Review

Intrauterine Device Insertion Failure After Misoprostol Administration
A Systematic Review

Laura R. Matthews, MD, Linda O’Dwyer, MA, MSLIS, and Erica O’Neill, MD, MSCR

OBJECTIVE: To examine rates of intrauterine device (IUD) insertion failure with and without prior misoprostol administration. Additional outcomes included difficulty of insertion, subjective pain, expulsion, and complications.

DATA SOURCES: Systematic searches were performed in PubMed MEDLINE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health Literature for articles with the following keywords: “misoprostol,” “intrauterine devices,” and “IUDs.”

METHODS OF STUDY SELECTION: A total of 161 unique results were retrieved. Titles, abstracts, and full-text articles were independently screened twice by two reviewers for content and relevance. Quality assessment was performed using previously established criteria. After screening and quality assessment, nine randomized controlled trials (RCTs) were obtained for inclusion. Six articles were designated high quality and three were designated low quality.

TABULATION, INTEGRATION, AND RESULTS: Six of six RCTs examining IUD insertion failure with misoprostol revealed no difference in this measure. Of nine RCTs examining difficulty of IUD insertion with misoprostol, seven revealed no difference in this measure and two revealed decreased difficulty of insertion with misoprostol administration. Of nine RCTs examining pain with IUD insertion, seven revealed no difference in pain measurement scores, one revealed increased pain with misoprostol administration, and one revealed decreased pain with misoprostol administration. Five studies examining rates of expulsion and two studies examining complications of IUD insertion revealed no difference in this measure.

CONCLUSION: No data support routine administration of misoprostol before IUD insertion. Success of insertion is high even among nulliparous women, and good-quality data do not demonstrate that misoprostol use increases success. These data similarly reveal no differences in difficulty of insertion, pain with insertion, or expulsion with prior administration of misoprostol. However, data for several outcomes are limited by lack of power.

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The intrauterine device (IUD) is a long-acting reversible contraceptive method used by 10.3% of reproductive-aged women in the United States.1 Intrauterine device use as a method of contraception has grown significantly over the past 10 years, partly as a result of a reversal of historical contraindications such as nulliparity and a history of pelvic infections. Comparing 2006-2010 with 2011-2013, IUD use increased 88%.1 Intrauterine device use is associated with very low failure rates: 0.2 per 100 woman-years with levonorgestrel-containing IUD use and 0.6 per 100 woman-years with copper-containing IUD use.2 Levonorgestrel-containing and copper-containing IUDs are associated with high 12-month continuation rates and very high rates of patient satisfaction, both when compared with other long-acting reversible contraceptive methods and nonlong-acting reversible contraceptive methods.3 Both types of IUDs are ideal for use in both multiparous and nulliparous women. Levonorgestrel-containing IUDs have overarching benefits in the treatment of gynecologic conditions occurring throughout the reproductive lifespan.
including dysfunctional uterine bleeding, pelvic pain from endometriosis and adenomyosis, and endometrial hyperplasia. In the setting of dysfunctional uterine bleeding, several studies have revealed the superiority of levonorgestrel-containing IUDs over surgical or ablative techniques on a variety of measures.\textsuperscript{4–6}

Several perceived drawbacks exist regarding IUD use. Of patients undergoing IUD insertion, 86% report anxiety and 41% report at least moderate discomfort during insertion.\textsuperscript{7} Moreover, insertion failure rates have been reported as high as 20% in nulliparous women and 14% of parous women.\textsuperscript{8} These factors may contribute to decreased promotion of this method by health care providers. In the recent past, more than 60% of health care providers reported reluctance in offering IUDs to nulliparous patients, with many citing concerns about safety and availability.\textsuperscript{9}

Misoprostol is a synthetic analog of prostaglandin E1 originally approved for treatment and prevention of gastric ulcers induced by nonsteroidal anti-inflammatory drugs.\textsuperscript{10} Misoprostol can be administered sublingually, orally, vaginally, or rectally. Vaginal administration has been associated with the highest peak serum levels of misoprostol, and overall bioavailability is greatest for sublingual and vaginal administration.\textsuperscript{11,12} When studied for use in first-trimester pregnancy termination, rectal administration of misoprostol has been shown to produce lower uterine tone and activity than other routes of administration.\textsuperscript{12} Misoprostol has well-known cervical ripening and uterotonic effects, naturally leading to its use as an adjunct in many gynecologic procedures.

