Clinical Use of Misoprostol in Nonpregnant Women: Review Article

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ABSTRACT

Misoprostol, a prostaglandin E₁ (PGE₁) derivative, has been widely used in nonpregnant women because of its cervical ripening and uterotonic effects. A large number of studies have demonstrated its effectiveness in enhancing ease of cervical dilation. This review article describes its pharmacokinetic profile and the relationship between prostaglandins and cervical ripening and uterine contraction and provides a review of the clinical use of misoprostol in nonpregnant women including cervical priming before hysteroscopy, before insertion of an intrauterine device, in endometrial biopsy, preoperatively in myomectomy, and before intrauterine insemination to improve pregnancy rates. Adverse effects are also described. Journal of Minimally Invasive Gynecology (2010) 17, 449–455 © 2010 AAGL. All rights reserved.

Keywords: Biopsy; Endometrium; Gynecology; Hysteroscopy; Intrauterine device; Intrauterine insemination; IUD; IUI; Misoprostol; Myomectomy

Misoprostol, a prostaglandin E₁ (PGE₁) derivative, was first approved in 1988 by the US Food and Drug Administration for prevention and treatment of gastric ulcers induced by nonsteroidal anti-inflammatory drugs [1]. It inhibits secretion of acid and pepsin in the stomach and has a mucosal protective effect on the gastrointestinal mucosa [2].

Because of its cervical ripening and uterotonic activity effects, misoprostol has been extensively used in obstetrics and gynecology for several years. A website, http://www.misoprostol.org/, is devoted to obstetric and gynecologic uses of misoprostol with an extensive bibliography. A large number of studies have demonstrated its effectiveness in termination of pregnancy in the first and second trimester [3–6]. Misoprostol has also been used for induction of labor and treatment of postpartum hemorrhage [7–9].

Misoprostol has been widely used in nonpregnant women as well. Many authors describe using the medication for cervical priming before hysteroscopy [10–13], before insertion of an intrauterine device (IUD), at endometrial biopsy [14], preoperatively in myomectomy [15], and before intrauterine insemination (IUI) to improve pregnancy rates [16].

For this review, electronic searches were undertaken in PubMed and SCOPUS using the keywords “Misoprostol,” “Pharmacokinetics,” “Cervical ripening,” “Uterine contraction,” “Nonpregnant women,” “Hysteroscopy,” “Intrauterine insemination,” “IUI,” “Endometrial biopsy,” “Intrauterine device,” “IUD insertion,” and “Myomectomy.”

Pharmacokinetics

Misoprostol (Cytotec; G.D. Searle & Co., Skokie, IL) is a 15-deoxy, 16-hydroxy, 16-methyl synthetic analogue of natural PGE₁ [1]. After oral administration, misoprostol is absorbed and undergoes rapid deesterification to misoprostol acid, its biologically active metabolite [17]. The pharmacokinetic profile is no different between pregnant and nonpregnant women [18]. Misoprostol can be administered sublingually, orally, vaginally, or rectally. The plasma concentration of misoprostol acid peaks less than 30 minutes after administration via the oral or sublingual route in pregnant women, after which the blood concentration decreases rapidly. Misoprostol acid levels peak approximately 1 hour after vaginal application. After 1 dose of misoprostol administered vaginally, the plasma concentration gradually decreases; however, it persists for at least 6 hours at substantially higher concentrations than when administered orally or sublingually. The area under the misoprostol acid concentration vs time curve indicates that the systemic bioavailability of sublingually administered misoprostol is significantly greater than with orally or vaginally administered misoprostol. There are no significant differences between sublingual and vaginal...
administration [19]. Rectally administered misoprostol is associated with a qualitatively similar absorption curve as that administered vaginally, but with lower bioavailability [20].

Misoprostol was originally manufactured for oral administration. Undissolved fragments of the misoprostol tablet are often found when administered vaginally because of incomplete dissolution [5,11,18,21,22]. Misoprostol is thought to liquefy better in an acidic medium. However, when compared with adding only water, Singh et al [23] failed to demonstrate any benefits of adding acetic acid, pH 2, to a 200-µg tablet of vaginal misoprostol administered 3 to 4 hours before vacuum aspiration for termination of first-trimester pregnancies.

