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## Review Article

# Use of Vaginal Misoprostol Prior to Placement of an Intrauterine Device: A Review

## Abstract

Intrauterine devices (IUD) are a highly effective and safe form of contraception. However, many individuals, particularly nulligravidas, elect against IUD use due to fear of pain associated with insertion. Misoprostol has been proposed as an agent to ease IUD insertion and decrease associated pain. However, its efficacy in the literature is inconclusive and its use varies widely between healthcare providers. We present a review on the efficacy of vaginal misoprostol in facilitating IUD insertion and reducing procedure-associated pain.

## Abbreviations

CDC – Centers for Disease Control; IUD – Intrauterine Device; LARC – Long-Acting Reversible Contraceptives; RCT – Randomized Controlled Trial

## Background

Intrauterine devices (IUD) are a highly effective, reliable, and safe form of contraception [1]. The use of long-acting reversible contraceptives (LARCs), including IUDs, has increased nearly five-fold in the last decade among 15 to 44-year-old women. According to a 2015 CDC National Center for Health Statistics data brief, women use LARCs at a higher rate if they have had at least one prior birth compared to nulliparous women. From 2011–2013, LARC use was three times greater in parous women than nulliparous women [2]. Many individuals, particularly nulligravidas, elect against IUD use due to concern regarding pain associated with insertion (1). However, it is unclear how much this may be due to provider-directed counseling. The Contraceptive Choice Project demonstrated that with scripted and efficacy-based counseling, 37% of teens (14 to 17 year olds) will choose an IUD [3]. Given the significant benefits of IUDs, modalities to decrease insertion difficulty and procedure-related pain are of high clinical relevance [1].

Misoprostol, a prostaglandin E1 analogue, is well known for its use as a cervical ripening agent in labor induction [1]. It is also used for cervical ripening prior to transcervical procedures such as hysteroscopy [4], dilation and curettage, and dilation and evacuation [5]. Misoprostol has also been proposed as an agent to ease IUD insertion and decrease procedure-associated

pain [1]. The use of misoprostol prior to IUD insertion varies between practitioners, and the literature regarding its efficacy in facilitating IUD insertion and decreasing pain is inconclusive. Misoprostol dose, route of administration, and timing of administration prior to procedure varies widely among available studies. Additionally, multiple studies in the current literature include multiple routes of misoprostol administration (sublingual, oral, rectal, and vaginal) and do not account for this in analysis. It is known that peak misoprostol plasma concentration occurs at significantly different time points depending on route of administration (< 30 minutes for sublingual use with rapid decrease compared to 1 hour for vaginal use with plasma levels remaining significantly elevated for at least 6 hours). Side effects also differ based on route of administration with milder side effects generally noted for vaginal administration [6]. Additionally, a previous study by Ziemann et al. suggested that systemic bioavailability with a vaginal route of administration is 3 times greater than with oral administration and that there are significant differences in the pharmacokinetics of misoprostol administered vaginally versus orally that could account for difference in clinical efficacy [7]. In contrast, a study by Meckstroth et al. concluded that although serum levels of misoprostol are indeed higher with vaginal administration than buccal administration, uterine tone and activity as measured by 2.5-mm pressure monitoring catheter is similar in both routes [8]. These factors make comparison between studies using multiple routes of misoprostol administration particularly difficult.

The objective of this review is to evaluate and summarize existing literature addressing the use of vaginal misoprostol

as an agent in facilitating IUD insertion, including ease of insertion, procedure-associated pain, and adverse effects.

## Methods

A PubMed database search was performed using the MeSH search terms “misoprostol” and “intrauterine device.” Relevant articles involving vaginal administration of misoprostol prior to IUD insertion were identified and are discussed below. Studies utilizing multiple routes of misoprostol administration or only non-vaginal misoprostol administration were excluded. Literature was reviewed through November 2016. Three randomized control trials and one case series of 8 women are summarized table 1.

