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Medications to ease intrauterine device insertion: a systematic review

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Abstract

Background: Potential barriers to intrauterine device (IUD) use include provider concern about difficult insertion, particularly for nulliparous women.

Objective: This study aims to evaluate the evidence on the effectiveness of medications to ease IUD insertion on provider outcomes (i.e., ease of insertion, need for adjunctive insertion measures, insertion success).

Search strategy: We searched the PubMed database for peer-reviewed articles published in any language from database inception through February 2016.

Selection criteria: We included randomized controlled trials (RCTs) that examined medications to ease interval insertion of levonorgestrel- releasing IUDs and copper T IUDs.

Results: From 1855 articles, we identified 15 RCTs that met our inclusion criteria. Most evidence suggested that misoprostol did not improve provider ease of insertion, reduce the need for adjunctive insertion measures or improve insertion success among general samples of women seeking an IUD (evidence Level I, good to fair). However, one RCT found significantly higher insertion success among women receiving misoprostol prior to a second IUD insertion attempt after failed attempt versus placebo (evidence Level I, good). Two RCTs on 2% intracervical lidocaine as a topical gel or injection suggested no positive effect on provider ease of insertion (evidence Level I, good to poor), and one RCT on diclofenac plus 2% intracervical lidocaine as a topical gel suggested no positive effect on provider ease of insertion (evidence Level I, good). Limited evidence from two RCTs on nitric oxide donors, specifically nitroprusside or nitroglycerin gel, suggested no positive effect on provider ease of insertion or need for adjunctive insertion measures (evidence Level I, fair).

Conclusions: Overall, most studies found no significant differences between women receiving interventions to ease IUD insertion versus controls. Among women with a recent failed insertion who underwent a second insertion attempt, one RCT found improved insertion success among women using misoprostol versus placebo.

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Keywords

Misoprostol; Lidocaine; Nitric oxide donors; Intrauterine devices; Insertion difficulty; Systematic review

1. Introduction

Intrauterine devices (IUDs) are highly effective contraceptive methods [1] that are generally safe for women, including adolescents and nulliparous women, based on the US Medical Eligibility Criteria for Contraceptive Use [2]. Although IUD use is increasing in the United States [3–5], rates remain lower than use of combined hormonal methods and condoms [4], which have higher failure rates due to greater dependence on user adherence. Potential barriers to IUD use include patient pain with insertion [6–8] and provider concern about difficult insertion, particularly for nulliparous women [9]. However, it has been shown that IUDs can be successfully inserted in nulliparous adolescents and young women, with high (96%) and similar first-attempt success rates as their parous counterparts [10]. Factors previously suggested to affect ease of IUD insertion or patient pain include age, parity, time of menses, time since last pregnancy, pregnancy delivery type, breastfeeding status, anticipated pain and IUD type [11–14], although findings are inconsistent. Identifying effective approaches to ease IUD insertion and reduce patient pain may increase IUD uptake by increasing the number and types of healthcare providers who perform IUD insertions.

Several systematic reviews have examined interventions to reduce pain with IUD insertion [15–18]. Medications examined have included nonsteroidal antiinflammatory drugs (NSAIDs), lidocaine, misoprostol and nitric oxide donors. Reviews have focused on patient outcomes including pain, side effects, adverse events and participant satisfaction. Provider outcomes such as ease of insertion, need for adjunctive insertion measures and insertion success have not been examined systematically. Since providers often initiate conversations about IUDs with women during contraceptive counseling [19] and may not discuss IUDs if there are concerns about difficult insertion, it is important to understand the effects of medications to ease IUD insertion on provider outcomes as well.

The US Centers for Disease Control and Prevention (CDC) publishes the US Selected Practice Recommendations for Contraceptive Use (US SPR) [20], which provides evidence-based guidance on a select group of common, yet sometimes complex, management issues around the initiation and use of specific contraceptive methods. Currently, the US SPR does not include recommendations for the provision of medications to ease IUD insertion. As part of a process to update the US SPR, the objective of this systematic review was to evaluate the evidence on the effectiveness of medications to ease IUD insertion on provider outcomes, to complement prior evidence [15] on the effectiveness of medications to ease IUD insertion on patient outcomes.

2. Materials and methods

We conducted this systematic review according to the PRISMA guidelines [21]. Our key question was whether patient use of a specific medication to ease IUD insertion improves provider outcomes compared with nonuse of the specific medication.

2.1. Literature search

We searched the PubMed database for peer-reviewed articles published in any language from database inception through February 2016 on the effect of medications to ease IUD insertion, using the following search strategy:

> ((((“Intrauterine Devices”[Mesh] OR “Intrauterine Devices, Copper”[Mesh] OR “Intrauterine Devices, Medicated” [Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR iucd OR IUS OR mirena OR skyla OR paragard OR “Copper T380” OR CuT380 OR “Copper T380a” OR “Cu T380a”) NOT (“Animals”[Mesh] NOT “Humans”[Mesh]))) AND insert*) AND (((((((“Pain”[Mesh])) OR “adverse effects”[Subheading]) OR “Drug-Related Side Effects and Adverse Reactions”[Mesh]) OR “Patient Satisfaction”[Mesh]) OR“Anxiety”[Mesh])) OR ((((“Intrauterine Devices”[Mesh] OR “Intrauterine Devices, Copper”[Mesh] OR “Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra- uterine) AND (device OR system OR contracept*)) OR IUD OR iucd OR IUS OR mirena OR skylab OR paragard OR “Copper T380” OR CuT380 OR “Copper T380a” OR “Cu T380a”) NOT (“Animals”[Mesh] NOT “Humans”[Mesh]))) AND insert*) AND (((((((“Pain”[Mesh])) OR “adverse effects”[Subheading]) OR “Drug-Related Side Effects and Adverse Reactions” [Mesh]) OR “Patient Satisfaction”[Mesh]) OR “Anxiety”[Mesh])) OR (pain OR “side effect*” OR “patient satisfaction” OR “ease of insertion” OR anxiety))

The search strategy was broad to capture all potential medications. Additionally, we hand-searched reference lists from articles identified by the search and key review articles.

2.2. Selection criteria

We reviewed titles as well as abstracts to identify studies examining medications to ease IUD insertion. We included studies that examined insertion of currently available levonorgestrel-releasing (LNG) IUDs or any copper T IUD ever approved by the US Food and Drug Administration and distributed in the United States (i.e., Copper T380A, Copper 7, Copper T200B), for women of any age and for any indication. We included studies that examined multiple IUD types if the majority of women received an IUD meeting the above-mentioned criteria. We only included studies that examined interval insertion, and we excluded those that examined postabortion or postpartum insertion. We included studies that examined provider outcomes (i.e., ease of insertion, generally measured by a visual analog scale; need for adjunctive insertion measures, including cervical dilation, ultrasound guidance or paracervical block; and insertion success) but excluded studies that only reported patient outcomes (e.g., pain, side effects, satisfaction). We included only randomized controlled trials (RCTs) given the number of interventions identified addressing ease of IUD insertion.

2.3. Study quality assessment and data synthesis

The evidence was summarized and systematically assessed by two authors independently. The quality of each individual piece of evidence was assessed using the grading system developed by the United States Preventive Services Task Force [22]. We focused on several study factors when assessing quality, including randomization procedures, blinding of providers, study population, medication details, consideration of confounders and outcome measurement. We did not compute summary measures of association due to heterogeneity across the included studies related to study population, medication details and outcome measurement.