Misoprostol use has been well studied in the hysteroscopy literature. Multiple well-designed studies have validated the efficacy of 200–400 micrograms vaginal or oral misoprostol before hysteroscopy in reducing pain with dilation, reducing the number of failed dilations, and increasing cervical canal diameter before dilation.\textsuperscript{13–15} Administration of misoprostol less than 4–6 hours before a procedure has not been shown to be beneficial when compared with placebo,\textsuperscript{16} whereas administration 8–24 hours before in varying regimens has been shown to incur the greatest benefit.\textsuperscript{13–15,17} Higher doses of misoprostol do not allow for additional cervical ripening over this timeframe when compared with studies using lower doses and may be associated with increased side effects.\textsuperscript{18} However, studies examining adjuvant misoprostol administration for office endometrial biopsy have not shown that misoprostol aids in the ease, pain, or success of this procedure.\textsuperscript{19}

Given these data, it is reasonable to hypothesize that pretreatment with misoprostol could aid in IUD insertion. Existing studies examining this question have asserted varied conclusions. In this systematic review, we examine whether misoprostol pretreatment affects rates of IUD insertion failure in women presenting for routine IUD insertion without risk factors for insertion failure. We sought to compare women receiving misoprostol pretreatment with women receiving either placebo or no misoprostol. We also examine insertion pain, ease of insertion, expulsion rates, and complications of insertion.

**SOURCES**

One author (L.O.) performed systematic searches in May 2014 in the following databases: PubMed MEDLINE (1940s–), EMBASE (1947–), Cochrane Central Register of Controlled Trials (1966–), ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health Literature (1982–). Searches were performed using search terms for both misoprostol and intrauterine devices. The search was updated in May 2015. A search of ClinicalTrials.gov was added in May 2016 by one of the authors (L.R.M.) (Fig. 1). A full list of search terms and strategies is provided in Box 1. No date or language limits were applied.

**STUDY SELECTION**

During the first screen, two authors (L.R.M. and E.O.) independently screened the titles and abstracts of all retrieved articles. During this process, we selected articles for inclusion if they compared outcomes of women with and without misoprostol pretreatment before IUD insertion. We excluded studies that did not examine at least one of the following: success of IUD insertion, ease of IUD insertion, pain with IUD insertion, complications of IUD insertion, and IUD expulsion rates. We included studies examining misoprostol in any dosage or route and insertion of any IUD type. We included studies examining patients of any parity. In an effort to investigate routine IUD insertion, we excluded articles examining only IUD removal or only insertion after previous failed insertion. We also excluded articles that were descriptive studies; reviews; not randomized controlled trials (RCTs), case–control, or cohort studies; or duplicate studies. In the case of duplicate studies, the study with a larger population or more recent publication date was included. We retained 17 articles for full-text retrieval and further review (Fig. 1).

Quality assessment of the articles was adapted from well-established criteria previously described (Table 1).\textsuperscript{20} These criteria examine detailed considerations
regarding quality for several types of study designs. After the second full-text screen by two independent reviewers (L.R.M. and E.O.), nine articles were retained. All were RCTs. Reasons for exclusion in the second screen included: failure to meet 50% of quality criteria for specific study type (zero studies), duplicate populations or data (six studies), or abstract-only form of publication (two studies; Fig. 1). Studies meeting all quality criteria for study type were designated “high quality”; studies meeting 50–99% were designated as “low quality.” Overall, six were designated as high quality and three were designated as low quality (Tables 1 and 2).

RESULTS
A total of 161 unique results were retrieved from both searches. We retrieved nine RCTs examining one or more of the following measures with and without misoprostol administration: success—failure of insertion, ease—difficulty of insertion, subjective pain scores, expulsion rates, and complication rates (Fig. 1). We designated six trials as high quality and three as low quality. In the studies examined, the most common route of administration was 400 micrograms total per vagina (five studies) followed by 400 micrograms total buccally (three studies). In one study, patients received 400 micrograms either buccally or per vagina. The timing of misoprostol administration varied across studies. Two studies administered misoprostol 1 hour before insertion, one study administered 1.5 hours prior, four studies administered 3–4 hours prior, and two studies provided ranges of administration times (2–4 hours and 2–8 hours). All six high-quality RCTs were double-blind and used a similarly administered placebo in comparison groups. Of three low-quality studies, one used a similarly administered placebo as a comparison and two used no placebo in comparison groups (Table 2).
Failure of IUD insertion with and without misoprostol pretreatment was examined in six studies. All were RCTs and all revealed no difference in this measure (Table 3). Five of these studies were high quality and five examined IUD insertion in nulliparous patients only.

