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Efficacy and safety of oral vs vaginal misoprostol for cervical priming before hysteroscopy: A systematic review and meta-analysis

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ABSTRACT

Background: There is great controversy regarding the most effective route for cervical priming before diagnostic or operative hysteroscopy.
Objective: To evaluate the evidence from published randomized clinical trials (RCTs) about the efficacy and safety of oral vs vaginal misoprostol for cervical priming before hysteroscopy.
Search strategy: Electronic databases including PubMed, Cochrane Library, Scopus and Web of Science were searched using the relevant keywords.
Selection criteria: All RCTs assessing the effect of oral vs vaginal misoprostol before hysteroscopy for cervical priming were considered. One hundred and ten studies were identified, of which eight studies were deemed eligible for this review.
Data collection and analysis: The extracted outcomes were: cervical canal width, ease of dilatation, time for cervical dilatation and adverse effects (nausea, vomiting, diarrhoea, bleeding, fever, abdominal pain/uterine cramping and any complications during the procedure). All statistical analyses were completed using RevMan.
Main results: Eight RCTs with 768 patients were included in this meta-analysis. Cervical canal width did not differ significantly between the two routes of misoprostol administration [mean difference −0.25 mm, 95% confidence interval (CI) −0.92–0.42; $p = 0.47$]. However, the vaginal route was significantly superior to the oral route for reducing the time for cervical dilatation (standardized mean difference 0.17, 95% CI 0.02–0.32; $p = 0.03$). No significant differences in adverse effects were found between the routes, except for diarrhoea which was significantly less prevalent with vaginal administration of misoprostol (risk ratio 2.48, 95% CI 1.17–5.26; $p = 0.02$).
Conclusions: Oral and vaginal administration of misoprostol before hysteroscopy were similar in terms of cervical canal width, ease of dilatation and various adverse effects, except that the vaginal route was associated with faster cervical dilatation and lower prevalence of diarrhoea.

Contents

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Introduction

Hysteroscopy is a minimally invasive procedure commonly used in the diagnosis and management of different gynaecological issues. It is often performed as an outpatient procedure. Uterine bleeding, deformities, synechiae and conception remnants are problems during hysteroscopy [1]. Approximately half of hysteroscopic complications occur during cervical entry, including cervical lacerations, false tract and uterine rupture [2]. Cervical priming before hysteroscopy is used to decrease the incidence of complications [2,3].

Prostaglandin analogues, particularly misoprostol, have been used before hysteroscopy in various randomized controlled trials (RCTs). Misoprostol can be administered by various routes – oral, sublingual or vaginal – to induce cervical dilatation. Misoprostol is as effective as laminaria for cervical priming before hysteroscopy, with less time needed for dilatation, lower cost and increased patient acceptability [4].

Clinical trials of the use of misoprostol by various routes have shown variable results. One study showed that vaginal misoprostol was more effective for maintaining better cervical ripening [5]. However, another clinical trial concluded that different routes of misoprostol were similar in efficacy [6]. No solid conclusion has been reached to date regarding the most effective route for cervical priming before diagnostic or operative hysteroscopy.

As such, the authors conducted this systematic review on the efficacy and safety of oral vs vaginal misoprostol for cervical priming before hysteroscopy.

Materials and methods

This systematic review and meta-analysis were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions [7]. The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during preparation of this review and meta-analysis [8]. No formal ethical approval was required.

Search strategy

A comprehensive computerized literature search of four electronic databases (PubMed, Cochrane Library, Scopus, ClinicalTrials.gov and ISI Web of Science) was undertaken in 2018 for all studies using the following keywords: (oral) AND (vaginal) AND (misoprostol OR Cytotec) AND (hysteroscopy OR uteroscope OR metroscope). The references cited in the identified publications were searched for additional studies.

Eligibility criteria

Only studies that met the following inclusion criteria were included:

(i) population: women aged >18 years who were undergoing hysteroscopy;
(ii) intervention: oral misoprostol at different doses;
(iii) comparator: vaginal misoprostol at different doses;
(iv) outcome parameters: efficacy outcomes including cervical canal width, ease of dilatation, time for cervical dilatation and adverse effects (including nausea, vomiting, diarrhoea, fever, bleeding, abdominal pain/uterine cramping and any complications during the procedure); and
(v) study design: RCT.

Observational studies, non-English studies, editorials and letters were excluded.

Study selection

Eligibility screening was undertaken in a two step-wise manner (title/abstract screening and full-text screening). Each phase was conducted by all authors and consensus was obtained after discussion in the case of controversy. All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention and results.