## Results

Scavuzzi et al. performed a randomized, double-blind controlled trial to evaluate effectiveness of vaginal administration of misoprostol in dilating the cervix prior to

IUD insertion in nulligravid women without history of prior uterine or cervical surgery. 179 menstruating women were included; 86 were given 400 micrograms of misoprostol vaginally 4 hours prior to copper T380A IUD placement and 93 were given a vaginal placebo. All medications were inserted by one provider. There were no significant differences between the groups at baseline. The primary end point of the study was difficulty of IUD insertion as evaluated subjectively by the principal investigator as either “difficult/very difficult versus easy.” Frequency of cervical dilation  $\leq 4$  mm measured by #4 Heger dilator immediately prior to IUD insertion, subjective pain during the procedure evaluated by visual analog scale and later dichotomized into “mild/absent versus moderate/severe,” and subjective procedure evaluation by study participants as “disagreeable or not disagreeable” were secondary end points. There was a significant difference between the groups with less subjective difficulty of IUD insertion when misoprostol was used (RR=0.49, 95% CI 0.33–0.72, NNT 3,  $p=0.00001$ ). Less occurrence of cervical dilation  $\leq 4$  mm was also reported

Table 1:

Authors	Study Design	Primary end point/aim	Comparison	Number of subjects	Outcome	Side effects
Scavuzzi et al (6)	RCT	IUD insertion in nulligravid (difficult/very difficult vs easy).	Misoprostol 400 mcg vaginally 4 hours prior to IUD vs placebo.	179 women: Misoprostol (n = 86, Placebo (n = 93).	Less subjective difficulty of IUD insertion when misoprostol was used (RR=0.49, 95% CI 0.33-0.72, NNT 3, $p=0.00001$ ).	No significant differences reported in complications during IUD insertion (bleeding, syncope, cramps, nausea, and vomiting, failed insertion). There was a significant increase in pre-procedure side effect of cramping with misoprostol use compared to placebo (RR=1.40, 95% CI 1.05-1.86, NNT 6, $p=0.002$ ).
Bahamondes et al (9)	RCT	Successful insertion of IUD and need for use of a cervical dilator in women with previous IUD insertion failure.	Misoprostol 200 mcg vaginally 10 and 4 hours prior to (clinic) IUD vs placebo.	100 women: misoprostol (n=55), placebo (n=45).	IUD insertion was successful in 87.5% of subjects receiving misoprostol as compared to 61.9% of those receiving placebo (evaluable population RR=1.41, 95% CI 8.2-43.0, $p=0.0066$ ). No significant difference in use of cervical dilators was found - use was required in 43.7% of those receiving misoprostol and 50% of the placebo group ( $p=0.804$ ).	5 women in the misoprostol group reported nausea, vomiting, diarrhea, or chills, and 6 women reported cramps.
Li et al (10)	Case series	8 women who previously failed IUD insertion.	400 micrograms of misoprostol was placed 1 day prior to IUD insertion.	8 women.	IUD insertion was successful without documented difficulty in all 8 women.	The only side effect reported was cramping in 3 women.
Dijkhuizen et al (11)	RCT	Primary endpoint of this study was failed IUD insertion.	400 micrograms of misoprostol or placebo vaginally 3 hours prior to procedure.	270 women: misoprostol (n=102), placebo (n=97) (Analysis was by intention-to-treat, although not all subjects randomized were included in the analysis: 71 subjects dropped out of the study after randomization (199 subjects analyzed as compared to 270 subjects randomized)).	Two of the misoprostol group insertions failed, and 1 failure in the placebo group (RR 1.9, 95% CI 0.02-20.6, $p=0.59$ ).	Significant side effects (headache, nausea/vomiting, cramping, fever, chills, and diarrhea) between groups, with a higher occurrence in the misoprostol group (RR 1.3, 95% CI 1.0-1.7, $p=0.05$ ), with most side effects reported as mild.

RCT: Randomized Controlled Trial

with misoprostol use (RR=0.49, 95% CI 0.33-0.70, NNT 4,  $p=0.00005$ ) as well as a 44% reduction in moderate-to-severe pain during the procedure compared to placebo (RR=0.56, 95% CI 0.41-0.76, NNT 3,  $p=0.00004$ ). Furthermore, there were fewer disagreeable procedure evaluations by study participants in the misoprostol group (RR=0.49, 95% CI 0.35-0.68, NNT 3,  $p=0.000004$ ) [6].

Regarding side effects, there were no significant differences reported in complications during IUD insertion (bleeding, syncope, cramps, nausea, Vomiting, failed insertion). There was a significant increase in pre-procedure side effect of cramping with misoprostol use compared to placebo (RR=1.40, 95% CI 1.05-1.86, NNT 6,  $p=0.002$ ). No additional significant differences between groups in pre-procedure side effects or side effects at 24 hours post-procedure were identified (nausea, vomiting, diarrhea, fever). Side effects were also evaluated at 30 days post-procedure (abnormal bleeding, cramps, acute pelvic inflammatory disease, expulsion) with no significant differences found. However, there was inadequate power to detect differences in IUD expulsion rates between the groups, a concern that has been previously raised with misoprostol use. The authors conclude the benefits of misoprostol use prior to IUD insertion outweigh the risks and suggested its use should become standard practice in nulligravid women [6]. This is the largest study evaluating use of vaginal misoprostol in nulligravidas identified for this review.

