Use of Misoprostol Before Hysteroscopy: A Systematic Review

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Abstract

Objective: To evaluate the effectiveness of administering misoprostol prior to hysteroscopy in achieving cervical dilatation and reducing complications including cervical laceration.

Data Sources: Computerized searches of MEDLINE, PubMed and EMBASE were conducted using the key words "hysteroscopy" and "misoprostol." References from identified publications were manually searched and cross-referenced to identify additional relevant articles.

Study Selection: We included randomized clinical trials that compared women undergoing hysteroscopy who received misoprostol before the procedure with those who received placebo. Studies were excluded if there was no control group, if placebo was not used, if women were not randomized, or if only the abstract was available. Ten of 19 articles identified met the criteria for systematic review.

Data Extraction and Synthesis: The two co-authors separately abstracted data. Any differences in data abstraction were resolved through discussion, and a consensus was reached. QUORUM guidelines for meta-analyses and systematic reviews of randomized controlled trials were followed.

In premenopausal women, misoprostol before hysteroscopy resulted in a reduced need for further cervical dilatation (relative risk [RR] = 0.61; 95% confidence interval [CI] = 0.51, 0.73), a lower rate of cervical laceration (RR 0.22; 95% CI 0.09, 0.56) and increased cervical dilatation (weighted mean difference 2.64; 95% CI 1.73, 3.54). In premenopausal women, misoprostol also resulted in a higher rate of side effects, including vaginal bleeding (RR 11.09; 95% CI 3.08, 40.00), cramping (RR 7.98; 95% CI 3.38, 18.84), and elevated temperature (RR 5.24; 95% CI 1.37, 20.09). For every four premenopausal women who received misoprostol prior to hysteroscopy, one woman avoided the need for further cervical dilatation. For every 12 premenopausal women receiving misoprostol, one cervical laceration was avoided.

Conclusion: In premenopausal women, misoprostol appears to be promising as a cervical ripening agent prior to hysteroscopy, although further research is needed to identify the ideal dose, route, and timing. Further research in postmenopausal women or those receiving GnRH agonists is also needed, to determine whether misoprostol is effective in cervical ripening in this population.

Key Words: Misoprostol, hysteroscopy, meta-analysis

Competing Interests: None declared.

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Résumé

Objectif : Évaluer l'efficacité de l'administration de misoprostol avant une hystéroscopie en vue d'obtenir une dilatation cervicale et de réduire les complications (y compris les lacérations cervicales).

Sources de données : Des recherches informatisées ont été menées dans MEDLINE, PubMed et EMBASE au moyen des mots clés *hysteroscopy* et *misoprostol*. Les références des publications identifiées ont fait l'objet d'une recherche manuelle et ont été recoupées en vue d'identifier des articles pertinents additionnels.

Sélection des études : Nous avons inclus les essais cliniques randomisés qui comparaient les femmes subissant une hystéroscopie qui recevaient du misoprostol avant l'intervention à celles qui recevaient un placebo. Les études étaient exclues si elles ne comptaient pas de groupes témoins, si elles ne faisaient pas appel à un placebo, si leurs participantes n'étaient pas randomisées ou si seul leur résumé était disponible. Dix des 19 articles identifiés ont satisfait aux critères de l'analyse systématique.

Extraction et synthèse des données : Les deux co-auteurs ont procédé séparément au résumé des données. Toutes les différences quant au résumé des données ont été résolues au moyen de discussions; ainsi, un consensus a pu être atteint. Les lignes directrices QUORUM visant les méta-analyses et les analyses systématiques d'essais comparatifs randomisés ont été respectées.

Chez les femmes préménopausées, l'administration de misoprostol avant l'hystéroscopie a entraîné une diminution de la nécessité de poursuivre la dilatation cervicale (risque relatif [RR] = 0,61; intervalle de confiance [IC] à 95 % = 0,51, 0,73), un taux moindre de lacération cervicale (RR : 0,22; IC à 95 % : 0,09, 0,56) et une dilatation cervicale accrue (différence moyenne pondérée : 2,64; IC à 95 % : 1,73, 3,54). Chez les femmes préménopausées, l'administration de misoprostol a également entraîné un taux accru d'effets indésirables, y compris les saignements vaginaux (RR : 11,09; IC à 95 % : 3,08, 40,00), les crampes (RR : 7,98; IC à 95 % : 3,38, 18,84) et une hausse de la température (RR : 5,24; IC à 95 % : 1,37, 20,09). Pour chaque groupe de quatre femmes préménopausées ayant reçu du misoprostol avant une hystéroscopie, une femme a pu éviter d'avoir besoin d'une dilatation cervicale accrue. Pour chaque groupe de 12 femmes préménopausées ayant reçu du misoprostol, un cas de lacération cervicale a pu être évité.