Data extraction

Two authors (AA, AG) extracted the data independently using an online data extraction form. The following data were collected: baseline characteristics of study population, risk-of-bias domains and study outcomes. Cervical canal width (in mm), ease of dilatation and time for cervical dilatation (in s) were selected as efficacy outcomes. Cervical canal width was the main outcome, taken as the diameter of the cervical canal measured by different Hegar dilators. Studies measured cervical width by performing cervical dilatation, starting with the smallest Hegar dilator and introducing larger Hegar dilatators through the internal os until resistance was sensed. Ease of dilatation was recorded by surgeons based on a five-point Likert scale. Time for cervical dilatation was assessed during the procedure. Various adverse effects which are common with misoprostol, namely nausea, vomiting, diarrhoea, bleeding, uterine cramping/abdominal pain, fever and any complications during the procedure (cervical laceration, false tract, uterine perforation, failed surgery) were selected as safety outcomes.

Data analysis

Efficacy outcomes were pooled as weighted mean difference (MD) or standardized mean difference (SMD) for continuous data. Pooled risk ratios (RR) using Mantel–Hansel's method with 95% confidence intervals (CI) were used for the dichotomous data of safety outcomes. All statistical analyses in this study were undertaken using RevMan Version 5.2 (Cochrane Collaboration, Oxford, UK).

Statistical heterogeneity was assessed by I^2 statistics [9], and values ≥50% indicated high heterogeneity. If significant heterogeneity was found, a random effects model was used; this was only needed for cervical canal width. Otherwise, a fixed effects model was adopted. A sensitivity analysis was undertaken for cervical canal width to consider the contribution of each included study to the pooled estimation of reported heterogeneity; the study by Nada et al. [10] was removed and the combined MD estimation was re-analysed for the remaining studies.

Risk-of-bias assessment

Quality assessment of the included RCTs was undertaken using the quality assessment table in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [[11], Part 2, Chapter 8.5]. This table contains the following fields: selection bias, performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias, reporting bias and other potential sources of bias. The authors' judgment is categorized as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'.

According to Egger et al., assessment of publication bias using the funnel plot method and Egger's test is not reliable for <10 included studies. Therefore, assessment of publication bias was not possible in this review due to the limited number of studies which met the inclusion criteria [12,13].

Dealing with missing data

The method of Hozo et al. was used to obtain mean and standard deviation (SD) from median and range to avoid exclusion of papers [14].

Results

Search results and characteristics of included studies

The search identified 110 studies from the electronic databases, of which 35 were duplicates. Of the remaining 75 studies, 65 studies were excluded based on title and abstract screening. Moreover, 10 studies were excluded during full-text screening. Eight studies [5,6,10,15–19] with a total of 768 patients met the inclusion criteria (Fig. 1). The reasons for exclusion were non-availability of the full-text article, retrospective study or observational study. The eight studies included in this review were conducted in the following countries: Egypt [10], South Korea [6,17], Thailand [16], Mexico [19], Turkey [5], Israel [15] and Greece [18]. All of the studies included premenopausal women alone, except the study by Herman et al. [15] which included both premenopausal and postmenopausal women. The references of the included RCTs were searched manually but no additional relevant records were identified. The characteristics of the included studies are summarized in Table 1.

Risk-of-bias assessment

The included RCTs were considered to be of moderate to high quality according to the Cochrane risk-of-bias assessment tool. The risk-of-bias summary is shown in Fig. 2.

Efficacy outcomes

Cervical canal width

No significant difference in cervical canal width was found between the two routes of misoprostol administration [MD -0.25 mm, 95% confidence interval (CI) −0.92–0.42; $p = 0.47$], as shown in Fig. 3A. Pooled studies were heterogeneous ($p < 0.00001$, $I^2 = 84\%$) so a random effects model was used. Heterogeneity was best resolved by performing a sensitivity analysis; exclusion of the study by Nada et al. ($p = 0.11$, $I^2 = 46\%$) showed no significant difference between the two routes of administration (MD -0.48 mm, 95% CI −0.99–0.03, $p = 0.07$) (Fig. 3B).

Ease of dilatation

No significant difference in ease of dilatation was found between the two routes of misoprostol administration (MD 0.00, 95% CI −0.15–0.15; $p = 0.96$). Pooled studies were homogenous ($p = 0.64$, $I^2 = 0\%$) (Fig. 4).

Time for cervical dilatation

The overall SMD showed that vaginal misoprostol was significantly associated with quicker cervical dilatation compared with oral misoprostol (SMD 0.17, 95% CI 0.02–0.32; $p = 0.03$) (Fig. 5). Pooled studies were homogeneous ($p = 0.18$, $I^2 = 35\%$).

Safety outcomes

Adverse effects

Nausea. No significant differences in nausea were found between the two routes of misoprostol administration (RR 1.74, 95% CI 0.97–3.13; $p = 0.06$) (Fig. 6). Pooled studies were homogenous ($p = 0.94$, $I^2 = 0\%$).

Vomiting. No significant differences in vomiting were found between the two routes of misoprostol administration (RR 3.24, 95% CI 0.99–10.57; $p = 0.05$). Pooled studies were homogenous ($p = 1.0$, $I^2 = 0\%$) (Fig. 7).

Diarrhoea. The vaginal route was associated with significantly lower prevalence of diarrhoea than the oral route (RR 2.48, 95% CI 1.17–5.26; $p = 0.02$). Pooled studies were homogenous ($p = 0.44$, $I^2 = 0\%$) (Fig. 8).

