Misoprostol prior to hysteroscopy in premenopausal and postmenopausal women. A systematic review and meta-analysis

N.P. Polyzos1,*, A. Zavos2, A. Valachis3, C. Dragamestianos2, C. Blockeel1, D. Stoop1, E.G. Papanikolaou4, H. Tournaye1, P. Devroey1, and I.E. Messinis2

1Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101-1090, Brussels, Belgium
2Department of Obstetrics and Gynaecology, University of Thessaly, Larissa, Greece 3Onkologkliniken Sörmland, Målarsjukhuset, Central Hospital of Eskilstuna, Eskilstuna, Sweden 4Biogenesis Medical Centre, Thessaloniki, Greece

*Correspondence address. Tel: +32-2-477-66-60; Fax: +32-2-477-66-49; E-mail: n.polyzos@gmail.com, nikolaos.polyzos@uzbrussel.be

Submitted on August 16, 2011; resubmitted on March 3, 2012; accepted on March 20, 2012

TABLE OF CONTENTS

- Introduction
- Methods
  - Search strategy and eligibility criteria
  - Outcomes tested
  - Subgroup analyses
  - Statistical analysis
  - Quality of trials and assessment of publication bias
- Results
  - Eligible trials characteristics
  - Primary outcomes
    - Need for further dilatation for the hysteroscopic procedure
    - Cervical width
  - Secondary outcomes
    - Complication rate
    - Rates of side effects
  - Quality of the Trials
    - Assessment of Publication Bias
- Discussion

BACKGROUND: Although several randomized controlled trials (RCTs) have examined the effect of misoprostol prior to hysteroscopy for cervical dilatation, no solid conclusion has been reached. We therefore set out to perform a meta-analysis of RCTs.

METHODS: We searched MEDLINE, the ISI Web of Science and the Cochrane Library to identify RCTs comparing misoprostol versus placebo or control prior to hysteroscopy. No restrictions on language or time were applied. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for all dichotomous outcomes, whereas mean differences (MDs) and 95% CIs were calculated for continuous outcomes using the Mantel–Haenszel or DerSimonian–Laird model according to the heterogeneity.
RESULTS: Of the initial 141 potentially relevant articles that were retrieved, 21 RCTs involving 1786 patients were included in the meta-analysis. Subgroup analyses were performed according to menopausal status and according to whether diagnostic or operative hysteroscopy was performed. Premenopausal women treated with misoprostol had a significantly lower risk for further cervical dilatation in the diagnostic setting [RR (95% CI): 0.56 (0.34–0.92)] and a significantly lower risk for cervical laceration in the operative setting [RR (95% CI): 0.22 (0.09–0.54)], compared with placebo. In contrast, post-menopausal patients did not experience any clear benefit from misoprostol compared with placebo regarding the need for further cervical dilatation [RR (95% CI): 0.99 (0.76–1.30)] and the cervical laceration rate [RR (95% CI): 1.15 (0.40–3.29)]. In addition, the mean cervical width prior to hysteroscopy was significantly higher in premenopausal women treated with misoprostol compared with placebo [MD (95% CI): 2.47 mm (1.81–3.13)] but did not differ among post-menopausal patients [MD (95% CI): 0.39 mm (−0.42 to 1.21)].

CONCLUSIONS: Misoprostol prior to hysteroscopy appears to facilitate an easier and uncomplicated procedure only in premenopausal women.

Key words: misoprostol / hysteroscopy / premenopausal / post-menopausal women / meta-analysis

Introduction

Hysteroscopy is the most widely used method to investigate intruterine pathology. The efficacy of hysteroscopy, either in the diagnostic or in the operative setting, among specific populations has been supported by several trials (Clark et al., 2002; El-Toukhy et al., 2008). In post-menopausal women with abnormal uterine bleeding, hysteroscopy with endometrial biopsy shows a high diagnostic accuracy in diagnosing endometrial cancer or hyperplasia (Clark et al., 2002), whereas premenopausal infertile patients with recurrent IVF failures may experience substantial benefits in terms of increased pregnancy rates (El-Toukhy et al., 2008).

However, despite the high efficacy of the procedure in the above-mentioned settings, both as a diagnostic or therapeutic tool, hysteroscopy may be associated with certain complications (Paschopoulos et al., 2006). Although the incidence of these complications is low, ~1–1.5% (Jansen et al., 2000), almost 50% of them are related to insertion of the hysteroscope or to the dilatation of the cervical canal (Jansen et al., 2000).