Conclusion : Chez les femmes préménopausées, le misoprostol semble prometteur en tant qu'agent de maturation du col avant une hystéroscopie. Cependant, de plus amples recherches s'avèrent requises pour en identifier la dose, la voie d'administration et la posologie idéales. De plus amples recherches chez les femmes postménopausées ou chez les femmes recevant des agonistes de la gonadolibérine s'avèrent

également requises, et ce, afin de déterminer l'efficacité du misoprostol pour la maturation cervicale chez cette population.

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INTRODUCTION

Hysteroscopy is a common gynaecologic procedure used to investigate and treat menstrual disorders, postmenopausal bleeding, infertility, and recurrent pregnancy loss.[1,2] The procedure requires that the cervical canal be dilated enough to allow passage of the hysteroscope. Complications of hysteroscopy include cervical laceration, uterine perforation, and creation of a false passage during the attempt to dilate the cervix, which may make completion of the procedure impossible.[2–4] Misoprostol, a prostaglandin E_1 analogue used in the prevention and treatment of gastric ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs), has been increasingly used in obstetrics and gynaecology as a cervical ripening agent.[5–7] The purpose of this meta-analysis was to evaluate the effectiveness of misoprostol prior to hysteroscopy in achieving preprocedural cervical dilatation and reducing the need for mechanical dilatation with its associated complications.

METHODS

Sources

We performed searches of MEDLINE, PubMed, and EMBASE using the keywords "hysteroscopy" and "misoprostol" to identify studies involving human subjects published in English between January 1980 and April 2005. References from these publications were searched manually and cross-referenced to identify additional relevant articles. Because of lack of details regarding study methods and results, abstracts and unpublished works were not included.

Study Selection

Studies considered eligible were randomized clinical trials that compared the effects of misoprostol and placebo given before the procedure in women undergoing hysteroscopy. Studies were ineligible if there was no control group, if placebo was not used, if treatment was not randomized, or if only the abstract was published. The primary outcome was the need for further mechanical cervical dilatation. Secondary outcomes were complications (particularly cervical laceration and uterine perforation), side effects (nausea, diarrhea, vaginal bleeding, cramping, and elevated temperature), and the continuous measure of cervical dilatation.

If an abstract described a study that did not meet eligibility criteria, it was not reviewed further. Papers for all other abstracts were reviewed in detail. The two co-authors separately abstracted the data for the primary and secondary outcomes. Any differences in data abstraction were resolved through discussion, and a consensus was reached.

QUORUM guidelines for meta-analyses and systematic reviews of randomized controlled trials were followed.[8] Statistical analyses were conducted using the computer program Review Manager 4.27 (Cochrane Collaboration, Oxford, UK). Heterogeneity among trials for each outcome was evaluated by chi-square analysis. A random effects model was used if there was significant heterogeneity ($P < 0.10$). For categorical data the relative risk of each outcome for each study was calculated, and a summary relative risk and 95% CI were calculated. For continuous data a weighted mean difference and 95% CI were calculated. A P value of less than 0.05 was considered significant. Analyses were planned in advance for (1) premenopausal women, (2) postmenopausal women and premenopausal women receiving GnRH agonists, and (3) both groups of women combined. The number of women needed to treat to avoid the need for cervical dilatation prior to hysteroscopy was calculated.[9] We performed post hoc analyses of premenopausal nulliparous women and of premenopausal women undergoing operative hysteroscopy.

Sample size of the meta-analysis for the primary outcome of need for cervical dilatation prior to hysteroscopy was based on a reduction in the primary outcome from 50% to 33%, with a two-tailed $\alpha = 0.05$ and $\beta = 0.20$, requiring 143 women per group.