Fever. The overall RR found no significant differences in fever between the two routes of misoprostol administration (RR 1.18, 95% CI 0.37–3.81, $p = 0.78$). Pooled studies were homogenous ($p = 0.96$, $I^2 = 0\%$) (Fig. 9).

Bleeding. The overall RR did not favour either of the two routes of misoprostol administration in terms of bleeding (RR 1.12, 95% CI 0.70–1.79; $p = 0.63$). Pooled studies were homogenous ($p = 0.92$, $I^2 = 0\%$) (Fig. 10).

Uterine cramping/abdominal pain. There were no significant differences in uterine cramping or abdominal pain between the two routes of misoprostol administration (RR 0.92, 95% CI 0.71–1.2; $p = 0.54$). Pooled studies were homogenous ($p = 0.78$, $I^2 = 0\%$) (Fig. 11).

Complications during the procedure

No significant differences in complications during hysteroscopy were found between the two routes of misoprostol administration (RR 1.7, 95% CI 0.74–3.92; $p = 0.21$). Pooled studies were homogenous ($p = 0.76$, $I^2 = 0\%$) (Fig. 12).

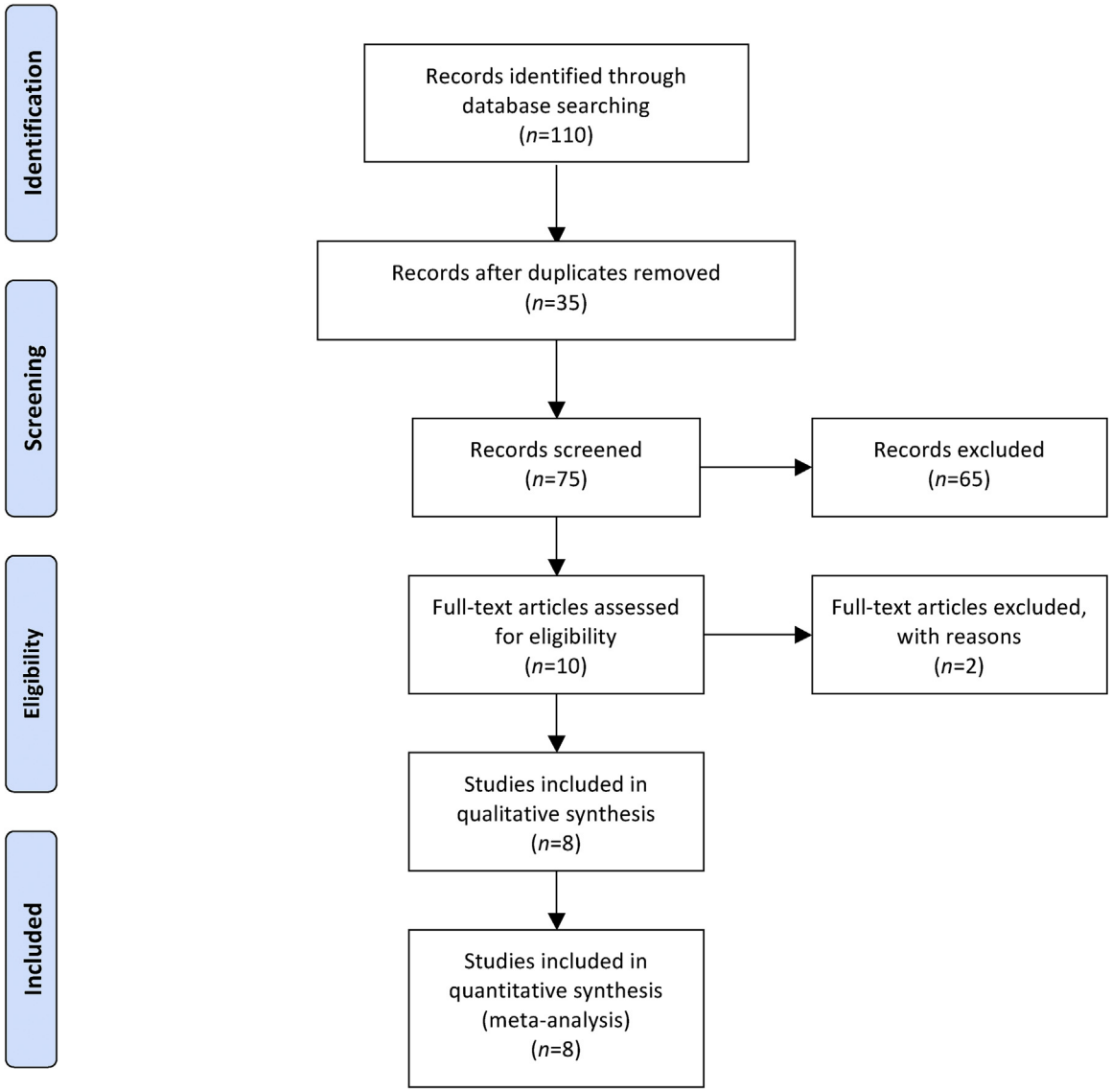

Fig. 1. PRISMA flow chart of study selection process.