Taking into account that an efficient method to facilitate an easier uncomplicated entry during the hysteroscopic procedure could substantially minimize the risk of complications, several modalities for cervical ripening prior to hysteroscopy have been adopted (Darwish et al., 2004; El-Toukhy et al., 2008; Lin et al., 2009). The prostaglandin analog misoprostol is the agent used most often for cervical preparation prior to hysteroscopy and has been tested in RCTs (Thomas et al., 2002; Preuthiphan and Herabutya, 2006).

The rationale behind the use of misoprostol prior to hysteroscopy is that it successfully ripens the cervix either when given for medical abortion during the first or second trimester of pregnancy (Goldberg et al., 2001), or when used for labor induction (Austin et al., 2010). Consequently, given its high efficacy in dilating the cervix in pregnant women one could hypothesize that misoprostol would also facilitate dilatation in women undergoing hysteroscopy.

To date, a significant amount of data has been published regarding the effect of misoprostol administration prior to the hysteroscopic procedures. Nonetheless, despite the large body of evidence, most of the available trials published in this field included small sample sizes, used different protocols, doses and routes of administration and have been applied to considerably diverse populations. Consequently, mainly because of this clinical diversity, the available data do not have sufficient power to allow solid conclusions to be drawn and clinical guidelines to be produced.

In order to assess the value of the use of misoprostol prior to hysteroscopy to increase the safety and the efficacy of this procedure, we performed a meta-analysis of RCTs using misoprostol versus control prior to diagnostic or operative hysteroscopy.

Methods

Search strategy and eligibility criteria

Two independent investigators (A.Z. and C.D.) searched the MEDLINE database (through PubMed), the Cochrane library and the ISI Web of Science without any restriction on language and year by using the search terms ‘hysteroscopy AND (misoprostol OR cytotec OR prostaglandin) AND (clinical trial OR randomized controlled trial OR double-blind OR single-blind OR random OR randomized OR placebo)’. Results were compared and a consensus was reached with the involvement of a third investigator (N.P.P.). In addition, hand searches were performed using the names of the first and the last investigator of each eligible trial in MEDLINE. Finally, all the references of previous systematic reviews were scrutinized in order to identify potentially eligible trials.

We considered RCTs that allocated patients to misoprostol at any dose versus placebo or no medication in a general female population undergoing hysteroscopy for various indications. All RCTs regardless of the dosage, route or timing of administration of misoprostol prior to hysteroscopy were eligible. Trials were excluded whenever patients were randomized to receive two different misoprostol therapeutic schemas (e.g. different doses or schedules or routes of administration of misoprostol) and no control arm existed. Finally, trials in which patients were allocated to a misoprostol treatment arm versus another regimen (e.g. dinoprostone or laminaria tents), other than placebo or no treatment, were excluded from the final analysis. In addition, non-randomized and quasi-randomized trials were also excluded from this systematic review.

Outcomes tested

The primary outcomes were the need for further cervical dilatation in order to perform the hysteroscopy and the cervical width prior to hysteroscopy. Secondary outcomes included the relative risk (RR) for major complications, such as cervical laceration or uterine perforation, and finally the RR for side effects rate, such as abdominal pain, diarrhea, vaginal bleeding and fever.
Effects of misoprostol before hysteroscopy

Subgroup analyses

Subgroup analyses based on two hypotheses prior to the data search were performed according to menopausal status and type of hysteroscopy (diagnostic or operative). The rationale behind the subgroup analyses for premenopausal and post-menopausal patients was that menopausal status appears to correlate with the effect of misoprostol on female cervix (Oppegaard et al., 2008), whereas no evidence exists regarding any beneficial effect of this agent in post-menopausal patients. In addition, subgroup analysis according to the type of hysteroscopy (diagnostic or operative hysteroscopy) was performed for two outcomes: need for cervical dilation and the complication rate. Such an analysis was implemented owing to the fact that the diameter of the hysteroscope differs significantly between the settings, with operative procedures requiring a larger diameter of the instrumentation.

Although our intention was to perform a subgroup analyses according to patients’ parity status, data regarding parity status were not available in the majority of the eligible trials and such an analysis could not be performed.

Statistical analysis

RR and 95% confidence intervals (CIs) were calculated for all dichotomous outcomes, whereas mean difference (MD) and 95% CIs were calculated for continuous outcomes. In the case of statistical homogeneity we used the Mantel–Haenszel model to analyze our results, while whenever statistical heterogeneity existed the DerSimonian–Laird model was used.

