Objective: To evaluate the efficacy and safety of vaginal misoprostol for cervical priming before diagnostic outpatient hysteroscopy (OH) without anesthesia.

Design: Double-blind randomized controlled trial.

Setting: University teaching hospital.

Patient(s): One hundred fifty patients requiring diagnostic OH for investigation of infertility or abnormal uterine bleeding in the reproductive age.

Intervention(s): Patients were randomly allocated into two equal groups (n = 75). In group I, 200 μg misoprostol was inserted into the posterior vaginal fornix 3 hours before OH; in group II (control), vaginal examination was performed without misoprostol administration. A rigid 30° 4-mm hysteroscope was used in the vaginoscopic technique.

Main Outcome Measure(s): Ease of cervical entry (Likert scale), procedural time, patient acceptability (Likert scale), and pain scoring (visual analog scale).

Result(s): Vaginal misoprostol significantly facilitated the procedure; cervical entry was easier, procedural time was shorter, patient acceptability was higher, and pain scoring was lower in group I compared with group II. Side effects of misoprostol were infrequent, minor, and transient. No complications were reported.

Conclusion(s): The regimen of 200 μg vaginal misoprostol administered 3 hours before diagnostic OH is a simple, effective, and safe method of cervical priming to facilitate the procedure without anesthesia. (Fertil Steril® 2011;96: 962–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Misoprostol, cervical priming, outpatient hysteroscopy

Hysteroscopy is considered the “gold standard” for diagnosing intrauterine pathology (1). With the invention of the miniature hysteroscope, it is possible to perform hysteroscopy in an office setting (outpatient hysteroscopy [OH]) without anesthesia for diagnostic indications and certain operative procedures (2). However, the experience of pain related to the procedure can be a major limitation for OH as a standard of care (3). This is often caused by the diameter of the hysteroscope and/or cervical resistance (4).

Several alternatives have been proposed to perform the procedure with an acceptable patient compliance. Local anesthetic reduces the pain experienced by women during OH. This occurs with paracervical and intracervical injections of anesthetic but not with transcervical and topical application; paracervical injection seems to be the most effective method of administering local anesthetic for the procedure (5). Nevertheless, the injection of paracervical anesthetic may cause pain and bleeding (6).

Cervical priming refers to dilating or softening of the cervix by mechanical (e.g., laminaria) or medical (e.g., prostaglandins) means before an intervention in pregnant (cervical ripening) or nonpregnant women (7). Misoprostol is a synthetic analogue of prostaglandin E1 which can be given orally, vaginally, sublingually, buccally, or rectally (8). There is evidence supporting the use of misoprostol as a cervical priming agent before some gynecologic procedures, such as intrauterine device insertion (9) and hysteroscopy (10).

The objective of the present study was to evaluate the efficacy and safety of vaginal misoprostol for cervical priming to facilitate the procedure of diagnostic OH without the use of anesthesia, in patients with infertility or abnormal uterine bleeding (AUB).

MATERIALS AND METHODS

This double-blind randomized controlled trial was conducted at the OH Clinic of the Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, from August 2009 to January 2011. The study population consisted of 150 patients requiring a diagnostic OH for investigation of infertility or AUB in the reproductive age. The study protocol was approved by the Scientific Research Committee of the department, and informed consent was obtained from each of the patients.

The exclusion criteria included: 1) contraindications to OH—marked cervical stenosis, recent or current pelvic inflammatory disease, known cervical malignancy, pregnancy, profuse uterine bleeding, or recent uterine perforation; 2) contraindications to prostaglandins—known sensitivity to prostaglandins, cardiovascular disease, hypertension, severe bronchial asthma, renal failure, or glaucoma; 3) previous cesarean delivery; 4) previous cervical surgery; and 5) neurologic disorders affecting the evaluation of pain.

The patients were allocated into two groups with a ratio of 1:1 by using computer-generated random numbers: group I (misoprostol group) and group II (control group). The patients were blinded to group allocation. All patients underwent vaginal examination 3
hours before OH. In group I, 200 µg misoprostol (Misotac; Sigma Pharm) moistened with saline solution was inserted into the posterior fornix during the examination; in group II, the vaginal examination was performed without misoprostol administration (no placebo was needed).

All patients underwent postmenstrual OH between days 7 and 11 of the cycle (except in patients with irregular bleeding). The operator performing the procedure was blinded to group allocation. A rigid 30° 4-mm hystroscope (Karl Storz Endoscopy) was used without anesthesia or analgesia. The uterine cavity was distended with normal saline solution at a pressure of 100–120 mm Hg. The vaginoscopic “no touch” technique was followed; no speculum or tenaculum was used.

