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

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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 intrauterine 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; Preutthipan 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.

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 dilatation 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, 105 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 dilatation.

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).

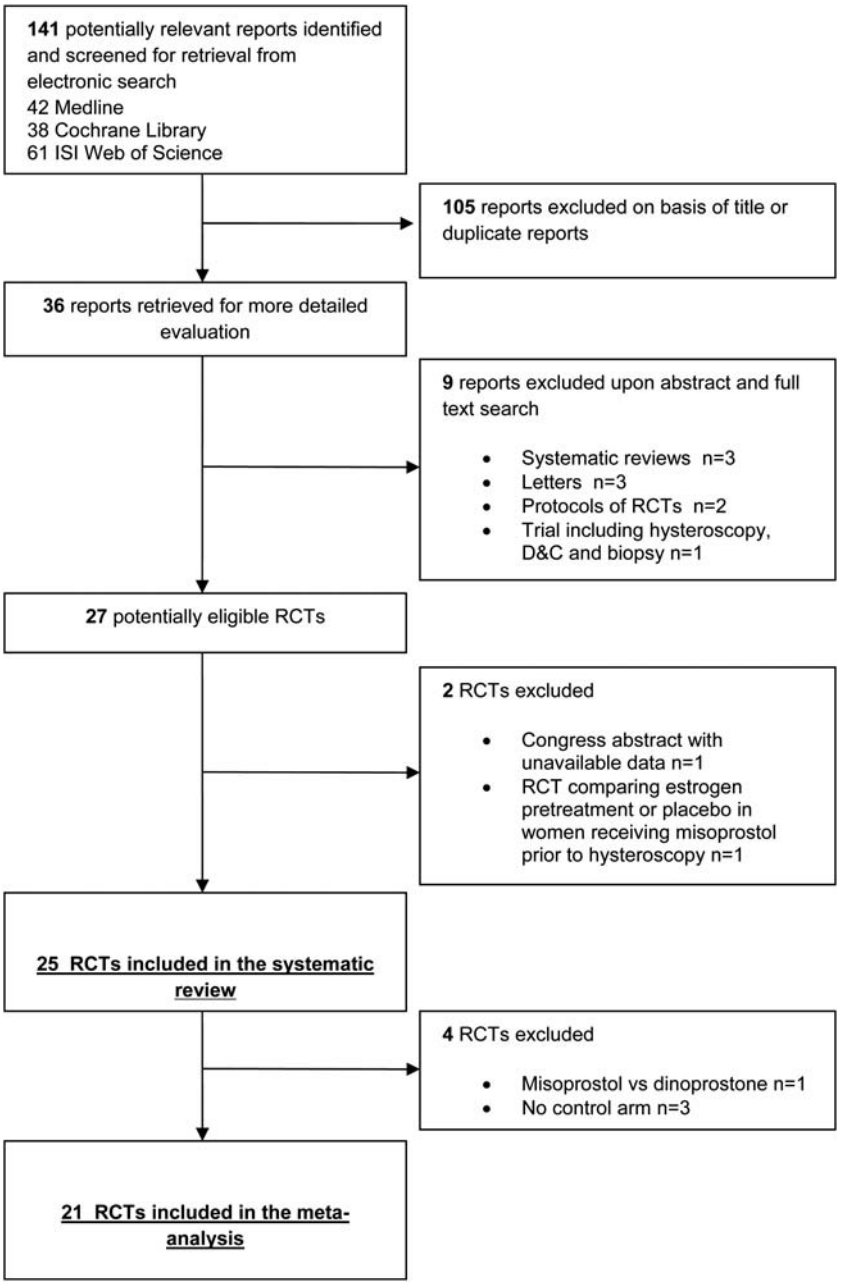

Figure 1 Flowchart diagram for the selection of RCTs studying the effects of misoprostol prior to hysteroscopy in premenopausal and post-menopausal women.

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

Table I Baseline characteristics from all the RCTs included in our systematic review of studies on the effects of misoprostol prior to hysteroscopy in premenopausal and post-menopausal women.