Comment

Hysteroscopy is used globally for the treatment of common gynaecological problems. Cervical priming of limited duration should be considered to ease hysteroscopy. Polyzos et al. [20] investigated the efficacy of misoprostol via various routes compared with placebo as a cervical priming agent. They found that misoprostol was associated with more comfortable and safer hysteroscopy in premenopausal women but not in postmenopausal women [20]. Furthermore, Nandhini et al. concluded that different routes of misoprostol administration were better than the control group for cervical priming to facilitate cervical entry with minimal side effects [21]. However, the latter study was vague regarding whether oral or vaginal administration of misoprostol was superior.

This meta-analysis found no differences in cervical canal width between the two routes of misoprostol administration. In addition, ease of dilatation, measured by a Likert scale, was also found to be similar for the two routes. Cervical dilatation was faster with vaginal misoprostol. No significant differences were found between the two routes in terms of adverse effects, except for diarrhoea; vaginal misoprostol was associated with a significantly lower prevalence of diarrhoea compared with oral misoprostol.

Regarding cervical canal width, Song et al. concluded that oral and vaginal misoprostol were equally effective for cervical priming before operative hysteroscopy, supporting the present results [6]. In addition, Choksuchat et al. found no difference in cervical canal width between oral and vaginal routes of misoprostol administration [16]. However, another study found that vaginal misoprostol induced a greater increase in cervical width compared with oral misoprostol, opposing the present results [5]. The cause of the reported heterogeneity in cervical canal width may be due to the use of sucrose as well as misoprostol by Nada et al. [10]. Moreover, differences in the hours of administration of misoprostol before hysteroscopy and different cervical parameters used in the included studies may be responsible for the reported heterogeneity in this outcome.

It is not fully understood how misoprostol causes cervical ripening. However, it has been shown that PGE2 (misoprostol) directly stimulates metalloproteinase 1 (MMP-1) activity in the cervical fibroblasts [22]. Other studies have reported that PGE2 might enable lysis of collagen due to its vasoactive effect, which

Table 1
Characteristics and results of included studies.

Study	Dose	Group: *n*	Mean age in years (SD)	Main outcome measures	End-point score (cervical canal width in mm after treatment): Mean (SD)	Conclusion
Batukan et al., 2008 [5]	400 μg both orally and vaginally	Oral: *n* = 39 Vaginal: *n* = 38	31.1 (5.1) 32.7 (6.8)	• Post-treatment cervical width • Time for cervical dilatation • Need for further dilatation • Operative time for all procedures • Operative time for polypectomy • Operative time for uterine septum	Oral: 6 (1.5) Vaginal: 7.3 (1.6)	Vaginal misoprostol was superior to oral misoprostol regarding faster cervical dilatation and shorter operative time, as well as need for cervical dilatation
Song et al., 2014 [6]	400 μg both orally and vaginally	Oral: *n* = 40 Vaginal: *n* = 40	38.2 (7.3) 36.6 (6.8)	• Cervical canal width	Oral: 7.62 (1.81) Vaginal: 7.60 (2.15)	All routes of misoprostol were equally effective in inducing proper cervical priming before operative hysteroscopy
Choksuchat et al., 2011 [16]	400 μg orally and 200 μg vaginally	Oral: *n* = 30 Vaginal: *n* = 30	43.7 (12.6) 37.80 (6.52)	• Cervical canal width	Oral: 5.10 (1.75) Vaginal: 5.60 (1.69)	Oral misoprostol 400 μg had the same efficacy for cervical ripening as vaginal misoprostol 200 μg
Herman et al., 2017 [15]	400 μg both orally and vaginally	Oral: *n* = 39 Vaginal: *n* = 40	47.4 (15.2) (12.6)	• Pre-operative cervical dilatation • Pre-operative cervical consistency • Subjective ease of cervical dilation • Time required to dilate cervix to Hegar 10 • Patient reported discomfort from misoprostol	Oral: 6.1 (2.0) Vaginal: 6.4 (2.1)	Cervical priming for operative hysteroscopy is achieved equally with all routes of misoprostol, with similar patient satisfaction and side effects
Lee et al., 2010 [17]	400 μg both orally and vaginally	Oral: *n* = 47 Vaginal: *n* = 47	43.2 (6) 41 (7.2)	• Cervical canal width after misoprostol administration • Time for cervical dilatation	Oral: 7.5 (1.9) Vaginal: 7.6(2.4)	All misoprostol routes were equally effective for cervical priming before hysteroscopic surgery
Nada et al., 2016 [10]	400 μg both orally and vaginally	Oral: *n* = 130 Vaginal: *n* = 130	33.80 (6.80) 33.20 (6.00)	• Width of endocervical canal • Ease of dilatation measured by Likert five-point scale • Time needed for dilatation from start point to Hegar 10	Oral: 4.79(1.07) Vaginal: 4.25 (0.71)	No significant difference between oral and vaginal misoprostol for cervical priming
Bakas et al., 2011 [18]	200 μg both orally and vaginally	Oral: *n* = 39 Vaginal: *n* = 36	34.8 (5.8) 35.6 (7.2)	• Degree of pre-operative cervical dilation required • Time needed for dilatation from start point to Hegar 5 • Development of uterine or cervical injury during procedure • Development of intrauterine bands as a result of the procedure	NA	Oral misoprostol 200 μg or vaginal misoprostol 200 μg can be used prior to hysteroscopy for cervical ripening
Sordia-Hernandez et al., 2011 [19]	600 μg orally and 400 μg vaginally	Oral: *n* = 22 Vaginal: *n* = 20	33.6 (19) 34.1 (6)	• Level of pelvic pain	NA	Vaginal misoprostol reduces pain and time needed for hysteroscopy