Whenever two or more different doses of misoprostol were compared with the control group, these patients’ groups were grouped together and we calculated the RR for the comparison of misoprostol at any dose versus the control group.

All parameters were analyzed in Revman 5 statistical software. All P-values were two-tailed. A P < 0.05 was considered significant.

Quality of trials and assessment of publication bias

The methodological quality of the trials was assessed by using the Cochrane’s risk of bias tool. Two independent investigators (A.Z. and A.V.) assessed the quality of trials and consensus was reached after discussing disagreements.

Publication bias was assessed by using contour-enhanced funnel plots and small-study effect bias by the Harbord’s test. Both analyses were performed using STATA SE 10.0 statistical software.

Results

Eligible trials characteristics

Among 141 potentially relevant reports, 106 were excluded on the basis of the title or owing to duplicate reports. Thirty-six publications were retrieved for more detailed evaluation. Among them, 9 reports were excluded (3 systematic reviews, 3 letters, 2 protocols of RCTs and 1 trial including dilation and curettage), leading to 27 potentially eligible RCTs. Nonetheless two studies were excluded, one because it was a congress abstract with unavailable data, and the other was an RCT comparing estrogen pretreatment or placebo in women receiving misoprostol prior to hysteroscopy. Overall 25 trials were considered eligible for the systematic review (Fig. 1). Although data were retrieved from all 25 trials (Table I), 4 trials were excluded from the final meta-analysis; 3 because they examined the effect of different doses of misoprostol or different routes of administration, without including a placebo or control arm (Choksuchat et al., 2006; Batukan et al., 2008; Lee et al., 2010) and 1 because misoprostol was compared with dinoprostone without a control arm (Preutthipan and Herabutya, 2006), leading to 21 trials.

The majority of the eligible trials compared misoprostol versus a placebo arm. Only three of the trials (Barcaite et al., 2005; Singh et al., 2009; El-Mazny and Abou-Salem, 2011) compared misoprostol versus a control (no treatment) arm. All of these trials were included only in the analysis regarding side effects, only one of them was included in the analysis regarding the cervical width prior to hysteroscopy (Barcaite et al., 2005), while none of them provided data regarding the need for further cervical dilation.

Eight of the eligible trials included patients undergoing operative hysteroscopy (Atay et al., 1997; Preutthipan and Herabutya, 2000; Thomas et al., 2002; Bisharah et al., 2003; Fernandez et al., 2004; Oppegaard et al., 2008; Uckuyu et al., 2008; Oppegaard et al., 2010). Eleven eligible trials included diagnostic hysteroscopy (Ngai et al., 1997; Ngai et al., 2001; Fung et al., 2002; Healey et al., 2007; da Costa et al., 2008; Valente et al., 2008; Waddell et al., 2008; Singh et al., 2009; Mulayim et al., 2010; El-Mazny and Abou-Salem, 2011; Sordia-Hernandez et al., 2011). Finally, two trials included both diagnostic and operative hysteroscopy (Preutthipan and Herabutya, 1999; Barcaite et al., 2005). Menopausal status was available in all of the trials with 11 trials included only premenopausal patients (Atay et al., 1997; Ngai et al., 1997; Preutthipan and Herabutya, 1999, 2000; Fernandez et al., 2004; Healey et al., 2007; Uckuyu et al., 2008; Valente et al., 2008; Mulayim et al., 2010; El-Mazny and Abou-Salem, 2011; Sordia-Hernandez et al., 2011), 5 included only post-menopausal (Ngai et al., 2001; Fung et al., 2002; da Costa et al., 2008; Oppegaard et al., 2010) and 4 included both premenopausal and post-menopausal patients (Thomas et al., 2002; Oppegaard et al., 2008; Waddell et al., 2008; Singh et al., 2009). One study that recruited premenopausal patients was included in the analysis for post-menopausal women as the administration of GnRH analogs in these patients induced an hypoestogenic status, similar to that of post-menopause (Bisharah et al., 2003). In addition, although two studies included post-menopausal women (Oppegaard et al., 2008, 2010), the authors have examined only the outcome of need for further cervical dilation at a threshold level of 5 mm and not the need for further dilatation for performing the procedure; thus, we considered this threshold as the threshold for performing diagnostic hysteroscopy and therefore these trials were included in the subgroup analyses for ‘diagnostic hysteroscopy’. Furthermore, in one of the trials including post-menopausal women, misoprostol and placebo arms received additional estrogen pretreatment for 14 days (Oppegaard et al., 2010); although the results of this trial were not pooled with the results of the other trials, sensitivity analysis was performed to test whether its inclusion significantly altered our conclusion.