The main outcome measures included: 1) ease of entry of the OH into the cervix recorded on a 5-point Likert scale (11); very difficult = 1, difficult = 2, fair = 3, easy = 4, and very easy = 5; 2) procedural time from introduction of the OH through the external cervical os and the visualization of the uterine cavity; 3) patient acceptability recorded by the patient on a 5-point Likert scale; 4) pain scoring recorded by the patient on a 10-point visual analog scale (VAS) (12); 5) side effects of misoprostol; and 6) complications of OH.

Statistical Analysis

Continuous data were expressed as mean ± SD and compared by using the Student t test. Categorical data were expressed as n (%) and compared by using the chi-square test or Fisher exact test as appropriate. All reported P values are two tailed, and the level of statistical significance was .05. Data analysis was performed by using the Statistical Package for the Social Sciences, v16.0 (SPSS).

RESULTS

The study population consisted of 150 patients allocated into two groups: group I (misoprostol group; 75 patients) and group II (control group; 75 patients). There was no statistically significant difference in the clinical characteristics (age, gravidity, parity, and nulliparous rate) between the two groups. The indications of hysteroscopy (primary infertility, secondary infertility, and AUB) were also not significantly different (Table 1).

The use of vaginal misoprostol significantly facilitated the procedure of OH. Cervical entry (Likert scale) was easier in group I (3.47 ± 1.05) than in group II (2.93 ± 1.02); P=.002. Procedural time (minutes) from introduction of the OH through the external cervical os and the visualization of the uterine cavity was shorter in group I (1.95 ± 0.47) than in group II (2.48 ± 0.56); P<.001. Patient acceptability (Likert scale) was higher in group I (2.87 ± 0.96) than in group II (2.51 ± 0.89); P=.019. Pain scoring (VAS) was lower in group I (3.26 ± 1.56) than in group II (4.87 ± 1.79); P<.001 (Table 2; Fig. 1).

Side effects of misoprostol were minor and transient; nausea was reported in seven patients (9.3%), vomiting in two patients (2.7%), abdominal pain in six patients (8.0%), diarrhea in four patients (5.3%), fever in three patients (4.0%) and shivering in three patients (4.0%). These side effects were also not significantly higher than in the control group (Table 3). There were no cases of vaginal bleeding or spotting related to misoprostol use. No complications were reported from the use of OH in our series.

DISCUSSION

The major technical improvements in the manufacturing of high-quality small-bore scopes (minihysteroscopes) and the consistent scientific data published over the past years could permit us to propose OH as a first-line diagnostic tool for the investigation of AUB (13) and uterine factor of infertility, especially before assisted reproductive techniques (14). However, the experience of pain can be a deterrent for patients offered OH; therefore, several efforts had been made to facilitate cervical dilation before the procedure (15).

Misoprostol has generally shown good efficacy in promoting cervical softness and facilitating hysteroscopic procedures. However, the vast majority of earlier studies on this topic investigated the use of vaginal misoprostol before conventional diagnostic or operative hysteroscopy under anesthesia. Presently, there are only a few published studies regarding the value of misoprostol before anesthesia-free OH; with variable doses, routes of administration, and time intervals before the procedure. In the present study, we evaluated the efficacy and safety of vaginal misoprostol for cervical priming at a dose of 200 µg 3 hours before diagnostic OH without anesthesia in patients with infertility or AUB. There was an overlap of patient samples with infertility in this study and our previous study about the value of OH as a routine investigation of uterine factor of infertility before assisted reproductive techniques (14).

Our results indicate that the use of vaginal misoprostol significantly facilitated the procedure of OH: Cervical entry was easier, procedural time was shorter, patient acceptability was higher, and pain scoring was lower in the misoprostol group compared with the control group. Misoprostol-related side effects (nausea, vomiting, abdominal pain, diarrhea, fever, and shivering) were infrequent, minor, and transient, and no complications were reported. Increasing the dose of vaginal misoprostol to >400 µg or increasing the interval beyond 3 hours has not improved the effect on cervical

