CLINICAL WHITE PAPER

Misoprostol Administration for IUD Placement

This white paper outlines research findings on the use of misoprostol to facilitate IUD placement.

Over the past 15 years, there has been consistent interest in using misoprostol as a cervical ripening agent in a variety of circumstances beyond use in medication abortion, which occurs in combination with mifepristone. While most studies have evaluated misoprostol's effectiveness and safety in pregnancy – including surgical abortion, miscarriage management, and labor induction – there also are several studies that have evaluated its use in non-pregnant patients as a pretreatment for hysteroscopy and to facilitate intrauterine device (IUD) placement.

EVIDENCE

Studies on the use of misoprostol before IUD placement fall into two categories: (1) *routine* administration of misoprostol before IUD placement; and (2) use of misoprostol in *select* patients following a failed first attempt at IUD placement. Three meta-analyses address these issues, though there are overlaps in the randomized controlled trial (RCT) studies included:

1. A 2016 Centers for Disease Control and Prevention (CDC) meta-analysis by Zapata et al.[1] identified 15 RCTs that met inclusion criteria (i.e., peer reviewed RCTs that examined medications to ease IUD insertion, published in any language through February 2016).
   - 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).
   - One double-blind RCT[2] found significantly higher insertion success among women receiving misoprostol prior to a second intrauterine contraceptive (IUC) insertion attempt (after a failed first attempt) as compared to women randomized to the placebo group (Evidence Level I, good). In this 2015 Brazilian study, Bahamondes et al. showed successful "second-try" placement in 87.5% in the treatment group compared to 61.9% of the placebo group. Women in the treatment group were instructed to insert one 200 mcg tablet of misoprostol vaginally 10 and 4 hours before returning to the health center for the second attempt of insertion.

Conclusions: Among women with a recent failed IUD insertion, data from one RCT demonstrated improved second insertion success among women using misoprostol versus placebo (Evidence Level I, good). Accordingly, Zapata et al. recommended that additional research 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 IUD insertion following a failed attempt.

2. A second meta-analysis published in 2016 by Matthews et al.[3] identified nine RCTs examining IUD insertion failure with and without prior routine misoprostol administration. Findings from the RCTs – six of which were designated as high quality and three of which were designated as low quality – revealed no difference in insertion failure with or without misoprostol. For inclusion, studies had to include two groups comparing misoprostol pretreatment with no misoprostol and had to examine at least one of the following: success of insertion, ease of insertion, insertion pain, expulsion rates, and complications of insertion. No date or language limits were applied.
   - Of nine RCTs examining difficulty of IUD insertion with and without misoprostol pretreatment, seven studies revealed no difference in this measure; two (one high-quality, one low-quality study) revealed decreased difficulty of insertion with misoprostol administration, as rated by health care providers.
   - Of nine RCTs examining pain with IUD insertion, seven studies revealed no difference in pain measurement scores, one (high-quality) study revealed increased pain with misoprostol administration, and one (high-quality) study revealed decreased pain with misoprostol administration.
   - Five studies examining rates of expulsion and two studies examining complications of IUD insertion revealed no difference with or without misoprostol pretreatment.

   Conclusions: No data supported routine administration of misoprostol before IUD insertion. Success of insertion was high even among nulliparous women and good quality data did not demonstrate that misoprostol use increases placement success. These data similarly revealed no differences in difficulty of insertion, pain with insertion, or expulsion with prior administration of misoprostol. However, data for several outcomes were limited by lack of power, meaning sample sizes were not large enough to conclusively answer the research questions of interest.

3. Tassi et al.[4] authored the most recent review of RCTs on use of misoprostol before IUD insertion. Completed in Italy, this systematic review and meta-analysis of published English language reports included trials published in MEDLINE, Scopus, the Cochrane Library, and ClinicalTrials.gov through October 2019. The primary outcome was IUD insertion failure; secondary outcomes included women's pain perception, use of cervical dilators to facilitate insertion, and prevalence of side effects. Fourteen studies were eligible for inclusion, focusing on one or more of the following: failure of

IUD insertion, women's perception of pain, need for cervical dilators prior to insertion, and development of side effects.

- Misoprostol premedication significantly reduced IUD insertion failure rates among women with previous caesarean section and previous IUD insertion failure. It also significantly reduced the use of cervical dilators among all subgroups.
- Buccal misoprostol administration (i.e., having misoprostol tablets dissolve between patients' gum and cheek) did not seem to be effective in reducing IUD insertion failure.
- Nulliparous women, as a group, did not benefit from misoprostol premedication.
- Misoprostol premedication significantly increased the prevalence of side effects, including nausea and other side effects or complications. Other side effects and complications considered were headache, abdominal pain or cramps, vomiting, diarrhea, fever, shivering, perforation, bleeding, vasovagal reaction, skin rash, bradycardia, and syncope.
- Visual analogue scale (VAS) pain scores were higher with both sublingual (i.e., applied under the tongue) and buccal misoprostol administration when IUD insertion took place less than 2.5 hours after misoprostol premedication, with a negative correlation between mean VAS pain score difference and time since misoprostol premedication.

Conclusions: Data demonstrated that misoprostol premedication reduced IUD insertion failure among women with previous caesarean section and those with previous IUD insertion failure, suggesting that misoprostol may be a reasonable choice for improving procedure success in these subgroups. Although misoprostol premedication reduced insertion failures, it significantly increased side effects and had a heterogeneous pattern of efficacy; thus, its routine use is not supported by the evidence.

RECOMMENDATIONS

1. While these meta-analyses utilized distinct methods and inclusion criteria, all three were consistent in concluding that routine administration of misoprostol before IUD insertion *does not* achieve the desirable outcomes of either lower failed insertion rates or reduction in pain scores during the IUD insertion procedure. *Consequently, misoprostol should not be administered* routinely *before IUD insertion, since there is no benefit in achieving successful insertion or reduced pain, but there are harms associated with misoprostol side effects such as intense uterine cramps, flushing, and diarrhea.*

2. Administration of misoprostol before IUD placement *does* appear to help select patients in two subgroups: patients with a history of a failed IUD placement and those with prior caesarean section.

3. If a clinician prescribes misoprostol to facilitate IUD placement for these subgroups or if a health center chooses to stock misoprostol tablets for use in these select circumstances, there should not be a problem with obtaining it.
   - Misoprostol is widely used – and Food and Drug Administration (FDA) approved – for the prevention and treatment of NSAID-induced gastric ulcers in patients taking NSAIDs who are at high risk for ulceration. It also has an indication (but not FDA approved) in the short-term treatment of active duodenal or gastric ulcers with other etiologies.
   - Use of misoprostol for obstetrical or gynecologic conditions, including those discussed in this paper, constitutes the use of an FDA-approved drug for non-approved indications, which may be done legally at the prerogative of the clinician.

REFERENCES

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This document was prepared by the National Family Planning & Reproductive Health Association (NFPRHA) and NFPRHA Clinical Fellow Michael Policar, MD, MPH. It is intended for informational purposes and does not constitute legal or medical advice or NFPRHA's endorsement of a specific product.

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