Finally, one study included perimenopausal and post-menopausal patients but was not used in the analysis comparing women based on their menopausal status (Barcaite et al., 2005).

As shown in Table I, the dose, route, schedule and timing of administration of misoprostol prior to hysteroscopy differed considerably among the available trials. Data regarding parity status of the patients enrolled were missing in the majority of the trials (Table I).
Primary outcomes

Need for further dilatation for the hysteroscopic procedure

Fourteen trials provided data regarding the need for further cervical dilatation prior to the hysteroscopic procedure. Due to high statistical heterogeneity, results for premenopausal women were pooled by using the random effects model. Premenopausal women pretreated with misoprostol appeared to experience a lower risk for the need for further cervical dilatation to complete diagnostic hysteroscopy, compared with placebo [RR (95% CI): 0.56 (0.34–0.92; 7 trials, 442 patients), $i^2 = 54\%$]. Although a tendency for a lower need for further cervical dilatation among premenopausal patients undergoing operative hysteroscopy was observed [RR (95% CI): 0.42 (0.08–2.21), $i^2 = 89\%$], this difference was not statistically significant because of the limited number of trials with events (Fig. 2, see 2.1). In contrast, misoprostol did not provide any significant benefit compared with placebo among post-menopausal women in the diagnostic setting [RR (95% CI): 0.99 (0.76–1.30; 3 trials, 243 patients), $i^2 = 41\%$] (Fig. 2, see 2.2). The only trial that reported significantly better outcomes with misoprostol administration in post-menopausal

Figure 1 Flowchart diagram for the selection of RCTs studying the effects of misoprostol prior to hysteroscopy in premenopausal and postmenopausal women.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Treatment</th>
<th>Nulliparous (%)</th>
<th>Route of administration</th>
<th>Dose (μg)</th>
<th>Time of administration before surgery (h)</th>
<th>Hysteroscope diameter (mm)</th>
<th>Setting (operative/diagnostic)</th>
<th>Menopausal status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atay 1997</td>
<td>Turkey</td>
<td>Misoprostol/Placebo</td>
<td>59/62</td>
<td>Vaginal</td>
<td>400</td>
<td>4</td>
<td>7</td>
<td>Operative (outpatient)</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Ngai 1997</td>
<td>China</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Oral</td>
<td>400</td>
<td>12</td>
<td>5</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Preuthipan 1999</td>
<td>Thailand</td>
<td>Misoprostol/placebo</td>
<td>100/100</td>
<td>Vaginal</td>
<td>200</td>
<td>9–10</td>
<td>5.5 diagnostic 7 or 9 operative</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Preuthipan 2000</td>
<td>Thailand</td>
<td>Misoprostol/placebo</td>
<td>100/100</td>
<td>Vaginal</td>
<td>200</td>
<td>9–10</td>
<td>5.5 diagnostic 7 or 9 operative</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Ngai 2001</td>
<td>China</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Oral</td>
<td>400</td>
<td>12</td>
<td>NA</td>
<td>Diagnostic</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Fung 2002</td>
<td>Hong Kong</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>800</td>
<td>&gt;5</td>
<td>5.5</td>
<td>Diagnostic</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Thomas 2002</td>
<td>Canada</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Oral</td>
<td>800</td>
<td>24 (400 μg) 12 (400 μg)</td>
<td>9–10</td>
<td>Operative</td>
<td>Premenopausal + GnRHa</td>
</tr>
<tr>
<td>Bisharah 2003</td>
<td>Canada</td>
<td>Misoprostol/placebo</td>
<td>100/100</td>
<td>Sublingual</td>
<td>100</td>
<td>12</td>
<td>9</td>
<td>Operative</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Fernandez 2004</td>
<td>France</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>200 400 800</td>
<td>4</td>
<td>4</td>
<td>Operative</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Barcaite 2005</td>
<td>Lithuania</td>
<td>Misoprostol/control</td>
<td>NA</td>
<td>Vaginal</td>
<td>400</td>
<td>12</td>
<td>8</td>
<td>Diagnostic</td>
<td>Perimenopausal</td>
</tr>
<tr>
<td>Da Costa 2007</td>
<td>Brazil</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>200</td>
<td>8</td>
<td>4</td>
<td>Diagnostic</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Healey 2007</td>
<td>Canada</td>
<td>Misoprostol/placebo</td>
<td>21.2/12.9</td>
<td>Oral</td>
<td>400</td>
<td>12</td>
<td>6</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Oppegaard 2008(*)</td>
<td>Norway</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>1000</td>
<td>12</td>
<td>10–11</td>
<td>Operative</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Singh 2008</td>
<td>India</td>
<td>Misoprostol/control</td>
<td>48/68</td>
<td>Vaginal</td>
<td>400</td>
<td>4–6</td>
<td>4</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Uckuyu 2008</td>
<td>Turkey</td>
<td>Misoprostol/placebo</td>
<td>100/100</td>
<td>Vaginal</td>
<td>400</td>
<td>12 (200 μg) 6 (200 μg)</td>
<td>10</td>
<td>Operative</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Valente 2008</td>
<td>Brasil</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>400</td>
<td>6</td>
<td>4</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Waddell 2008</td>
<td>Canada</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>400 12–24</td>
<td>5.5</td>
<td></td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Mulayim 2010</td>
<td>Turkey</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Sublingual</td>
<td>200</td>
<td>2</td>
<td>5.5</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>Oppegaard 2010(*)</td>
<td>Norway</td>
<td>E2 + misoprostol/E2 + placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>1000</td>
<td>12</td>
<td>NA</td>
<td>Operative</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Sordia-Hernades 2010</td>
<td>Mexico</td>
<td>Misoprostol/placebo</td>
<td>42/36</td>
<td>Oral</td>
<td>600</td>
<td>24 (200 mg every 8 h)</td>
<td>5</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
<tr>
<td>El-Mazny 2011</td>
<td>Egypt</td>
<td>Misoprostol/placebo</td>
<td>NA</td>
<td>Vaginal</td>
<td>200</td>
<td>3</td>
<td>4</td>
<td>Diagnostic</td>
<td>Premenopausal</td>
</tr>
</tbody>
</table>

