a Open Access Full Text Article

ORIGINAL RESEARCH The use of misoprostol for cervical priming prior to hysteroscopy: a systematic review and analysis

Ying Hua Wenwen Zhang Xiaoli Hu Ansu Yang Xueqiong Zhu

Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, People's Republic of China

Correspondence: Xueqiong Zhu Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Wenzhou Medical University, No 109 Xueyuan Xi Road, Wenzhou, Zhejiang, 325027, People's Republic of China Tel +86 577 8800 2796 Fax +86 577 8883 2693 Email zjwzzxg@163.com



Abstract: The effects of misoprostol use on cervical priming prior to hysteroscopy have been controversial. Therefore, a systematic literature review and meta-analysis of studies were conducted to assess the effect of misoprostol on cervical priming prior to hysteroscopy. All studies published before July 2014 with data related to the use of misoprostol for cervical priming compared with placebo or no medication prior to hysteroscopy, were identified. Twenty-five randomized controlled trials involving 2,203 females were systematically analyzed. The results showed that, compared with placebo or no medication, the use of misoprostol prior to hysteroscopy led to a significant relief of the need for cervical dilatation, resulted in a significantly greater cervical width, had fewer hysteroscopy complications, and mild and insignificant side effects. Subgroup analyses revealed that the regimen of 200 or 400 μ g vaginal misoprostol may be a simple and effective method for cervical priming, especially prior to operative hysteroscopy. Keywords: misoprostol, hysteroscopy, cervical priming, cervical dilatation, complications, systematic review

Introduction

Hysteroscopy is a minimally invasive approach for observing the uterine cavity for a variety of gynecological problems, and has become a valuable diagnostic and therapeutic procedure.^{1,2} Also, hysteroscopy is potentially useful for female sterilization and offers promise as an investigative tool for studying the intratubal milieu.³ However, many patients undergoing the procedure are at risk for cervical dilatation complications, such as cervical laceration, uterine perforation, and creation of false passages.⁴ Fortunately, the incidence of these complications may be reduced if the cervix is ripened beforehand.

Misoprostol, a prostaglandin E1 analog, which was initially used for the treatment of peptic ulcers, has been widely applied in obstetrics and gynecology because of its ripening effect on cervix during the induction of abortion or labor.^{5,6} The primary advantages of the drug include its thermostability, low cost, and the ease of administration.⁷ Moreover, misoprostol is available in many formulations: tablets or gelcaps, at doses of 200, 400, 800, and 1,000 µg, and can be administered by mouth or sublingually, as well as via the rectal or vaginal route.⁸⁻¹⁰ Because of its effect on cervical ripening in pregnant females, misoprostol has also been used for cervical priming prior to hysteroscopy by surgeons. While numerous studies indicated the efficacy of misoprostol for achieving cervical dilatation in patients undergoing hysteroscopy,^{10–15} some reports concluded that the use of misoprostol before hysteroscopy did not facilitate cervical dilatation.^{8,9,16–18} The discrepancy may be due to small sample sizes, differences in the route of administration of misoprostol, the types of

Drug Design, Development and Therapy 2016:10 2789-2801

2789

© 2016 Hua et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, large accept and a commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, large see paragraph 4.2 and 5 of our Terms (http://www.dovepress.com/terms.php).

hysteroscopy (operative or diagnostic hysteroscopy), and/or different populations under study.

To more systematically evaluate the efficacy and safety of misoprostol for cervical priming prior to hysteroscopy, we conducted a meta-analysis on randomized controlled trials (RCTs) comparing misoprostol versus placebo or no medication before diagnostic or operative hysteroscopy in females receiving hysteroscopy. In addition, we hope that such analyses would help in determining the optimal dose and route of administration for the application of misoprostol in hysteroscopy.

Methods

Search strategy

We searched (published up to July 2014) the three most popular databases – MEDLINE (via PubMed), EMBASE (via embase.com), and Cochrane – for articles in any language. The search strategy used the terms "hysteroscopy" AND "misoprostol". In addition, the references of the relevant articles and previous systematic reviews were checked to identify potentially eligible trials.

Selection criteria

We included RCTs for cervical priming using misoprostol prior to diagnostic or operative hysteroscopy in females regardless of age, parity, or other characteristics. The intervention in the trials was the use of misoprostol compared with placebo or no medication before hysteroscopy. No restriction was placed on dose, route, or timing of misoprostol administration. We excluded studies without a placebo or no medication group, as well as those comparing misoprostol to another method (laminaria tents or dinoprostone). Nonrandomized trials such as case–control studies were also excluded.

Data extraction and quality assessment

Two reviewers, YH and WWZ, independently extracted the data that were retrieved from the search. The results were then compared and disagreements were resolved by discussion. If the two primary reviews could not reach a consensus the third reviewer (XLH) was be consulted. Information of the authorship, publication year, patient demographics, type of intervention, and outcomes were extracted. To assess the validity of the included trials, two investigators (YH and WWZ) independently examined the study quality using the *Cochrane Handbook for Systematic Reviews of Interventions* with respect to the generation of random sequences, allocation concealment, blinding, incomplete outcome data, and selective reporting.¹⁹ The risk of publication bias was assessed using funnel plots.

Outcomes

The outcomes of interest for this article included the following variables: number of females who required cervical dilatation, cervical width at the start of hysteroscopy, hysteroscopy complications such as cervical tears and uterine perforation, and the incidence of misoprostol side effects such as abdominal pain, nausea, diarrhea, genital bleeding, and fever.

Data synthesis

Statistical analyses were performed with the use of Review Manager (RevMan), Version 5.1 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). To calculate the risk ratio (RR) for dichotomous data and the mean differences (MD) for continuous data with 95% confidence intervals (CIs), the fixed effects model was used. Statistical significance was set at a *P*-value of <0.05. We evaluated statistical heterogeneity by employing *P*-values, chi-square, and *I*² tests.²⁰ If significant heterogeneity was found (*P*≤0.10, *I*²>50%), a random effects model was applied to limit the effects of heterogeneity. A subgroup analysis was also performed to reveal the possible reasons for the heterogeneity.

Results Description of studies

A total of 2,203 females requiring hysteroscopy from 25 RCTs were included in this meta-analysis. A flow diagram for the literature search is presented in Figure 1A.

We identified 25 randomized studies comparing misoprostol versus placebo or no medication prior to hysteroscopy. Table 1 summarizes the characteristics of these studies, which include seven studies of operative hysteroscopy,^{8–10,13,14,21,22} 13 studies of diagnostic hysteroscopy,^{16–18,23–32} and five studies on both diagnostic and operative hysteroscopy.^{11,12,15,33,34} Additionally, the route of misoprostol administration was oral (four studies), vaginal (18 studies), sublingual (four studies), or rectal (one study). Table 1 shows that the dose of misoprostol administration prior to hysteroscopy differed considerably among the available trials and the outcomes.