Author	Country	Treatment	Nulliparous (%)	Route of administration	Dose (μg)	Time of administration before surgery (h)	Hysteroscope diameter (mm)	Setting (operative diagnostic)	Menopausal status
Atay 1997	Turkey	Misoprostol/Placebo	59/62	Vaginal	400	4	7	Operative (outpatient)	Premenopausal
Ngai 1997	China	Misoprostol/placebo	NA	Oral	400	12	5	Diagnostic	Premenopausal
Preutthipan 1999	Thailand	Misoprostol/placebo	100/100	Vaginal	200	9–10	5.5 diagnostic 7 or 9 operative	Diagnostic Operative	Premenopausal
Preutthipan 2000	Thailand	Misoprostol/placebo	100/100	Vaginal	200	9–10	5.5 diagnostic 7 or 9 operative	Operative	Premenopausal
Ngai 2001	China	Misoprostol/placebo	NA	Oral	400	12	NA	Diagnostic	Post-menopausal
Fung 2002	Hong Kong	Misoprostol/placebo	NA	Vaginal	800	>5	5,5	Diagnostic	Post-menopausal
Thomas 2002	Canada	Misoprostol/placebo	NA	Oral	800	24 (400 μg) 12 (400 μg)	9–10	Operative	Premenopausal Post-menopausal Premenopausal + GnRHa
Bisharah 2003	Canada	Misoprostol/placebo	100/100	Sublingual	100	12	9	Operative	Premenopausal + GnRHa
Fernandez 2004	France	Misoprostol/placebo	NA	Vaginal	200 400 800	4	4	Operative	Premenopausal
Barcaite 2005	Lithuania	Misoprostol/control	NA	Vaginal	400	12	8	Diagnostic Operative	Perimenopausal Post-menopausal
Da Costa 2007	Brazil	Misoprostol/placebo	NA	Vaginal	200	8	4	Diagnostic	Post-menopausal
Healey 2007	Canada	Misoprostol/placebo	21.2/12.9	Oral	400	12	6	Diagnostic	Premenopausal
Oppegaard 2008(*)	Norway	Misoprostol/placebo	NA	Vaginal	1000	12	10–11	Operative	Premenopausal Post-menopausal
Singh 2008	India	Misoprostol/control	48/68	Vaginal	400	4–6	4	Diagnostic	Premenopausal Post-menopausal
Uckuyu 2008	Turkey	Misoprostol/placebo	100/100	Vaginal	400	12 (200 μg) 6 (200 μg)	10	Operative	Premenopausal
Valente 2008	Brasil	Misoprostol/placebo	NA	Vaginal	400	6	4	Diagnostic	Premenopausal
Waddell 2008	Canada	Misoprostol/placebo	NA	Vaginal	400	12–24	5,5	Diagnostic	Premenopausal Post-menopausal
Mulayim 2010	Turkey	Misoprostol/placebo	NA	Sublingual	200	2	5,5	Diagnostic	Premenopausal
Oppegaard 2010(*)	Norway	E2 + misoprostol/ E2 + placebo	NA	Vaginal	1000	12	NA	Operative	Post-menopausal
Sordia-Hernades 2010	Mexico	Misoprostol/placebo	42/36	Oral Vaginal	600	24 (200 mg every 8 h)	5	Diagnostic	Premenopausal
El-Mazny 2011	Egypt	Misoprostol/control	NA	Vaginal	200	3	4	Diagnostic	Premenopausal

Continued

Table I *Continued*

Author	Country	Treatment	Nulliparous (%)	Route of administration	Dose (μg)	Time of administration before surgery (h)	Hysteroscope diameter (mm)	Setting (operative diagnostic)	Menopausal status
Trials excluded from the meta-analysis									
Preutthipan 2000	Thailand	Misoprostol/ Dinoprostone	100/100	Vaginal	200	9–10	5.5 diagnostic 7 or 9 operative	Operative	Premenopausal
Choksuchat 2006	Thailand	Misoprostol/ Misoprostol	NA	Oral	200	12	5,5	Diagnostic	Premenopausal
Batukan 2008	Turkey	Misoprostol/ Misoprostol	50/53.8	Vaginal	400	10–12	9	Operative	Premenopausal
Lee 2010	Korea	Misoprostol/ misoprostol misoprostol	NA	Vaginal Oral Sublingual	400	6–8	10	Operative	Premenopausal