3. Results

The search strategy identified 1855 articles, of which 15 [23–37] met our inclusion criteria. Excluded studies were mainly review papers and papers not relevant to our key question. Two studies were excluded because they examined nonmedication interventions to ease IUD insertion (i.e., use of inhaled lavender [38] or having a full bladder [39]). Four studies were excluded because either they only included IUDs never available in the United States [40–42] or the majority of IUDs studied were never available in the United States [43]. Thirteen studies [13,14,44–54] were excluded because they only reported on patient outcomes (e.g., pain during IUD insertion) and have already been summarized in a recent systematic review [15]. One case series that examined second-attempt insertion success among women receiving misoprostol after a failed first-attempt insertion was excluded due to study design [55]. Of the 15 RCTs included in our systematic review, 10 examined misoprostol [23–32], 2 examined intracervical 2% lidocaine [33,35], 1 examined diclofenac plus intracervical 2% lidocaine [37] and 2 examined nitric oxide donors [34,36]. Four RCTs [27,34–36] included only LNG IUDs, three [28,31,37] included only copper (Cu) IUDs and eight [23–26,29,30,32,33] included both LNG and Cu IUDs but did not stratify results by IUD type. Of the 12 RCTs that included LNG IUDs, 1 specifically reported including only 52 mg LNG IUDs [23]; it is unlikely that any of the other RCTs included the newer, smaller LNG IUD (13.5 mg) since most completed data collection before it became available [24–26,29,30,32–34,36,37]. The indication for IUD use was for contraception in nine RCTs [25,26,30–32,34–37], contraception or therapeutic treatment in three RCTs [24,27,33] and unknown in three RCTs [23,28,29].

3.1. Misoprostol

Of the 10 misoprostol trials, 7 were among women without prior vaginal delivery [25,26,28–32], 2 were among women with and without prior vaginal delivery [24,27] and 1 was among women with a recent failed insertion [23] (Table 1). We rated two studies as good quality [23,26] and eight studies as fair quality [24,25,27–32]. Each examined 400 mcg of misoprostol, but the route and timing of administration differed in each trial. All studies compared misoprostol versus placebo, except one [28] that compared misoprostol plus oral diclofenac versus diclofenac alone. Sample sizes ranged from 40 [25] to 274 women [28].

3.1.1. Women without prior vaginal delivery only—Of the seven misoprostol trials among women without prior vaginal delivery, five [25,26,28,29,32] found no significant

differences between misoprostol and control groups in provider ease of insertion, need for adjunctive insertion measures or insertion success. In the first of these studies [25], 40 nulliparous women requesting an IUD were randomized to receive either misoprostol (400 mcg, buccal, 1.5 h before IUD insertion; n=20) or placebo (n=20). IUD insertion technique was standardized, and IUDs were inserted by residents in obstetrics and gynecology and staff physicians. IUD types were LNG IUDs (≥75%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among women attempting IUD insertion and included in analyses (n=17 in intervention group; n=18 in control group), there were no significant differences between misoprostol and control groups in procedure time (mean=5.1 versus 5.5 min, respectively), provider ratings of ease of insertion (mean=24 versus 29, respectively, on a 100-mm visual analog scale ranging from 0=easy to 100=extremely difficult) or need for cervical dilation (0% versus 16%, respectively) or paracervical block (0% versus 12%, respectively). Also, insertion success was similar between misoprostol and control groups with 0% and 1% failed insertions, respectively (significance testing not conducted).

In the second of the five studies [32], 108 nulliparous women requesting an IUD were randomized to receive either misoprostol (400 mcg, vaginal or buccal by patient choice, 3–4 h before IUD insertion; n=54) or placebo (n=54). IUDs were inserted by experienced providers who had placed ≥10 IUDs in the past year. IUD types were LNG IUDs (74%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among women attempting IUD insertion and included in analyses (n=54 in intervention group; n=51 in control group), there were no significant differences between misoprostol and control groups in provider ratings of ease of insertion (mean=25.0 versus 27.4, respectively, on a 100-mm visual analog scale ranging from 0=extremely easy to 100=impossible); need for cervical dilation (9% versus 10%, respectively), ultrasound guidance (2% versus 6%, respectively) or paracervical block (6% versus 0%, respectively); or insertion success (4% versus 6% failed insertions, respectively).

In the third of the five studies [28], 274 parous women who had previously delivered only by elective cesarean section requesting an IUD were randomized to either intervention group (400 mcg misoprostol, sublingual, plus 100 mg diclofenac, 1 h before IUD insertion; n=137) or control group (diclofenac alone; n=137). IUDs were inserted following menstruation (timing otherwise not reported) and were inserted by obstetrician-gynecologists with ≥3 years of experience inserting IUDs. All IUDs were Cu IUDs. Cervical dilation was measured up to 4 mm in all women prior to IUD insertion. Among women attempting IUD insertion and included in analyses (n=130 in intervention group; n=125 in control group), there were no significant differences between misoprostol and control groups in procedure time (mean=4.1 min for both groups), provider ratings of ease of insertion (easy, usual, difficult/failed; 92% versus 90% of insertions were rated as easy, respectively), cervical dilation (median=4 mm in both groups), need for analgesia (30% versus 29%, respectively) or additional cervical dilation (1% versus 2%, respectively) or insertion success (2% versus 4% failed insertions, respectively).

In the fourth of the five studies [29], 73 nulliparous women requesting an IUD were randomized to receive either misoprostol (400 mcg, buccal, 2–4 h before IUD insertion;

n=37) or placebo (*n*=36). IUDs were inserted by obstetrician-gynecologists with advanced training in family planning. IUD types were LNG IUDs (71%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among all women randomized, there were no significant differences between misoprostol and control groups in provider ratings of ease of insertion (median=21 for both groups, on a 100-mm visual analog scale ranging from 0=extremely easy to 100=impossible); need for cervical dilation (14% versus 8%, respectively), ultrasound guidance (3% versus 0%, respectively) or paracervical block (3% versus 0%, respectively); or insertion success (5% versus 0% failed insertions, respectively).

In the last of the five studies [26], 83 nulliparous women requesting an IUD were randomized to receive either misoprostol (400 mcg, buccal, 2–8 h before IUD insertion; *n*=42) or placebo (*n*=40). IUD insertion technique was standardized, and IUDs were inserted by five attending physicians skilled in IUD insertion (physician specialties not reported). IUD types were LNG IUDs (≥86%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among all women randomized, there were no significant differences between misoprostol and control groups in provider ratings of ease of insertion (mean=2.2 versus 2.5, respectively, on a 10-cm visual analog scale ranging from 0=easy to 10=extremely difficult), need for cervical dilation or ultrasound guidance (14% versus 25%, respectively; data not reported separately for each adjunctive insertion measure) or insertion success (all women had successful IUD placement).

In two trials [30,31], providers reported significantly easier insertion among women receiving misoprostol versus placebo 2–4 h before insertion. In the first of these studies [30], 61 nulliparous women requesting an IUD were randomized to receive either misoprostol (400 mcg, vaginal or buccal, 2 h before IUD insertion; *n*=30) or placebo (*n*=31). IUD insertion technique was standardized, and IUDs were inserted by residents in obstetrics and gynecology and attending physicians. IUD types were LNG IUDs (≥70%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among all women randomized, providers reported significantly ($p<.05$) easier insertion among women receiving misoprostol versus placebo (mean=24.1 versus 33.4, respectively, on a 100-mm visual analog scale ranging from 0=easiest to 100=most difficult insertion). No differences between misoprostol and control groups were found in the need for adjunctive insertion measures (only one woman in the control group required cervical dilation; significance testing not conducted) or insertion success (all women had successful IUD placement).

