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Effects of prophylactic misoprostol administration prior to intrauterine device insertion in nulliparous women

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Abstract

Background: This study was conducted to examine the effects of prophylactic misoprostol prior to intrauterine device (IUD) placement in nulliparous women.
Study Design: Nulliparous, reproductive-aged women desiring an IUD for contraception were randomized to receive 400 mcg of buccal misoprostol or placebo 90 min prior to IUD insertion. Subjects completed a series of 100-mm visual analogue scales (VAS, anchors: 0=*none*, 100 mm=*worst imaginable*) to measure their perceived pain at several times points (anticipated pain, leg positioning, speculum placement, tenaculum placement, IUD insertion, equipment removal and 5 min postinsertion). Secondary outcomes included provider "ease of placement" (100-mm VAS, anchors: 0=*easy*, 100 mm=*extremely difficult*), side effects and retention of the IUD after 1 month (self-report or clinic visit). The study had 80% power (α=0.05, one-sided) to detect a reduction with treatment of 20 mm in VAS scores with a combined sample size of 34.
Results: A total of 40 subjects were randomized to receive either misoprostol or placebo, and 35 completed the study. Five subjects withdrew (four prior to receiving study medication and one declined IUD). Baseline characteristics were similar between groups. There were no significant differences in patient-reported pain with IUD placement [misoprostol 65 mm (SD 21), placebo 55 mm (SD 21), p=.83] or at any other time point. Moreover, the misoprostol group reported significantly more preinsertion nausea (29% vs. 5%, p=.05) and cramping (47% vs. 16%, p=.04) than the placebo group. While provider-reported ease of insertion was not significantly different between groups, three placebo patients required additional dilation vs. none in the misoprostol group. All 35 subjects underwent follow-up at least 1 month postinsertion, and no expulsions were reported.
Conclusion: Prophylactic misoprostol prior to IUD placement in nulliparous women did not reduce patient perceived pain, but it did appear to increase preinsertion side effects.

Keywords: Intrauterine device; Prophylactic misoprostol; Nulliparous; Prostaglandins; Cervical priming

1. Introduction

Until recently, intrauterine devices (IUDs) were thought to be only appropriate for multiparous women, largely based on the alleged increased risk of pelvic inflammatory disease (PID) resulting in infertility. Although a causal link between IUD use and PID has been disproven [1] and nulliparity is no longer a contraindication for IUD use [2,3], many health care providers continue to limit IUD access in nulliparous women due to concerns surrounding potential insertion difficulties [4].

While not evidence-based, many providers have adopted the routine use of misoprostol, a prostaglandin E1 analog, to improve success with IUD placement in nulliparous women. Originally approved for the prophylaxis of nonsteroidal anti-inflammatory drug-induced ulcers and commonly used "off-label" for cervical ripening for labor induction, misoprostol has also gained acceptance for cervical preparation for a number of office-based gynecologic procedures including hysteroscopy, endometrial biopsy and abortion [5–8]. These observations have led to recommendations for routine use of misoprostol prior to IUD insertion to make the experience easier for women (particularly nulliparas) and providers. While a randomized study from Sweden found that providers rated insertion to be

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easier in subjects pretreated with misoprostol, there was no difference in the subjective experience of pain reported by patients and no difference in the overall success of IUD insertion [9]. Two other studies have also failed to find that misoprostol improves the success of insertion or reduces patient pain [10,11]. However, all three published reports included research designs that may have affected their study outcomes including using a Hegar dilator to evaluate initial dilation [9,11] or the inclusion of only repeat IUD users [10]. While misoprostol offers many potential benefits, it is not without side effects including diarrhea, vomiting, fever and abdominal pain [12,13]. In fact, some studies have found that these side effects significantly outweigh the beneficial cervical effects in gynecological procedures that require little dilation, i.e., endometrial biopsy [14]. Moreover, prostaglandins not only soften the cervix, but they also increase uterine contractility; whether this could increase expulsion risk has not been studied.