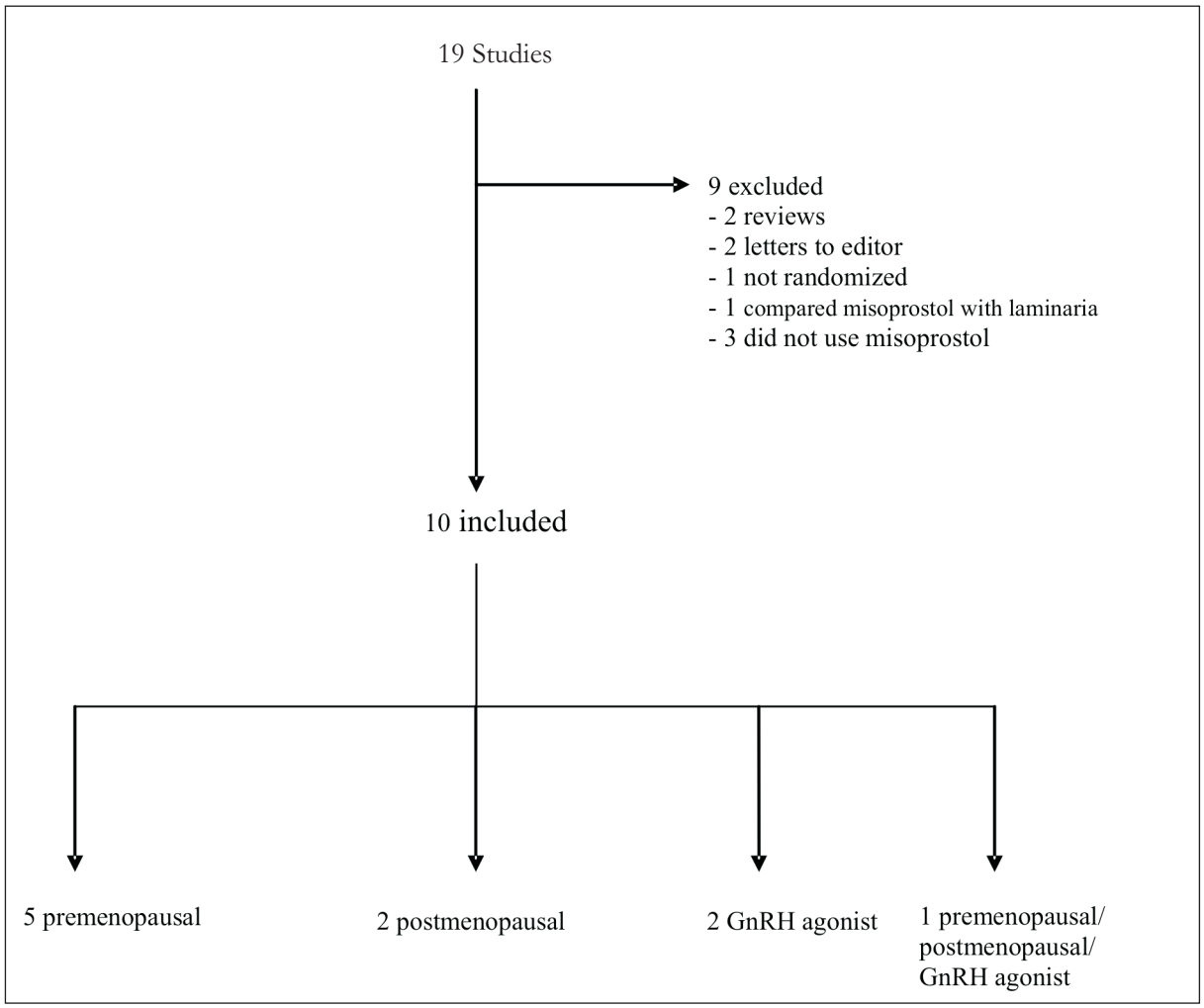
RESULTS

Of the 19 studies[2–5,10–24] identified from the literature search, ten[10–19] were included in the meta-analysis (Figure). Nine studies were excluded: two were reviews,[5,23] two were letters to the editor commenting on previous randomized clinical trials,[21,22] one study was not randomized,[20] one study compared misoprostol with laminaria,[24] and three studies did not use misoprostol.[2–4] One author was contacted to clarify information presented in the published study.[18]

Table 1 summarizes the ten randomized clinical trials included in the meta-analysis. Five of the studies included premenopausal women,[10–14] four studies included postmenopausal women or those receiving GnRH agonists,[15–17,19] and one study included both groups of women.[18] Some trials studied diagnostic hysteroscopy,[10,16,17] others studied operative hysteroscopy,[11,13–15,18,19] and one study evaluated both.[12]