Continued
Women was the trial in which patients were pretreated with estrogens for 14 days preoperatively [RR (95% CI): 0.65 (0.48–0.87)] (Oppegaard et al., 2010). This trial was not included in the meta-analysis plot owing to the fact that patients received a completely different regimen. Sensitivity analysis with the inclusion of this trial has improved the cumulative relative risk [RR (95% CI): 0.88 (0.70–1.27)], without reaching statistical significance (P = 0.06), a result which further justifies the fact that estrogen pretreatment may be of value for post-menopausal women treated with misoprostol.

Cervical width

Results regarding the MD in the cervical width prior to the hysteroscopic procedure were in accordance with results for the need for further dilatation. Due to high statistical heterogeneity, meta-analysis was performed by using the random effects model. Premenopausal patients receiving misoprostol had a significantly greater cervical width compared with patients receiving placebo or no treatment [MD (95% CI): 2.47 mm (1.81–3.13; 7 trials, 536 patients), I² = 90%] (Fig. 3, see 3.1). However, there was no significant difference in the cervical width in post-menopausal women receiving misoprostol compared with placebo: MD (95% CI): 0.39 mm (0.21–1.21; 6 trials, 364 patients, I² = 90%; Fig. 3, see 3.2). Sensitivity analysis with the exclusion of one trial in which misoprostol was compared with a control arm (not placebo) (Barcule et al., 2005) did not significantly alter the results [MD (95% CI): 0.03 mm (–0.48–0.53), I² = 67%].

Complication rate

Misoprostol supplementation prior to hysteroscopy resulted in a significantly lower rate of cervical laceration versus placebo [RR (95% CI): 0.40 (0.21–0.74; 15 trials, 1119 patients), I² = 2%]. When analyzing the results according to menopausal status, again this risk was significantly lower only in premenopausal women [RR (95% CI): 0.22 (0.09–0.52; 10 trials, 691 patients), I² = 0%] (Fig. 4, see 4.1). On the contrary, post-menopausal patients experienced no benefit from the use of misoprostol, with a laceration rate comparable to placebo either in a diagnostic or in an operative setting [RR (95% CI): 1.15 (0.40–3.29; 6 trials, 428 patients), I² = 93% (Fig. 4, see 4.2). The risk for uterine perforation did not differ among patients receiving either misoprostol or placebo [RR (95% CI): 0.69 (0.28–1.72; 11 trials, 1040 women), I² = 0%]. Yet, no definite conclusions can be drawn because of the small number of events occurring in both treatment arms.

