after.

The main outcome measures included the following: (1) ease of entry of the OH into the cervix recorded on a 5-point Likert scale: "very difficult," "difficult," "fair," "easy," and "very easy"; (2) procedural time from the beginning of cervical dilatation to the visualization of the uterine cavity; (3) baseline cervical width at the beginning of the procedure assessed by the largest number of Hegar dilator that could be inserted into the cervix without resistance; (4) pain scoring recorded by the patient on a 10-point visual analog scale (VAS)[5]; (5) side effects of misoprostol; and (6) complications of OH.

Data were analyzed using SPSS software, version 15.0 (SPSS Inc, Chicago, Illinois). Continuous variables were expressed as the mean value ± SD. After using the Kolmogorov-Smirnov distribution function, parametric variables were evaluated by $\chi^2$ test and Student *t* test, while nonparametric variables were evaluated by the Mann-Whitney *U* test. A *P* value of $<0.05$ was considered statistically significant.

## Results

Demographic and clinical characteristics of the patients are presented in Table 1. The study population consisted of 60 patients allocated into 3 groups: group I (control group; 20 patients), group II (200-mcg misoprostol group; 20 patients), and group III (400-mcg misoprostol group; 20 patients). All 3 groups were matched for age and body mass index ($P > 0.05$).

The use of vaginal misoprostol significantly facilitated the procedure of OH (Table 2). Ease of cervical entry was significantly easier in group II when compared with the control group (3.8 ± 0.52 versus 2.85 ± 0.67) and also in group III when again compared with the control group (3.9 ± 0.65 versus 2.85 ± 0.67) ($P < 0.05$). Procedural time was shorter in group II when compared with the control group (71.3 ± 39.69 min versus 244.7 ± 100.6 min) and also in group III when again compared with the control group (55.25 ± 25.9 min versus 244.7 ± 100.6 min) ($P < 0.05$). Baseline cervical width was larger in group II when compared with the control group (5.85 ± 1.08 mm versus 4.15 ± 1.63 mm) and also in group III when again compared with the control group (6.5 ± 0.51 mm versus 4.15 ± 1.63 mm) ($P < 0.05$). Pain scoring was lower in group II when compared with the control group (2.75 ± 2.14 versus 4.8 ± 2.35) and also in group III when again compared with the control group (2.8 ± 1.5 versus 4.8 ± 2.35) ($P < 0.05$).

When the administration of 200 mcg vaginal misoprostol (group II) was compared with the administration of 400 mcg vaginal misoprostol (group III), ease of cervical entry (3.8 ± 0.52 versus 3.9 ± 0.65), baseline cervical width (5.85 ± 1.08 mm versus 6.5 ± 0.51 mm), and pain scoring (2.75 ± 2.14 versus 2.8 ± 1.5) were similar between groups ($P > 0.05$) (Table 2). Although the procedural time was longer in group II (71.3 ± 39.69 min versus 55.25 ± 25.9 min), the difference was not statistically significant ($P > 0.05$) (Table 2).

No major side effects of misoprostol or complications from OH were reported.

## Discussion

In the present study, the use of vaginal misoprostol, both in doses of 200 mcg and 400 mcg, significantly facilitated the procedure of OH: cervical entry was easier; procedural time was shorter; baseline cervical width was larger; and pain scoring was lower in the misoprostol groups compared with the control group. On the other hand, increasing the dose of vaginal misoprostol from 200 mcg to 400 mcg did not improve the effect on cervical dilation.

In more recent RCTs, in which different doses and routes of misoprostol were evaluated before OH without anesthesia, Thomas *et al*[6] randomly allocated either placebo or 400 mcg of oral misoprostol to their patients 12 and 24 hours before OH. The misoprostol group demonstrated an increased ease of cervical dilation. There were no differences between the 2 groups in the time required for

*Table 1 Demographic and clinical characteristics of the patients*[a]

| Variable | Group I (control group) n = 20 | Group II (200 mcg miso) n = 20 | Group III (400 mcg miso) n = 20 | *P* value |
|---|---|---|---|---|
| Age (y) | 30.15 ± 4.23 | 32.75 ± 5.37 | 30.35 ± 6.38 | NS |
| Body mass index (kg/m$^2$) | 25.3 ± 3.2 | 24.4 ± 4.2 | 26.2 ± 1.2 | NS |
| Duration of infertility (mo) | 55.37 ± 52.59 | 62.50 ± 53.38 | 56.70 ± 53.27 | NS |

Miso, misoprostol; NS, nonsignificant.