Quality of trials and assessment of publication bias

Two investigators independently assessed the risk of bias of the eligible trials by using the *Cochrane Handbook for Systematic Reviews of Interventions*,¹⁹ and a consensus was reached after discussion. As demonstrated in Figure 1B,

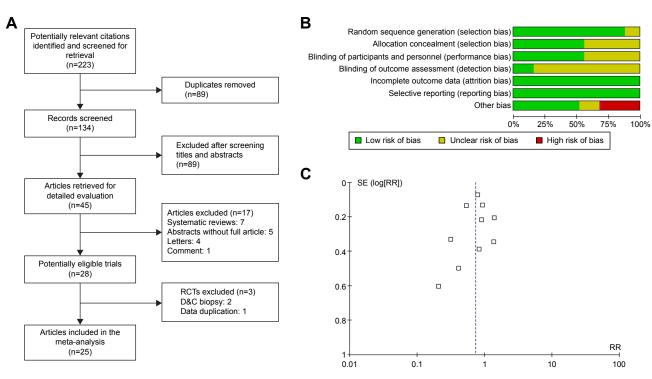


Figure I Flow diagram and quality of the selected study.

Notes: (A) Flow diagram for study selection. (B) Risk of bias assessment. (C) Funnel plot of comparison: need for cervical dilatation. Abbreviations: D&C, dilatation and curettage; RCTs, randomized controlled trials; RR, risk ratio; SE, standard error.

most of the included trials had properly randomized their participants and 60% had adequate randomization allocations. With regard to performance bias, 60% had adequate blinding. All papers were judged to be free of attrition and reporting biases.

As shown in Figure 1C, the funnel plots appeared to be symmetrical, which indicated that there was no obvious publication bias.

Outcomes

Need for cervical dilatation

Data on the need for cervical dilatation before hysteroscopy were reported in ten studies that included a total of 930 females. Due to the high statistical heterogeneity, results were pooled using the random effects model. Compared with placebo or no medication, misoprostol administration prior to hysteroscopy reduced the need for cervical dilatation to a statistically significant degree (RR 0.75; 95% CI 0.58–0.96; *P*=75% Figure 2A).

By subgroup analysis, when only operative hysteroscopy was examined, the need for cervical dilatation in the misoprostol group was significantly decreased compared to the placebo or no medication groups (RR 0.79; 95% CI 0.69-0.91 Figure 3A), while the need for cervical dilatation was not significantly decreased before diagnostic hysteroscopy (RR 0.97; 95% CI 0.80–1.17; *I*²=32% Figure 3B). The need

for cervical dilatation after vaginal misoprostol administration was significantly decreased compared to placebo or no medication (RR 0.68; 95% CI 0.51–0.92; *P*=76% Figure 2B), while after sublingual (RR 0.81; 95% CI 0.22-3.00; I2=84%) Figure 4A) and oral (RR 0.90; 95% CI 0.59–1.38; Figure 4B) misoprostol administration, the need for cervical dilatation was not significantly decreased.

Cervical width

Fourteen trials provided data on the MD in the cervical width before the hysteroscopy. Patients receiving misoprostol appeared to have a significantly greater cervical width compared with placebo or no medication (MD 1.34 mm; 95% CI 0.55-2.14; *I*²=98% Figure 5A). The cervical width after vaginal misoprostol administration was significantly greater than that in the placebo or no medication group (MD 1.64 mm; 95% CI 0.93-2.35; *I*²=95% Figure 5B), but after sublingual (MD 0.40 mm; 95% CI -0.80 to 1.61; I²=98% Figure 6A) or oral (MD -0.20 mm; 95% CI -1.31 to 0.91; Figure 6B) misoprostol administration cervical width was not significantly greater. In addition, in the 200 µg subgroup (MD 2.20 mm; 95% CI 1.21–3.19; *I*²=94% Figure 7A) or the 400 µg subgroup (MD 2.20 mm; 95% CI 1.14–3.26; I²=92% Figure 7B), the cervical width was significantly greater than that in the placebo or no medication group, while it was not

Study (year)	Country	Participants	Setting (operative/	Dose (µg)	Route of	Outcomes
		(females)	diagnostic)		administration	
Atay et al ["]	Turkey	Patients undergoing	Diagnostic +	400	Vaginal	Number of patients with adequate cervical ripening (7 mm hysteroscopic sheath
(1997)		hysteroscopy	operative			or 6 mm Hegar fits), dilatation time, dilatation pain score (in comparison with menstrual pain), cervical bleeding, cervical laceration, uterine perforation (while introducing hysteroscopic sheath)
Preutthipan and	Thailand	Nonpregnant females	Diagnostic +	200	Vaginal	Cervical width. duration of hysteroscopy. need for cervical dilatation. cervical
Herabutya ¹²		before hysteroscopy	operative		0	tear, side effects (mild lower abdominal pain, slight vaginal bleeding, nausea,
(6661)						watery diarrhea, perceived increase in body temperature)
Preutthipan and	Thailand	Nulliparous females	Operative	200	Vaginal	Cervical width, need for cervical dilatation, time for cervical dilatation to
Herabutya ¹³						Hegar 9, duration of operative hysteroscopy, complications (cervical tear,
	:		i			creation of a faise track, uterine perforation)
Ngai et al'° (2001)	Hong Kong	Postmenopausal females	Diagnostic	400	Oral	Cervical dilatation, cumulative force, duration of operation, blood loss, side effects (nausea, dizziness, fatigue, lower abdominal pain, vaginal bleeding,
~						vomiting, diarrhea)
Fung et al ¹⁷	Hong Kong	Postmenopausal females	Diagnostic	800	Vaginal	Extra needed dilatation, cervical width, operative time, operative complications
(2002)						(cervical tear, uterine perforation), side effects (lower abdominal pain, fever, diarrhea)
Thomas et al ¹⁴	Canada	Patients undergoing	Onerative	800	Oral	Time required for dilatation ease of dilatation no complications cervical
(2002)	n7n - n)	hysteroscopy		2	Ð	lacerations perforation, side effects (nausea, bleeding, diarrhea, cramps)
Bisharah et al ⁸	Canada	Nulliparous females	Onerative	100	Sublingual	Baseline cervical diameter degree of difficulty to dilate time to dilate to
(2003)	3				0	9 mm, side effects and complications of the procedure (cervical tear, uterine
						perforation, creation of false passage, bleeding, mild abdominal cramps)
Fernandez et al ⁹	France	Premenopausal females	Operative	200/400/800	Vaginal	Cervical width, subjective ease of cervical dilatation, the time required for
(2004)						dilatation up to Hegar No 10, preoperative pain, complications (perforation, cervical brearation false track)
Barcaite et al ¹⁵	l ithuania	Perimenonausal +	Diagnostic +	400	Vaginal	Number of females who needed extra cervical dilatation, cervical width (no
(2005)		nostmenonalisal females	ODerative		0	Hegar). operative time. complications. side effects (abdominal pain)
Healev et al ¹⁸	Canada	Premenonalisal females	Diagnostic	400	Oral	Need to further dilate the cervix preprocedural dilatation time required to
(2007)	5				5	further dilate cervix. Dostprocedural dilatation. side effects (nausea, vomiting.
~						diarrhea, abdominal pain, menstrual cramps, vaginal bleeding, vaginal spotting,
						headache)
Da Costa et al ²³	Brazil	Postmenopausal females	Diagnostic	200	Vaginal	The need for additional cervical dilation, degree of pain during procedure,
(2008)						procedure duration, side effects (genital bleeding, nausea, vomiting, diarrhea,
						hyperthermia), complications (uterine perforation, false passages, cervical
						lacerations, and infections)
Uckuyu et al ²¹	Turkey	Females who have	Operative	400	Vaginal	Cervical width, complication (uterine perforation, false passages, bleeding cervical
(2008)		undergone cesarean				lacerations), failure rates
		section and no vaginal deliveries				
Valente et al ²⁴	Brazil	Females of reproductive	Diagnostic	400	Vaginal	Pain, side effects (bleeding, nausea, vomiting, diarrhea, fever), complications
(2008)		age				(uterine perforation, creation of a false cervical passage, cervical laceration, infection, cramping, genital discharge)

