Title

Prophylactic ibuprofen does not improve pain with IUD insertion: a randomized trial.

Journal

Contraception, 91(3)

ISSN

1879-0518

Authors

Bednarek, Paula H

Creinin, Mitchell D

Reeves, Matthew F

et al.

Publication Date

2015-03-25

Peer reviewed

ELSEVIER

Contraception 91 (2015) 193 – 197

Contraception

Original research article

Prophylactic ibuprofen does not improve pain with IUD insertion: a randomized trial☆

Paula H. Bednarek[a,*], Mitchell D. Creinin[b], Matthew F. Reeves[c], Carrie Cwiak[d], Eve Espey[e], Jeffrey T. Jensen[a], for the Post-Aspiration IUD Randomization (PAIR) Study Trial Group

[a]*Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA*
[b]*Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, CA, USA*
[c]*National Abortion Federation, Washington, DC, USA*
[d]*Department of Gynecology and Obstetrics, Emory University, Atlanta, GA, USA*
[e]*Department of Obstetrics and Gynecology, University of New Mexico, Albuquerque, NM, USA*

Received 6 August 2014; revised 15 November 2014; accepted 17 November 2014

Abstract

Objective: To evaluate if ibuprofen 800 mg reduces pain with intrauterine device (IUD) insertion among U.S. women.
Study design: We conducted a randomized, double-blind, placebo-controlled trial of women undergoing IUD insertion approximately 2–6 weeks following first-trimester uterine aspiration. Subjects were randomized to receive ibuprofen 800 mg or placebo 30–45 min prior to IUD insertion. A 100-mm visual analog scale (VAS) was administered to measure pain after speculum insertion (baseline) and immediately following IUD insertion.
Results: A total of 202 women were enrolled, with 101 randomized to each group (ibuprofen or placebo). Sociodemographic characteristics and baseline VAS scores were similar between groups. The median pain score with IUD insertion was 41.5 mm in the placebo group and 38.0 mm in the ibuprofen group (p=.50). Mean and median pain scores did not differ between placebo and ibuprofen when nulliparous and parous women were analyzed independently. Overall, median pain scores were 17.5 mm higher in nulliparous women than parous women (p=.004). Median pain scores did not differ by age, IUD-type, history of dysmenorrhea or time since aspiration.
Conclusions: Administration of ibuprofen 800 mg prior to IUD insertion does not reduce pain associated with the procedure for U.S. women. Overall, nulliparous women report more pain with IUD insertion than multiparous women.

Keywords: IUD; Intrauterine device; Ibuprofen; Pain

1. Introduction

Inconsistent use and discontinuation of contraceptives are major causes of unintended pregnancy [1]. The failure rate of the pill, patch or ring is 20 times higher than that of long-acting reversible contraceptives (LARCs) [2]. Increasing acceptability and use of LARC methods like the intrauterine device (IUD) is an important strategy to reduce the risk of unintended pregnancy [3].

Despite well-established safety and efficacy profiles, IUDs are still underutilized in the United States. Concerns about pain and difficulty with insertion are currently a major barrier to IUD use, especially among nulliparous women [4,5].

Although nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used prior to IUD insertion to decrease pain, no data support the utility of this practice, including use specifically in nulliparous women [6,7]. The largest trial of NSAIDs prior to IUD insertion used ibuprofen 400 mg, a dose lower than is commonly recommended in the United States [7]. Interestingly, NSAIDs are often recommended prior to other office-based gynecologic procedures, such as colposcopy [8], endometrial biopsy [9] and dilation and curettage [10–12], though data are mixed about their effectiveness with these procedures as well.

☆ Trial registration: Clinicaltrials.gov Identifier: NCT00562276.

* Corresponding author. Department of Obstetrics and Gynecology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, UHN 50, Portland, OR 97239, USA. Tel.: +1-503-418-2582.
E-mail address: bednarek@ohsu.edu (P.H. Bednarek).

http://dx.doi.org/10.1016/j.contraception.2014.11.012
0010-7824/

The goal of this study was to determine if ibuprofen 800 mg administered prophylactically prior to IUD placement reduces pain with the insertion procedure among U.S. nulliparous and multiparous women choosing either the copper T380A IUD or the LNG 52 mg IUS.