In the second of two studies that found significant differences in provider ease of insertion between misoprostol and control groups [31], 190 nulligravida women requesting an IUD were randomized to receive either misoprostol (400 mcg, vaginal, inserted by a provider into the posterior vaginal fornix 4 h before IUD insertion; *n*=95) or placebo (*n*=95). IUD insertion technique was standardized, and all IUDs were inserted by a single provider. All IUDs were Cu IUDs and inserted during menstruation. Cervical dilation was measured up to 4 mm in all women prior to IUD insertion. The provider rated insertion as easy or difficult/very difficult. Among women attempting IUD insertion and included in analyses (*n*=86 in intervention group; *n*=93 in control group), the provider reported significantly ($p<.0001$) fewer insertions as difficult/very difficult for women receiving misoprostol versus placebo (27% versus 55%, respectively; relative risk [RR]=0.49, 95% confidence interval [CI]=0.33,

0.72). Women receiving misoprostol versus placebo also had significantly (p<.0001) reduced risk of cervical dilation measurement ≤4 mm (28% versus 58%, respectively; RR=0.48, CI=0.33, 0.70) No significant differences in insertion success were found between misoprostol and control groups (5% versus 3% failed insertions, respectively).

3.1.2. Women with and without prior vaginal delivery—Of the two misoprostol trials among women with and without prior vaginal delivery, one examined the effect of sublingual misoprostol (400 mcg, 3 h before IUD insertion) versus placebo among 89 women requesting immediate insertion of a subsequent IUD after removal of a prior IUD; 9% of women in the intervention group were nulliparous compared with 2% in the control group [27]. IUD insertion was conducted according to normal clinical practice including cervical dilation as a standard procedure in one of six sites, and IUDs were inserted by 11 providers experienced in IUD insertion. All IUDs were LNG IUDs. Among women attempting IUD insertion and included in analyses (n=43 in intervention group; n=46 in control group; total number of women randomized was not reported), no significant differences in provider ratings ease of insertion (easy or difficult) were found between misoprostol and control groups (93% versus 91% of insertions were rated as easy, respectively) nor were there differences in the need for cervical dilation (19% versus 20%, respectively) or local anesthesia (2% for both groups).

In the second trial, 270 women requesting an IUD were randomized to receive either vaginal misoprostol (400 mcg, 3 h before IUD insertion; n=136) or placebo (n=134); nearly half of women in both study groups were nulliparous [24]. IUDs were inserted by 38 providers with a range of experience including interns, residents, midwives and obstetrician-gynecologists. IUD types were LNG IUDs (90%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Some IUD types (b8%) were not available in the United States. Among women attempting IUD insertion and included in analyses (n=102 in intervention group; n=97 in control group), there were no significant differences between misoprostol and control groups in provider ratings of ease of insertion (mean=2.9 versus 2.8, respectively, on a 10-cm visual analog scale ranging from 0=extremely easy to 10=extremely) or insertion success (2% versus 1% failed insertions, respectively). For both outcomes, findings did not differ when stratified by parity (data not reported).

3.1.3. Women with a recent failed insertion—The last misoprostol trial examined the effect of misoprostol among women with a recent failed insertion [23]. The study included 100 women with IUD insertion failure at first attempt. Three providers highly experienced in IUD insertion were called to assist providers unsuccessful with the first insertion attempt, who tried insertion again as part of the first attempt. These same highly experienced providers made the second insertion attempt (timing after initial attempt not reported). Women were randomized to receive misoprostol vaginally (200 mcg 10 h before insertion and 200 mcg 4 h before insertion) or placebo. IUD types were LNG IUDs (92%) and Cu IUDs; all women in the intervention group chose LNG IUDs versus 82% in the control group. Among the intervention group (n=55), 48 women attempted insertion and 7 never returned. Among the control group (n=45), 42 women attempted insertion and 3 never returned. Among women who attempted a second IUD insertion (excluding those who never

returned to the clinic), there were significant differences in successful insertions between misoprostol (88%) and control (62%) groups (RR=1.41, CI=8.2, 43.0). Among intent-to-treat women (including those who never returned to the clinic), there were differences in successful insertions between misoprostol (76%) and control (58%) groups, but findings were not statistically significant (RR=1.32, CI=0.3, 36.0). There were no significant differences in the need for cervical dilation between groups (44% versus 50%, respectively). Also, among women who attempted a second insertion, receiving placebo versus misoprostol was significantly associated with failed insertion after adjustment for age, delivery history, uterus position, uterine sound measure and provider type (prevalence ratio [PR] = 2.90, CI=1.13, 7.42).

3.2. Intracervical 2% lidocaine

Two trials examined the effect of intracervical 2% lidocaine (inserted into the cervical canal or injected into the cervical stroma) on provider ease of insertion (Table 2) [33,35]. One was rated as having good quality [33], and one was rated as having poor quality [35].

The first trial examined the effect of 2% lidocaine as a topical gel inserted into the cervical canal with an angiocatheter 3 min before IUD insertion (n=75) versus a placebo gel (n=75) among 150 women requesting an IUD; 70% had a prior vaginal delivery, 23% had a prior cesarean section and 7% were nulliparous [33]. IUD insertion technique was standardized, and IUDs were inserted by 37 providers with a range of experience including nurse practitioners, residents in obstetrics and gynecology and attending physicians. IUD types were LNG IUDs (86%) and Cu IUDs, and the distribution of IUD type did not differ by study group. Among women attempting IUD insertion and included in analyses (n=72 in intervention group; n=73 in control group), there were no significant differences between lidocaine and control groups in procedure time (median=111.0 versus 99.5 s, respectively) or provider ratings of ease of insertion (67% versus 66% of insertions were rated as easy, 29% versus 31% were rated as average and 4% versus 3% were rated as easy, respectively).

The second trial examined the effect of 2% lidocaine as an intracervical block injected 5 min before IUD insertion (n=50) versus 400 mg of ibuprofen taken 1 h before insertion (n=50) among 100 women requesting an IUD for the first time; 56% had a prior cesarean section and 44% were nulliparous [35]. IUD insertion technique was standardized, and IUDs were inserted between days 1 and 5 of menses by a single provider. All IUDs were LNG IUDs. Among women attempting IUD insertion and included in analyses (n=50 in intervention group; n=48 in control group), there were no significant differences in provider ratings of ease of insertion (rated as easy of difficult) between lidocaine and control groups (90% versus 83% of insertions were rated as easy, respectively).

3.3. Diclofenac plus intracervical 2% lidocaine

One trial rated as having good quality examined the effect of diclofenac plus intracervical 2% lidocaine on provider ease of insertion, (Table 2) [37]. Women requesting an IUD (n=90) were randomized to receive 100 mg of diclofenac 1 h before IUD insertion plus 2% lidocaine as a topical gel inserted into the cervical canal with a cotton swab 3 min before IUD insertion (n=45) or placebo tablets plus a placebo gel (n=45). The majority (78%) of

women had a prior vaginal delivery. IUD insertion technique was standardized, and IUDs were inserted by eight experienced gynecologists. All IUDs were Cu IUDs. Among all women randomized, there were no significant differences between diclofenac plus lidocaine and control groups in provider ratings of ease of insertion (mean=2.2 versus 2.4, respectively, on a 10-cm visual analog scale ranging from 0=very easy to 10=extremely difficult).

3.4. Nitric oxide donors

Two trials examined the effect of nitric oxide donors on provider ease of insertion and need for adjunctive insertion measures, both rated as having fair quality (Table 2) [34,36].

The first trial examined the effect of nitroprusside gel applied intracervically immediately prior to IUD insertion (n=13) versus a placebo gel (n=11) among 24 nulliparous women requesting an IUD with no prior IUD use or attempted placement [34]. IUD insertion technique was standardized; however, the experience level of inserting physicians was not reported. All IUDs were LNG IUDs. Among all women randomized, there were no significant differences between nitroprusside gel and control groups in provider ratings of ease of insertion (mean=32.4 versus 26.5, respectively; range and description of visual analog scale not reported) or the need for cervical dilation (8% versus 9%, respectively) or paracervical block (0% versus 0%, respectively).