As IUD use is increasing in nulliparous women, further research focusing on improving the insertion experience is warranted. The goal of this study was to determine whether prophylactic misoprostol prior to IUD insertion reduces patient-perceived pain and improves provider ease of insertion in nulliparous women, and to examine the side effects and adverse events with its use.

2. Materials and methods

A double-blind, randomized, placebo-controlled study was conducted at Oregon Health and Science University (OHSU) in Portland, OR, from February 2007 to March 2010. The OHSU Institutional Review Board approved the study protocol. All patients underwent informed written consent.

Nulliparous women aged 18–45 years requesting an IUD for contraception were recruited. Potential subjects were ineligible if they had a prior pregnancy greater than 20 weeks of duration; were pregnant within 6 weeks of study entry; had a prior attempted or successful IUD insertion; had a history of a cervical procedure such as cone biopsy, Loop electrosurgical excision procedure, or cryotherapy and/or any World Health Organization Medical Eligibility Criteria category 3 or 4 precaution to an IUD [15]. Women could choose between either of the currently available IUDs in the United States (levonorgestrel-releasing or copper T380A). Preprocedure counseling and evaluation were consistent with standard clinic protocols. Participants completed a demographics form prior to their IUD insertion.

Randomization allocation was obtained by phone from a research coordinator once consent was obtained. The randomization scheme was computer-generated and was inaccessible to providers enrolling subjects. Study participants and providers were blinded to group allocation. Participants were randomized to receive either misoprostol 400 mcg or placebo, and instructed to take the medication buccally 90 min prior to their appointment time. The dose, route and timing of misoprostol were based on prior cervical priming research performed in first-trimester abortions [16–18]. The placebo was similar in shape, size, taste and color and was given to patients in an opaque envelope. The IUD insertion was performed in a standardized fashion; local anesthesia was placed at the tenaculum site (benzocaine spray or 1–2 mL of 1% lidocaine injected), a tenaculum was placed, a sound was used to measure length of endometrial cavity and the IUD was placed according to the recommendations of the manufacturer. Any prophylactic analgesics or additional cervical analgesia (e.g., paracervical block) was documented. Obstetric and gynecologic residents and staff physicians performed the IUD insertions.

Subjects rated their pain using a 100-mm visual analog scale (VAS; anchors: 0=*none*, 100 mm=*worst imaginable*) at several time points: anticipated pain (prior to IUD insertion), pain experienced with leg positioning in stirrups (baseline), speculum placement, tenaculum placement, IUD insertion, equipment removal and 5 min postinsertion. A research assistant collected the VAS data from the subject concurrently with each step and not from memory. Any side effect experienced by the patient following study drug dosing was collected immediately prior to IUD insertion. The time interval from study drug dosing until insertion and for the IUD insertion procedure (speculum insertion until removal) was documented. Immediately following the IUD insertion, providers recorded their assessment of the ease of insertion using a VAS scale (VAS, anchors: 0=*easy*, 100 mm=*extremely difficult*). The experience level of the inserting physician and additional information regarding the insertion process (i.e., was cervical dilation required) were also recorded.

Approximately 1 month following IUD insertion, participants were contacted via email, phone or clinic visit to assess any potential complications and to confirm if they had successfully identified their IUD strings. If a string check had not yet been performed, participants were encouraged to check for their IUD strings and were contacted again at a later date for confirmation.

For the primary outcome of pain with IUD insertion, we elected to use a one-tailed test of hypothesis that misoprostol would decrease pain with the procedure. The study had an 80% power at an α of 0.05 (one-sided) to identify a 20-mm decrease in pain in the misoprostol group [19]. Thirty-four subjects were required to achieve this level of power. To allow for attrition or disqualification of participants, sample size was increased to 40 subjects, translating to a sample size of 20 in each study group. All analyses were performed based on intent to treat. As the data were normally distributed, categorical and continuous data were analyzed using χ^2 and Student's t tests, respectively. One-sided analysis was used for the pain outcomes, but all other tests were two-sided. Statistical analyses were performed with SPSS software, version 17 (SPSS Inc., Chicago, IL).

3. Results

Of the 40 women randomized in the study, 35 completed the study (Fig. 1). While there were no statistically