GnRHa, GnRH analogs.
(*) Although the trials by Oppegaard *et al.* (2008, 2010) have tested the effect of misoprostol in the operative setting, the authors reported the number of women that needed further cervical dilatation at a threshold level of 5 mm and not the number of women needing further cervical dilatation in order to complete the procedure. This level was considered the level for performing diagnostic hysteroscopy and therefore these trials were included in the subgroup analyses for 'diagnostic hysteroscopy' for the outcome 'need for further dilatation'.

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), $I^2 = 90\%$] (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 (−0.42–1.21; 6 trials, 364 patients, $I^2 = 90\%$; Fig. 3, see 3.2). Sensitivity analysis with the exclusion of one trial in which misoprostol was compared with a control arm (not placebo) (Barcaite *et al*, 2005) did not significantly alter the results [MD (95% CI): 0.03 mm (−0.48–0.53), $I^2 = 67\%$].

Secondary outcomes

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), $I^2 = 2\%$]. 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), $I^2 = 0\%$] (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), $I^2 = 0\%$] (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), $I^2 = 0\%$]. Yet, no definite conclusions can be drawn because of the small number of events occurring in both treatment and control arms.

Rates of side effects

The rates of side effect 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 2.63 to 6.88 depending on the type of complication. Results did not differ even when excluding three trials that compared misoprostol with a control (no treatment) arm and restricting our analysis to trials comparing misoprostol versus a placebo arm, with an RR ranging from 2.21 to 5.90 for a higher side-effect rate in misosprostol-treated women (Table II).