Rates of side effects

The rates of side effects were significantly higher in misoprostol-treated women. As shown in Table II, misoprostol significantly increased abdominal cramping, diarrhea, nausea, fever and bleeding with an RR ranging from 2.21 to 5.90 for a higher side-effect rate in misoprostol-treated women (Table II).
Quality of the trials

The quality of the eligible trials was assessed using Cochrane’s risk of bias tool (Higgins et al., 2008). Two independent investigators assessed separately the risk of bias of each individual trial and a consensus was reached after discussion. Although several methodological parameters of the trials were satisfactory, with more than half of them reporting an adequate method of randomization, allocation concealment or blinding (Fig. 5), only eight trials (38%) demonstrated a low risk for bias.

Sensitivity analysis was performed for the primary outcomes pertaining only to trials with low risk of bias (n = 8). The cervical width was significantly higher in the misoprostol-treated premenopausal women than placebo [MD (95% CI): 2.29 mm (1.17–3.42); P < 0.0001] (Ngai et al., 1997; Fernandez et al., 2004; Oppegaard et al., 2008; Uckuyu et al., 2008). Although no significant difference was observed in the need for further cervical dilatation or risk of cervical laceration [RR (95% CI): 0.66 (0.26–1.66)] (Healey et al., 2007; Oppegaard et al., 2008) and [RR (95% CI): 0.19 (0.03–1.08)] (Fernandez et al., 2004; Oppegaard et al., 2008; Uckuyu et al., 2008), respectively, this finding can mainly be attributed to the limited number of high-quality trials for these outcomes, rather than to the lack of any effect of treatment.
Assessment of publication bias

The presence of publication bias was assessed using the contour-enhanced funnel plots. A contour funnel plot was constructed for the outcome of need for further cervical dilatation and included all the trials that provided results for this outcome. There is a strong suggestion of asymmetry in the funnel plot. As demonstrated in Fig. 6, studies appear to be missing on the right-hand side of the plot. The area where missing studies are perceived includes regions of both low and high statistical significance. This suggests that studies showing misoprostol administration to be not significantly and significantly less effective compared with placebo are missing. Consequently, publication bias cannot be considered the only reason for the funnel asymmetry.

However, small-study effect bias is unlikely to exist because the Harbord’s test for small-study effect bias had a \( P \)-value of 0.976, suggesting the absence of such a bias.

Discussion

Our meta-analysis indicates that misoprostol may have a role as a cervical-ripening agent prior to hysteroscopy. Although we have to acknowledge the fact that a subgroup analyses performed may reduce the statistical power, it appears that the efficacy of misoprostol is related to the menopausal status of patients. Premenopausal women receiving misoprostol prior to undergoing diagnostic hysteroscopy are more likely to avoid the need of cervical dilation, whereas those undergoing an operative procedure are expected to have an easier dilatation and are less likely to experience cervical laceration during the procedure. On the contrary, available data suggest that post-menopausal women may not experience any substantial benefit by using misoprostol alone prior to the hysteroscopic procedure and therefore, its efficacy in these patients is questionable.

Our results are in contrast with a recent meta-analysis published on the same subject (Gkrozou et al., 2011). Although Gkrozou et al., (2011) concluded that no significant difference exists, either in post-menopausal or in premenopausal women, regarding the need for further dilatation or the complication rates, our meta-analysis shows that premenopausal women may experience substantial benefits after pretreatment with misoprostol. A potential explanation for this discrepancy may simply be the fact that in the Gkrozou et al., (2011) systematic review three trials, including cumulatively 250 patients, have been omitted (Atay et al., 1997; Oppegaard et al., 2010; Sordia-Hernandez et al., 2011). These trials involve almost 14% of the total patients included in the present meta-analysis and their inclusion appears to completely alter the results.

The difference between the effects of misoprostol according to patients’ menopausal status has been previously underlined by other investigators. To date, misoprostol has been shown to effectively ripen the cervix in premenopausal patients, either in the first or in the second trimester medical abortion (Goldberg et al., 2001) or as a labor-induction agent (Austin et al., 2010). The high efficacy observed in premenopausal compared with post-menopausal women may be attributed to a different consistency of the cervix in these two subpopulations of patients (Oppegaard et al., 2010).