Prostaglandins and Cervical Ripening or Uterine Contraction

The complex biochemical process of cervical ripening and the mediators associated with this mechanism are still largely unknown. It has not yet been conclusively established how prostaglandins produce cervical ripening. Ripening of the uterine cervix is related to changes in collagen, glycosaminoglycans, and collagenolytic activity. Connective-tissue biopsy specimens from the lower part of the uterine cervix in pregnant women at various gestational stages have demonstrated that the concentrations of collagen, sulfated glycosaminoglycans, and hyaluronic acid decrease during pregnancy.

When compared with nonpregnant women, the concentrations of collagen are approximately 70% at 10 weeks of gestation, and approximately 30% at term. The collagenolytic activity increases with advancing gestational age. The 2,4-dinitrophenyl-Pro-Gln-Gly-Ile-Ala-Gly-Gln-D-Arg hydrolytic activity (collagenase) and the leukocyte elastase concentration increase gradually by a factor of 10. One study found that cervical dilation time during spontaneous labor was longer in women with high concentrations of collagen, and shorter in women with low concentrations of collagen [24].

el-Rafaey et al [25] demonstrated a similar alteration in cervical connective tissue after vaginal administration of misoprostol or gemeprost (an aloprostadi prostaglandin analogue) [25]. Electron microscopy and histochemical studies of cervical tissue revealed that mean proline incorporation per microgram of protein (i.e., collagen metabolism) increased significantly, whereas collagen density, estimated using light intensity, decreased significantly. In addition, the diameter of collagen fibers was smaller after PGE1 application. Dilation of the cervix at parturition in guinea pigs also involves collagenase-mediated degradation of cervical collagen [26].

Prostaglandins are capable of inducing production of hyaluronic acid by cervical fibroblasts, causing increased hydration and alteration of the composition of glycosaminoglycan and proteoglycan [27]. Prostaglandins may act as chemotactic agents, promoting the infiltration of leukocytes and macrophages into the cervical stroma. These inflammatory cells could be the source of the specific degradative enzymes that cause the changes in the extracellular matrix that are associated with ripening of the cervix [28].

Prostaglandins act synergistically with nitric oxide (NO), and have an important role in cervical ripening by causing changes in the extracellular matrix that are associated with ripening of the cervix [29]. Nitric oxide may regulate the activity of metalloproteinases responsible for collagen degradation, and induce prostaglandin production by stimulating cyclooxygenase activity [30].

Prostaglandin E1 can induce release of cervical NO. The level of NO metabolites increased significantly for 1 to 3 hours after administration of 400 and 25 µg of vaginal misoprostol in early and late stages of pregnancy [31]. However, the same study demonstrated that 400 µg of vaginal misoprostol had no effect on cervical fluid NO metabolites in nonpregnant women. There is no information on whether a higher dosage of misoprostol or a longer time would have resulted in release of cervical NO in nonpregnant women. Nevertheless, cervical ripening at approximately 10 hours after misoprostol administration has been demonstrated in many studies [11–13,32–35].

Prostaglandins have potent uterotonic activity caused by their effect of increasing intracellular calcium and activating myosin light-chain kinase, leading in turn to actin and myosin undergoing conformational changes that enable them to slide over each other, causing shortening of the muscle cells and inducing uterine contractions [28].

Use of Misoprostol in Nonpregnant Women

Preoperative Use for Hysteroscopy

Many patients require cervical dilation before hysteroscopy. There have been some reports of cervical tears, false tracts, bleeding, or uterine perforation during the dilation procedure [36,37]. Misoprostol can be used to ripen the cervix, resulting in a softer, more easily dilated cervical canal, which in turn can decrease the number of women who require further mechanical cervical dilation before surgery [10] (Table 1).

Misoprostol in Premenopausal Women

Studies in premenopausal women have demonstrated that baseline cervical canal diameter is significantly greater when misoprostol is used compared with placebo groups. One meta-analysis found that the mean cervical diameter 12 hours after misoprostol administration was approximately 6.0 to 7.5 mm, and the need for further cervical dilation was reduced (relative risk, 0.61; 95% confidence interval, 0.51–0.73) [10]. Clinical data from several studies suggest that the efficacy of 200 µg of vaginal misoprostol or 400 µg of oral misoprostol is comparable with laminaria and is more effective than dinoprostone for cervical priming before hysteroscopy [33,39]. However, 1 study demonstrated that more patients needed cervical dilation in a misoprostol group compared with a group prepared with a laminaria.
tent [43]. Another study found that the force needed to dilate a cervix to 6 mm was less when 400 \( \mu g \) of vaginal misoprostol was administered 12 to 24 hours before hysteroscopy [50]. Furthermore, in women who had undergone cesarean section and no vaginal deliveries, 400 \( \mu g \) of vaginal misoprostol at 6 and 12 hours before operative hysteroscopy led to a significantly greater cervical width and fewer failed cervical dilations than in a control group [51].