The second trial examined nitroglycerin gel applied vaginally 30–45 min before IUD insertion (n=12) versus a placebo gel (n=12) among 24 nulliparous women requesting an IUD for contraception with no prior IUD use or attempted placement [36]. Of note, 92% of women in the intervention group versus 50% in the control group premedicated with 800 mg of ibuprofen (p=.07). IUD insertion technique was standardized, and IUDs were inserted by three attending physicians. All IUDs were LNG IUDs. Among all women randomized, there were no significant differences between nitroglycerin gel and control groups in provider ratings of ease of insertion (mean=29.4 versus 22.8, respectively, on a 100-mm visual analog scale ranging from 0=easy to 100= very difficult) or the need for cervical dilation (8% in both groups). One woman needed a paracervical block, but the study group was not reported.

4. Discussion

We included 15 RCTs in our systematic review that examined the effect of misoprostol [23–32], intracervical 2% lidocaine [33,35], diclofenac plus intracervical 2% lidocaine [37] or nitric oxide donors [34,36], on provider outcomes including ease of insertion, need for adjunctive insertion measures and/or insertion success. Of nine RCTs [24–32] that examined the effect of misoprostol on provider ease of insertion (measured by visual analog scales, 2- or 3-point rating scales or total procedure time), seven [24–29,32] found no significant differences between study groups. Two RCTs [30,31] found significantly easier insertion among women receiving misoprostol versus placebo 2–4 h before IUD insertion; however, all insertions were considered to be easy in one trial [30], and results may have been confounded in the other [31] given that providers measured cervical dilation in all women prior to IUD insertion that may have influenced provider ratings of ease of insertion. Of

seven RCTs [25–30,32] that examined the effect of misoprostol on need for adjunctive insertion measures (e.g., cervical dilation, ultrasound guidance, paracervical block), none found differences between study groups. Of eight RCTs [24–26,28–32] that examined the effect of misoprostol on insertion success among general samples of women seeking an IUD, none found differences between study groups. However, among women with a recent failed insertion, one RCT found that, among women who attempted insertion again, insertion success was significantly higher among women receiving misoprostol 10 h and 4 h prior to the second IUD insertion attempt [23]. For 2% intracervical lidocaine as a topical gel or injection used 3–5 min before IUD insertion versus placebo gel or ibuprofen, neither of two RCTs [33,35] found significant differences in provider ratings of ease of insertion (measured by 2- or 3-point rating scales) between lidocaine and control groups. For diclofenac 1 h before IUD insertion plus 2% intracervical lidocaine as a topic gel used 3 min before IUD insertion versus placebo, the one RCT identified found no significant differences in provider ratings of ease of insertion (measured by a visual analog scale) between study groups [37]. For nitric oxide donors, specifically nitroprusside gel applied intracervically immediately before IUD insertion or nitroglycerin gel applied vaginally 30–45 min before IUD insertion versus placebo, neither of two RCTs [34,36] found significant differences in provider ratings of ease of insertion (measured by visual analog scales) or need for adjunctive insertions measures (i.e., cervical dilation, paracervical block).

This body of evidence has several limitations. For RCTs examining misoprostol, one study did not describe randomization procedures [30], two studies did not describe whether or not allocation sequence procedures were concealed [29,30] and one study did not include a placebo for misoprostol [28]. Four studies used misoprostol formulated specifically for the study [26,29,30,32], and two did not report the source of the misoprostol [24,25]; it is possible that the pharmacokinetics of the study misoprostol may have differed from those of commercially formulated misoprostol. Misoprostol medication adherence was assumed in seven RCTs [23–26,29,30,32], and patient use of premedication (e.g., NSAIDs) was either not reported or assessed [29–31] or occurred but the distribution by study group was not reported [24]. In five studies, it was unknown if IUD insertion procedures were standardized [23,24,28,29,32], and the experience level of inserting physicians was not considered or adjusted for in three studies [24,25,30]. Three RCTs included limited response options when measuring provider ratings of ease of insertion [27,28,31]. Five studies were not powered to detect differences in outcomes of interest [25,26,29,30,32], with sample sizes ranging from 40 [25] to 108 [32], and intent-to-treat analyses were not performed in six studies [24,25,27,28,31,32]. One study included IUD types not available in the United States (b8%) and did not stratify results by IUD type [24]. One study included both LNG IUDs and Cu IUDs with differential distribution by study group [23]. Last, two studies were among prior IUD users who had undergone a previous successful insertion [24,27] and these women may not be generalizable to the population of women seeking a first IUD.

For RCTs examining 2% intracervical lidocaine, one study did not blind participants or providers to group allocation and did not include a placebo for lidocaine injection (e.g., saline injection) [35]. Both RCTs included limited response options when measuring provider ratings of ease of insertion, were not powered to detect differences in outcomes of interest and did not perform intent-to-treat analyses [33,35]. The RCT that examined

diclofenac plus 2% intracervical lidocaine assumed diclofenac adherence, did not report patient premedication with nonstudy drugs (e.g., NSAIDs) and was not powered to detect differences in outcomes of interest [37]. For RCTs examining nitric oxide donors, study groups were not comparable related to premedication with ibuprofen in one study [36], and the experience level of inserting physicians was not reported and may have differed in the other study [34]. Neither of the two RCTs were powered to detect differences in outcomes of interest and were conducted among small (n=24) samples of women [34,36].

A recent systematic review examined interventions to reduce patient pain and improve other patient outcomes [15]. RCTs that evaluated any intervention to reduce IUD insertion pain were included, as well as studies that examined any IUD type, regardless of past or present availability in the United States. A total of 33 RCTs were included and some metaanalyses conducted. Conclusions from the review were that misoprostol, 2% lidocaine gel and most NSAIDs did not help reduce pain at the time of insertion. In fact, several studies, including a metaanalysis of four trials, found significantly higher pain during IUD insertion among women receiving misoprostol versus placebo. Several studies also found increased side effects (e.g., cramping, shivering, headache, abdominal pain) among women receiving misoprostol versus placebo. The review suggested that paracervical block with lidocaine may reduce patient pain based on two RCTs [47,49] that found significantly reduced pain at either tenaculum placement or IUD insertion among women receiving paracervical block with 1% lidocaine 3–5 min before IUD insertion. The review also suggested that tramadol and naproxen may have some effect on reducing IUD insertion-related pain, but the RCTs [40,41] examining these medications included IUDs not available in the United States (i.e., Dalkon Shield, Multiload copper 375).

In conclusion, overall, most studies found no significant differences between women receiving interventions to ease IUD insertion versus controls. Evidence suggests that misoprostol does not improve provider ease of insertion (7/9 RCTs), reduce the need for adjunctive insertion measures (7/7 RCTs) or improve insertion success (8/8 RCTs), among general samples of women seeking an IUD (body of evidence grading Level I, good to fair). However, among women with a recent failed insertion who underwent a second insertion attempt, one RCT found improved insertion success among women using misoprostol versus placebo (body of evidence grading Level I, good). Limited evidence from one RCT on diclofenac plus 2% intracervical lidocaine as a topical gel suggests no positive effect on provider ease of insertion (body of evidence grading Level I, good). Limited evidence from two RCTs on 2% intracervical lidocaine as a topical gel or injection suggests no positive effect on provider ease of insertion (body of evidence grading Level I, good to poor). Limited evidence from two RCTs on nitric oxide donors, specifically nitroprusside or nitroglycerin gel, suggests no positive effect on provider ease of insertion or need for adjunctive insertion measures (body of evidence grading Level I, fair). Additional research in this area should not focus on routine use of misoprostol for IUD insertion but rather on other medications that may improve provider and patient outcomes with IUD insertion, as well as the use of misoprostol for insertion after failed IUD insertion attempt. The information from all but one RCT [37] summarized in this review, along with findings from a complementary review on the effectiveness of medications to ease IUD insertion on patient

outcomes [15], was presented to an expert panel in August 2015 at a meeting held by the CDC and will be incorporated into the forthcoming update of the US SPR.