Force needed to dilate cervix, pain-related measurements, complications (vaginal bleeding, cervical laceration, uterine perforation), side effects (nausea, diarrhea, headache, pelvic cramp, fever, or shivering) The need for cervical dilatation, a pain score on a visual analog scale of 0–10, side effects (nausea, vomiting, diarrhea, increase in body temperature, lower	abdominal pain, or vaginal bleeding) Cervical dilatation, number of females achieving cervical dilatation >5 mm, difficult dilatation, dilatation time, exposure to capsules, frequency of complications, side effects (bleeding, shivering, diarrhea, nausea, vaginal discharge) Cervical dilatation at hysteroscopy, difference in dilatation at recruitment and before hysteroscopy, number of patients achieving cervical dilatation >5 mm, difficult dilatation, exposure to capsules, frequency of preoperative complications, complications within 14 days after hysteroscopy, no adverse effects, lower	bleeding, vaginal discharge Need for cervical dilatation, time required for dilatation, ease of dilatation, complications (cervical tear, uterine perforation, cervical suture) Ease of cervical entry, procedural time, patient acceptability, pain scoring, side effects (nausea, vomiting, abdominal pain, diarrhea, fever, shivering)	Pain score on a visual analog scale of 0–10, surgical time, side effects (nausea, diarrhea, and abdominal pain) Need for cervical dilatation, cervical width, complications (cervical tear, creation of false cervical track, uterine perforation, bleeding), side effects (nausea, diarrhea, and abdominal pain)	,	Cervical width, complications (cervical tear, creation of false cervical track, bleeding) Leeding) Ease of cervical entry, baseline cervical width, pain scoring, procedural time
Vaginal Vaginal	Vaginal Vaginal	Sublingual Vaginal	Oral/vaginal Sublingual	Vaginal Sublingual/rectal	Vaginal Vaginal
400 400	0000'I	200	600/400 200	200 400/400	200 200/400
Diagnostic Diagnostic	Operative Operative	Diagnostic Diagnostic	Diagnostic Diagnostic	Diagnostic + operative Diagnostic + operative	Diagnostic Diagnostic
Postmenopausal and premenopausal females aged 18 years or older Females undergoing hysteroscopy	Premenopausal and postmenopausal females Postmenopausal females	Premenopausal females Females in the reproductive age	Infertile females Premenopausal and postmenopausal females	Postmenopausal females Premenopausal females	Females who have only undergone cesarean section Patients with infertility mtrolled trial.
Canada India	Norway Norway	Turkey Egypt	Mexico Tunisia	India Egypt	Greece Turkey T. randomized cc
Waddell et al ²⁵ (2008) Singh et al ²⁶ (2009)	Oppegaard et al ¹⁰ (2008) Oppegaard et al ¹² (2010)	Mulayim et al ²⁷ (2010) El-Mazny and Abou-Salem ²⁸	(2011) Sordia- Hernández et al ³⁹ (2011) Mathlouthi et al ²⁹ (2011)	Kant et al ³³ (2011) Shawky Moiety and Azzam ³⁴ (2012)	Kalampokas Greece Females v Kalampokas Greece Females v et al ³¹ (2012) undergon Bastu et al ³² Turkey Patients v (2013) Abbreviation: RCT, randomized controlled trial.

A	Study or subgroup	Experim events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, random, 95% Cl	Risk ratio M–H, random, 95% Cl	
	Barcaite et al ¹⁵ (2005)	27	51	53	54	14.4	0.54 (0.42, 0.70)	-	
	Da Costa et al 23 (2008)	10	60	12	60	6.8	0.83 (0.39, 1.78)		
	Fung et al ¹⁷ (2002)	32	47	35	48	14.5	0.93 (0.72, 1.21)	-	
	Healey et al ¹⁸ (2007)	17	30	17	27	11.6	0.90 (0.59, 1.38)		
	Kant et al ³³ (2011)	7	25	22	25	8.2	0.32 (0.17, 0.61)	_ _	
	Mathlouthi et al ²⁹ (2011)	5	54	12	54	4.9	0.42 (0.16, 1.10)		
	Shawky Moiety and Azzam ³⁴ (2012)	0	0	0	0	4.0	Not estimable		
	Mulayim et al ²⁷ (2010)	21	27	14	25	12.0	1.39 (0.93, 2.08)		
	Preutthipan and Herabutya ¹² (1999)	3	46	14	-0 45	3.7	0.21 (0.06, 0.68)		
	Preutthipan and Herabutya ¹³ (2000)	5 55	73	75	79	16.2	0.79 (0.69, 0.91)		
	Singh et al 26 (2009)	15	50	11	50	7.8	1.36 (0.70, 2.67)		
	Thomas et al ¹⁴ (2002)	0	0	0	0	1.0	Not estimable		
	Total (95% CI)		463		467	100	0.75 (0.58, 0.96)		
	Total events	192		265				•	
	Heterogeneity: τ^2 =0.10; χ^2 =35.50, <i>dt</i> Test for overall effect: Z=2.24 (<i>P</i> =0.0		001); <i>I</i> ²=	75%			0.	I I I I I I I I I I I I I I I I I I I)
В	Study or subgroup	Experim events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, random, 95% Cl	Risk ratio M–H, random, 95% Cl	
	Barcaite et al ¹⁵ (2005)	27	51	53	54	20.3	0.54 (0.42, 0.70)	+	
	Da Costa et al ²³ (2008)	10	60	12	60	9.4	0.83 (0.39, 1.78)	_ _	
	Fung et al ¹⁷ (2002)	32	47	35	48	20.3	0.93 (0.72, 1.21)	+	
	Kant et al ³³ (2011)	7	25	22	25	11.3	0.32 (0.17, 0.61)		
	Preutthipan and Herabutya ¹² (1999)	3	46	14	45	5.0	0.21 (0.06, 0.68)		
	Preuthipan and Herabutya ¹³ (2000)	55	73	75	79	22.8	0.79 (0.69, 0.91)	-	
	Singh et al ²⁶ (2009)	15	50	11	50	10.8	1.36 (0.70, 2.67)	- +- -	
	Total (95% CI)		352		361	100	0.68 (0.51, 0.92)	•	
	Total events	149		222					

Heterogeneity: τ^2 =0.10; χ^2 =25.28, *df*=6 (*P*<0.0003); *l*²=76% Test for overall effect: *Z*=2.53 (*P*=0.01)

Figure 2 Comparison of the need for cervical dilatation between the misoprostol group and the placebo or no medication group, including both operative and diagnostic hysteroscopy studies.