When a comparison was made between oral and vaginal administration, 400 \( \mu g \) of oral misoprostol had similar efficacy in cervical ripening as 200 \( \mu g \) of vaginal misoprostol [11]. However, at the same dose of 400 \( \mu g \), another study found vaginal misoprostol to be more effective than oral misoprostol [40]. Mean (SD) cervical width in the vaginal misoprostol group was significantly greater than in the oral group (7.3 [1.6] mm vs 6.0 [1.5] mm). Also in this study, the percentage of women with an initial cervical width of 9 mm was statistically significantly higher in the vaginal misoprostol group (36.8% vs 5.1%) [40].

The time between misoprostol administration and operation may affect its efficacy. Some studies have found an interval of 4 to 6 hours between administration of misoprostol and surgery did not alter the need for cervical dilation and it did not facilitate hysteroscopic surgery [34,42]. Another study found no benefit with a dose up to 800 \( \mu g \) at this interval [34]. However, other studies have found that administration of 200 to 400 \( \mu g \) of misoprostol 8 to 12 hours before surgery resulted in a better outcome, with cervical width of roughly 5.6 to 7.5 mm [11–13,33,35,39,40]. One of these studies, by Darwish et al [33], demonstrated that 8 hours after administration of 200 \( \mu g \) of vaginal misoprostol, the cervical diameter was comparable with the cervical diameter in women using laminaria.

It is not necessary to increase the amount of vaginal misoprostol to prime the cervix to more than 400 \( \mu g \) if it is administered at least 12 hours before surgery. Studies have found that higher dosages of misoprostol did not provide greater cervical response than lower dosages. One study found that mean (SD) cervical dilation was 6.4 (2.4) mm vs 4.8 (2.0) mm in a randomized controlled trial comparing 1000 \( \mu g \) of vaginal misoprostol with placebo 12 hours before operative hysteroscopy [41]. The change in cervical diameter after using 200 \( \mu g \) of vaginal misoprostol or 400 \( \mu g \) of oral misoprostol 12 hours before surgery was approximately 3 mm wider. A systematic analysis in another study revealed that misoprostol increased cervical dilation (weighted mean difference, 2.64