RCTs, randomized controlled trials; NA, not available.

would simplify the expression of more MMP-8-rich neutrophils in the cervix [23].

Herman et al. reported that ease of dilatation was equivalent for both vaginal and oral routes, supporting the present results [24]. Moreover, Song et al. showed no significant difference in ease of dilatation between the two routes [6]. Nada et al. found no differences in time of cervical dilatation between the routes of misoprostol administration [10]. However, Batukan et al. reported that vaginal misoprostol was associated with faster cervical dilatation compared with oral misoprostol, supporting the present results [5]. Vaginal misoprostol may also be associated with a shorter procedure time due to the significant reduction in time needed for cervical dilatation.

Nada et al. found that the two routes of misoprostol administration were therapeutically safe, harmless and showed no difference in terms of nausea, cramps, vomiting, bleeding, fever, diarrhoea and complications [10]. Moreover, Lee et al. established that side effects did not differ between oral and vaginal administration [17]. Choksuchat et al. found that oral misoprostol was linked with more cases of diarrhoea than vaginal misoprostol [16]. Based on the present findings, the oral route may be linked with more cases of diarrhoea due to the high dose of oral misoprostol prescribed for patients in the included studies. Diarrhoea is a very common side effect of misoprostol. One study suggested that oral misoprostol was linked to excess side effects due to metabolism of the drug with focusing on different organs impending various adverse effects systemically as diarrhoea [25].

Although oral misoprostol is used widely, many pharmacokinetic studies have concluded that the plasma concentration of the active metabolite of misoprostol remains high for longer after vaginal administration than oral administration [26,27]. Regarding sublingual misoprostol, an RCT suggested that it could lead to more side effects as instead of passing through the gastrointestinal tract, the drug would reach the circulation directly through the internal jugular vein and could be absorbed more quickly, causing a higher peak concentration in blood. This feature might be

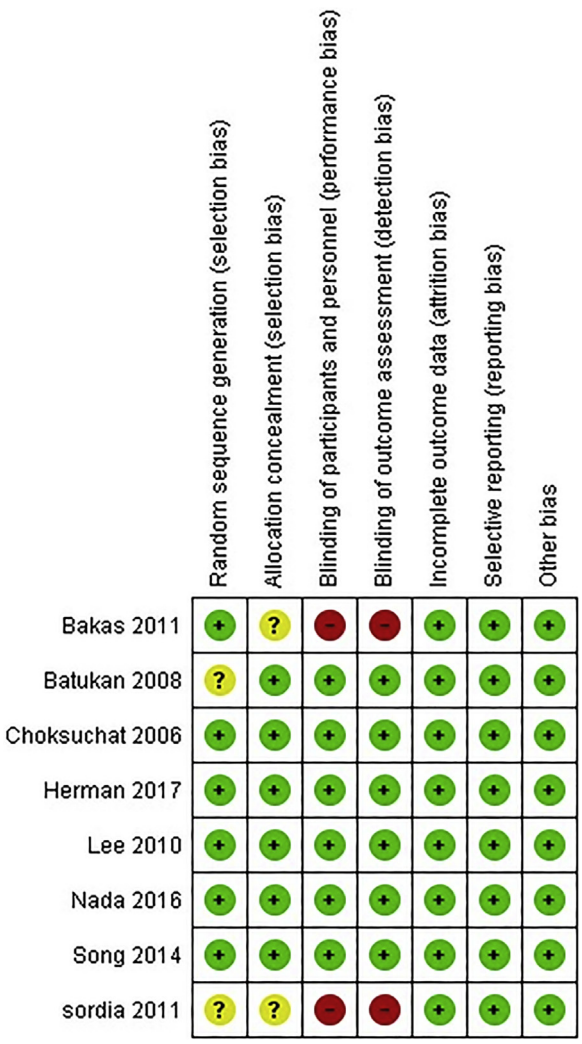

Fig. 2. Risk-of-bias summary graph.

responsible for more frequent adverse events with this route of administration [25].