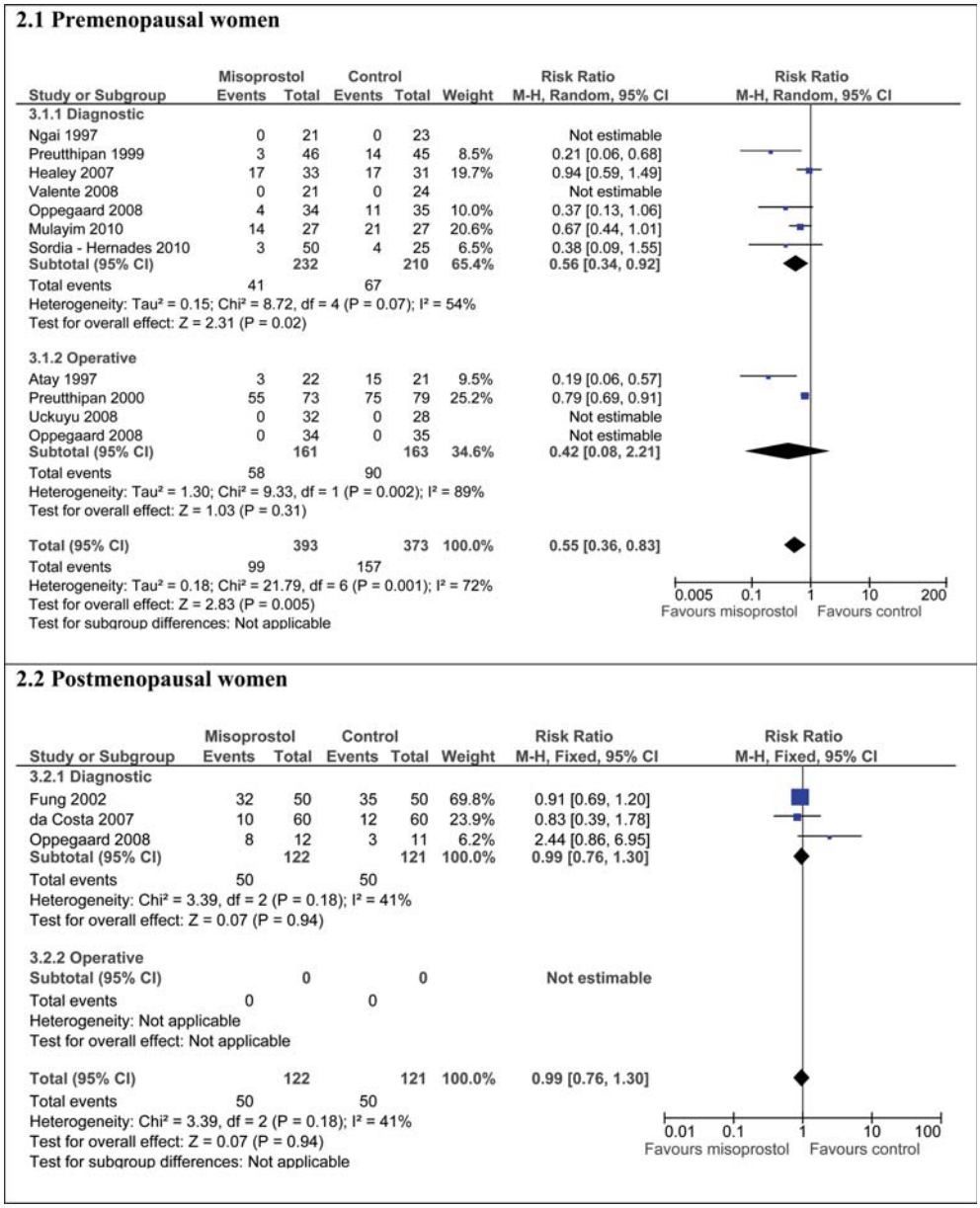

Figure 2 Forest plots for the outcome "need for further cervical dilatation". Subgroup analyses were performed according to menopausal status (2.1 and 2.2) and according to whether diagnostic or operative hysteroscopy was performed.

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.

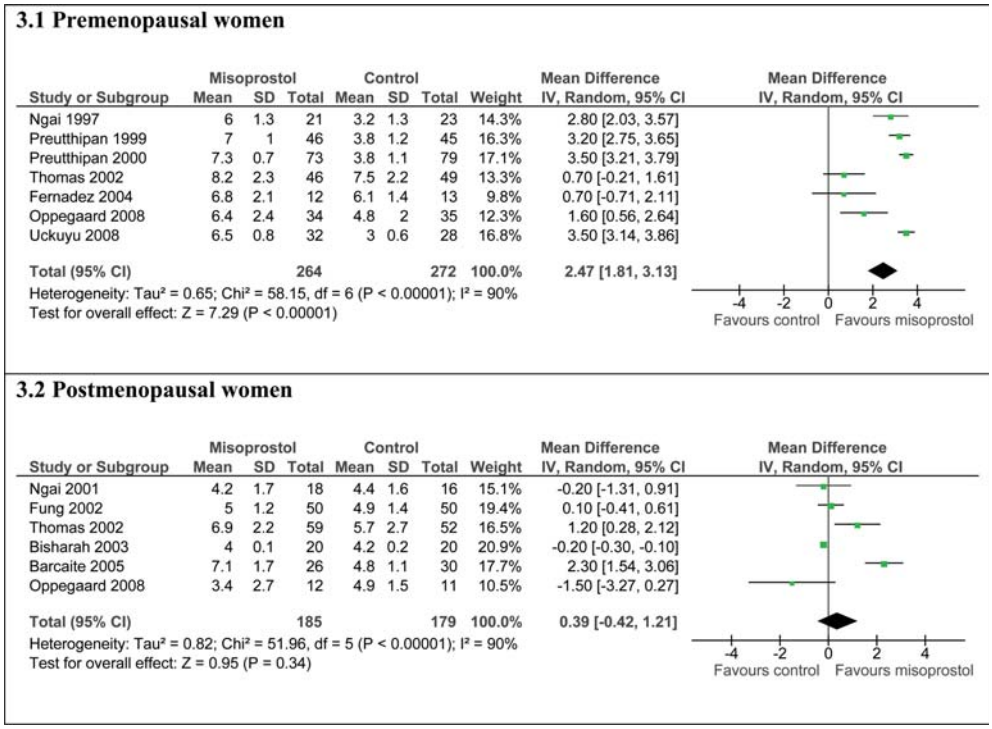

Figure 3 Forest plots for the cervical width prior to hysteroscopy in premenopausal and post-menopausal women.