Notes: (A) Irrespective of the route of misoprostol administration. (B) Vaginal misoprostol administration.

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

in the 800 μg subgroup (MD 0.16 mm; 95% CI –0.33 to 0.66; *I*²=0% Figure 8A) or the 1,000 μg subgroup (MD 0.60 mm; 95% CI –0.73 to 1.94; *I*²=76% Figure 8B).

Complication of hysteroscopy

There was no significant difference between the misoprostol group and the placebo or no medication group when assessing the uterine perforation rate. However, the analysis of 14 trials, including 1,358 females, showed that the use of misoprostol prior to hysteroscopy resulted in a statistically significant decrease in the rate of cervical lacerations compared to placebo or no medication. When analyzing false passage, the risk was also significantly lower in the misoprostol group. All effect estimates for the above hysteroscopy complications with 95% CIs and *P*-values are shown in Table 2.

In addition, compared with placebo or no medication, hysteroscopy complications (cervical lacerations and false

passage) after vaginal misoprostol (RR 0.36; 95% CI, 0.19–0.66; ten trials, 848 patients in Figure 9A; RR 0.37; 95% CI, 0.16–0.88; six trials, 520 patients in Figure 10A) administration were significantly decreased, but not after sublingual and oral (RR 0.48; 95% CI, 0.22–1.03; four trials, 381 patients in Figure 9B; RR 0.2; 95% CI, 0.02–1.66; one trial, 54 patients in Figure 10B) misoprostol administration.

0.01

0.1

Favors

experimental

10

Favors

control

100

Side effects of misoprostol

The pooled analysis ruled out that misoprostol side effects such as mild abdominal pain, bleeding, nausea, diarrhea, and fever were significantly more frequent in the misoprostol group compared with placebo or no medication. These side effects were generally minor, transient, and tolerable without the need for further treatment. All the patients were discharged on the day of the procedure.

0.5 0.7 1 1.5 Favors Favors experimental control Risk ratio
Favors Favors experimental control Risk ratio
Favors Favors experimental control Risk ratio
Favors Favors experimental control Risk ratio
M–H, fixed, 95% Cl
•

Figure 3 Comparison of the need for cervical dilatation between the misoprostol group and the placebo or no medication group, including vaginal, oral, sublingual administration routes.

Notes: (A) Operative hysteroscopy. (B) Diagnostic hysteroscopy.

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

All effect estimates for misoprostol side effects with 95% CIs and *P*-values are shown in Table 2.

Discussion

This meta-analysis indicates that misoprostol prior to hysteroscopy may facilitate cervical dilatation. Misoprostol, when given vaginally, was more effective when compared with oral and sublingual administration. The mean cervical width was significantly larger in the misoprostol group. In addition, hysteroscopy complications such as cervical laceration and false passage were significantly less frequent in the misoprostol group with the exception of uterine perforation.

A	Study or subgroup	Experim events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, random, 95% Cl	Risk ratio M–H, ran	o dom, 95% Cl
	Mathlouthi et al ²⁹ (2011)	5	54	12	54	44.3	0.42 (0.16, 1.10)		
	Mulayim et al 27 (2010)	21	27	14	25	55.7	1.39 (0.93, 2.08)	- +	-
	Total (95% CI)		81		79	100	0.81 (0.22, 3.00)		
	Total events	26		26			,,		
	Heterogeneity: τ^2 =0.75; Test for overall effect: Z=			0.01); /²=84	4%			0.01 0.1 1 Favors experimental	10 100 Favors control
В	Study or subgroup	Experim events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% Cl	Risk ratio M–H, fixe	o ed, 95% Cl
	Healey et al ¹⁸ (2007)	17	30	17	27	100	0.90 (0.59, 1.38)		_
	Total (95% CI) Total events Heterogeneity: not applic Test for overall effect: Z=		30	17	27	100	0.90 (0.59, 1.38)	0.1 0.2 0.5 1	► 2 5 10
		-00 (7 -0	.00)					Favors experimental	Favors control

Figure 4 Comparison of the need for cervical dilatation between the misoprostol group and the placebo or no medication group. Notes: (A) Sublingual misoprostol administration. (B) Oral misoprostol administration. Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

Study or	Experi			Contro			Weight		Mean difference
subgroup	mean	SD	Total	mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Barcaite et al ¹⁵ (2005)	7.6	1.4	51	5	1.1	54	5.5	2.60 (2.12, 3.08)	
Bastu et al ³² (2013)	5.85	1.08	20	4.15	1.63	20	5.3	1.70 (0.84, 2.56)	
Bastu et al ³² (2013)	6.5	0.51	20	4.15	1.63	20	5.3	2.35 (1.60, 3.10)	
Bisharah et al ⁸ (2003)	4	0.1	20	4.2	0.2	20	5.6	-0.20 (-0.30, -0.10)	-
Fernandez et al ⁹ (2004)	6.3	1.4	12	6.1	1.4	13	5.1	0.20 (-0.90, 1.30)	_
Fernandez et al ⁹ (2004)	5.7	2	12	6.1	1.4	13	4.8	-0.40 (-1.76, 0.96)	
Fernandez et al ⁹ (2004)	6.8	2.1	10	6.1	1.4	13	4.7	0.70 (-0.81, 2.21)	
Fung et al ¹⁷ (2002)	5	1.2	47	4.9	1.4	48	5.5	0.10 (-0.42, 0.62)	- - -
Kalampokas et al ³¹ (2012)	6.6	1.3	30	5.5	0.9	25	5.5	1.10 (0.52, 1.68)	
Kant et al ³³ (2011)	7.7	1.7	25	4.5	1.8	25	5.2	3.20 (2.23, 4.17)	
Shawky Moiety and Azzam ³⁴ (2012)	4.25	0.98	71	3.22	1.03	70	5.6	1.03 (0.70, 1.36)	
Shawky Moiety and Azzam ³⁴ (2012)	4.27	0.79	71	3.22	1.03	70	5.6	1.05 (0.75, 1.35)	-
Ngai et al ¹⁶ (2001)	4.2	1.7	18	4.4	1.6	16	5.1	-0.20 (-1.31, 0.91)	
Oppegaard et al ¹⁰ (2008)	6.4	2.4	34	4.8	2	31	5.1	1.60 (0.53, 2.67)	
Oppegaard et al ¹⁰ (2008)	3.4	2.7	11	4.9	1.5	10	4.3	-1.50 (-3.35, 0.35)	
Oppegaard et al ²² (2010)	5.7	1.6	33	4.7	1.5	34	5.4	1.00 (0.26, 1.74)	
Preutthipan and Herabutya ¹² (1999)	7	1	46	3.8	1.2	45	5.5	3.20 (2.75, 3.65)	-
Preutthipan and Herabutya ¹³ (2000)	7.3	0.7	73	3.8	1.1	79	5.6	3.50 (3.21, 3.79)	-
Uckuyu et al ²¹ (2008)	6.5	0.8	32	3	0.6	28	5.6	3.50 (3.14, 3.86)	-
Total (95% CI)			636			634	100	1.34 (0.55, 2.14)	•
Heterogeneity: τ^2 =2.93; χ^2 =1,172.94	, <i>df</i> =18	(P<0.0	00001);	l²=98%					-4 -2 0 2
Test for overall effect: Z=3.31 (P=0.0	009)								Favors Favors experimental control