All RCTs included in this review examined the difficulty of IUD insertion with and without misoprostol pretreatment (Table 3). Seven of these nine studies revealed no difference in difficulty of insertion. Of these, five were high quality and five included nulliparous patients only. Methods used to determine ease of insertion as judged by health care providers were heterogeneous.

Conversely, two studies describe decreased difficulty of IUD insertion with misoprostol pretreatment. Scavuzzi et al examined difficulty of IUD insertion in 179 nulliparous patients with and without vaginal misoprostol pretreatment in a high-quality study. Insertion was deemed “difficult or very difficult” by health care providers in 26.7% of patients receiving misoprostol compared with 54.8% receiving placebo (P<.001). Additionally, these authors noted a significantly large proportion of women presenting for IUD insertion with cervical dilation greater than 4 mm when misoprostol was given. Sääv et al examined 80 nulliparous women undergoing IUD insertion with or without buccal misoprostol pretreatment. Of note, this is a low-quality study without a placebo control group. The proportion of insertions judged as “intermediate or difficult” by health care providers was 25.6% in the misoprostol group compared with 45% in the control group (P=.039).

All RCTs also examined the effect of misoprostol on pain during or immediately after IUD insertion. Seven of these nine studies revealed no difference in patient-reported pain measures with and without misoprostol administration (Table 3). Four studies were high quality and five included nulliparous patients only. Most used visual analog or 10-point scales to quantify patients’ perception of pain.

Two of the nine RCTs revealed significant differences in patient-reported pain scores between intervention groups. Lathrop et al reported several patient-reported pain measures in nulliparous patients undergoing insertion with or without buccal misoprostol. Using visual 100-point scales, the authors reported significantly increased pain with misoprostol pretreatment as compared with the control group, both immediately after insertion (46 compared with 34; P=.044) and before discharge from the clinic (35.5 compared with 20.5; P=.024). Conversely, Scavuzzi et al examined overall patient-reported pain scores and noted that pain scores of “moderate” or “severe” were 37% in the vaginal misoprostol group compared with 67% in women in a control group (P<.001).

Expulsion rates were examined in five RCTs. In all of these studies, expulsion rates were low and no significant difference was found in rates of expulsion with or without misoprostol pretreatment (Table 3). Complications of IUD insertion such as uterine perforation, pelvic inflammatory disease, heavy bleeding during insertion, and vasovagal reactions were discussed in two studies.

### Table 1. Quality Criteria Used for Assessment of Included Articles

<table>
<thead>
<tr>
<th>Quality Criterion</th>
<th>No. of Studies Meeting Criterion</th>
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<tbody>
<tr>
<td>Were patients randomized?</td>
<td>9</td>
</tr>
<tr>
<td>Was randomization concealed?</td>
<td>9</td>
</tr>
<tr>
<td>Were patients blinded to group allocation?</td>
<td>7</td>
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<tr>
<td>Were clinicians blinded to group allocation?</td>
<td>9</td>
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<tr>
<td>Were outcome assessors blinded to group allocation?</td>
<td>9</td>
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<tr>
<td>Were patients analyzed in the groups to which they were randomized?</td>
<td>7</td>
</tr>
<tr>
<td>Was follow-up complete?</td>
<td>9</td>
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Box 1. Search Terms and Strategies


("Intrauterine Devices"[Mesh] OR “intrauterine device”[all fields] OR "IUD"[all fields]) AND (“Misoprostol”[Mesh] OR “misoprostol”[all fields])

EMBASE search May 28, 2014; updated May 2015

("intraterine contraceptive device"/exp OR “intrauterine device” AND “intraterine devices” OR “intrauterine devices” OR “iud” OR “iuds”) AND (“misoprostol”/exp OR misoprostol)

Cochrane Library search May 28, 2014; updated May 2015

("intraterine device",ab OR IUD:ti,ab,kw OR MeSH descriptor: [Intrauterine Devices]) AND (misoprostol:ti,ab,kw OR MeSH descriptor: [Misoprostol])

CINAHL search May 28, 2014; updated May 2015

(MH “Intrauterine Devices” OR “intrauterine devices” OR “intraterine device” OR “IUD”) AND (MH “Misoprostol” OR “misoprostol”)

ClinicalTrials.gov search May 2016

("Misoprostol") AND (“Intrauterine device” OR “IUD”)

CINAHL, Cumulative Index to Nursing and Allied Health Literature.
No significant differences between rates of complications were noted.