Owing to the hypoestrogenic status, the tissue of post-menopausal...
women is more fibrotic and less elastic and the hormone receptor sensitivity in the cervix is decreased (Barcaite et al., 2005). Furthermore, estrogens may directly regulate leucocyte function in the cervix, and thus the inflammatory process, during cervical ripening (Oppegaard et al., 2010). Consequently, misoprostol, which is a prostaglandin analog, successfully dilates the cervix in premenopausal patients but has no effect in post-menopausal women.

This theory appears to be the most convincing given that a recent RCT has shown that the addition of estrogens to the misoprostol taken by post-menopausal patients prior to hysteroscopy significantly increased cervical width prior to the procedure and reduced the need for further dilatation (Oppegaard et al., 2010). Similar conclusions can additionally be derived from an earlier small RCT, which has shown that although misoprostol treatment alone is not effective in achieving cervical priming in post-menopausal women, local estrogen pretreatment ameliorates misoprostol cervical priming in these patients (Atmaca et al., 2005). Nonetheless, future trials should be conducted to confirm these initial findings. Furthermore, given that hysteroscopy after menopause aims to identify cancerous or precancerous endometrial lesions, an approach such as the one described, should be regarded with caution given that we are unaware of whether even the short-term administration of estrogens may increase the risk of endometrial cancer (Key and Pike, 1988).

Although our analysis identified specific subgroups of patients that appear to experience a substantial benefit with misoprostol, the main weakness of the available evidence is the overall clinical diversity (e.g. different populations under study, different regimens, doses and routes of administration of misoprostol). This may be further reflected...
Table II RR of complications between women in the misoprostol versus the placebo/control arm.

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>5.20 (2.66, 10.17)</td>
<td>21</td>
<td>1786</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.68 (3.36, 13.27)</td>
<td>21</td>
<td>1786</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.63 (1.68, 4.12)</td>
<td>21</td>
<td>1786</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fever</td>
<td>5.53 (1.45, 21.15)</td>
<td>21</td>
<td>1786</td>
<td>0.01</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4.75 (1.89, 11.95)</td>
<td>21</td>
<td>1786</td>
<td>0.0009</td>
</tr>
<tr>
<td><strong>Excluding trials without a placebo arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>4.64 (2.22, 9.74)</td>
<td>18</td>
<td>1431</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.88 (2.76, 12.54)</td>
<td>18</td>
<td>1431</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.21 (1.36, 3.58)</td>
<td>18</td>
<td>1431</td>
<td>0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>5.90 (1.05, 33.13)</td>
<td>18</td>
<td>1431</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4.12 (1.67, 10.20)</td>
<td>18</td>
<td>1431</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Figure 5 Risk of bias assessment among the RCTs, which were eligible for inclusion in the meta-analysis.

Figure 6 Contour-enhanced funnel plot for the assessment of publication bias.

by the high statistical heterogeneity that has been identified for outcomes such as the cervical width ($I^2 = 90\%$), which may be considered too high to make recommendations. However, a more thorough scrutiny of figure 3.1, shows that, at least for premenopausal women, the vast majority of the trials clearly favor misoprostol in terms of mean cervical width, with significantly higher cervical width in five out of seven trials, and borderline non-significant differences in favor of misoprostol for the other 2 trials. Hence, this statistical heterogeneity is mainly attributed to the different degree of beneficial effect of misoprostol on the final outcome, rather than the lack of effect of misoprostol in several of the trials. This is further supported by the very strong $p$ value ($P < 0.00001$) and the narrow confidence intervals for the cumulative mean difference for cervical width in premenopausal women, as well as, by the more robust results for other outcomes such as cervical laceration, showing a strong beneficial effect of misoprostol in premenopausal women ($P < 0.0005$) without any statistical heterogeneity ($I^2 = 0\%$), figure 4.1. Nevertheless, it is a fact that, despite that 21 trials have been published up to now, the heterogeneity among the regimens, the routes of administration and the exact timing of administration, makes analysis of the data very difficult and prevent us from providing solid guidelines regarding the optimal route, dosing schedule or scheme of administration of misoprostol. Although a previous trial suggested that misoprostol doses between 200 and 800 µg appear to have no significant difference in terms of cervical dilatation (Fernandez et al., 2004), based on the pharmacodynamics/kinetics of misoprostol, repetitive doses may give a higher impact on cervical priming. Finally, the vaginal route appears to be superior to the oral route (Batukan et al., 2008).