Bahamondes et al. analyzed the use of vaginal misoprostol versus placebo prior to IUD insertion among women that had had a previous insertion attempt and failure via a double-blind, randomized controlled trial. 100 women with previous IUD insertion failure were randomized to receive either vaginal misoprostol ( $n=55$ ) or placebo ( $n=45$ ). The women were instructed to insert one 200 microgram misoprostol tablet or placebo tablet 10 hours prior to clinic appointment time and again 4 hours prior to appointment time. There were no significant differences between the groups at baseline. Endpoints of the study included successful insertion of IUD and need for use of a cervical dilator. Analysis was intention-to-treat (all subjects randomized) as well as evaluable population (all subjects returning for insertion appointment after randomization). IUD insertion was successful in 87.5% of subjects receiving misoprostol as compared to 61.9% of those receiving placebo (evaluable population RR=1.41, 95% CI 8.2-43.0,  $p=0.0066$ ). No significant difference in use of cervical dilators was found - use was required in 43.7% of those receiving misoprostol and 50% of the placebo group ( $p=0.804$ ). Multiple regression analysis showed history of at least 1 Cesarean section and use of placebo to be associated with failure of IUD insertion ( $p=0.020$  and  $p=0.026$ , respectively). Regarding side effects, 5 women in the misoprostol group reported nausea, vomiting, diarrhea, or chills, and 6 women reported cramps [9].

This study demonstrated misoprostol being significantly better than placebo in facilitating IUD insertion among women with a previous IUD insertion failure. This is important as many studies previously finding that misoprostol was not useful randomized women prior to first attempt at IUD insertion.

Given that most IUD insertions do not fail on first attempt, it is difficult to elucidate whether misoprostol may actually be useful in improving difficult insertion. The study authors concluded misoprostol use is only indicated when there has been a previous IUD insertion failure. Limitations of this study included the majority of women choosing a Levonorgestrel-releasing device with only 7 women choosing a copper IUD (0 misoprostol and 7 placebo). Additionally, only 240 (9.5%) of women in the study had never given birth (9 in misoprostol group and 10 in placebo) [9]. This is the only study in this review to limit the population of subjects to those with prior IUD insertion failure with a placebo group included.

Prior to the above study, Li et al. conducted a case series of 8 patients who had previously failed IUD insertion. 7 of these women were identified as having cervical stenosis with a history of prior cesarean section and no prior vaginal deliveries. 1 patient was an adolescent identified as having a small cervix. None of the women had a history of prior cervical surgery. 6 women received copper IUDs and 2 received Levonorgestrel-releasing IUDs. 400 micrograms of misoprostol was placed 1 day prior to IUD insertion. In all 8 women IUD insertion was successful without documented difficulty. The only side effect reported was cramping in 3 women. No expulsion of the IUDs was noted in follow-up. The authors conclude that misoprostol had a beneficial effect among this group [10].

Dijkhuizen et al. performed a double-blind, multicenter, randomized controlled trial in which 270 patients requesting an IUD were randomized to self-administer 400 micrograms of misoprostol or placebo vaginally 3 hours prior to procedure. 102 women (age  $\geq 18$ ) received misoprostol and 97 were given placebo. 89.9% of subjects received Levonorgestrel-releasing IUDs with 10.1% receiving copper IUDs. Insertions were performed by 38 providers. There were no significant differences between the groups at baseline. The primary endpoint of this study was failed IUD insertion with secondary outcomes of complications, pain (reported by participants using visual analog scale), side effects, and difficulty of insertion (as reported by provider using a 10 point scale). Analysis was by intention-to-treat, although not all subjects randomized were included in the analysis: 71 subjects dropped out of the study after randomization (199 subjects analyzed as compared to 270 subjects randomized) [11].