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Table 1

Evidence on misoprostol to ease IUD insertion

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
Women without prior vaginal delivery only					
Edelman, 2011 [25] No external funding [54] USA, Oregon Health and Science University	RCT; 2 study groups 40 nulliparous women aged 18–45 years requesting an IUD for contraception IUD types included LNG (≥75%) or copper T380A Intervention group: 20 randomized; 17 attempted insertion and included in analyses (3 withdrew prior to IUD insertion); mean age=25±5 years Control group: 20 randomized; 19 attempted insertion (1 declined IUD after vagal reaction); 1 withdrew prior to IUD insertion; 17 included in analyses; mean age=27±6 years 35/40 (88%) completed study through clinic discharge	400 mcg misoprostol, buccal, vs. placebo, 1.5 h prior IUDs inserted by OB/GYN residents and staff physicians IUD insertion technique was standardized	Failed insertion Use of adjunctive insertion measures * Procedure time Provider ease of insertion measured by VAS immediately after IUD insertion (0=easy, 100 mm= extremely difficult)	• No differences in failed insertions between misoprostol and control groups (0% vs. 1%); significance testing NR • No significant differences in use of adjunctive insertion measures between misoprostol and control groups (cervical dilation: 0% vs. 16%; and paracervical block: 0% vs. 12%) • No significant differences in procedure time between misoprostol and control groups (mean minutes [SD]=5.1 [2.3] vs. 5.5 [2.4]) • No significant differences in provider ease of insertion between misoprostol and control groups (mean [SD] score= 24 [19] vs. 29 [21])	I, fair Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Excluded women with prior attempted or successful IUD insertion • Misoprostol and placebo were similar • High completion rate (88%) • Study groups comparable related to baseline characteristics (age, BMI, race/ethnicity, pregnancy history, dysmenorrhea) and nonoutcome procedural details (use of premedication, IUD type, local anesthesia placed at tenaculum site) Weaknesses • Source of misoprostol NR (commercially formulated or formulated for study) • Medication adherence assumed • Experience level of inserting physicians may have differed • Study not powered to detect differences in outcomes of interest • Intent-to-treat analyses not performed
Swenson, 2012 [32] No external funding [54] USA, University of Utah	RCT; 2 study groups 108 nulliparous women aged ≥18 years requesting an IUD for contraception	400 mcg misoprostol, vaginal or buccal by patient	Failed insertion	• No significant differences in failed insertions between misoprostol and	I, fair Strengths

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
	IUD types included LNG (74%) or copper T380A Intervention group: 54 randomized, attempted insertion and included in analyses; mean age=25±4 years Control group: 54 randomized; 53 attempted insertion (1 failed to return for insertion); 51 included in analyses (2 excluded for benzodiazepine or narcotic use); mean age=25±4 years 105/108 (97%) completed study through clinic discharge	choice, vs. placebo, 3–4 h prior; 94% chose to insert pills vaginally Misoprostol and placebo were formulated by study pharmacist IUDs inserted by experienced providers (placed ≥10 IUDs in past year)	Use of adjunctive insertion measures* Provider ease of insertion measured by VAS after IUD insertion (0=extremely easy, 100 mm=impossible)	control groups (4% vs. 6%) • No significant differences in use of adjunctive insertion measures between misoprostol and control groups (cervical dilation: 9% vs. 10%; ultrasound guidance: 2% vs. 6%; or paracervical block: 6% vs. 0%) • No significant differences in provider ease of insertion between misoprostol and control groups (mean [SE] score= 25.0 [3.5] vs. 27.4 [3.5])	• Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Misoprostol and placebo were identical • Minimal variation in IUD insertion skill level between providers • High completion rate (97%) • Study groups comparable related to baseline characteristics (age, race, pregnancy history) and nonoutcome procedural details (use of premedication, IUD type, route of pill administration) Weaknesses • Possible difference in pharmacokinetics between commercially formulated misoprostol and misoprostol used in study • Medication adherence assumed • Unknown if insertion procedures standardized • Study not powered to detect differences in outcomes of interest • Intent-to-treat analyses not performed
Ibrahim, 2013 [28] Funding source NR Egypt, Gynecology Clinic of the Suez Canal University Hospital	RCT; 2 study groups 274 parous women who delivered only by elective cesarean section requesting an IUD IUD type: copper T380A Intervention group: 137 randomized; 130 attempted insertion and included in analyses; mean age=29±6 years Control group: 137 randomized;	400 mcg misoprostol, sublingual, plus 100 mg diclofenac, oral, vs. 100 mg diclofenac, 1 h prior IUDs inserted by OB/GYNs with ≥ 3 years of experience inserting IUDs	Failed insertion Use of adjunctive insertion measures* Cervical dilation ≤4 mm measured by inserting Hegar dilator through internal orifice of cervix prior to IUD insertion Procedure time	• No significant differences in failed insertions between misoprostol and control groups (2% vs. 4%) • No significant differences in use of adjunctive insertion measures between misoprostol and control groups (analgesia: 30% vs.	I, fair Strengths • Randomization computer-generated • Providers blinded to group allocation • Allocation sequence concealed • Misoprostol was commercially formulated

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
	125 attempted insertion and included in analyses; mean age=30±7 years 255/274 (93%) completed study through clinic discharge	IUDs inserted following menstruation	Provider ease of insertion judged by resistance of internal cervical os (easy, usual, difficult/failed)	29%; dilation: 1% vs. 2%) • No significant differences in median cervical dilation between misoprostol and control groups (4 mm vs. 4 mm) • No significant differences in mean duration of procedure (4.1±1.6 vs. 4.1±2.8 min) between misoprostol and control groups • No significant differences in provider ease of insertion between misoprostol and ontrol groups (easy: 92% vs. 90%; usual: 6% vs. 6%)	• Medication adherence known (given by clinic nurse 1 h prior to procedure) • Minimal variation in IUD insertion skill level between providers • High completion rate (93%) • Large sample size although unknown if power calculations conducted • Study groups comparable related to baseline characteristics (age, BMI, pregnancy history) <u>Weaknesses</u> • Time after sublingual misoprostol administration may not have been sufficient to achieve peak effect • Placebo for misoprostol not given • Unknown if insertion procedures standardized • Limited response options for measurement of provider ease of insertion • Intent-to-treat analyses not performed
Lathrop, 2013 [29] No external funding [54] USA, Emory University	RCT; 2 study groups 73 nulliparous women aged ≥18 (mean=25.9) years requesting an IUD IUD types included LNG (71.3%) or copper T380A Intervention group: 37 randomized, attempted insertion and included in analyses; mean age=26 years Control group: 36 randomized, attempted insertion and included in analyses; mean age=26 years 71/73 (97%) completed study through clinic discharge	400 mcg misoprostol, buccal, vs. placebo, 2–4 h prior Misoprostol and placebo were formulated by study pharmacist IUDs inserted by 5 OB/GYNs with advanced training in family planning	Failed insertion Use of adjunctive insertion measures * Provider ease of insertion measured by VAS after IUD insertion (0=extremely easy, 100 mm=impossible)	• No significant differences in failed insertions between misoprostol and control groups (5% vs. 0%) • No significant differences in use of adjunctive insertion measures between misoprostol and control groups (cervical dilation: 14% vs. 8%; ultrasound guidance: 3% vs. 0%; or paracervical block: 3% vs. 0%)	I, fair <u>Strengths</u> • Randomization computer-generated • Participants and providers blinded to group allocation • Misoprostol and placebo were identical • Minimal variation in IUD insertion skill level between providers • High completion rate (97%) • Study groups comparable related to baseline characteristics (age, race, marital status, pregnancy