Study or	Experi	imenta	al	Contro	ol		Weight	Mean difference	Mean difference
subgroup	mean	SD	Total	mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Barcaite et al ¹⁵ (2005)	7.6	1.4	51	5	1.1	54	7.2	2.60 (2.12, 3.08)	
Bastu et al ³² (2013)	5.85	1.08	20	4.15	1.63	20	6.8	1.70 (0.84, 2.56)	
Bastu et al ³² (2013)	6.5	0.51	20	4.15	1.63	20	6.9	2.35 (1.60, 3.10)	
Fernandez et al ⁹ (2004)	6.8	2.1	10	6.1	1.4	13	5.6	0.70 (-0.81, 2.21)	_ _
Fernandez et al ⁹ (2004)	6.3	1.4	12	6.1	1.4	13	6.4	0.20 (-0.90, 1.30)	_ -
Fernandez et al ⁹ (2004)	5.7	2	12	6.1	1.4	13	5.9	-0.40 (-1.76, 0.96)	
Fung et al ¹⁷ (2002)	5	1.2	47	4.9	1.4	48	7.2	0.10 (-0.42, 0.62)	
Kalampokas et al ³¹ (2012)	6.6	1.3	30	5.5	0.9	25	7.1	1.10 (0.52, 1.68)	
Kant et al ³³ (2011)	7.7	1.7	25	4.5	1.8	25	6.6	3.20 (2.23, 4.17)	
Oppegaard et al ¹⁰ (2008)	3.4	2.7	11	4.9	1.5	10	5.0	-1.50 (-3.35, 0.35)	
Oppegaard et al ¹⁰ (2008)	6.4	2.4	34	4.8	2	31	6.4	1.60 (0.53, 2.67)	_ _
Oppegaard et al ²² (2010)	5.7	1.6	33	4.7	1.5	34	6.9	1.00 (0.26, 1.74)	_ _
Preuthipan and Herabutya ¹² (1999)	7	1	46	3.8	1.2	45	7.3	3.20 (2.75, 3.65)	
Preutthipan and Herabutya ¹³ (2000)	7.3	0.7	73	3.8	1.1	79	7.4	3.50 (3.21, 3.79)	-
Uckuyu et al ²¹ (2008)	6.5	0.8	32	3	0.6	28	7.4	3.50 (3.14, 3.86)	-
Total (95% CI)			456			458	100	1.64 (0.93, 2.35)	•
Heterogeneity: τ^2 =1.74; χ^2 =269.25, o	df=14 (F	> <0.00	001); <i>I</i> ²	=95%					
Test for overall effect: Z=4.53 (P<0.0	00001)								
									Favors Favors experimental control

Figure 5 Comparison of the cervical width prior to hysteroscopy between the misoprostol group and the placebo or no medication group. Notes: (A) Irrespective of the route of misoprostol administration. (B) Vaginal misoprostol administration.

Abbreviations: CI, confidence interval; *df*, degrees of freedom; IV, independent variable; SD, standard deviation.

The main outcome such as cervical width has a high degree of heterogeneity (I^2 =98% Figure 5A) that could not be explained by either subgroup analysis or sensitivity analysis because of clinical diversity, including different populations under study, different regimens, doses, time intervals, and administration routes of misoprostol. However, when only patients pretreated with misoprostol vaginally were examined, the cervical width was significantly larger in the misoprostol group. Furthermore, the subgroup analysis indicated that the lower doses of 200 or 400 µg vaginal misoprostol produced a more beneficial effect in the outcome of cervical width than the higher doses. Therefore, 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.

Because the type of hysteroscopy is closely associated with the diameter of cervical dilatation, we conducted a subgroup analysis based on the type of hysteroscopy. When only diagnostic hysteroscopy was examined, there appeared to a lower need for cervical dilation, but this did not reach statistical significance. However, it appeared that females receiving misoprostol prior to operative hysteroscopy were more likely to avoid the need for cervical dilation.

•	Study or subgroup	Exper mean		tal Total	Contr mean		Total	•	Mean difference IV, random, 95% Cl	Mean differen IV, random, 95	
	Bisharah et al ⁸ (2003)	4	0.1	20	4.2	0.2	20	50.9	-0.20 (-0.30, -0.10)	-	
	Shawky Moiety and Azzam ³⁴ (2012)	4.25	0.98	71	3.22	1.03	70	49.1	1.03 (0.70, 1.36)		
	Total (95% CI) Heterogeneity: τ^2 =0.74; χ^2 =48.52, <i>df</i> =1 Test for overall effect: <i>Z</i> =0.66 (<i>P</i> =0.51)	(<i>P</i> <0.00	0001);	91 /²=989	6		90	100	0.40 (–0.80, 1.61)	Favors	5 1 Favors control
;	Study or subgroup	Exper mean			Contr mean		Total	•	Mean difference IV, fixed, 95% Cl	Mean difference IV, fixed, 95% CI	
3	· · · · , ·						Total	•			

Figure 6 Comparison of the cervical width prior to hysteroscopy between the misoprostol group and the placebo or no medication group. Notes: (A) Sublingual misoprostol administration. (B) Oral misoprostol administration.

Abbreviations: CI, confidence interval; df, degrees of freedom; IV, independent variable; SD, standard deviation.

Thus, misoprostol appears to be more beneficial for operative hysteroscopy.

The route of misoprostol administration for cervical dilatation can be oral, vaginal, or sublingual. Among the three routes, vaginal administration has higher bioavailability,³⁵ less severe gastrointestinal side effects, and longer sustained effect.³⁶ Batukan et al found that vaginal administration was more effective than the oral route for preoperative cervical ripening,³⁷ while other studies found no difference between the two routes,³⁸ or among the three routes.³⁹ In the present study, compared with the placebo or no medication group, the need for cervical dilatation, the mean cervical width,

4	Study or	Exper mean			Contr		Total		Mean difference	Mean diffe	
	subgroup	mean	30	Total	mean	30	Total	(%)	IV, random, 95% CI	IV, randon	n, 95% CI
	Bastu et al ³² (2013)	5.85	1.08	20	4.15	1.63	20	16.2	1.70 (0.84, 2.56)		
	Fernandez et al ⁹ (2004)	6.3	1.4	12	6.1	1.4	13	15.0	0.20 (-0.90, 1.30)	_	-
	Kalampokas et al ³¹ (2012)	6.6	1.3	30	5.5	0.9	25	17.3	1.10 (0.52, 1.68)		
	Kant et al ³³ (2011)	7.7	1.7	25	4.5	1.8	25	15.6	3.20 (2.23, 4.17)		
	Preutthipan and Herabutya ¹² (1999)	7	1	46	3.8	1.2	45	17.7	3.20 (2.75, 3.65)		+
	Preutthipan and Herabutya ¹³ (2000)	7.3	0.7	73	3.8	1.1	79	18.1	3.50 (3.21, 3.79)		•
	Total (95% CI)			206			207	100	2.20 (1.21, 3.19)		•
	Heterogeneity: τ^2 =1.38; γ^2 =85.63, df=5	(<i>P</i> <0.00	001);	² =94%	5						
	Test for overall effect: Z=4.35 (P<0.000	1)	,,							-4 -2 0	2 4
	Υ. Υ.	,								Favors experimental	Favors control