Table 2 summarizes the outcomes of misoprostol administration before hysteroscopy for all women, revealing a significant reduction in the need for further dilatation prior to hysteroscopy and a lower rate of cervical laceration. There were higher rates of side effects with misoprostol, including

Studies included in the meta-analysis



nausea, diarrhea, cramping, and fever. The use of misoprostol appears to be beneficial in premenopausal women (Table 3), who had significant reductions in rates of cervical laceration and need for dilatation, and there was greater preprocedural cervical dilatation (weighted mean difference = 2.6; 95% CI 1.7, 3.5, $P < 0.0001$, random effects model) in this group. These reductions were not evident when postmenopausal women or those receiving GnRH agonists were studied (Table 4). In this group of women there was no significant difference in cervical dilatation with the use of misoprostol (weighted mean difference = 0.1; 95% CI 0.4, 0.6, $P = 0.62$, random effects model). For every four premenopausal women receiving misoprostol prior to hysteroscopy, one woman avoided the need for further cervical dilatation.[9] For every 12 premenopausal women receiving misoprostol, one cervical laceration was avoided.[9]

Further post hoc subgroup analyses were performed evaluating premenopausal nulliparous women and premenopausal women undergoing operative hysteroscopy. As only one study evaluated diagnostic hysteroscopy in premenopausal women,[10] we did not have adequate sample size to comment further on this particular subgroup. Among premenopausal nulliparous women, the use of misoprostol reduced the need for further cervical dilation[12,13] (RR = 0.70; 95% CI = 0.59, 0.82, $P = 0.007$) and the occurrence of cervical laceration[10,12,13] (RR = 0.14; 95% CI = 0.03,0.74, $P = 0.02$). The mean cervical dilatation was also greater in the misoprostol group (weighted mean difference 3.36; 95% CI = 3.12, 3.59, fixed effects model). Among premenopausal women undergoing operative laparoscopy, the use of misoprostol reduced the need for cervical dilatation[11,13] (RR = 0.68; 95% CI = 0.58,80, $P = 0.001$) and the occurrence of cervical laceration[11,13,14] (RR = 0.22; 95% CI = 0.08, 0.60, $P = 0.003$), and resulted in an

Table 1. Studies of misoprostol prior to hysteroscopy

Author	Year	Patient population	Misoprostol dose	Treatment	Control
Ngai et al.[10]	1997	Premenopausal	400 µg po 12h pre-op	21	23
Atay et al.[11]	1997	Premenopausal	400 µg pv 4h pre-op	22	21
Preutthipan et al.[12]	1999	Premenopausal	200 µg pv 9–10h pre-op	46	45
Preutthipan et al.[13]	2000	Premenopausal	200 µg pv 9–10h pre-op	73	79
Fernandez et al.[14]	2004	Premenopausal	200 µg pv 4h pre-op 400 µg pv 4h pre-op 800 µg pv 4h pre-op	12 12 10	13
Cooper et al.[15]	1996	GnRH agonist	1000 µg pv 2–4h pre-op	32	32
Ngai et al.[16]	2001	Postmenopausal	400 µg po 12h pre-op	18	16
Fung et al.[17]	2002	Postmenopausal	800 µg pv 5h pre-op	47	48
Thomas et al.[18]	2002	Premenopausal and Postmenopausal/GnRH Agonist	400 µg po 24h and 12h pre-op	46 59	49 52
Bisharah et al.[19]	2003	GnRH agonist	100 µg sl 12h pre-op	20	20

increased mean cervical dilatation[13] (weighted mean difference = 3.50; 95% CI = 3.21, 3.79, fixed effects model). As only one study presented data specific for premenopausal nulliparous women undergoing operative hysteroscopy,[13] we are unable to comment further on this subgroup.

When further subgroup analyses assessing the types of hysteroscopy (operative or diagnostic) were performed for postmenopausal women or those receiving GnRH agonists, no benefits with misoprostol were seen.