### Table 1
Use of misoprostol for preoperative cervical dilation before hysteroscopy

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>Regimen, ( \mu g )</th>
<th>Mean interval, hr</th>
<th>Before medication</th>
<th>After medication</th>
<th>Need for further dilation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ngai [35]</td>
<td>44</td>
<td>400 PO vs placebo</td>
<td>12</td>
<td>NA</td>
<td>6.0 (1.3) vs 3.2 (1.3)^a</td>
<td>NA</td>
</tr>
<tr>
<td>Preuthipan [12]</td>
<td>91</td>
<td>200 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>7.0 (1.0) vs 3.8 (1.3)^a</td>
<td>31.1 vs 6.5</td>
</tr>
<tr>
<td>Preuthipan [13]</td>
<td>120</td>
<td>200 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>7.3 (0.7) vs 3.8 (1.1)^a</td>
<td>94.9 vs 75.3^a</td>
</tr>
<tr>
<td>Thomas [38]</td>
<td>220</td>
<td>400 PO vs placebo</td>
<td>12 and 24</td>
<td>NA</td>
<td>8.2 (2.3) vs 7.5 (2.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Darwish [33]</td>
<td>144</td>
<td>200 Vg vs laminaria</td>
<td>8</td>
<td>NA</td>
<td>7.5 (1.2) vs 7.6 (1.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Fernandez [34]</td>
<td>48</td>
<td>Placebo vs 200 Vg vs 400 Vg vs 800 Vg</td>
<td>4</td>
<td>NA</td>
<td>6.1 (1.4) vs 6.3 (1.4) vs 5.79 (2.0) vs 6.8 (2.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Preuthipan [39]</td>
<td>310</td>
<td>200 Vg vs dinoprostone</td>
<td>9–10</td>
<td>NA</td>
<td>7.4 (0.8) vs 7.0 (0.9)^a</td>
<td>70.4 vs 80.4^a</td>
</tr>
<tr>
<td>Choksuchat [11]</td>
<td>60</td>
<td>400 PO vs 200 Vg</td>
<td>12</td>
<td>2.00 (1.90) vs 2.37 (1.83)</td>
<td>5.10 (1.75) vs 5.60 (1.69)</td>
<td>3.10 (1.79) vs 3.23 (1.74)^b</td>
</tr>
<tr>
<td><strong>Postmenopause</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Batukan [40]</td>
<td>77</td>
<td>400 PO vs 400 Vg</td>
<td>10–12</td>
<td>NA</td>
<td>6.0 (1.5) vs 7.3 (1.6)^a</td>
<td>94.9 vs 63.2^a</td>
</tr>
<tr>
<td>Oppegaard [41]</td>
<td>69</td>
<td>1000 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>6.4 (2.4) vs 4.8 (2.0)^a</td>
<td>NA</td>
</tr>
<tr>
<td>Singh [42]</td>
<td>100</td>
<td>400 Vg vs placebo</td>
<td>4–6</td>
<td>NA</td>
<td>NA</td>
<td>30 vs 22^a</td>
</tr>
<tr>
<td>Lin [43]</td>
<td>117</td>
<td>400 PO vs laminaria</td>
<td>12 and 24</td>
<td>NA</td>
<td>8.0 (3.7) vs 12.1 (3.2)</td>
<td>70.2 vs 28.3^a</td>
</tr>
<tr>
<td>Mulayim [44]</td>
<td>52</td>
<td>200 SL vs placebo</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>56 vs 77.7^c</td>
</tr>
<tr>
<td><strong>Post-GnRH agonists administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ngai [45]</td>
<td>37</td>
<td>400 PO vs placebo</td>
<td>12</td>
<td>NA</td>
<td>4.2 (1.7) vs 4.4 (1.6)</td>
<td>NA</td>
</tr>
<tr>
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<td>220</td>
<td>400 PO vs placebo</td>
<td>12 and 24</td>
<td>NA</td>
<td>6.9 (2.2) vs 5.7 (2.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Fung [46]</td>
<td>98</td>
<td>800 Vg vs placebo</td>
<td>7</td>
<td>NA</td>
<td>5.2 (1.2) vs 5.0 (1.4)</td>
<td>68.1 vs 72.9</td>
</tr>
<tr>
<td>Barcaite [32]</td>
<td>105</td>
<td>400 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>7.6 (1.4) vs 5.0 (1.1)^a</td>
<td>52.9 vs 98.1^a</td>
</tr>
<tr>
<td>Oppegaard [44]</td>
<td>24</td>
<td>1000 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>3.4 (2.7) vs 4.9 (1.5)</td>
<td>NA</td>
</tr>
<tr>
<td>da Costa [47]</td>
<td>120</td>
<td>200 Vg vs placebo</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>17.2 vs 20.3</td>
</tr>
<tr>
<td><strong>Preutthipan [12]</strong></td>
<td>91</td>
<td>200 Vg vs placebo</td>
<td>12</td>
<td>NA</td>
<td>7.0 (1.0) vs 3.8 (1.3)^a</td>
<td>94.9 vs 75.3^a</td>
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<td>NA</td>
<td>6.1 (1.4) vs 6.3 (1.4) vs 5.79 (2.0) vs 6.8 (2.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable; PO = oral administration; SL = sublingual administration; Vg = vaginal administration.

^a p < .05.

^b Comparison of cervical width difference between oral and vaginal administration.

^c Comparison of need for cervical dilation.

^d Comparison of peak force at each diameter during dilation, and no significant difference in cervical resistance was detected.
mm; 95% confidence interval, 1.73–3.54), and 1 in 4 premenopausal women who received misoprostol before hysteroscopy did not require further cervical dilation [10].

The incidence of cervical tears from mechanical dilation was significantly less in 2 studies in the misoprostol group compared with the placebo or dinoprostone groups [13,39]. The operative time in another study was significantly shorter after cervical priming with misoprostol compared with placebo [12,13].

In conclusion, we recommend a dose of 200 to 400 μg of vaginal misoprostol administered 10 to 12 hours before hysteroscopy in premenopausal women to facilitate cervical dilation.

