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REVIEW ARTICLE

A systematic review and meta-analysis of randomized controlled trials on the effectiveness of cervical ripening with misoprostol administration before hysteroscopy

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ABSTRACT

Background: Misoprostol is an effective cervical ripening agent. *Objectives:* To determine the effect of misoprostol on cervical ripening before hysteroscopy. *Search strategy:* Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched for pertinent studies published before November 2014, using the search terms "hysteroscopy," "ripening," and "misoprostol." *Selection criteria:* Randomized controlled trials published in English were included that compared the effects of misoprostol versus placebo on cervical dilatation before diagnostic or operative hysteroscopy. *Data collection and analysis:* Random-effects models were used to calculate odds ratios or mean differences (MDs) with 95% confidence intervals (CIs). *Main results:* The analysis included 32 trials. Misoprostol had significant effects on the need for further cervical dilatation (odds ratio 0.29, 95% CI 0.17–0.50), the cervical width (MD 1.53, 95% CI 0.92–2.13), and the time taken for cervical dilatation (MD −0.35, 95% CI −0.50 to −0.20). Corresponding observations were made in the subgroup of premenopausal women, but not in the subgroup of postmenopausal women. Adverse effects were significantly more common with misoprostol than with placebo (risk difference 0.07, 95% CI 0.01–0.12). *Conclusions:* Misoprostol had a significant effect on cervical ripening before hysteroscopy, except in the postmenopausal population. However, it also resulted in more adverse effects.

1. Introduction

Hysteroscopy has become the most important diagnostic and operative tool for direct viewing of the uterine cavity and biopsy sampling of intrauterine lesions [1]. However, the process of cervical dilatation before diagnostic or therapeutic hysteroscopy is associated with complications such as cervical bleeding, the formation of false tracts, and cervical tears [2,3]—particularly in nulligravidas, postmenopausal women, and women with cervical stenosis [4]. Traditional methods of cervical dilatation before hysteroscopy comprise laminaria tents, osmotic dilators, and Hegar dilators. However, these methods can lead to considerable discomfort and bleeding, and can interfere with the operator's view during hysteroscopy.

Misoprostol is a synthetic E1 prostaglandin analog that is used for the treatment and prevention of peptic ulcer. It is also an effective cervical ripening agent that is administered orally, vaginally, or sublingually in both pregnant and nonpregnant patients [5,6]. The optimum route of administration, dosage, and timing of administration before transcervical procedures such as hysteroscopy has yet to be determined.

Misoprostol is potentially effective for cervical dilatation before hysteroscopy [6]. Several randomized controlled trials (RCTs) have compared the effect of misoprostol given orally, vaginally, or sublingually before operative or diagnostic hysteroscopy, with that of placebo. However, whether misoprostol reduces the complications associated with hysteroscopy is unclear because the studies were not powered to detect this effect.

The aim of the present systematic review and meta-analysis of RCTs was to obtain a more objective appraisal of the evidence regarding the effect of misoprostol given before hysteroscopy, especially with regard to the effects on cervical ripening and the complications associated with hysteroscopy.

2. Materials and methods

2.1. Search strategies

Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched for all studies published between January 1, 1966, and November 30, 2014, that examined the effectiveness of misoprostol, given via various routes of administration, for cervical ripening before diagnostic or operative hysteroscopy. The search was conducted using the terms "hysteroscopy," "ripening," and "misoprostol."

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In addition, the reference sections of all relevant studies in any language were searched manually, as were key journals and abstracts from the major annual meetings in the fields of obstetrics and gynecology.

2.2. Selection criteria

The inclusion criteria were: the study was an RCT comparing misoprostol with placebo; the study evaluated the effect of misoprostol before diagnostic or operative hysteroscopy; the article reported data on the effect on cervical dilatation; and participants had given informed consent for study recruitment. Articles were excluded from the analysis if they were a review or letter to the editor, they described animal studies, they described fundamental research (e.g. biological or cellular research), the women in the study were exposed to other known pathogenic factors or disorders that might have affected the outcome, and the language of the article was not English.

The titles and abstracts were screened to identify potentially relevant studies. Two reviewers (Z.Z. and H.Y.), who were not masked to the names of the original investigators and the sources of the publications, identified and selected articles that met the inclusion and exclusion criteria. The reviewers worked independently and in duplicate. Disagreements were resolved by consensus or arbitration by X.J.

2.3. Data abstraction

After the identification of eligible studies, data were independently extracted and reviewed by Z.Z. and H.Y., using a unified extracting form. Any disagreements during the abstraction were discussed with X.J. until a resolution was reached. The abstracted data covered the participant characteristics (number of participants, age, and medical history), information about interventions (time, administration approach and dose of misoprostol, and combinations with other drugs), and the outcomes of interest. The primary outcomes of interest were cervical diameter, the need for further dilatation, the time taken for cervical dilatation, and the ease of cervical dilatation. Other outcomes assessed were the duration of hysteroscopic procedure, the visual analog scale score of pain during the procedure, and the patient acceptability rated on a Likert scale. The morbidity of the complications and adverse effects (cervical laceration, false tract formation, cervical bleeding, uterine perforation, abdominal cramping, diarrhea, nausea, vaginal bleeding, fever, vomiting, shivering, and posthysteroscopy infection) was calculated.