DISCUSSION

Studies of misoprostol suggest that it is very effective in initiating uterine contractions and inducing labour in the second and third trimesters of pregnancy.[6,7,25,26] It has also been shown to be useful in cervical ripening before surgical abortion, making the procedure easier to perform by increasing cervical dilatation and ease of dilatation.[5,25–30]

Previous studies of misoprostol as a cervical ripening agent before hysteroscopy found conflicting results depending on the population studied. The small sample sizes of the individual studies meant that they lacked the statistical power to demonstrate significant differences in some of the outcomes evaluated, such as cervical laceration and the need for cervical dilatation. The current meta-analysis determined a priori the sample size required to detect a 33% reduction in the need for further cervical dilation (from 50% to 33%). We found that misoprostol in premenopausal women was an effective cervical ripening agent because it reduced the need for further cervical dilatation and lowered the rate of cervical laceration. There were higher rates of complications in women who used misoprostol, including vaginal bleeding, cramping, and elevated temperature, but these side effects were transient. We found subgroups of premenopausal women in whom misoprostol was of benefit: women undergoing operative hysteroscopy and women who were nulliparous. This is not surprising, as operative hysteroscopy requires greater preprocedural dilation, and nulliparous women are more likely to have a narrow cervical canal.

It is important to address the shortcomings of this meta-analysis. A variety of protocols with different doses, routes, and frequencies of administration were used in the studies included in the meta-analysis. The population of women evaluated also varied. Some studies evaluated premenopausal women,[10–14] others evaluated postmenopausal women[16,17] or those receiving GnRH agonists,[15,19] and others studied a combination of these groups.[18] Hysteroscopes of different sizes also were used, and some studies evaluated misoprostol before operative

Table 2. Outcomes of misoprostol prior to hysteroscopy (all women)

Outcome	Number of studies	Misoprostol (%)	Control (%)	Relative risk	95% CI	*P*
Need for further dilatation	5[11–13, 17,18]	128/275 (46.5%)	186/274 (67.9%)	0.66	0.47, 0.94*	0.02
Cervical laceration	9[10–14,16–19]	9/368 (2.4%)	24/346 (6.9%)	0.39	0.19, 0.77**	0.007
Uterine perforation / false passage	8[10,11,13–18]	5/334 (1.5%)	6/313 (1.9%)	0.70	0.24, 2.02**	0.51
Nausea	5[11–13,16,18]	24/245 (9.8%)	8/241 (3.3%)	2.65	1.28, 5.47**	0.008
Diarrhea	6[11–13,16–18]	29/295 (9.8%)	3/291 (1.0%)	6.49	2.47, 17.03**	0.0001
Vaginal bleeding	5[12,13,16,18,19]	52/243 (21.4%)	9/240 (3.8%)	5.31	0.93, 30.19*	0.06
Abdominal cramping	6[12,13,16–19]	77/293 (26.3%)	7/290 (2.4%)	8.87	4.51, 17.43**	< 0.0001
Fever	4[11–13,17]	15/191 (7.9%)	2/195 (1.0%)	5.54	1.63, 18.80**	0.006

CI: Confidence interval. * Random effects model; ** Fixed effects model

Table 3. Outcomes of misoprostol administration prior to hysteroscopy in premenopausal women

Outcome	Number of studies	Misoprostol (%)	Control (%)	Relative risk	95% CI	*P*
Need for further dilatation	3[11–13]	60/141 (42.6%)	104/145 (71.7%)	0.61	0.51, 0.73*	< 0.0001
Cervical laceration	5[10–14]	4/196 (2.0%)	20/181 (11.0%)	0.22	0.09, 0.56*	0.001
Uterine perforation/ false passage	4[10,11,13,14]	2/150 (1.3%)	4/136 (2.9%)	0.39	0.08, 1.85*	0.24
Nausea	3[11–13]	7/141 (5.0%)	1/145 (0.7%)	5.23	0.92, 29.65*	0.06
Diarrhea	3[11–13]	6/141 (4.3%)	0/145 (0%)	7.20	0.90, 57.56*	0.06
Vaginal bleeding	2[12,13]	26/119 (21.8%)	2/124 (1.6%)	11.09	3.08, 40.00*	0.0002
Abdominal cramping	2[12,13]	41/119 (34.5%)	5/124 (4.0%)	7.98	3.38, 18.84*	< 0.0001
Fever	3 [11–13]	12/141 (8.5%)	2/145 (1.4%)	5.24	1.37, 20.09	0.02

* Fixed effects model

Table 4. Outcomes of misoprostol prior to hysteroscopy in postmenopausal women or those receiving GnRH agonists