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

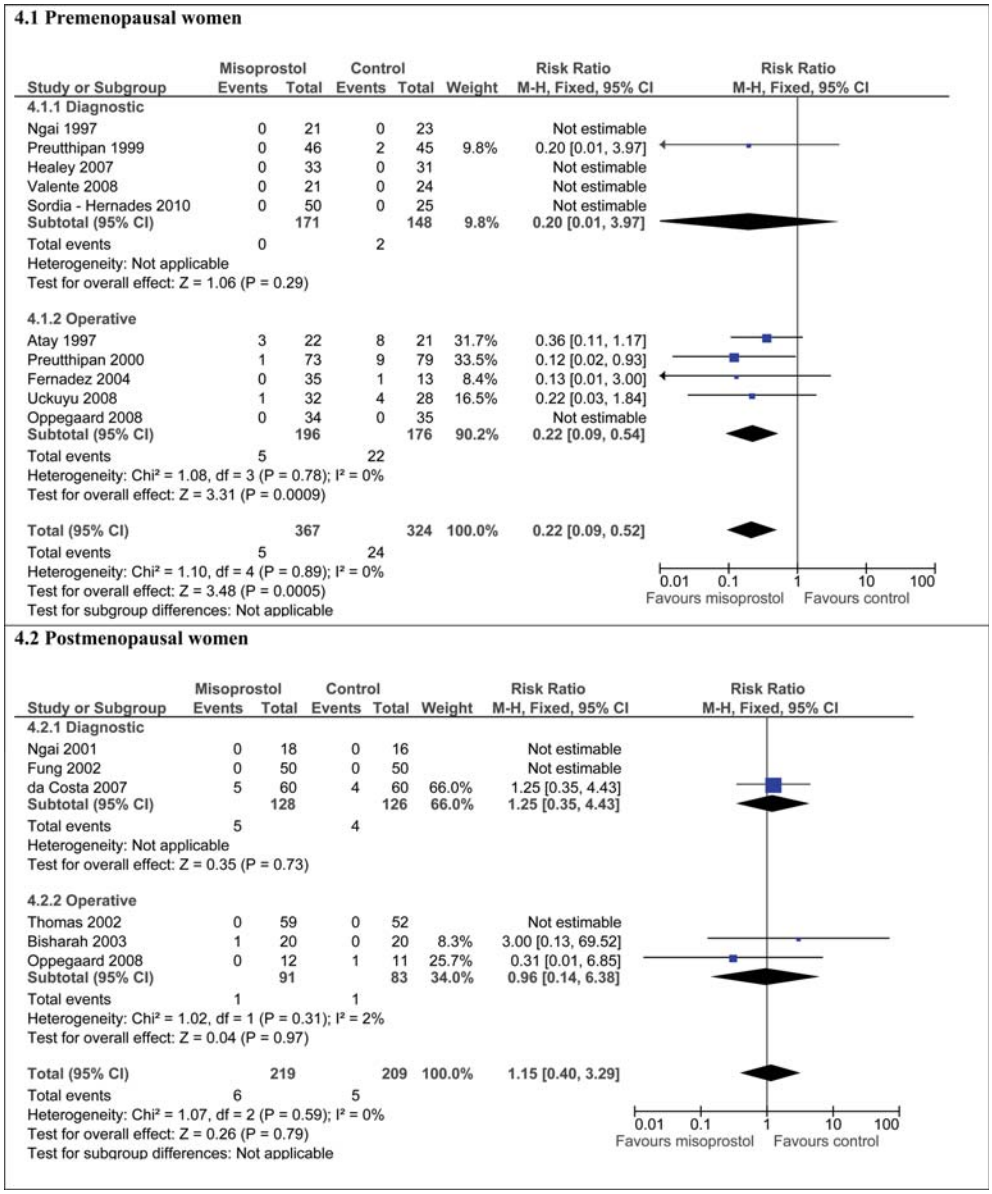

Figure 4 Forest plots for cervical laceration in premenopausal and post-menopausal women.