**Misoprostol in Postmenopausal Women**

Most studies that have examined the use of misoprostol in postmenopausal women before hysteroscopy have failed to demonstrate any benefits [38,41,45–47]. One study showed that administration of 400 μg of vaginal misoprostol in perimenopausal and postmenopausal women 12 hours before hysteroscopy produced a greater cervical diameter and less need for further dilation than in the placebo group [32]. In contrast, however, 3 randomized control trials did not show any benefits with 200 or 800 μg of vaginal misoprostol at approximately 8 hours or 1000 μg of vaginal misoprostol at 12 hours before hysteroscopy [41,46,47]. In addition, sequential doses of 400 μg of oral misoprostol at 12 and 24 hours before surgery did not demonstrate any advantage insofar as cervical dilation [38].

We hypothesize that hypoestrogenic status may be related to poor cervical response to misoprostol in postmenopausal women because estrogen receptors are present in the human cervix [52]. Although interstitial collagenase is believed to have a key role in the mechanism of cervical ripening, gonadal steroids are assumed to be involved in cervical changes. Prostaglandin E₂ interacts with gonadal steroid receptors, and this interaction results in production of collagenase and increased remodeling of the cervical connective tissue, involving changes to proteoglycan metabolism and composition [53]. One study found that estradiol demonstrated a stimulative effect on the procollagenase transcription via a prostaglandin-dependent pathway in cervical fibroblasts in guinea pigs [54]. Further evidence in support of this assumption can be found in a study that found that misoprostol had a greater priming effect on the estrogen-pretreated cervix in postmenopausal women undergoing endometrial curettage [55].

In conclusion, it seems that there is still not enough evidence to support a positive effect for misoprostol on cervical dilation in postmenopausal women.

**Misoprostol and Administration of Gonadotropin-Releasing Hormone Agonists**

Few studies have examined the cervical effects of misoprostol in women receiving treatment with gonadotropin-releasing hormone (GnRH) agonists. Cooper et al [48] found no benefit from 1000 μg of vaginal misoprostol administered 2 to 4 hours before hysteroscopy in a group of such women. Although sublingual administration provides the highest systemic bioavailability, a study showed that cervical dilation in women using 100 μg of sublingual misoprostol at 12 hours before surgery was not different from that in a placebo group [49].

In general, GnRH agonists induce a state of hypogonadotropic hypogonadism by downregulating the pituitary GnRH receptors [56]. This condition also occurs in postmenopausal women [57]. Therefore, we speculate that the effects of misoprostol in patients receiving GnRH agonists are similar to the effects observed in postmenopausal (hypogonadal) women.

In conclusion, there is only limited evidence to support a useful role for misoprostol in cervical dilation in women receiving treatment with GnRH agonists.

**Misoprostol in IUI**

Prostaglandin is thought to help transport sperm by enhancing uterine and fallopian tube contractility [16,58]. Prostaglandin E may also have an important role during the implantation period [59]. However, this substance may be removed from the semen during the process of sperm preparation for IUI. Brown et al [16] used vaginal misoprostol, 400 μg, mixed with 5 mL of inert triglyceride administered via suppository at IUI and found that the cumulative pregnancy rate with misoprostol therapy was significantly greater than with placebo (17% vs 9% per cycle). A significant difference was noted in clomiphene cycles but not in clomiphene/follicle-stimulating hormone or natural cycles. However, these same authors later reported uterine cramping, uterine bleeding, and unfavorable pregnancy rates in patients who received vaginal misoprostol without mixing with a triglyceride base [16]. In contrast, Moslemizadeh et al [60] did not find any benefits of 200 μg of vaginal misoprostol in the clomiphene citrate/human menopausal gonadotropin cycle; clinical pregnancy rates were 15.15% vs 18.2% in the treatment and control groups, respectively. Furthermore, 400 μg of vaginal misoprostol not only has no benefit for IUI outcomes, but it also increases vaginal bleeding and abdominal cramping [61].

In conclusion, at this time, there is limited evidence to support the use of misoprostol in an IUI procedure.

**Misoprostol in Endometrial Biopsy**

Endometrial biopsy is essential to evaluate intrauterine disease in many gynecologic patients. In most situations, the gynecologist must deal with a narrow cervix. Perrone et al [14] evaluated use of 400 μg of oral misoprostol or a placebo 3 hours before an office endometrial biopsy in women aged 35 to 77 years (mean age, approximately 46 years in both groups). Women in the misoprostol group experienced significant uterine cramping 1 ½ hours after the procedure,
and more uterine cramping and pain associated with the procedure. No other cervical effects were noted [14].

In conclusion, with only 1 study to date, it seems that more evidence is needed to support this application.