Outcome	Number of studies	Misoprostol (%)	Control (%)	Relative risk	95% CI	*P*
Need for further dilatation	1[17]	32/47 (68.1%)	35/48 (72.9%)	0.93	0.72, 1.21*	0.61
Cervical laceration	3[16,17,19]	1/85 (1.2%)	0/84 (0%)	3.00	0.13, 69.52*	0.49
Uterine perforation/ false passage	3[15–17]	1/97 (1.0%)	0/96 (0%)	3.00	0.13, 71.00*	0.50
Nausea	1[16]	1/18 (5.6%)	0/16 (0%)	2.68	0.12, 61.58*	0.54
Diarrhea	2[16,17]	1/68 (1.5%)	0/66 (0%)	3.00	0.13, 71.92*	0.50
Vaginal bleeding	2[16,19]	6/38 (15.8%)	6/36 (16.7%)	0.91	0.36, 2.27*	0.83
Abdominal cramping	3[16,17,19]	5/88 (5.7%)	1/86 (1.2%)	2.54	0.61, 10.64*	0.20
Fever	1[17]	3/50 (6.0%)	0/50 (0%)	7.00	0.37, 132.10*	0.19

CI: Confidence interval. * Fixed effects model

hysteroscopy and others before diagnostic hysteroscopy. Despite these heterogeneous groups, a significant difference was found in the primary outcome in the premenopausal group. This meta-analysis suggests that in premenopausal women (and, in particular, nulliparous women or those undergoing operative hysteroscopy), misoprostol administration before hysteroscopy improves preprocedural cervical dilatation and reduces cervical laceration. Because of variations in protocols, however, we are not able to determine the ideal dosing regimen. Other shortcomings of the studies included in this meta-analysis are also evident. The studies did not provide further details on specific dilators used, or the cause of cervical lacerations (i.e., the tenaculum or the dilators). The hysteroscopies were performed in a variety of settings, ranging from outpatient offices without analgesia to operating rooms with use of general anaesthesia. Studies in premenopausal women did not specify the timing of hysteroscopy in relation to the menstrual cycle. The rate of serious complications such as uterine perforation or creation of a false passage was low (1.9% in the control group) and so one would need a very large sample size (n = 2515 per group) to detect a 50% reduction (2% to 1%) in this outcome. However, the need for further cervical dilatation and cervical laceration may be considered surrogate markers for more serious complications.

The benefit of using misoprostol in postmenopausal women or in those receiving GnRH agonists is less clear. In this group of women, only one study suggested benefit,[18] and when these studies were combined in this meta-analysis there was no evident benefit. Unfortunately, data from the only study suggesting benefit were not presented in a way that allowed incorporation as a dichotomous outcome in the meta-analysis.[18] It is possible that the dosing protocol of the study that suggested improvement in cervical dilatation (400 μg by mouth, given at 24 hours and 12 hours prior to hysteroscopy) may provide the appropriate timing and dose to allow cervical ripening in these women. The overall lack of benefit seen in hypoestrogenic women suggests that either estrogen or progesterone plays an important role in prostaglandin-induced cervical ripening. When further subgroup analyses were performed (postmenopausal women versus those using GnRH agonists, or operative hysteroscopy only), no subgroup of postmenopausal women was found to benefit, although with small sample sizes we did not have adequate statistical power to evaluate the outcomes of interest in these subgroups.

CONCLUSION

Misoprostol has promise for use as a cervical ripening agent before hysteroscopy in premenopausal women, particularly nulliparous women or those undergoing operative hysteroscopy, because it reduces the need for further mechanical cervical dilatation and reduces the rate of cervical laceration. Further research is needed to identify the ideal dose, route, and timing of misoprostol prior to the procedure and to determine if misoprostol is effective in cervical ripening in postmenopausal women or those receiving GnRH agonists.