The current systematic review did not assess the effect of misoprostol on pain reduction in women undergoing outpatient hysteroscopy. This outcome has been assessed in a recent systematic review including six randomized trials (Cooper et al., 2011), concluding that misoprostol is beneficial when dilating the cervix beyond 5 mm. This observation is in accordance with our conclusion that the maximum benefit with misoprostol should be anticipated in the operative setting, in which higher diameter hysteroscopes are utilized. Although in the report by Cooper et al. (2011) it is suggested that this benefit might be greater in post-menopausal women, this conclusion is based on only one trial and should be interpreted with great caution, especially given that our meta-analysis has shown that post-menopausal women do not appear to experience substantial benefits.

A limitation of the current study is the fact that the overall quality of several of the RCTs was suboptimal, with less than half of the trials having a low risk of bias. Given that inclusion of trials with high or unclear risk of bias has been previously reported to lead to inflated outcomes in favor of the experimental arm (Polyzos et al., 2010), we cannot exclude that methodological quality may have affected our results. However, even when pertaining only to trials with a low risk of bias, our results did not substantially change and the mean cervical width remained significantly higher in premenopausal women pre-treated with misoprostol.

In addition, we cannot omit the fact that publication bias may be present in our analysis, as shown by the contour-enhanced funnel plot. Publication bias has been previously highlighted in the field of reproductive medicine, suggesting that trials with negative results are more likely to be left unpublished (Polyzos et al., 2011). Consequently, it may be likely that RCTs that have not reported significant results in
favor of misoprostol may not have reached publication, something which may have led to inflated outcomes in favor of misoprostol.

Although misoprostol appears to have a role in premenopausal patients, we have to highlight that in certain circumstances, especially when diagnostic hysteroscopy is performed in multiparous women using a 3 mm microhysteroscope, the need for cervical dilatation may be superfluous (Marwah and Bhandari, 2003). Although the lack of data from individual studies prevented us from performing an analysis according to parity status, in multiparous women diagnostic hysteroscopy may be easily performed without the need for any dilatation, without any discomfort for the patient and certainly without the need of cervical priming. The vaginoscopic approach appears to be an effective method for performing diagnostic hysteroscopy with significantly less pain (Marwah and Bhandari, 2003), whereas on the other hand, paracervical anesthesia is an excellent method for controlling pain during outpatient hysteroscopy and therefore misoprostol may not have a role in such a setting (Marwah and Bhandari, 2003; Cooper et al., 2010). However, in cases in which a higher diameter of hysteroscope is used, the operative setting or when difficulty in dilating the cervix might be expected, for example, in nulliparous women or women who have undergone Caesarean section (Preuthiphan and Herabutya, 2000; Uckuyu et al., 2008), misoprostol may be useful because it appears to increase the likelihood of a safer and easier hysteroscopic procedure.

In conclusion, misoprostol administration prior to hysteroscopy appears to have a beneficial role in premenopausal patients undergoing hysteroscopy in both the diagnostic and operative setting. In cases in which cervical dilatation is considered as easy, misoprostol may not be routinely administered as it may only increase patients’ discomfort without any substantial benefit. Misoprostol alone is not recommended in post-menopausal patients, given that its effect as a cervical-ripening agent appears to be ineffective. Pretreatment with estrogens in addition to misoprostol might be considered in post-menopausal patients. However, data to support this treatment approach are limited. Furthermore, based on the available evidence, no solid guideline can be provided with regards to the dose, the route or the timing of misoprostol prior to the hysteroscopic procedure. Future large RCTs, including carefully selected populations and a uniform administration, route and dosage schedule and schema, should be performed in order to identify which treatment protocol may be ideal for premenopausal women undergoing hysteroscopy and whether estrogen pretreatment prior to misoprostol may be beneficial in post-menopausal patients.

**Authors’ roles**

N.P.P. had the original concept for the study, which was subsequently developed and planned by A.Z., A.V. and C.D. performed the literature searches and extracted the data, A.Z. and A.V. performed the trials quality assessment, N.P.P. and A.Z. performed the analyses, N.P.P. and A.Z. wrote the initial draft of the manuscript. All authors were involved in interpreting the results, writing the final draft of the manuscript and approving the final version.

**Funding**

None

**Conflict of interest**

None to declare.

**References**