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.

	RR (95% CI)	Number of trials	Number of patients	*P*-value
All trials				
Abdominal cramping	5.20 (2.66, 10.17)	21	1786	<0.00001
Diarrhea	6.68 (3.36, 13.27)	21	1786	<0.00001
Nausea	2.63 (1.68, 4.12)	21	1786	<0.0001
Fever	5.53 (1.45, 21.15)	21	1786	0.01
Bleeding	4.75 (1.89, 11.95)	21	1786	0.0009
Excluding trials without a placebo arm				
Abdominal cramping	4.64 (2.22, 9.74)	18	1431	<0.00001
Diarrhea	5.88 (2.76, 12.54)	18	1431	<0.00001
Nausea	2.21 (1.36, 3.58)	18	1431	0.001
Fever	5.90 (1.05, 33.13)	18	1431	0.04
Bleeding	4.12 (1.67, 10.20)	18	1431	0.002

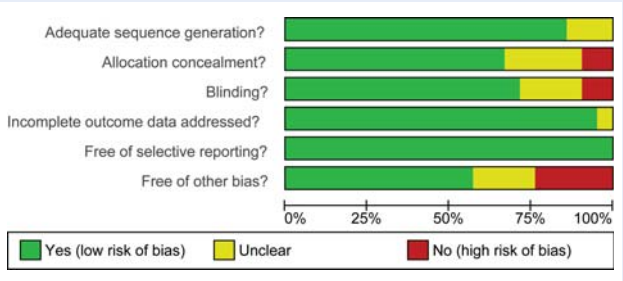

Figure 5 Risk of bias assessment among the RCTs, which were eligible for inclusion in the meta-analysis.

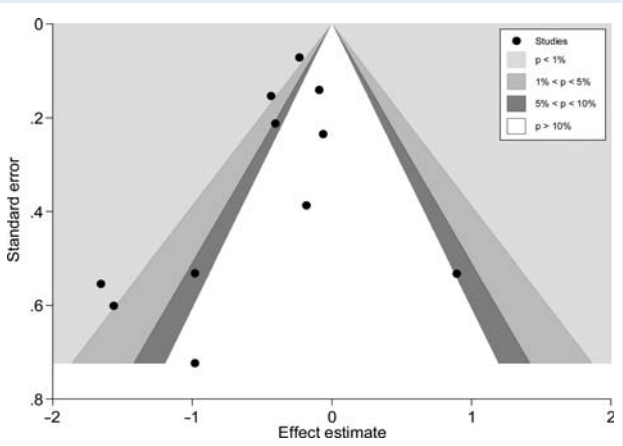

Figure 6 Contour-enhanced funnel plot for the assessment of publication bias.

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 pretreated 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 women, 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 (Preutthipan 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.Z. 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.

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Conflict of interest

None to declare.

References

Atay V, Duru NK, Pabuccu R, Ergün A, Tokac G, Aydin BA. Vaginal misoprostol for cervical dilatation before operative office hysteroscopy. *Gynaecol Endosc* 1997; **6**:47–49.

Atmaca R, Kafkasli A, Burak F, Germen AT. Priming effect of misoprostol on estrogen pretreated cervix in postmenopausal women. *Tohoku J Exp Med* 2005; **206**:237–241.

Austin SC, Sanchez-Ramos L, Adair CD. Labor induction with intravaginal misoprostol compared with the dinoprostone vaginal insert: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2010;**202**:624 e1–9.

Barcaite E, Bartusevicius A, Railaite DR, Nadisauskiene R. Vaginal misoprostol for cervical priming before hysteroscopy in perimenopausal and postmenopausal women. *Int J Gynaecol Obstet* 2005;**91**:141–145.