REFERENCES

1. Baggish MS. Operative hysteroscopy. In: Rock JA, Thompson JD, editors. TeLinde's operative gynecology. Philadelphia: Lippincott – Raven Publishers;1997, p. 415–42.
2. Bradley LD. Complications in hysteroscopy: prevention, treatment and legal risk. Curr Opin Obstet Gynecol 2002;14:409–15.
3. Loffer FD. Complications of hysteroscopy - their cause, prevention and correction. J Am Assoc Gynecol Larparosc 1995;3:11–26.
4. Vilos GA, Vilos EC, King JH. Experience with 800 hysteroscopic endometrial ablations. J Am Assoc Gynecol Laparosc 1996;4:33–8.
5. Goldberg AB, Carusi DA, Meckstroth KR. Misoprostol in gynecology. Curr Womens Health Rep 2003;3:475–83.
6. Alfirevic Z. Oral misoprostol for induction of labour (Cochrane review). In the Cochrane Library Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.
7. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour (Cochrane review). In: The Cochrane Library, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.
8. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of meta-analyses of randomized controlled trials: the QUORUM statement. Quality of reporting of meta-analyses. Lancet 1999;354:1896–900.
9. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine – how to practice and teach EBM. New York: Churchill Livingston; 1997, p.179–81.
10. Ngai SW, Chan YM, Liu KL, Ho PC. Oral misoprostol for cervical priming in non-pregnant women. Hum Reprod 1997;12:2373–5.
11. Atay V, Duru NK, Pabuccu R, Ergun A, Tokac G, Aydin BA. Vaginal misoprostol for cervical dilatation before operative office hysteroscopy. Gynecol Endoscopy 1997;6:47–9.
12. Preutthipan S, Herabutya Y. A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. Obstet Gynecol 1999;94:427–30.
13. Preutthipan S, Herabutya Y. Vaginal misoprostol for cervical priming before operative hysteroscopy: a randomized controlled trial. Obstet Gynecol 2000;96:890–4.
14. Fernandez H, Alby JD, Tournoux C, Cheuveaud-Lambling A, DeTayrae R, Frydman R, et al. Vaginal misoprostol for cervical ripening before operative hysteroscopy in premenopausal women: a double-blind, placebo-controlled trial with three dose regimes. Hum Reprod 2004; 9:1618–21.
15. Cooper KG, Pinion SB, Bhattacharya S, Parkin DE. The effects of the gonadotropin releasing hormone analogue (goseralin) and prostaglandin E (misoprostol) on cervical resistance prior to transcervical resection of the endometrium. Br J Obstet Gynaecol 1996;103:375–8.
16. Ngai SW, Chan YM, Ho PC. The use of misoprostol prior to hysteroscopy in postmenopausal women. Hum Reprod 2001;16:1486–8.
17. 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;109:561–5.

18. Thomas JA, Leyland N, Durand N, Windrim RC. The use of oral misoprostol as a cervical ripening agent in operative hysteroscopy: a double-blind, placebo-controlled trial. Am J Obstet Gynecol 2002;186:876–9.

19. Bisharah M, Al-Fozan H, Tulandi T. A randomized trial of sublingual misoprostol for cervical priming before hysteroscopy. J Am Assoc Gynecol Laparosc 2003;10:390–1.

20. Darwish A. Modified hysteroscopic myomectomy of large submucous fibroids. Gynecol Obstet Invest 2003;56:192–6.

21. Sharma S, El-Rafaey H. The use of misoprostol as a cervical ripening agent in operative hysteroscopy. Am J Obstet Gynecol 2003;18:297–8.

22. Scott P, Magos A. Vaginal misoprostol for cervical priming before operative hysteroscopy: a randomized controlled trial. Obset Gynecol 2001;97:640–1.

23. Lichtenberg ES. Complications of osmotic dilators. Obstet Gynecol Surv 2004; 59:528–36.

24. Darvish AM, Ahmad RM, Mohammad AM. Cervical priming prior to operative hysteroscopy: a randomized comparison of laminaria versus misoprostol. Hum Reprod 2004; 19:2391–4.

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

26. Blanchard K, Clark S, Winikoff B, Gaines G, Kaoni G, Shannon C. Misoprostol for women's health: a review. Obstet Gynaecol 2002;99:316–22.

27. Fong YF, Singh K, Prasad RN. A comparative study using two dose regimens (200 ug or 400 ug) of vaginal misoprostol for pre-operative cervical dilatation in first trimester nulliparae. Br J Obstet Gynaecol 1998;105:413–7.

28. Singh K, Fong YF, Prasad RN, Dong F. Randomized trial to determine optimal dose of vaginal misoprostol for preabortion cervical priming. Obstet Gynecol 1998;92:795–8.

29. MacIsaac L, Grossman D, Balistreri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstet Gynecol 1999;93:766–70.

30. Singh K, Fong YF, Prasad RN, Dong F. Evacuation interval after vaginal misoprostol for preabortion cervical priming: A randomized clinical trial. Obstet Gynecol 1999;94:431–4.