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
				• No significant differences in provider ease of insertion between misoprostol and control groups (median [range] score= 21 [0–100] and 21 [0–68])	history, STI history, income) and nonoutcome procedural details (IUD type) • Intent-to-treat analyses performed Weaknesses • Allocation sequence concealment NR • Possible difference in pharmacokinetics between commercially formulated misoprostol and misoprostol used in study • Medication adherence assumed • Patient use of premedication (e.g., NSAIDs) NR • Unknown if insertion procedures standardized • Study not powered to detect differences in outcomes of interest
Lotke, 2013 [30] No external funding [54] USA, University of Arizona	RCT; 2 study groups 61 nulliparous women aged ≥18 years requesting an IUD for contraception IUD types included LNG (≥70%) or copper T380A Intervention group: 30 attempted insertion and included in analyses; mean age=25±4 years; number randomized NR Control group: 31 attempted insertion and included in analyses; mean age=26±4 years; number randomized NR 61/62 (98%) completed study through clinic discharge	400 mcg misoprostol, vaginal or buccal by patient choice, vs. placebo, 2 h prior; 57% of misoprostol group took medication vaginally vs. 37% of placebo group Misoprostol and placebo were formulated by university pharmacist IUDs inserted by OB/GYN residents and attending physicians IUD insertion technique was standardized	Failed insertion Use of adjunctive insertion measures* Provider ease of insertion measured by VAS after IUD insertion (0=easiest insertion, 100 mm=most difficult)	• All patients had successful IUD placement • Only 1 patient in control group required adjunctive insertion measures (cervical dilation) • Providers reported significantly (p=.04) easier insertion among misoprostol vs. control group (mean [SD] score= 24.1 [14.2] vs. 33.4 [20.3])	I, fair Strengths • Participants and providers blinded to group allocation • Misoprostol and placebo were similar • High completion rate (98%) • Study groups comparable related to baseline characteristics (age, BMI, race/ethnicity, relationship status, education, pregnancy history, number of sexual partners in last six months) and nonoutcome procedural details (IUD type, route of pill administration, mean time from taking medication to IUD insertion) • Intent-to-treat analyses performed Weaknesses

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
					• Randomization procedures NR • Allocation sequence concealment NR • Possible difference in pharmacokinetics between commercially formulated misoprostol and misoprostol used in study • Medication adherence assumed • Experience level of inserting physicians may have differed • Patient use of premedication (e.g., NSAIDs) not assessed • Study not powered to detect differences in outcomes of interest
Scavuzzi, 2013 [31] Instituto de Medicina Integral Prof. Fernando Figueira Brazil	RCT; 2 study groups 190 nulligravida women aged 16–45 years requesting an IUD for contraception IUD type: copper T380A Intervention group: 95 randomized; 87 attempted insertion (1 declined) and included in analyses; 86 analyzed; mean age=25±6 years Control group: 95 randomized; 93 attempted insertion and included in analyses; mean age=25±6 years 179/190 (94%) completed study through clinic discharge	400 mcg misoprostol, vaginal, vs. placebo, 4 h prior (inserted by provider into posterior vaginal fornix) IUDs inserted by single provider All women were menstruating at time of IUD insertion IUD insertion technique was standardized	Failed insertion Cervical dilation ≤4 mm measured by inserting Hegar dilator through internal orifice of cervix prior to IUD insertion Provider ease of insertion (easy vs. difficult/very difficult)	• No significant differences in failed insertions between misoprostol and control groups (5% vs. 3%) • Misoprostol group had significantly (p<.0001) reduced risk of cervical dilation <4 mm vs. control group (RR=0.48; CI=0.33, 0.70; 28% vs. 58%) • Provider reported significantly (p<.0001) fewer insertions as difficult/very difficult for misoprostol vs. control group (RR=0.49 (27% vs. 55%), CI=0.33, 0.72)	I, fair Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and provider blinded to group allocation • Misoprostol and placebo were similar • Misoprostol commercially formulated • Medication adherence known (inserted vaginally by provider) • No variation in IUD insertion skill level (single provider) • High completion rate (94%) • Study groups comparable related to baseline characteristics (age, education) and procedural details (day of menstrual cycle, uterus position) • Target sample size determined by power calculations Weaknesses

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
					• Limited response options (with no neutral option) for measurement of provider ease of insertion • Patient use of premedication (e.g., NSAIDs) NR • Intent-to-treat analyses not performed
Espey, 2014 [26] No external funding [54] USA, University of New Mexico	RCT; 2 study groups 83 nulliparous women requesting an IUD for contraception IUD types included LNG (≥86%) or copper T380A Intervention group: 42 randomized, attempted insertion and included in analyses; mean age=24±4 years Control group: 40 randomized, attempted insertion and included in analyses; mean age=24±5 years 80/83 (96%) completed study through clinic discharge	400 mcg misoprostol, buccal, vs. placebo, 2–8 h prior Misoprostol and placebo were formulated by university pharmacist IUDs inserted by 5 attending physicians skilled in IUD insertion IUD insertion technique was standardized	Failed insertion Use of adjunctive insertion measures * Provider ease of insertion measured by VAS after IUD insertion (0=easy, 10 cm= extremely difficult)	• All patients had successful IUD placement • No significant differences in need for adjunctive insertion measures (dilation/ ultrasound) between misoprostol and control groups (14% vs. 25%). • No significant differences in provider ease of insertion between misoprostol and control groups (mean [SD]=2.2 [2.2] vs. 2.5 [2.2])	I, good Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Misoprostol and placebo were similar • Minimal variation in IUD insertion skill level between providers • High completion rate (96%) • Study groups comparable related to baseline characteristics (age, race/ethnicity, marital status, education, pregnancy history, STI history) and nonoutcome procedural details (use of premedication, IUD type) • Intent-to-treat analyses performed Weaknesses • Possible difference in pharmacokinetics between commercially formulated misoprostol and misoprostol used in study • Medication adherence assumed • Study not powered to detect differences in outcomes of interest
Women with and without prior vaginal delivery					

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
Heikinheimo, 2010 [27] Bayer-Schering Pharma, Berlin, Germany 6 clinics in Finland, Sweden	RCT; 2 study groups 89 women aged 23–45 years requesting immediate insertion of a subsequent IUD after removal of a prior IUD for contraception (~70%) or menorrhagia treatment (~30%) (number randomized NR) IUD type: LNG Intervention group: 43 attempted insertion; mean age=38±5 years; 9% nulliparous Control group: 46 attempted insertion; mean age=39±5 years; 2% nulliparous Completion rate NR	400 mcg misoprostol, sublingual, vs. placebo, 3 h prior IUDs inserted by 11 providers experienced and trained in IUD insertion IUD insertion was done according to normal clinical practice (cervical dilation included in standard procedure at 1 site)	Use of adjunctive insertion measures * Provider ease of insertion (easy or difficult)	• No significant differences in use of adjunctive insertion measures between misoprostol and control groups (cervical dilation: 19% vs. 20%; and use of local anesthesia: 2% vs. 2%) • No significant differences in provider ease of insertion between misoprostol and control groups (easy insertion: 93% vs. 91%)	I, fair <u>Strengths</u> • Multicenter • Randomization computer-generated, stratified by site • Allocation sequence concealed • Participants and providers blinded to group allocation • Misoprostol was commercially formulated • Medication adherence known (given by study nurse 3 h prior to procedure) • Misoprostol and placebo were similar • Minimal variation in IUD insertion skill level between providers • Target sample size determined by power calculations • Study groups appear comparable related to most baseline characteristics (age, BMI, number of pregnancies, number of births, years first IUD used) and nonoutcome procedural details (use of premedication, main indication for IUD), but statistical testing NR <u>Weaknesses</u> • Number of women randomized NR; unable to calculate completion rate • Prior IUD users (who had undergone a previous successful insertion) may differ from general population of women seeking first IUD • Limited response options (with no neutral option) for measurement of provider ease of insertion • Higher proportion of intervention group were