Batukan C, Ozgun MT, Ozcelik B, Aygen E, Sahin Y, Turkyilmaz C. Cervical ripening before operative hysteroscopy in premenopausal women: a randomized, double-blind, placebo-controlled comparison of vaginal and oral misoprostol. *Fertil Steril* 2008;**89**:966–973.

Bisharah M, Al-Fozan H, Tulandi T. A randomized trial of sublingual misoprostol for cervical priming before hysteroscopy. *J Am Assoc Gynecol Laparosc* 2003; **10**:390–391.

Choksuchat C, Cheewadhanaraks S, Getpook C, Wootipoom V, Dhanavoravibul K. Misoprostol for cervical ripening in non-pregnant women: a randomized double-blind controlled trial of oral versus vaginal regimens. *Hum Reprod* 2006; **21**:2167–2170.

Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. *J Am Med Assoc* 2002;**288**:1610–1621.

Cooper NA, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis. *Br Med J* 2010;**340**:c1130.

Cooper NA, Smith P, Khan KS, Clark TJ. Does cervical preparation before outpatient hysteroscopy reduce women's pain experience? A systematic review. *BJOG* 2011;**118**:1292–1301.

da Costa AR, Pinto-Neto AM, Amorim M, Paiva LH, Scavuzzi A, Schettini J. Use of misoprostol prior to hysteroscopy in postmenopausal women: a randomized, placebo-controlled clinical trial. *J Minim Invasive Gynecol* 2008;**15**:67–73.

Darwish AM, Ahmad AM, Mohammad AM. Cervical priming prior to operative hysteroscopy: a randomized comparison of laminaria versus misoprostol. *Hum Reprod* 2004;**19**:2391–2394.

El-Mazny A, Abou-Salem N. A double-blind randomized controlled trial of vaginal misoprostol for cervical priming before outpatient hysteroscopy. *Fertil Steril* 2011;**96**:962–965.

El-Toukhy T, Sunkara SK, Coomarasamy A, Grace J, Khalaf Y. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. *Reprod Biomed Online* 2008;**16**:712–719.

Fernandez H, Alby JD, Tournoux C, Chauveaud-Lambling A, DeTayrac R, Frydman R, Porcher R. Vaginal misoprostol for cervical ripening before operative hysteroscopy in pre-menopausal women: a double-blind, placebo-controlled trial with three dose regimens. *Hum Reprod* 2004; **19**:1618–1621.

Fung TM, Lam MH, Wong SF, Ho LC. A randomised placebo-controlled trial of vaginal misoprostol for cervical priming before hysteroscopy in postmenopausal women. *BJOG* 2002;**109**:561–565.

Gkrozou F, Koliopoulos G, Vrekoussis T, Valasoulis G, Lavasidis L, Navrozoglou I, Paschopoulos M. A systematic review and meta-analysis of randomized studies comparing misoprostol versus placebo for cervical ripening prior to hysteroscopy. *Eur J Obstet Gynecol Reprod Biol* 2011;**158**:17–23.

Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. *N Engl J Med* 2001;**344**:38–47.

Healey S, Butler B, Kum FN, Dunne J, Hutchens D, Crane JM. A randomized trial of oral misoprostol in premenopausal women before hysteroscopy. *J Obstet Gynaecol Can* 2007;**29**:648–652.

Higgins JPT, Green S, Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, West Sussex; Hoboken, NJ: Wiley-Blackwell, 2008.

Jansen FW, Vredevoogd CB, van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. *Obstet Gynecol* 2000;**96**:266–270.

Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 1988;**57**:205–212.

Lee YY, Kim TJ, Kang H, Choi CH, Lee JW, Kim BG, Bae DS. The use of misoprostol before hysteroscopic surgery in non-pregnant premenopausal women: a randomized comparison of sublingual, oral and vaginal administrations. *Hum Reprod* 2010;**25**:1942–1948.

Lin YH, Hwang JL, Seow KM, Huang LW, Chen HJ, Hsieh BC. Laminaria tent vs misoprostol for cervical priming before hysteroscopy: Randomized study. *J Minim Invasive Gynecol* 2009;**16**:708–712.

Marwah V, Bhandari SK. Diagnostic and interventional microhysteroscopy with use of the coaxial bipolar electrode system. *Fertil Steril* 2003;**79**:413–417.