No studies examined differences in these outcome measures between IUD types and no differences in outcome measures were noted between studies examining solely levonorgestrel-containing or copper-containing IUDs (Table 3).

**DISCUSSION**

Through this systematic review examining potential benefits of misoprostol administration before IUD insertion, we have explored relevant patient and health care provider factors in detail. We conclude that no benefit in patient-reported pain, health care provider-reported difficulty of insertion, failure of insertion, or expulsion rates can be substantiated based on the current available data. Most good-quality data report no benefit in any outcome with misoprostol administration. However, many are underpowered to detect differences in these outcomes. Few studies report misoprostol-related differences in difficulty of insertion or insertion-related pain, and these are flawed studies that should be interpreted with caution.

All six trials examining differences in rates of failed IUD insertion found no difference in this measure, our primary outcome. It is noteworthy that all trials had extremely high rates of successful insertions; each reported insertion success in at least 94% of patients in each arm. Because most studies included only nulliparous patients, who tend to experience more failed insertions in the literature, caution is needed in interpreting these success rates. In two studies, success or failure of insertion was described as a primary outcome by the authors. However, both studies were largely underpowered to detect differences in insertion failure. Again, caution should be taken in consideration of these results. Large numbers of patients would be required in future prospective randomized trials to achieve adequate power to detect these differences. Additionally, inclusion of populations with lower predicted insertion success, such as those with a prior failed attempt, may be associated with lower overall success and larger differences. Nevertheless, we can conclude that no current benefit exists for misoprostol pretreatment in reducing failed IUD insertions.

Although a minority of studies report a benefit in reducing overall difficulty of IUD insertion after misoprostol pretreatment, these should be interpreted with caution in the context of this systematic review. Of the two studies asserting this conclusion, only one is...
designated as high quality after our quality assessment and both studies contain methodologic flaws including lack of precision in reporting this outcome. One study contained a control group who did not receive a placebo. The other study assumed a 45% rate of subjective difficulty during IUD insertion in nulliparous patients in the power calculation, which is significantly lower than in other reports. Furthermore, both studies reported only 45–55% of insertions as “easy” in their outcome data; this greatly influences interpretation of results. It is clear that the benefit of misoprostol pretreatment cannot be confirmed by these reports.