3	Study or	Exper	iment	al	Contr	ol		Weight	Mean difference		Mear	n differe	nce	
	subgroup	mean	SD	Total	mean	SD	Total	(%)	IV, random, 95% CI		IV, ra	ndom, 9)5% C	3
	Barcaite et al ¹⁵ (2005)	7.6	1.4	51	5	1.1	54	27.2	2.60 (2.12, 3.08)				•	
	Bastu et al ³² (2013)	6.5	0.51	20	4.15	1.63	20	25.2	2.35 (1.60, 3.10)				-	
	Fernandez et al ⁹ (2004)	5.7	2	12	6.1	1.4	13	19.5	-0.40 (-1.76, 0.96)					
	Uckuyu et al ²¹ (2008)	6.5	0.8	32	3	0.6	28	28.0	3.50 (3.14, 3.86)				•	
	Total (95% CI)			115			115	100	2.20 (1.14, 3.26)			•	•	
	Heterogeneity: τ^2 =1.01; χ^2 =36.87, <i>df</i> =3	(P<0.00	001);	I2=92%	6								+-	+
	Test for overall effect: Z=4.07 (P<0.0001)	,.							-10	-5	0	5	10
	, ,									ex	Favor perime			Favors control

Figure 7 Comparison of the cervical width prior to hysteroscopy between the misoprostol group and the placebo or no medication group. **Notes:** Vaginal administration of misoprostol (**A**) 200 μg and (**B**) 400 μg.

Abbreviations: Cl, confidence interval; df, degrees of freedom; IV, independent variable; SD, standard deviation.

Study or subgroup	Experi mean	mental SD	Total	Control mean	SD	Total	Weight (%)	Mean difference IV, fixed, 95% CI	Mean difference IV, fixed, 95% CI
Fernandez et al ⁹ (2004)	6.8	2.1	10	6.1	1.4	13	10.8	0.70 (-0.81, 2.21)	
Fung et al ¹⁷ (2002)	5	1.2	47	4.9	1.4	48	89.2	0.10 (-0.42, 0.62)	-#-
Total (95% CI)			57			61	100	0.16 (–0.33, 0.66)	•
Heterogeneity: $\chi^2=0.54$, a	lf=1 (P=0.	46); /²=	=0%					_	
Test for overall effect: Z=	0.65 (P=0.	51)							–2 –1 0 1 2 Favors Favors
									experimental control
Study or subgroup	Experi mean	mental SD	Total	Control mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Oppegaard et al ¹⁰ (2008)	3.4	2.7	11	4.9	1.5	10	24.4	-1.50 (-3.35, 0.35)	_ _
Oppegaard et al ¹⁰ (2008)	6.4	2.4	34	4.8	2	31	35.4	1.60 (0.53, 2.67)	│ — _ ∎—
Oppegaard et al ²² (2010)	5.7	1.6	33	4.7	1.5	34	40.1	1.00 (0.26, 1.74)	
Total (95% CI)			78			75	100	0.60 (–0.73, 1.94)	-
Listeregeneity =2-1.01;	² =8.19, df	=2 (P=	0.02); <i>I</i> 2:	=76%				—	+ + + + - +
Heterogeneity: τ^2 =1.01; χ									
Test for overall effect: $Z=$		38)							-4 -2 0 2 Favors Favors

Figure 8 Comparison of the cervical width prior to hysteroscopy between the misoprostol group and the placebo or no medication group. **Notes:** Vaginal misoprostol administration (**A**) 800 µg and (**B**) 1,000 µg.

Abbreviations: Cl, confidence interval; df, degrees of freedom; IV, independent variable; SD, standard deviation.

and hysteroscopy complications (cervical laceration and false passage) after vaginal misoprostol administration reached statistical significance, but they did not after sublingual and oral misoprostol administration. Therefore, the vaginal route appeared to be superior to the oral or sublingual routes.

To determine the optimal doses of vaginal misoprostol administration, we performed another subgroup analysis. Compared with the placebo or no medication group, the mean cervical width after vaginal misoprostol administration was significantly greater in the 200 and 400 μ g subgroups, while in the 800 and 1,000 μ g subgroups, the mean cervical width was not significantly different. Therefore, 200 or 400 μ g of vaginal misoprostol prior to hysteroscopy is the optimal regimen.

It should be pointed out that all the misoprostol side effects such as diarrhea, fever, nausea, mild abdominal pain, and bleeding are significantly increased after the use of misoprostol. However, these side effects are generally minor, transient, and well tolerated by patients. Misoprostol side effects are related to dosage, interval, and route of administration. Increasing the dose and interval of vaginal misoprostol does not improve the effect on cervical dilatation but does increase the side effects.²⁸ In addition, misoprostol, when administered vaginally, has fewer side effects compared with oral or sublingual administration.^{15,38,40}

Compared with the meta-analysis by Polyzos et al⁴¹ and Gkrozou et al⁴² our meta-analysis identified 25 eligible

Table 2 Effect estimates on complication	ns of hysteroscopy an	d side effects of misoprostol
--	-----------------------	-------------------------------

Complication	Studies (number	Relative risk or mean	P-value	
	of participants)	difference (95% CI)		
I.I Cervical tear	14 (1,358)	0.46 (0.30, 0.73)	0.0008	
1.2 Uterine perforation	9 (885)	0.67 (0.29, 1.53)	0.34	
1.3 False passage	7 (628)	0.33 (0.15, 0.74)	0.007	
2.1 Mild abdominal pain	14 (1,423)	5.49 (3.76, 8.00)	< 0.00001	
2.2 Bleeding	(1,150)	6.97 (3.95, 12.29)	< 0.00001	
2.3 Nausea	12 (1,164)	2.26 (1.42, 3.61)	0.0006	
2.4 Diarrhea	11 (1,256)	6.53 (3.23, 13.22)	< 0.00001	
2.5 Fever	7 (786)	6.36 (2.23, 18.13)	0.0005	

Note: I, complications of hysteroscopy; 2, side effects of misoprostol. **Abbreviation:** Cl. confidence interval.