Strengths and limitations

To the authors' knowledge, this is the first meta-analysis on oral vs vaginal misoprostol administration for cervical priming before hysteroscopy. The PRISMA guidelines were followed. Limitations of this meta-analysis are the small number of included studies and the small sample size, which may have affected the heterogeneity of certain outcomes. Furthermore, women due to undergo either diagnostic or operative hysteroscopy were included. Subgroup analysis was not undertaken to show the differences in premenopausal and postmenopausal women for these two routes of misoprostol, as most of the included studies only included premenopausal women.

Clinical and research recommendations

Based on the study findings, vaginal administration of misoprostol is recommended before hysteroscopy, instead of oral misoprostol, as it was associated with faster cervical dilatation leading to a shorter procedure time, and less diarrhoea. There is a need to perform more double-blind randomized controlled trials on this topic with large sample sizes to confirm these findings. Future studies should state the recommended time for misoprostol administration for cervical priming before hysteroscopy as this is still unknown, and the included studies varied regarding this important point. Furthermore, future studies should investigate the difference in administration of misoprostol by different routes on cervical dilation in postmenopausal and premenopausal women; this was not possible in this review as most of the included studies were performed in premenopausal patients.

Conclusion

This systematic review found no difference between oral and vaginal misoprostol for cervical priming before hysteroscopy in terms of cervical canal width. However, vaginal administration led

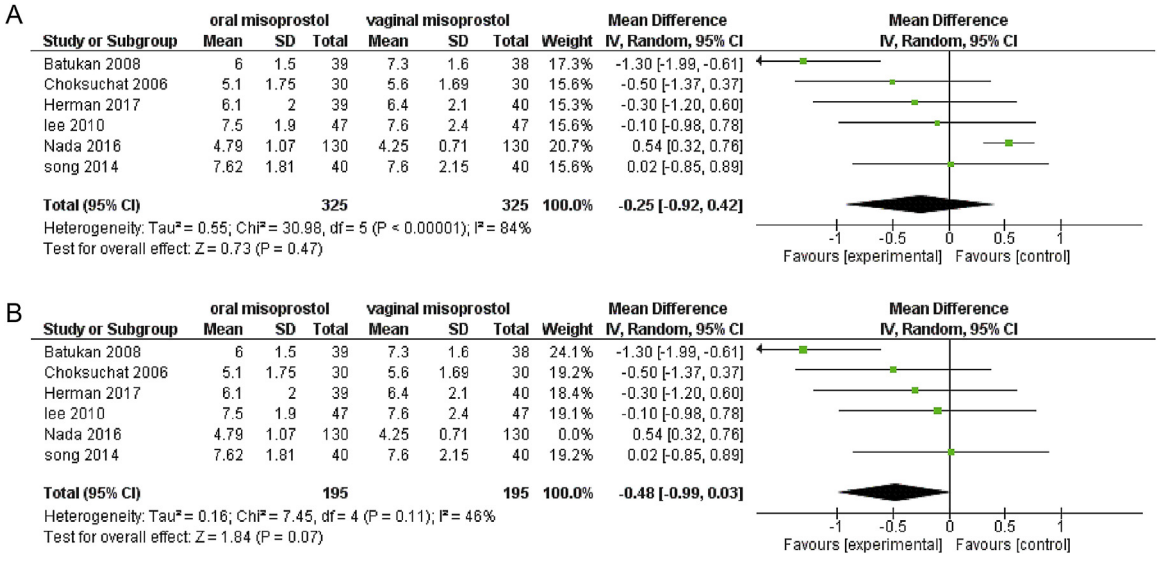

Fig. 3. A. Forest plot for cervical canal width. B. Forest plot for cervical canal width after removal of heterogeneity.

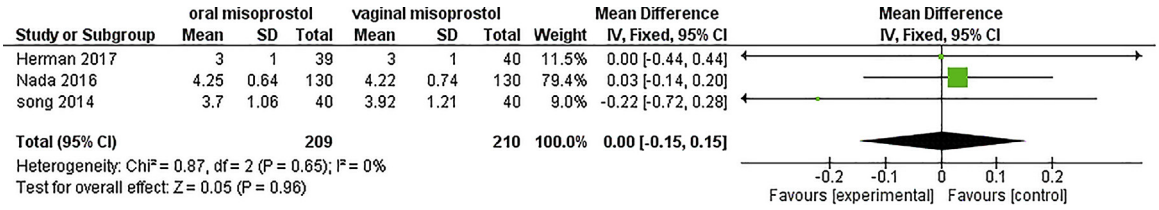

Fig. 4. Forest plot for ease of cervical dilatation.