2.4. Assessment of methodological quality

The risk of bias in the selected studies was assessed by evaluating randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals, as in the study by Dale et al. [7]. All studies were evaluated by three independent reviewers (Z.Z., H.Y., and X.J.) and disagreements were resolved by consensus.

The quality of the included studies was assessed according to the Cochrane guidelines [8]. Specifically, blinding, allocation concealment, intention-to-treat analysis, and standard of follow-up were analyzed for the trials. Blinding was recorded as yes, no, or not reported. Allocation concealment was deemed adequate, unclear, or inadequate. Intention-to-treat analysis was recorded as yes or no. Follow-up analysis was recorded as adequate, unclear, or inadequate.

2.5. Statistical analysis

Meta-analysis was conducted using RevMan 5.2 (Cochrane Collaboration, Oxford, UK). Mean differences (MDs) and odds ratios (ORs) were calculated using Revman 5.2 (The Cochrane Collaboration, London, UK). The Cochran Q statistic was calculated to measure the heterogeneity between studies, with $P \le 0.05$ representing statistical homogeneity. In the presence of unexplained statistical heterogeneity, the random-effects model was used. $P < 0.05$ was considered statistically significant.

Additionally, subgroup analyses were performed to assess the effect of misoprostol given before diagnostic or operative hysteroscopy among premenopausal and postmenopausal women.

3. Results

3.1. Study characteristics

The initial search yielded 255 records (Fig. 1). A total of 32 trials were potentially suitable for inclusion in the meta-analysis [9–40]. The other trials were excluded because data on cervical ripening were not available in the papers and could not be obtained from the original investigators.

In total, 32 studies (n = 3349) conformed to the inclusion and exclusion criteria and were included in the present analysis. Supplementary Material S1 summarizes the quality of these trials. The main characteristics of the populations, the type of hysteroscopy (diagnostic/operative), the diameter of the hysteroscope, the interventions and comparisons, the inclusion and exclusion criteria, and the outcomes obtained in the trials are summarized in Supplementary Material S2.

No study included in the system review and meta-analysis evaluated cervical ripening as a study endpoint, and none was powered to detect differences in cervical dilatation. The outcome measures in the included studies were the duration of the dilatation, the duration of hysteroscopy, the visual analog scale score of pain during the procedure, difficulty in dilatation, hysteroscopy complications, and adverse effects. The populations studied in the different trials were heterogeneous for several demographic characteristics.

3.2. Primary outcomes

In total, 19 RCTs including 2238 women provided data on the cervical diameter before the hysteroscopic procedure. Because of a high degree of heterogeneity across these studies, the data were analyzed using a random-effects model. The results demonstrated a greater benefit in terms of cervical width for misoprostol than for placebo (MD 1.53 [95% confidence interval (CI) 0.92–2.13], $P < 0.001$) (Fig. 2). In the subgroup analysis of premenopausal women, misoprostol treatment also had a beneficial effect on cervical width (diagnostic hysteroscopy: MD 2.07 [95% CI 0.77–3.36], $P = 0.001$; operative hysteroscopy: MD 1.34 [95% CI 0.47–2.20], $P < 0.001$). In postmenopausal women, the cervical width after misoprostol treatment before operative hysteroscopy was also larger (MD 0.86 [95% CI −0.63 to 2.35]), but the difference was not statistically significant ($P = 0.26$). Data for diagnostic hysteroscopy in postmenopausal women were not available.

Results on the need for further dilatation before the hysteroscopic procedure were provided in 14 RCTs, which included 1780 women. In agreement with the results on cervical width, misoprostol treatment in the population overall reduced the need for further cervical dilatation to a statistically significant degree (OR 0.29 [95% CI 0.17–0.50], $P < 0.001$) (Fig. 3). The need for additional cervical dilatation was also reduced in the subgroup of premenopausal women receiving misoprostol (diagnostic hysteroscopy: OR 0.27 [95% CI 0.19–0.38], $P < 0.001$; operative hysteroscopy: OR 0.14 [95% CI 0.03–0.61], $P < 0.001$). Among postmenopausal women, the difference in the need for further dilatation before operative hysteroscopy was not statistically significant (OR 0.29 [95% CI 0.06–1.47], $P = 0.14$); data on diagnostic hysteroscopy were not available.

In a meta-analysis of the findings from 12 RCTs and 1803 women, the time taken for cervical dilatation was significantly shorter in the misoprostol group than in the control group (MD −0.35 [95% CI −0.50 to −0.20], $P < 0.001$) (Fig. 4). The difference between the groups was less pronounced but still significant in the analysis including premenopausal women only (diagnostic hysteroscopy: MD −0.53 [95% CI −0.80 to −0.26], $P < 0.001$; operative hysteroscopy: MD−0.26 [95% CI −0.44 to −0.07], $P < 0.001$). In the analysis including postmenopausal women

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