2. Materials and methods

This randomized, double-blind, placebo-controlled trial was conducted as a planned substudy of a multicenter trial evaluating IUD insertion following first-trimester uterine aspiration. Subjects were enrolled from June 2007 to February 2009 at four U.S. academic medical centers: Oregon Health and Science University, the University of Pittsburgh, Emory University and the University of New Mexico. The methods and outcomes of the main study have been previously described [13]. Briefly, women 18 years and older requesting a first-trimester uterine aspiration for induced or spontaneous abortion who also desired an IUD were enrolled in the main study. Each participant chose to receive an LNG 52 mg IUS (Mirena, Bayer HealthCare Pharmaceuticals) or a copper T380A IUD [ParaGard T380A; Teva Pharmaceuticals (formerly Duramed Pharmaceuticals)]; the diameters of the inserters were 4.75 mm and 4.5 mm, respectively. Subjects were randomized to insertion immediately following the aspiration procedure (immediate) or 2–6 weeks following the procedure (delayed). Women in the delayed insertion group who returned for the insertion procedure and did not have an allergy to ibuprofen or renal impairment were offered participation in this substudy. The institutional review boards of each institution approved the study protocol, and all study subjects gave written consent prior to enrollment.

Subjects in this substudy were randomized to receive ibuprofen 800 mg or placebo 30–45 min prior to IUD insertion. Randomization was performed using computer-generated blocks with varying sizes, stratified by center with equal allocation to the two treatment arms. Sequentially numbered opaque envelopes were prepared by study staff not involved in conducting the trial. The placebo and ibuprofen capsules were created to be identical in appearance and were prepared and packaged at a central site. The pharmacy dispensed the study medication based on the randomization scheme to ensure allocation concealment.

The IUD was inserted by an experienced study investigator, using the standard manufacturer approved technique for each IUD type, including placement of a tenaculum and uterine sounding. No cervical dilation or misoprostol was used for any IUD insertion in this study. Subjects rated their pain using a 100-mm visual analog scale (VAS) (anchors: 0=no pain, 100=worst imaginable) at the time of speculum insertion and immediately following deployment of the IUD (prior to cutting the threads). As this study was designed to specifically evaluate pain with the insertion process, pain assessments were not performed after the procedure and pain medication usage was not evaluated.

2.1. Statistical analyses

Several studies demonstrate that a change of 9–14 mm on a 100-mm VAS is a minimal clinically important difference in perceived pain that is reproducible among patients experiencing both mild and severe forms of pain [14–17]. When designing this study, we anticipated that 266 women would be randomized to delayed IUD insertion in the main study and return for IUD insertion. Using a two-sample *t* test, this estimated sample size would provide 80% power at an alpha of 0.05 to identify a 7-mm difference on a 100-mm VAS assuming a standard deviation of 20 mm.

Baseline characteristics were compared according to treatment group to assess for significant differences using a Fisher's Exact Test, Chi-square test or *t* test where appropriate. To be consistent with common clinical reporting of VAS results to convey clinical relevance for average treatment effect, we compared mean VAS scores. A *t* test was used to evaluate the primary outcome, mean pain with IUD insertion measured on a 100-mm VAS. However, the data were not normally distributed; thus, we also report median scores. Univariate and multivariable mixed effects regression analyses were used to evaluate potential confounders and to determine independent predictors of insertional pain. All analyses were completed using SPSS (version 17.0) and SAS (version 9.2).

3. Results

A total of 222 women returned for their IUD insertion appointment, of which 3 had an allergy to NSAIDs and 7 had already taken pain medicine prior to the appointment, leaving 212 potential subjects. Of these, 202 were enrolled, with 101 randomized to ibuprofen and 101 randomized to placebo (Fig. 1). There were no significant differences in baseline characteristics between the two treatment groups (Table 1) or in the baseline pain reported with placement of the speculum (Table 2). All IUDs were placed successfully upon first attempt.