Mulayim B, Celik NY, Onalan G, Bagis T, Zeyneloglu HB. Sublingual misoprostol for cervical ripening before diagnostic hysteroscopy in premenopausal women: a randomized, double blind, placebo-controlled trial. *Fertil Steril* 2010; **93**:2400–2404.

Ngai SW, Chan YM, Liu KL, Ho PC. Oral misoprostol for cervical priming in non-pregnant women. *Hum Reprod* 1997;**12**:2373–2375.

Ngai SW, Chan YM, Ho PC. The use of misoprostol prior to hysteroscopy in postmenopausal women. *Hum Reprod* 2001;**16**:1486–1488.

Oppegaard KS, Nesheim BI, Istre O, Qvigstad E. Comparison of self-administered vaginal misoprostol versus placebo for cervical ripening prior to operative hysteroscopy using a sequential trial design. *BJOG* 2008;**115**:663 e1–9.

Oppegaard KS, Lieng M, Berg A, Istre O, Qvigstad E, Nesheim BI. A combination of misoprostol and estradiol for preoperative cervical ripening in postmenopausal women: a randomised controlled trial. *BJOG* 2010;**117**:53–61.

Paschopoulos M, Polyzos NP, Lavasidis LG, Vrekoussis T, Dalkalitsis N, Paraskevaidis E. Safety issues of hysteroscopic surgery. *Ann N Y Acad Sci* 2006; **1092**:229–234.

Polyzos NP, Polyzos IP, Zavos A, Valachis A, Mauri D, Papanikolaou EG, Tzioras S, Weber D, Messinis IE. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. *Br Med J* 2010;**341**:c7017.

Polyzos NP, Valachis A, Patavoukas E, Papanikolaou EG, Messinis IE, Tarlatzis BC, Devroey P. Publication bias in reproductive medicine: from the European Society of Human Reproduction and Embryology annual meeting to publication. *Hum Reprod* 2011;**26**:1371–1376.

Preutthipan S, Herabutya Y. A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. *Obstet Gynecol* 1999;**94**: 427–430.

Preutthipan S, Herabutya Y. Vaginal misoprostol for cervical priming before operative hysteroscopy: a randomized controlled trial. *Obstet Gynecol* 2000;**96**:890–894.

Preutthipan S, Herabutya Y. A randomized comparison of vaginal misoprostol and dinoprostone for cervical priming in nulliparous women before operative hysteroscopy. *Fertil Steril* 2006;**86**:990–994.

Singh N, Ghosh B, Naha M, Mittal S. Vaginal misoprostol for cervical priming prior to diagnostic hysteroscopy–efficacy, safety and patient satisfaction: a randomized controlled trial. *Arch Gynecol Obstet* 2009;**279**:37–40.

Sordia-Hernandez LH, Rosales-Tristan E, Vazquez-Mendez J, Merino M, Iglesias JL, Garza-Leal JG, Morales A. Effectiveness of misoprostol for office hysteroscopy without anesthesia in infertile patients. *Fertil Steril* 2011;**95**:759–761.

Thomas JA, Leyland N, Durand N, Windrim RC. The use of oral misoprostol as a cervical ripening agent in operative hysteroscopy: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 2002;**186**:876–879.

Uckuyu A, Ozcimen EE, Sevinc FC, Zeyneloglu HB. Efficacy of vaginal misoprostol before hysteroscopy for cervical priming in patients who have undergone cesarean section and no vaginal deliveries. *J Minim Invasive Gynecol* 2008;**15**:472–475.

Valente EP, de Amorim MM, Costa AA, de Miranda DV. Vaginal misoprostol prior to diagnostic hysteroscopy in patients of reproductive age: a randomized clinical trial. *J Minim Invasive Gynecol* 2008;**15**:452–458.

Waddell G, Desindes S, Takser L, Beauchemin MC, Bessette P. Cervical ripening using vaginal misoprostol before hysteroscopy: a double-blind randomized trial. *J Minim Invasive Gynecol* 2008;**15**:739–744.