Table 3. Outcome Measures of Articles Selected for Inclusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Insertion Failure</th>
<th>Difficulty of Insertion</th>
<th>Pain During Insertion</th>
<th>Other Outcomes</th>
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<tr>
<td>Dijkhuizen et al, 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>No difference (2.0% vs 1.0%; P=.59)</td>
<td>No difference (1–10 scale; 2.9 vs 2.8; P=.77)</td>
<td>No difference (VAS; 46 vs 40; P=.14)</td>
<td>Complications: no difference (21.8% vs 19.1%, P=.65)</td>
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<td>Edelman et al, 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>No difference (VAS; 24 mm vs 29 mm; P=.5)</td>
<td>No difference (VAS; 65 mm vs 55 mm; P=.83)</td>
<td>No difference (VAS; 5.8 vs 5.9; P=.94)</td>
<td>Expulsion: no difference (0% in both groups)</td>
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<td>Espey et al, 2014&lt;sup&gt;22&lt;/sup&gt;</td>
<td>No difference (0% in both groups)</td>
<td>No difference (VAS; 2.2 vs 2.5; P=.54)</td>
<td>No difference (VAS; 35.5 vs 20.5; P=.024)</td>
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<td>Lathrop et al, 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>No difference (5.4% vs 0%; P=.49)</td>
<td>No difference (VAS; 21 mm vs 21 mm; P=.75)</td>
<td>Pain immediately after insertion: increased with misoprostol (VAS; 46 vs 34; P=.044)</td>
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<td>Scavuzzi et al, 2013&lt;sup&gt;24&lt;/sup&gt;</td>
<td>No difference (4.7% vs 3.2%; P=.91)</td>
<td>Decreased with misoprostol (&quot;Difficult or very difficult&quot;; 26.7% vs 54.8%; P&lt;.001)</td>
<td>Decreased with misoprostol (&quot;Moderate or severe&quot;; 37.2% vs 66.7%; P&lt;.001)</td>
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<td>Swenson et al, 2012&lt;sup&gt;25&lt;/sup&gt;</td>
<td>No difference (4% vs 6%; P=.68)</td>
<td>No difference (VAS; 25 mm vs 27.4 mm; P=.64)</td>
<td>No difference (VAS; 58.4 mm vs 56.9 mm; P=.74)</td>
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<tr>
<td>Heikinheimo et al, 2010&lt;sup&gt;28&lt;/sup&gt;</td>
<td>No difference (&quot;Difficult&quot;; 7.0% vs 6.7%; P=1.0)</td>
<td>No difference (&quot;severe&quot;; 23.3% vs 10.9%; no P value given)</td>
<td>Need for cervical dilation to 4 mm: decreased with misoprostol (72.1% vs 41.9%; P&lt;.001)</td>
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<td>Ibrahim and Sayed Ahmed, 2013&lt;sup&gt;26&lt;/sup&gt;</td>
<td>No difference (1.5% vs 4%, P&gt;.05)</td>
<td>No difference (&quot;not easy&quot;; 7.7% vs 9.6%; P=.8)</td>
<td>No difference (VAS; 7 vs 6.5, P=.8)</td>
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<tr>
<td>Säjäv et al, 2007&lt;sup&gt;29&lt;/sup&gt;</td>
<td>No difference (&quot;intermediate or difficult&quot;; 25.6% vs 45%; P=.039)</td>
<td>Decreased with misoprostol (&quot;Intermediate or difficult&quot;; 25.6% vs 45%; P=.039)</td>
<td>Cervical dilation: no difference (4 mm in both groups; P=.4)</td>
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<td></td>
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<td></td>
<td>Cervical dilation at insertion: no difference (4 mm vs 4 mm; P=.44)</td>
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<td></td>
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<td>Expulsion: no difference (0% in both groups)</td>
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VAS, visual analog scale.
Bold indicates primary outcome conclusions for each study.
Significantly, the majority of studies examined reveal no difference in patient-reported pain scores with and without misoprostol pretreatment. Although the agent’s effects at the cellular level are long proven, its softening and ripening effects do not appear to translate into improved patient symptomatology. However, many of these studies contain insufficient power to determine differences in this outcome. It is noteworthy that one study determined that misoprostol improved patient-reported pain scores during insertion, and one study concluded the opposite, that pain scores were sustainably increased during IUD insertion after misoprostol pretreatment. Clearly, the majority of the data do not replicate these assertions.

The conclusion of increased pain after misoprostol administration in one investigation is likely related to side effects of misoprostol, which include nausea, diarrhea, and abdominal cramping. The incidence of cramping may be related to route of administration. Although we have shown no significant benefit of misoprostol administration, our study did not thoroughly address these risks of misoprostol administration that could potentially deter its use in this outpatient setting. These potential side effects should be carefully examined in the consideration of misoprostol use before IUD insertion, given that we are unable to prove its benefits.

There are several limitations to this systematic review. Given that we were unable to complete a meta-analysis as a result of heterogeneity of the methods and outcomes of our data, our conclusions are not held to the same rigorous standards as a statistically driven review. Furthermore, many outcomes examined are limited by a lack of power in each study. Large RCTs are still lacking. Our data examine outcomes associated with misoprostol administration in varying routes and doses. We reviewed data examining different populations, different types of IUDs, and using different statistical analyses. Although this makes our conclusions grounded in a diverse set of data, it does not address nuances that may arise regarding the potential benefits of misoprostol in unique situations and in unique populations.

It is important to note that no data exist examining insertion failures, difficulty, or pain when misoprostol is administered at a time much longer (12–24 hours) before the IUD insertion. Given that the hysteroscopy literature has reported improved outcomes with such long-term misoprostol pretreatment, these data would be vital for inclusion in future studies.

The results of this study have practical implications for clinical practice. The routine use of misoprostol before IUD insertion in multiparous or nulliparous patients is not advised. Certain clinical situations may call for consideration of misoprostol use as part of the treatment plan such as anatomic distortion, cervical stenosis, a prior failed IUD insertion attempt, or insertion in postmenopausal women. Further studies may be necessary to delineate which patient factors are associated with a benefit in misoprostol before IUD insertion.

REFERENCES