Two of the misoprostol group insertions failed with 1 failure in the placebo group (RR 1.9, 95% CI 0.02-20.6,  $p=0.59$ ). Insertion complications (failed insertion, vasovagal reaction, heavy bleeding, expulsion) were not significantly different between groups with 21.8% of those receiving misoprostol having complications compared to 19.1% of those getting placebo (RR 1.1, 95% CI 0.7-2.0,  $p=0.65$ ). Perforation or major bleeding did not occur with only 1 IUD expulsion noted in a subject who received placebo. Similarly, pain scores and insertion difficulty did not significantly differ between groups ( $p=0.14$  and  $p=0.77$ , respectively). There was a significant difference in side effects (headache, nausea/vomiting, cramping, fever, chills, and diarrhea) between groups, with a higher occurrence in the misoprostol group (RR 1.3, 95% CI 1.0-

1.7,  $p=0.05$ ), with most side effects reported as mild. Subgroup analysis was performed to compare multiparous individuals ( $n=99$ ) to nulliparous individuals ( $n=87$ ). A significantly higher pain score was found in nulliparous subjects than multiparous subjects in both misoprostol and placebo groups ( $p<0.0001$ ) as well as increased insertion difficulty in the nulliparous group ( $p<0.001$ ). Side effects did not differ between groups in the subgroup analysis ( $p=0.34$ ). Therefore, this study concluded that there is no benefit for misoprostol use in the context of IUD insertion as it did not decrease the number of failed insertions, which are rare, or pain, and that its side effects may cause harm [11].

Additional randomized studies of misoprostol use in nulliparous women utilizing a uniform route of administration (namely buccal) were reviewed [12-14]. All of these showed no benefit on ease of insertion, rate of successful insertion, or insertional pain.

## Discussion

There are few studies in the literature investigating exclusively a vaginal route of misoprostol administration prior to IUD insertion. Many reviews conclude that the overall majority of studies find no significant differences between women receiving misoprostol and placebo prior to IUD insertion, notably a 2015 Cochrane review by Lopez et al. reporting misoprostol did not help with pain in meta-analysis and may even increase procedure pain [1]. A 2016 review by Matthews et al. found no data in favor of misoprostol decreasing IUD insertion difficulty or pain and advised against its routine use, even in nulliparous women [15]. However most reviews include studies with different routes and doses of misoprostol administration and do not account for this in comparisons. This is a significant shortcoming in the current literature. Of the 3 randomized controlled trials and 1 case series found utilizing solely vaginal misoprostol, dose was consistent across all studies, but timing of administration prior to procedure differed in all studies. Further studies comparing vaginal misoprostol administration at various time points prior to procedure will be of significant benefit to the current literature. Additionally, insertion protocol in which women self-administer misoprostol at home prior to clinic arrival are not standardized, and further studies with standardized insertion protocols will help further elucidate effect.

Of particular interest is that the Bahamondes et al. trial and the Li et al. case series looked at subjects with a history of prior IUD insertion failure, and both found significant improvement in facilitating IUD insertion [9,10]. Bahamondes et al. highlighted that because the rate of failed IUD insertion on first attempt is generally very low, randomizing subjects prior to first attempt of IUD insertion could falsely conclude that misoprostol was not of benefit in a population that may actually benefit from misoprostol [9]. Dijkhuizen et al. also noted that their study was powered on a high failure insertion rate which was not actually demonstrated, thus this could be influencing precision of effect [11]. Further research should be conducted in the specific population of individuals with prior IUD insertion failure.

Also of relevance is the use of pre-IUD misoprostol in nulligravid women compared to multiparous women, as many nulligravidas fear IUD use due to concern of pain associated with insertion [1]. Of the above studies and case series, only Dijkhuizen et al. had similar numbers of multiparous and nulliparous subjects and were able to perform subgroups analysis. Pain and insertion difficulty were significantly increased in nulliparous women regardless of medication use [11]. Further studies of vaginal misoprostol comparing these 2 populations will be clinically relevant.

Significant concerns cited by healthcare providers regarding pre-procedure misoprostol use often include concern for higher rates of IUD expulsion and other negative side effects of misoprostol [6]. Of the above studies, rates of expulsion were either very low or not addressed. Additionally, providers often prescribe pre-insertion misoprostol for women with medical history of diseases such as endometriosis that they feel will cause increased pain during the procedure. None of the above studies evaluated the medical history of subjects.

Ultimately, the efficacy of vaginal misoprostol prior to IUD insertion remains inconclusive in the available literature, although current reviews suggest it is unlikely to be beneficial as a general practice in multiparous women without prior failed attempt [1, 15]. Differences in route of administration, dose, Timing of medication administration prior to procedure, parity, and medical history among study subjects make comparison between studies difficult and clinical application difficult to interpret.

## Conclusion

The use of vaginal misoprostol to facilitate IUD insertion remains inconclusive given the limited evidence: variable inclusion/exclusion criteria, methods, and inconsistent outcome measures. Further studies are needed, especially among patients with prior documented IUD insertion failure. In deciding whether to use vaginal misoprostol prior to IUD insertion in practice, clinicians should be thoughtful of the specific populations in which individual studies have demonstrated benefit (e.g. prior insertion failure).

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