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I: misoprostol (n = 75)</th>
<th>Group II: control (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29.53 ± 6.12</td>
<td>30.16 ± 5.74</td>
<td>.517</td>
</tr>
<tr>
<td>Gravidity</td>
<td>1.98 ± 0.45</td>
<td>2.11 ± 0.63</td>
<td>.148</td>
</tr>
<tr>
<td>Parity</td>
<td>0.87 ± 0.19</td>
<td>0.92 ± 0.31</td>
<td>.236</td>
</tr>
<tr>
<td>Nulliparous rate</td>
<td>42 (56.0)</td>
<td>39 (52.0)</td>
<td>.623</td>
</tr>
<tr>
<td>Primary infertility</td>
<td>37 (49.3)</td>
<td>32 (42.6)</td>
<td>.413</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>15 (20.0)</td>
<td>17 (22.7)</td>
<td>.690</td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
<td>23 (30.7)</td>
<td>26 (34.7)</td>
<td>.602</td>
</tr>
</tbody>
</table>

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

dilation, but it has increased side effects, mainly diarrhea and shivering (16).

In agreement with our results, Sordia-Hernández et al. (17) reported that vaginal misoprostol at a dose of 200 μg inserted 12 hours apart, starting 24 hours before OH without anesthesia for investigation of infertility, considerably reduces pain and the time needed for hysteroscopy compared with oral misoprostol administration and placebo. They reported only one patient with nausea and two patients with referred abdominal pain in the vaginal misoprostol group (n = 20). Choksuchat et al. (18) also found that 200 μg vaginal misoprostol 12 hours before conventional diagnostic hysteroscopy had efficacy similar to 400 μg oral misoprostol for cervical ripening, with lesser side effects.

Darwish et al. (19) reported that 200 μg intravaginal misoprostol and endocervical laminaria were equally effective in inducing proper cervical priming before operative hysteroscopy in patients with diagnosed intrauterine lesions. Nevertheless, they observed that misoprostol may be superior, owing to easy application, reduced cost, and patient convenience and acceptability. Preuthipan et al. (20) also found that vaginal misoprostol is more effective than dinoprostone for cervical priming in nulliparous women before hysteroscopic surgery. Although more side effects were observed in the misoprostol-treated patients, they were mild.

Batukan et al. (21) reported that 400 μg vaginal misoprostol 10–12 hours before operative hysteroscopy is more effective than the oral route for preoperative cervical ripening in premenopausal women. Da Costa et al. (22) also found that 200 μg of vaginal misoprostol reduced pain severity during diagnostic hysteroscopy in postmenopausal women. However, Oppegaard et al. (23) concluded that 1,000 μg vaginal misoprostol 12 hours before operative hysteroscopy has a significant cervical ripening effect compared with placebo in premenopausal but not postmenopausal women.

In contrast to our results, Fernandez et al. (24) found that vaginal misoprostol applied 4 hours before operative hysteroscopy in premenopausal women, at three different doses (200, 400, or 800 μg), did not reduce the need for cervical dilation, did not facilitate hysteroscopic surgery, and increased preoperative pain. Valente et al. (25) also observed that with the dose used in their

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**TABLE 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I: misoprostol (n = 75)</th>
<th>Group II: control (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of cervical entrya</td>
<td>3.47 ± 1.05</td>
<td>2.93 ± 1.02</td>
<td>.002</td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>1.95 ± 0.47</td>
<td>2.48 ± 0.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patient acceptabilitya</td>
<td>2.87 ± 0.96</td>
<td>2.51 ± 0.89</td>
<td>.019</td>
</tr>
<tr>
<td>Pain scoringb</td>
<td>3.26 ± 1.56</td>
<td>4.87 ± 1.79</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Note: Values presented as mean ± SD.

*a According to 5-point Likert scale.

*b According to 10-point visual analog scale.

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**FIGURE 1**

Main outcome measures.
study (400 μg); vaginal misoprostol induced vaginal bleeding and precluded diagnostic anesthesia-free hysteroscopy in patients of reproductive age. Singh et al. (26) found that 400 μg vaginal misoprostol 4–6 hours before diagnostic hysteroscopy did not facilitate cervical dilation. Although it did effect a reduction in pain scores, there was no difference in patient satisfaction, need for analgesia, or sedation.

In conclusion, our results indicate that the use of vaginal misoprostol as a cervical priming agent is a simple method to facilitate the procedure of diagnostic OH without anesthesia in patients with infertility or AUB. Reduction of misoprostol dosage (200 μg) with shortening of the time interval between misoprostol administration and the procedure (3 hours) has been proven to be an effective regimen with minimal side effects.

## REFERENCES