[a]Values presented as mean ± SD.

*Table 2 Comparison of misoprostol groups with the control group*[a]

| Variable | Group I (control group) n = 20 | Group II (200 mcg miso) n = 20 | Group III (400 mcg miso) n = 20 | Group I and group II *P* value | Group I and group III *P* value | Group II and group III *P* value |
|---|---|---|---|---|---|---|
| Ease of cervical entry[b] | 2.85 ± 0.67 | 3.8 ± 0.52 | 3.9 ± 0.65 | <0.05 | <0.05 | 0.986 |
| Procedural time (min) | 244.7 ± 100.6 | 71.3 ± 39.69 | 55.25 ± 25.9 | <0.05 | <0.05 | 0.289 |
| Baseline cervical width (mm) | 4.15 ± 1.63 | 5.85 ± 1.08 | 6.5 ± 0.51 | <0.05 | <0.05 | 0.06 |
| Pain scoring[c] | 4.8 ± 2.35 | 2.75 ± 2.14 | 2.8 ± 1.5 | <0.05 | <0.05 | 0.327 |

Miso, misoprostol.

[a]Values presented as mean ± SD.

[b]According to 5-point Likert scale.

[c]According to 10-point visual analog scale.

dilation. Fernandez *et al*[7] assigned patients to receive either placebo or vaginal misoprostol in doses of 200, 400, or 800 mcg 4 hours before OH. The groups did not differ significantly in the time required for dilation and ease of dilation. Preoperative pain was greater in the treatment groups. In a trial by Oppegaard *et al*,[8] patients were randomized to either 1000 mcg of self-administered vaginal misoprostol or self-administered vaginal placebo the evening before OH. Study findings revealed that there was a significant cervical ripening effect compared with placebo. Sordia-Hernández *et al*[9] evaluated the effectiveness of both oral and vaginal misoprostol, by giving 600 mcg oral misoprostol to one group, 400 mcg vaginal misoprostol to another, and placebo to the control group. They argued that 400 mcg vaginal misoprostol given the day before OH considerably reduced the time needed for hysteroscopy and the pain during OH. El-Mazny and Abou-Salem[10] compared 200-mcg vaginal misoprostol with the control group in which placebo was not used; they found that cervical entry was easier, procedure time was shorter, patient acceptability was higher, and pain scoring was lower in the misoprostol group, which is in line with our findings. In a very recent study, Bakas *et al*[11] administered 200 mcg oral misoprostol to one group (12 hours before), 200 mcg vaginal misoprostol (12 hours before) to another, and 200 mcg vaginal misoprostol (4 hours before) to a third group. Their results support the preoperative use of 200 mcg of vaginal misoprostol 12 hours before the OH, again in line with the findings of the present study. Since 200 mcg and 400 mcg doses of vaginal misoprostol presented similar results in our study, a dose of 200 mcg may be preferable to avoid unnecessary usage of a higher dose such as 400 mcg. Therefore, potential side effects of high-dose drug usage can be prevented in advance.

Because of the positive impact of misoprostol on cervical priming, 200 mcg of vaginal misoprostol administered 12 hours before the OH has been routine clinical practice in our infertility clinic since the beginning of 2012.

## Conclusion

Misoprostol is a promising analog to use for cervical priming before OH. Since doses of 200 mcg and 400 mcg vaginal misoprostol 12 hours before the OH both have proven to be effective regimens, 200 mcg may be preferred. However, before routine clinical usage, further research is needed to determine whether misoprostol reduces complications in OH, through large RCTs that are powered to detect a difference in complications. In such trials, optimal dose, route (vaginal or oral), and timing of misoprostol administration have to be well established.

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