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
					nulliparous, but statistical testing NR • Intent-to-treat analyses not performed (number randomized NR)
Dijkhuizen, 2011 [24] Leiden University Medical Center 5 hospitals, Netherlands	RCT; 2 study groups 270 women aged ≥ 18 years requesting IUD for contraception (~85%) or therapeutic treatment (~15%); 1 woman sought subsequent IUD after removal of a prior IUD IUD types included LNG (90%) or copper (Multiload 275: *n*=4; T-safe Cu380: *n*=6; Flexi-T: *n*=4; frameless: *n*=1; other: *n*=5) Intervention group: 136 randomized; 102 attempted insertion and included in analyses; mean age=32±9 years; 48% nulliparous Control group: 134 randomized; 97 attempted insertion and included in analyses; mean age=31±8 years; 47% nulliparous 199/270 (74%) completed study through clinic discharge	400 mcg misoprostol, vaginal, vs. placebo, 3 h prior IUDs inserted by 38 providers (interns [little experience], residents, midwives, OB/GYNs [at least average experience])	Failed insertion Provider ease of insertion measured by VAS immediately after IUD insertion (0=extremely easy, 10 cm=extremely difficult)	• No significant differences in failed insertions between misoprostol and control groups (2% vs. 1%); RR=1.9, CI=0.2, 20.6; did not differ by parity • No significant differences in provider ease of insertion between misoprostol and control groups (mean [SD]=2.9 [2.8] vs. 2.8 [2.6]); did not differ by parity	I, fair <u>Strengths</u> • Multicenter • Randomization computer-generated, stratified by parity • Allocation sequence concealed • Participants and providers blinded to group allocation • Misoprostol and placebo were similar • Target sample size determined by power calculations • Study groups appear comparable related to most baseline characteristics (age, ethnicity, weight, parity, pregnancy history, menses during insertion, main indication for IUD) and procedural details (IUD type), but statistical testing NR <u>Weaknesses</u> • Some women were prior IUD users (who had undergone a previous successful insertion) and may differ from general population of women seeking first IUD • Source of misoprostol NR (commercially formulated or formulated for study) • Medication adherence assumed; known that 5 (3%) did not follow protocol but ≥70% of misoprostol group had remains of tablets present in vagina • Unknown if insertion procedures standardized

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
					• Experience level of inserting providers differed • Some IUD types included not available in USA; results not stratified • Completion rate <85%, although rate did not differ between study group • Use of premedication (*n*=3) and local anesthesia before insertion (*n*=1) occurred, but distribution by study group NR • Study groups appear dissimilar related to proportion of women breastfeeding (17% vs. 10% in misoprostol and control groups), but statistical testing NR • Intent-to-treat analyses not performed
Women with a recent failed insertion					
Bahamondes, 2015 [23] Brazilian National Research Council, Fundacao de Amparo a Pesquisa do Estado de Sao Paulo Brazil, University of Campinas Medical School	RCT; 2 study groups 100 women requesting an IUD with recent failed IUD insertion (mean age=37±7 years) IUD types included LNG (92%) or copper T380A Intervention group: 55 randomized; 48 attempted insertion; 16% nulliparous; 100% chose LNG IUD Control group: 45 randomized; 42 attempted insertion; 22% nulliparous; 82% chose LNG IUD 90/100 (90%) completed study through clinic discharge	400 mcg misoprostol, vaginal, vs. placebo, 10 (200 mcg) and 4 (200 mcg) hours prior to second insertion attempt 3 providers highly experienced in IUD insertion were called to assist providers unsuccessful with first insertion attempt; same 3 highly experienced providers made second insertion attempt	Successful insertion Use of adjunctive insertion measures*	• Among women who attempted a second IUD insertion (vs. intent to treat), there were significant differences in successful insertions between misoprostol and control groups (88% vs. 62%, p=.007; RR=1.41, CI=8.2, 43.0) • Among intent-to-treat women, there were differences in successful insertions between misoprostol and control groups (76% vs. 58%, significance testing NR) but RR=1.32, CI=0.3, 36.9 • Among women who attempted a second IUD insertion,	I, good Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Misoprostol and placebo were similar • Misoprostol was commercially formulated • Minimal variation in IUD insertion skill level between providers • High completion rate (90%); rate did not differ between misoprostol and control groups (87% vs. 93%) • Target sample size determined by power calculations • Intent-to-treat analyses performed

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
				receiving placebo (PR=2.90, CI=1.13, 7.42) was significantly associated with failed insertion after adjustment for age, delivery history, uterus position, uterine sound measure and provider type • No significant differences in need for cervical dilation between misoprostol and control groups (44% vs. 50%, p=. 8); no pain medication was given	• Study groups appear comparable related to most baseline characteristics (age, pregnancy and delivery history) and nonoutcome procedural details (uterus position, uterine sound measure), but statistical testing NR <u>Weaknesses</u> • Medication adherence assumed • Unknown if insertion procedures standardized • Study groups dissimilar related to IUD type (LNG: 100% vs. 82% in misoprostol and control groups), but statistical testing NR

BMI, body mass index; CI, 95% confidence interval; IUD, intrauterine device; LNG, levonorgestrel-releasing; NR, not reported; NSAID, nonsteroidal antiinflammatory drug; OB/GYN, obstetrics and gynecology; PR, prevalence ratio; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation; SE, standard error; STI, sexually transmitted infection; USA, United States of America; VAS, visual analog scales.

* Cervical dilation or use of os finder or soft endometrial biopsy, use of ultrasound guidance or additional anesthesia or analgesia during procedure to facilitate insertion.