Study or subgroup	Experin events		Control events		Weight (%)	Risk ratio M–H, fixed, 95% C	I	Risk ra M–H, fi	itio ixed, 95% Cl	
Atay et al ¹¹ (1997)	3	22	8	21	23.3	0.36 (0.11, 1.17)				
Barcaite et al ¹⁵ (2005)	0	51	0	54		Not estimable				
Da Costa et al ²³ (2008)	5	60	4	60	11.4	1.25 (0.35, 4.43)		_		
Fernandez et al ⁹ (2004)	0	34	1	13	6.1	0.13 (0.01, 3.08)				
Kalampokas et al ³¹ (2012)	1	30	2	25	6.2	0.42 (0.04, 4.33)				
Oppegaard et al ¹⁰ (2008)	0	45	1	41	4.5	0.30 (0.01, 7.27)				
Preutthipan and Herabutya ¹² (1999)	0	46	2	45	7.2	0.20 (0.01, 3.97)				
Preutthipan and Herabutya ¹³ (2000)	1	73	9	75	25.3	0.11 (0.01, 0.88)			_	
Uckuyu et al ²¹ (2008)	1	32	4	28	12.1	0.22 (0.03, 1.84)	_			
Waddell et al ²⁵ (2008)	0	43	1	50	4.0	0.39 (0.02, 9.25)				
Total (95% CI)		436		412	100	0.36 (0.19, 0.66)		•	•	
Total events	11		32							
Heterogeneity: χ^2 =5.73, <i>df</i> =8 (<i>P</i> =0.6 Test for overall effect: Z=3.30 (<i>P</i> =0.6	<i>,</i> ,	, 0					0.005 F	0.1 =avors	1 10 Favors	20
0 , , , ,	<i>,</i> ,	, D					F			20
Test for overall effect: $Z=3.30$ ($P=0.0$ Study or	(DO10) Experin	nental	Control		Weight	Risk ratio	Fexpe	Favors erimental Risk ra	Favors control	
Test for overall effect: Z=3.30 (P=0.0)010)	nental Total	Control events		(%)		Fexpe	Favors erimental Risk ra	Favors control	
Test for overall effect: $Z=3.30$ ($P=0.0$ Study or	(DO10) Experin	nental				Risk ratio	Fexpe	Favors erimental Risk ra	Favors control	
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup	Experin events	nental Total	events	Total	(%)	Risk ratio M–H, fixed, 95% C	Fexpe	Favors erimental Risk ra	Favors control	
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al [®] (2003)	Experin events	nental Total 20	events 0	Total 20	(%) 2.6	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52)	Fexpe	Favors erimental Risk ra	Favors control	1
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al ⁸ (2003) Shawky Moiety and Azzam ³⁴ (2012)	Experin events 1 3	nental Total 20 71	events 0 9	Total 20 70	(%) 2.6 46.5	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52) 0.33 (0.09, 1.16)	Fexpe	Favors erimental Risk ra	Favors control	1
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al ⁸ (2003) Shawky Moiety and Azzam ³⁴ (2012) Mulayim et al ²⁷ (2010)	Experin events 1 3 4	nental Total 20 71 27	events 0 9 1	Total 20 70 25	(%) 2.6 46.5 5.3	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52) 0.33 (0.09, 1.16) 3.70 (0.44, 30.94)	Fexpe	Favors erimental Risk ra	Favors control	1
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al ⁸ (2003) Shawky Moiety and Azzam ³⁴ (2012) Mulayim et al ²⁷ (2010) Thomas et al ¹⁴ (2002) Total (95% CI) Total events	Experin events 1 3 4 1	nental Total 20 71 27 73 191	events 0 9 1	Total 20 70 25 75	(%) 2.6 46.5 5.3 45.6	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52) 0.33 (0.09, 1.16) 3.70 (0.44, 30.94) 0.11 (0.01, 0.88)	Fexpe	Favors erimental Risk ra	Favors control	1
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al ⁸ (2003) Shawky Moiety and Azzam ³⁴ (2012) Mulayim et al ²⁷ (2010) Thomas et al ¹⁴ (2002) Total (95% CI) Total events Heterogeneity: χ^2 =7.11, <i>df</i> =3 (P=0.0	Experin events 1 3 4 1 9; /2=58'	nental Total 20 71 27 73 191	events 0 9 1 9	Total 20 70 25 75	(%) 2.6 46.5 5.3 45.6	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52) 0.33 (0.09, 1.16) 3.70 (0.44, 30.94) 0.11 (0.01, 0.88)	F exp(Favors erimental Risk ra M–H, fi	Favors control	-
Test for overall effect: Z=3.30 (P=0.0 Study or subgroup Bisharah et al ⁸ (2003) Shawky Moiety and Azzam ³⁴ (2012) Mulayim et al ²⁷ (2010) Thomas et al ¹⁴ (2002) Total (95% CI) Total events	Experin events 1 3 4 1 9; /2=58'	nental Total 20 71 27 73 191	events 0 9 1 9	Total 20 70 25 75	(%) 2.6 46.5 5.3 45.6	Risk ratio M–H, fixed, 95% C 3.00 (0.13, 69.52) 0.33 (0.09, 1.16) 3.70 (0.44, 30.94) 0.11 (0.01, 0.88)	F expr I 0.01	Favors erimental Risk ra	Favors control	

Figure 9 The complication of hysteroscopy: cervical laceration in the misoprostol group compared to the placebo or no medication group. Notes: (A) Vaginal misoprostol administration. (B) Sublingual and oral misoprostol administration. Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

studies that included more RCT studies. They had different emphasis such as menopausal status. Polyzos et al concluded that misoprostol may have a role as a cervical-ripening agent prior to hysteroscopy, and the efficacy of misoprostol is related to the menopausal status of patients.⁴¹ Whereas our meta-analysis shows that the efficacy of misoprostol is related to the type of hysteroscopy and route of administration. Although Gkrozou et al concluded that neither the need for cervical dilatation nor the complication of hysteroscopy was different between the misoprostol group and the placebo group.⁴² Our meta-analysis shows that females may experience substantial benefits after pretreatment with misoprostol, especially prior to operative hysteroscopy and vaginal administration.

However, it is a fact that, although there have been 25 RCTs published to date, the heterogeneity among the regimens, doses, time intervals, and route of administration makes analysis of the data very difficult. Ultimately, it prevented us from providing a solid guideline regarding the

optimal schedule of misoprostol administration, especially in patients who differ in terms of parity (nulliparous or parous), means of delivery (vaginal delivery or cesarean section), and estrogen status (pre- or postmenopausal period). Future RCTs covering more study subjects from carefully selected populations and a uniform administration route and dosage schedule of misoprostol should be performed to identify the ideal conditions for the use of misoprostol prior to hysteroscopy.

Conclusion

The use of misoprostol prior to hysteroscopy may facilitate cervical dilatation and decrease hysteroscopy complications (cervical laceration and false passage). On the other hand, the side effects of misoprostol were relatively mild and insignificant. Our meta-analysis recommends for obstetricians and therapists that the regimen of 200 or 400 μ g vaginal misoprostol may be optimal, especially prior to operative hysteroscopy.