**Misoprostol in IUD Insertion**

The difficulty of insertion of IUDs arises in part from a constricted cervix, especially in nulliparous women. Cervical priming using misoprostol might help resolve this problem; however, to our knowledge, only 1 study has examined this possible treatment, and found that insertion of a copper IUD in women treated with 400 µg of sublingual misoprostol 1 hour before the procedure was judged to be easier than in nontreated women. However, shivering and diarrhea were more frequent adverse effects [62].

In conclusion, it seems that misoprostol may be an effective way to ease IUD insertion; however the dosage and duration of misoprostol therapy in this role need further study to minimize adverse effects.

**Misoprostol in Myomectomy**

Prostaglandins increase myometrial contractions and lead to reduction in myometrial hemorrhage [63]. Misoprostol, a PGE₁ analogue, causes decreased uterine artery blood flow when used in early pregnancy [64]. Celik and Sapmaz [15] demonstrated that a single dose of 400 µg of vaginal misoprostol significantly reduced blood loss, operative time, and the need for postoperative blood transfusion in myomectomy procedures. This use of misoprostol as an effective method to decrease blood loss during myomectomy is also noted in the Cochrane database [65]; however, because of the small sample size in the Cochrane reference, only 13 women in the study group and 12 in the control group, more data are needed to validate this outcome.

There has been concern about the variation of prostanoid receptors present in the myometrium that may be related to the phase of the menstrual cycle [66]. However, a later retrospective analysis from Celik [15] found no significant differences between women who were in the follicular phase or the luteal phase of the cycle.

In conclusion, more studies are needed to establish the benefits of misoprostol when used in myomectomy procedures before routine use of this application is recommended.

### Table 2

<table>
<thead>
<tr>
<th>Misoprostol, µg/route</th>
<th>Abdominal pain/uterine cramping, %</th>
<th>Abnormal vaginal bleeding, %</th>
<th>Fever/shivering, %</th>
<th>Nausea, %</th>
<th>Diarrhea, %</th>
<th>Fatigue, %</th>
<th>Dizziness, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 Vg</td>
<td>32–63</td>
<td>19–30</td>
<td>3–11</td>
<td>4–10</td>
<td>3–6</td>
<td>0–20</td>
<td>0–10</td>
</tr>
<tr>
<td>400 Vg</td>
<td>36–79</td>
<td>2–63</td>
<td>7–17</td>
<td>2–10</td>
<td>4–7</td>
<td>2–16</td>
<td>7</td>
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<tr>
<td>400 PO</td>
<td>6–65</td>
<td>5–47</td>
<td>0–3</td>
<td>0–40</td>
<td>0–33</td>
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<td>0–20</td>
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<tr>
<td>800 Vg</td>
<td>100</td>
<td>100</td>
<td>43</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>1000 Vg</td>
<td>7–12</td>
<td>8–21</td>
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<tr>
<td>400 PO</td>
<td>25.6 (2/39)</td>
<td>5.1 (10/39)</td>
<td>NA</td>
<td>5.1 (2/39)</td>
<td>2.6 (1/39)</td>
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</tbody>
</table>

NA = not applicable; PO = oral administration; Vg = vaginal administration.

*a* Comparison between 400 µg of vaginal and oral misoprostol 10–12 hours before operative hysteroscopy [40].

Abnormal vaginal bleeding, lower abdominal pain or uterine cramping, and fever or shivering are the major adverse effects of misoprostol, with nausea, diarrhea, and dizziness the more common minor adverse effects. Various reports indicate that the vaginal route of administration leads to more uterine cramping and abnormal vaginal bleeding compared with the oral route. One study found that the systemic bioavailability of misoprostol acid 6 hours after vaginal administration was greater than with oral administration; however, the difference was not significant [19]. There are no current data about concentrations of misoprostol acid in the myometrial or endometrial tissue after use of misoprostol, and this is an area in which further studies might be useful in helping us to understand the association between various routes and dosages of misoprostol and adverse effects.

In conclusion, appropriate use of misoprostol in each patient should be considered individually.

### Conclusion

There is a broad spectrum of misoprostol use nowadays in nonpregnant women, with mixed results. In premenopausal
women, misoprostol is capable of ripening the cervix before hysteroscopy, although more research is required to identify the optimal dosage and the timing and route of administration. Further studies in postmenopausal women or those receiving GnRH agonists are also needed to determine whether misoprostol is effective for cervical ripening in this population. Other potential applications exist; however, more evidence is necessary before adopting the use of misoprostol in routine practice.

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