Table 2

Evidence on other medications to ease IUD insertion

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
Intracervical 2% lidocaine					
Allen, 2013 [33] Society of Family Planning USA, Brown University	RCT; 2 study groups 150 women aged 18–41 years requesting an IUD for contraception or abnormal uterine bleeding; 70% had prior vaginal delivery, 23% had prior cesarean section and 7% were nulliparous; no prior IUD use IUD type: LNG (86%) or copper T380A Lidocaine group: 75 randomized; 72 included in analyses (3 had protocol violations) Control group: 75 randomized; 73 included in analyses (2 had protocol violations) 145/150 (97%) completed study	2% lidocaine gel vs. placebo gel (water-based lubricant), 6 mL (inserted into cervical canal via angiocatheter 3 min prior to insertion; 3 mL placed on anterior lip of cervix and remaining placed at internal os); no women used nonstudy, preinsertion analgesics, anxiolytics or misoprostol IUDs inserted by 37 providers (nurse practitioners, OB/GYN residents, attending physicians) IUD insertion technique was standardized	Procedure time Provider ease of insertion (easy, average or difficult)	• No significant differences in duration of procedure time in seconds between lidocaine and control groups (median [range]= 111.0 [64.0–569.0] vs. 99.5 [52.01719.0]) • No significant differences in provider ease of insertion between lidocaine and control groups (easy: 67% vs. 66%; average: 29% vs. 31%; difficult: 4% vs. 3%)	I, good Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Study groups comparable related to baseline characteristics (age, race/ethnicity, insurance, BMI, gravida, parity, delivery history, breastfeeding, dysmenorrhea, self-rated pain tolerance) and procedural details (IUD type, timing of insertion, uterine position, provider type) • High completion rate (97%) Weaknesses • Limited response options for measurement of provider ease of insertion • Study not powered to detect differences in outcomes of interest • Intent-to-treat analyses not performed
Castro, 2014 [35] National Institute of Hormones and Women's Health, National Council for Scientific and Technological Development Brazil, University of Sao Paulo	RCT; 2 study groups 100 women aged 18–45 years requesting an IUD for the first time for contraception; 56% had prior cesarean section and 44% were nulliparous IUD type: LNG Lidocaine group: 50 randomized, attempted insertion and included in analyses; mean age=30±6 years Control group: 50 randomized; 48 attempted insertion and included	2% lidocaine injection (1.8 mL) 5 min prior to insertion (injected into cervix at 3-, 6-, 9-, 12-o'clock positions using carpule syringe and 27-gauge needle) vs. 400 mg ibuprofen 1 h prior IUDs inserted by single provider	Provider ease of insertion (easy or difficult)	• No significant differences in provider ease of insertion between lidocaine and control groups (easy: 90% vs. 83%; difficult: 10% vs. 17%)	I, poor Strengths • Randomization computer-generated • Allocation sequence concealed • No variation in IUD insertion skill level (single provider) • High completion rate (98%) • Study groups comparable related to baseline characteristics (age,

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
	in analyses; mean age=31±6 years 98/100 (98%) completed study	IUD insertion technique was standardized IUDs inserted between days 1–5 of menses			BMI, blood pressure, parity, prior use of HC, education, income, smoker status) Weaknesses • Participants and provider not blinded to group allocation • No placebo (e.g., saline injection) • Unclear if women delivering by cesarean section experienced labor/cervical dilation • Limited response options (with no neutral option) for measurement of provider ease of insertion • Study not powered to detect differences in outcomes of interest • Intent-to-treat analyses not performed
Diclofenac plus intracervical 2% lidocaine					
Fouda, 2016 [37,33] Funding source NR Egypt, Cairo University	RCT; 2 study groups 90 parous women aged 18–50 years requesting an IUD for contraception; 78% had prior vaginal delivery; no prior IUD use IUD type: copper T380A Diclofenac+lidocaine group: 45 randomized, received IUD and included in analyses Control group: 45 randomized, received IUD and included in analyses 90/90 (100%) completed study	Diclofenac (2–50 mg tablets), 1 h prior +2% lidocaine gel, 6 mL vs. placebo tablets+placebo gel (water-based lubricant); gel inserted into cervical canal via cotton swab 3 min prior to insertion (3 mL placed on anterior lip of cervix and remaining placed at internal os); IUDs inserted by 8 experienced gynecologists IUD insertion technique was standardized	Provider ease of insertion measured by VAS after IUD insertion (0=very easy, 10 cm=extremely difficult)	• No significant differences in provider ease of insertion between diclofenac +lidocaine and control groups (mean [SD]= 2.2 [1.5] vs. 2.4 [2.0])	I, good Strengths • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Study groups comparable related to baseline characteristics (age, BMI, gravida, parity, delivery history, time since last delivery, breastfeeding, dysmenorrhea, baseline anxiety scores) and procedural details (uterine position) • High completion rate (100%) • Intent-to-treat analyses conducted Weaknesses • Medication adherence assumed

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
					• Patient premedication with nonstudy drugs (e.g., NSAIDs) NR • Study not powered to detect differences in outcomes of interest
Nitric oxide donors					
Bednarek, 2013 [34] Society of Family Planning USA, Oregon Health and Science University and Planned Parenthood Columbia Willamette	RCT; 2 study groups 24 nulliparous women aged 18–45 years requesting an IUD for contraception; no prior IUD use or attempted placement IUD type: LNG Nitroprusside gel group: 13 randomized and included in analyses Control group: 11 randomized and included in analyses 23/24 (96%) completed study	10 mg nitroprusside gel (1 mL) vs. placebo gel, applied intracervically immediately prior to IUD insertion IUD insertion technique was standardized and included local anesthesia placed at tenaculum site	Need for cervical dilation or paracervical block Provider ease of insertion measured by VAS after IUD insertion (scale NR)	• No significant differences between nitroprusside gel and control groups in need for cervical dilation (8% vs. 9%); no women needed paracervical block • No significant differences in provider ease of insertion between nitroprusside gel and control groups (mean [SD]= 32.4 [22.7] vs. 26.5 [27.2])	I, fair Strengths • Multiple centers • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Excluded women with prior attempted or successful IUD insertion • Nitroprusside and placebo gels were identical • High completion rate (96%) • Study groups comparable related to most baseline characteristics (age, BMI, race/ethnicity, current menstruation, dysmenorrhea) and nonoutcome procedural details (use of premedication, expected pain, anxiety level, uterine position) • Intent-to-treat analyses for outcomes of interest performed Weaknesses • Experience level of inserting physicians NR and may have differed • Unable to calculate participation rate • Study not powered to detect differences in outcomes of interest

Reference, funding, country	Study design, population	Intervention	Outcome	Results	Quality, Strengths, Weaknesses
Micks, 2014 [36] American College of Obstetricians and Gynecologists/Bayer Healthcare Pharmaceuticals Research Award in Long-Term Contraception USA, Oregon Health and Science University and Planned Parenthood Columbia Willamette	RCT; 2 study groups 24 nulliparous women aged 18–45 years requesting an IUD for contraception; no prior IUD use or attempted placement IUD type: LNG Nitroglycerin gel group: 12 randomized and included in analyses Control group: 12 randomized and included in analyses 24/24 (100%) completed study	0.5 mg nitroglycerin gel (1 mL) vs. placebo gel, applied vaginally 30–45 min prior to IUD insertion; women given the option of premedication with ibuprofen (800 mg) prior to receiving study gel (92% vs. 50% in nitroglycerin and control groups, p=.07) IUDs inserted by 3 attending physicians IUD insertion technique was standardized	Need for cervical dilation or paracervical block Provider ease of insertion measured by VAS (0=easy, 100 mm=very difficult)	• No significant differences between nitroglycerin gel and control groups in need for cervical dilation (8% vs. 8%); 1 needed paracervical block (study group NR) • No significant differences in provider ease of insertion between nitroglycerin gel and control groups (mean [SD]=29.4 [23.8] vs. 22.8 [29.9])	I, fair Strengths • Multiple centers • Randomization computer-generated • Allocation sequence concealed • Participants and providers blinded to group allocation • Excluded women with prior attempted or successful IUD insertion • Nitroglycerin and placebo gels were identical • Minimal variation in IUD insertion skill level between providers • High completion rate (100%) • Target sample size determined by power calculations • Study groups comparable related to most baseline characteristics (age, BMI, race/ethnicity, current menstruation, dysmenorrhea) and nonoutcome procedural details (expected pain, anxiety level, uterine position) • Intent-to-treat analyses conducted (1 women had copper vs. LNG IUD inserted) Weaknesses • Unable to calculate participation rate • Study groups not comparable related to premedication with ibuprofen (92% vs. 50% in nitroglycerin gel and control groups) • Study not powered to detect differences in outcomes of interest

BMI, body mass index; HC, hormonal contraception; IUD, intrauterine device; LNG, levonorgestrel-releasing; NR, not reported; OB/GYN, obstetrics and gynecology; RCT, randomized controlled trial; SD, standard deviation; USA, United States of America; VAS, visual analog scales.