Α	Study or subgroup	Experim events	nental Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% C	Risk ratio I M–H, fixe	o ed, 95% Cl	
	Da Costa et al ²³ (2008)	3	60	4	60	22.4	0.75 (0.18, 3.21)			
	Fernandez et al ⁹ (2004)	0	34	1	13	12.0	0.13 (0.01, 3.08)		<u> </u>	
	Kalampokas et al ³¹ (2012)	1	30	1	25	6.1	0.83 (0.05, 12.66)			
	Oppegaard et al ¹⁰ (2008)	0	45	2	41	14.6	0.18 (0.01, 3.70)			
	Preutthipan and Herabutya ¹³ (2000)	1	73	5	79	26.9	0.22 (0.03, 1.81)	_	_	
	Uckuyu et al ²¹ (2008)	1	32	3	28	17.9	0.29 (0.03, 2.65)		<u> </u>	
	Total (95% CI)		274		246	100	0.37 (0.16, 0.88)	•		
	Total events	6		16						
	Heterogeneity: χ^2 =2.15, df=5 (P=0.8)	3); /²=0%						├ ─── ├ ───	<u> </u>	
	Test for overall effect: Z=2.26 (P=0.0	02)						0.005 0.1 Favors experimental	1 10 Favors control	200
в	Study or subgroup	Experimental events Total		Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% C	Risk ratio	o ad, 95% Cl	

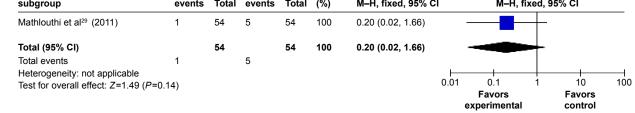


Figure 10 The complication of hysteroscopy: false passage in the misoprostol group compared to the placebo or no medication group. Notes: (A) Vaginal misoprostol administration. (B) Sublingual and oral misoprostol administration.

Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Acknowledgments

This work was sponsored by the Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents. The study sponsors had no involvement in the collection, analysis, and interpretation of data, or in the writing of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

- 1. Birinyi L, Daragó P, Török P, et al. Predictive value of hysteroscopic examination in intrauterine abnormalities. *Eur J Obstet Gynecol Reprod Biol.* 2004;115(1):75–79.
- Wortman M, Daggett A, Ball C. Operative hysteroscopy in an officebased surgical setting: review of patient safety and satisfaction in 414 cases. J Minim Invasive Gynecol. 2013;20(1):56–63.
- Valle RF, Sciarra JJ. Current status of hysteroscopy in gynecologic practice. *Fertil Steril*. 1979;32(6):619–632.
- 4. Bradley LD. Complications in hysteroscopy: prevention, treatment and legal risk. *Curr Opin Obstet Gynecol*. 2002;14(4):409–415.
- Lin CJ, Chien SC, Chen CP. The use of misoprostol in termination of second-trimester pregnancy. *Taiwan J Obstet Gynecol*. 2011;50(3): 275–282.
- Thaisomboon A, Russameecharoen K, Wanitpongpan P, Phattanachindakun B, Changnoi A. Comparison of the efficacy and safety of titrated oral misoprostol and a conventional oral regimen for cervical ripening and labor induction. *Int J Gynaecol Obstet*. 2012;116(1): 13–16.

- Blanchard K, Clark S, Winikoff B, Gaines G, Kabani G, Shannon C. Misoprostol for women's health: a review. *Obstet Gynecol*. 2002;99(2): 316–332.
- 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(3):390–391.
- Fernandez H, Alby JD, Tournoux C, et al. 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(7):1618–1621.
- Oppegaard KS, Nesheim BI, Istre O, Qvigstad E. Comparison of selfadministered vaginal misoprostol versus placebo for cervical ripening prior to operative hysteroscopy using a sequential trial design. *BJOG*. 2008;115(5):663, e1–e9.
- 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(1):47–49.
- Preutthipan S, Herabutya Y. A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. *Obstet Gynecol*. 1999;94(3):427–430.
- Preutthipan S, Herabutya Y. Vaginal misoprostol for cervical priming before operative hysteroscopy: a randomized controlled trial. *Obstet Gynecol.* 2000;96(6):890–894.
- 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(5):876–879.
- 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(2): 141–145.
- Ngai SW, Chan YM, Ho PC. The use of misoprostol prior to hysteroscopy in postmenopausal women. *Hum Reprod.* 2001;16(7): 1486–1488.

- Fung TM, Lam MH, Wong SF, Ho LC. A randomized placebo-controlled trial of vaginal misoprostol for cervical priming before hysteroscopy in postmenopausal women. *BJOG*. 2002;109(5):561–565.
- 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(8):648–652.
- Higgins JPT, Douglas GA. Assessing risk of bias in included studies. In: Higgins JPT, Sally G, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons Ltd; 2008: 188–235.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a metaanalysis. Stat Med. 2002;21(11):1539–1558.
- 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(4):472–475.
- 22. 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 randomized controlled trial. *BJOG*. 2010;117(1):53–61.
- 23. 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(1):67–73.
- 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(4):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(6):739–744.
- 26. 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(1):37–40.
- 27. 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(7):2400–2404.
- 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(4):962–965.
- Mathlouthi N, Saodi O, Ben Temime R, Makhlouf T, Attia L, Chachia A. Sublingual misoprostol for cervical ripening before diagnostic hysteroscopy: a randomized and prospective study about 108 cases. *Tunis Med.* 2011;89(11):825–829.

- Sordia-Hernández LH, Rosales-Tristan E, Vazquez-Mendez J, et al. Effectiveness of misoprostol for office hysteroscopy without anesthesia in infertile patients. *Fertil Steril*. 2011;95(2):759–761.
- Kalampokas E, Sofoudis C, Antonogeorgos G, et al. A randomized controlled trial for cervical priming using vaginal misoprostol prior to hysteroscopy in women who have only undergone cesarean section. *Arch Gynecol Obstet*. 2012;286(4):853–857.
- 32. Bastu E, Celik C, Nehir A, Dogan M, Yuksel B, Ergun B. Cervical priming before diagnostic operative hysteroscopy in infertile women: a randomized, double-blind, controlled comparison of 2 vaginal misoprostol doses. *Int Surg.* 2013;98(2):140–144.
- Kant A, Divyakumar, Priyambada U. A randomized trial of vaginal misoprostol for cervical priming before hysteroscopy in postmenopausal women. *J Midlife Health*. 2011;2(1):25–27.
- Shawky Moiety FM, Azzam A. Prostaglandins prior to hysteroscopy. *Gynecol Surg.* 2012;9(1):169–173.
- Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *Int J Gynaecol Obstet*. 2007;99(2):S160–S167.
- Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod*. 2002;17(2):332–336.
- 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(4):966–973.
- 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(8):2167–2170.
- Lee YY, Kim TJ, Kang H, et al. 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(8):1942–1948.
- Tanha FD, Salimi S, Ghajarzadeh M. Sublingual versus vaginal misoprostol for cervical ripening before hysteroscopy: a randomized clinical trial. *Arch Gynecol Obstet*. 2013;287(5):937–940.
- Polyzos NP, Zavos A, Valachis A, et al. Misoprostol prior to hysteroscopy in premenopausal and post-menopausal women. A systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(4):393–404.
- 42. Gkrozou F, Koliopoulos G, Vrekoussis T, et al. 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(1):17–23.

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peerreviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are the features of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/drug-design-development-and-therapy-journal

Dovepress