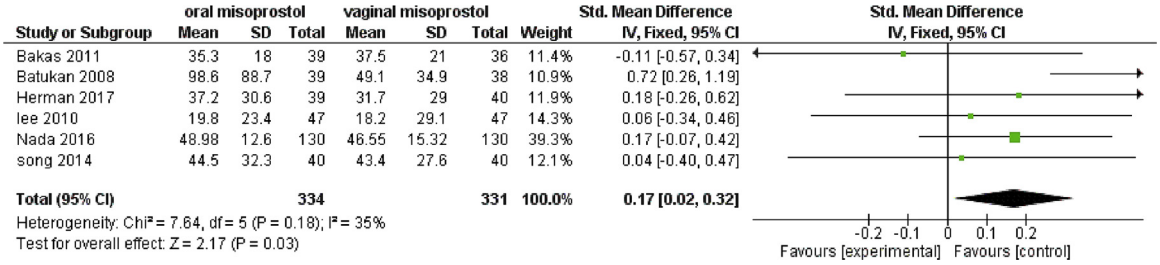

Fig. 5. Forest plot for time for cervical dilatation.

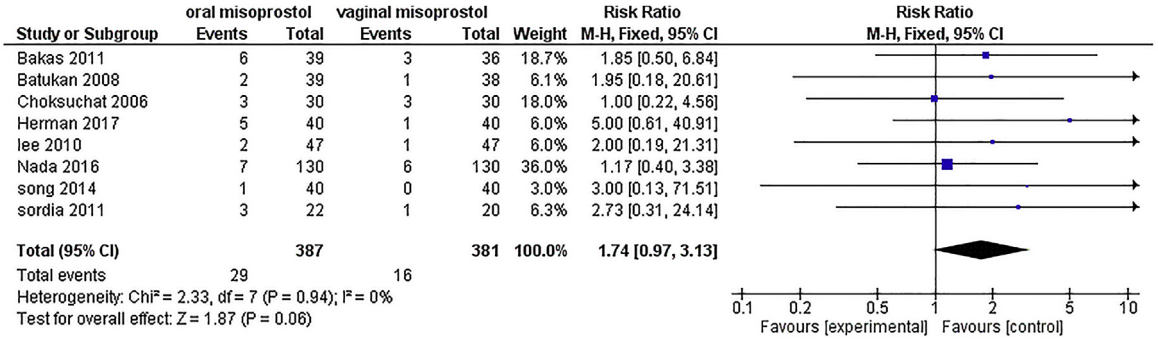

Fig. 6. Forest plot for occurrence of nausea.

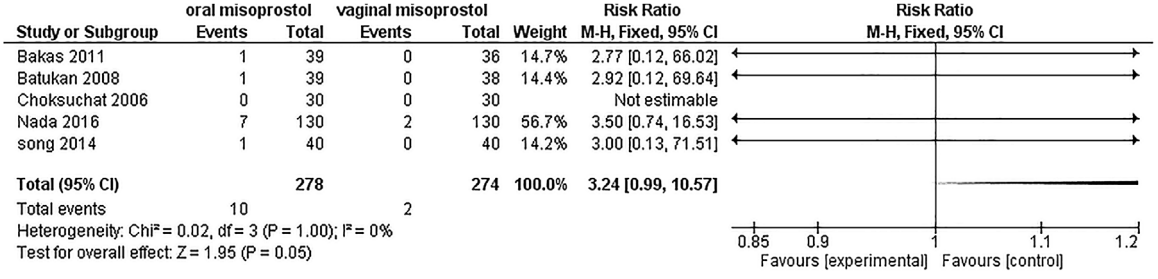

Fig. 7. Forest plot for occurrence of vomiting.

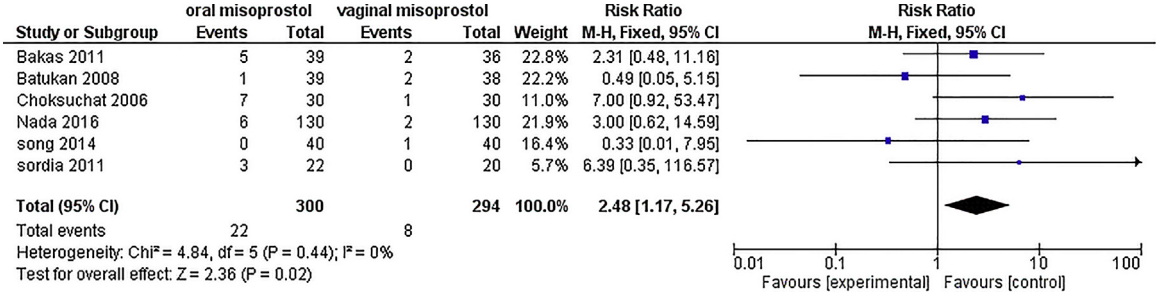

Fig. 8. Forest plot for occurrence of diarrhoea.

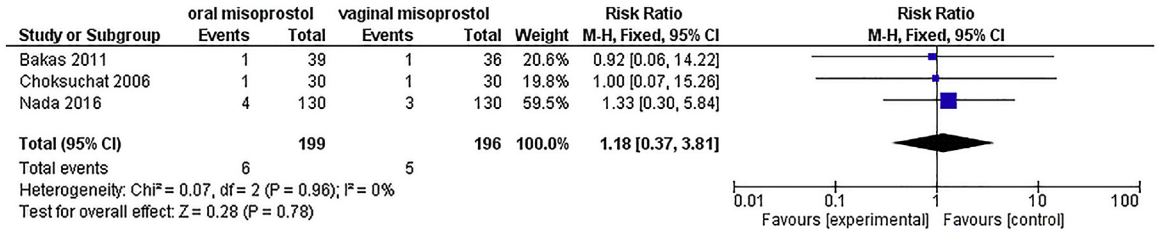

Fig. 9. Forest plot for occurrence of fever.

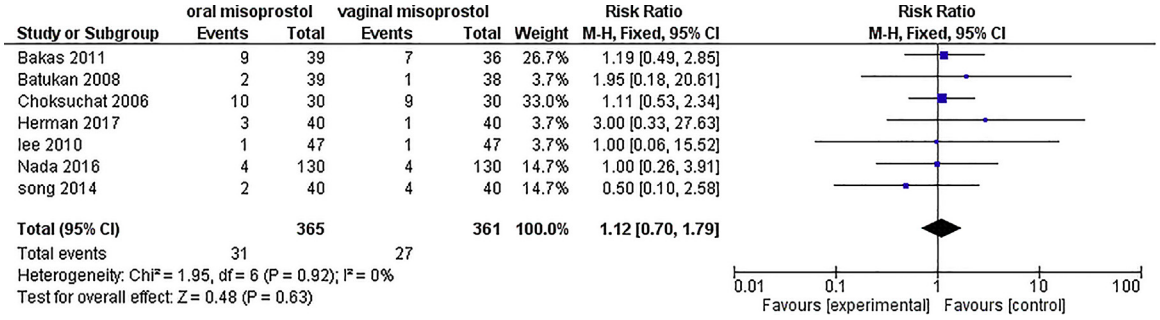

Fig. 10. Forest plot for occurrence of bleeding.

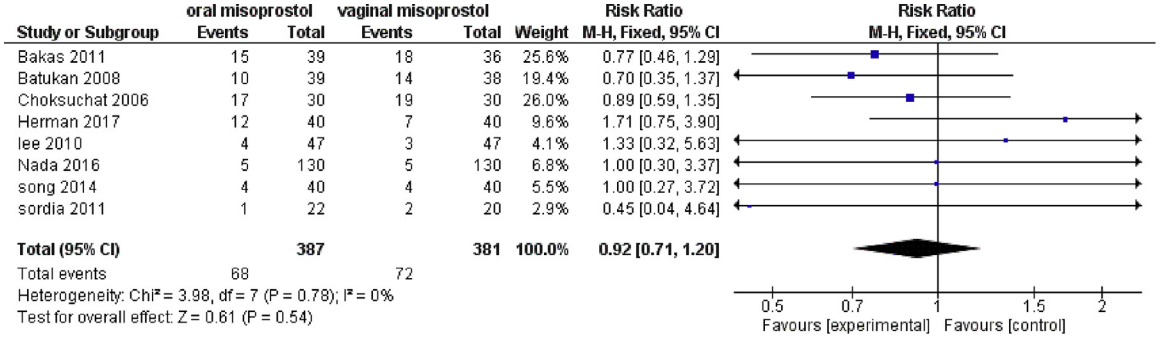

Fig. 11. Forest plot for occurrence of uterine cramping/abdominal pain.

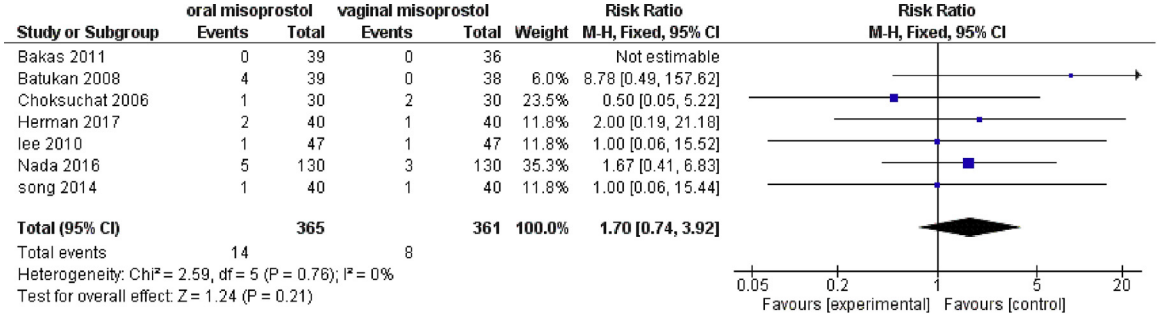

Fig. 12. Forest plot for occurrence of any complication during the procedure.

to faster cervical dilatation. No differences in adverse effects were found between the two routes of administration, except for diarrhoea which was significantly less prevalent with vaginal administration.

Funding

None.

Declaration of Competing Interest

None declared.

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