Overall, there was no significant difference in mean or median pain scores for IUD placement between women who received ibuprofen or placebo (Table 2). Similarly, there was no significant difference in pain scores with IUD placement when only nulliparous or parous women were evaluated separately. Similar results were noted when evaluating median pain scores (Table 2). A small number of parous women had no prior vaginal delivery, of whom 11 were in the ibuprofen group and 6 were in the placebo group. When pain with IUD insertion was evaluated for the population as a whole, median pain scores for the 17 women who were parous and had no vaginal delivery (median 56 mm, range 7–100; mean 53.9 mm, S.D. 27.4) were more similar to the nulliparous women (59.5 mm, range 0–100; mean 54.6 mm, S.D. 25.3) than the other parous women (median 29.0 mm, range 1–96; mean 32.1 mm, S.D. 23.2). All subjects

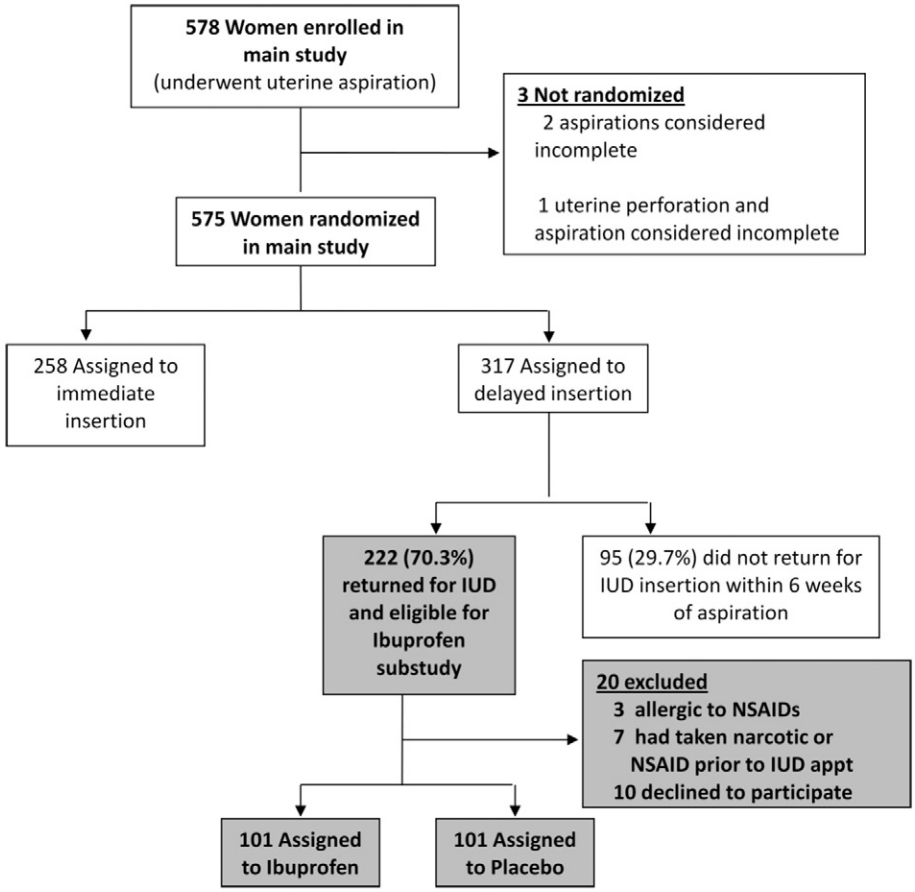

Fig. 1. Flow of study participants.

reported a higher pain score following IUD insertion than with speculum placement.

Both parity and pain with speculum insertion were associated independently with IUD insertional pain in univariate analysis (both p<.0001). In multivariable analysis, only parity remained a strong predictor of pain, with pain decreasing in a linear pattern as parity increases from 0 to ≥3. There were no differences in pain scores based on age (p=.07), body mass index (p=.13), IUD-type (p=.62), history of dysmenorrhea (p=.35), previous IUD use (p=.62), number of days since aspiration (p=.31) or any sociodemographic characteristic listed in Table 1.

4. Discussion

This trial demonstrated that ibuprofen 800 mg administered 30–45 min prior to IUD insertion does not decrease pain with the procedure among U.S. women receiving either an LNG 52 mg IUS or a copper T380A IUD. Additionally, no difference was found when the data were stratified by parity. Harms of providing a medication such as ibuprofen without evidence of benefit include elevated risk of side effects and anxiety about expected pain and increased complexity of scheduling.

Although we did not enroll the number of women originally estimated, the final sample still provided a strong ability to detect a difference; whereas the original sample size would have detected a difference in mean VAS scores of 7 mm, the final sample had 80% power to detect a difference of approximately 8 mm using a *t* test of proportions with an alpha of 0.05 (Power and Precision release 4.1). Moreover, the sample size of nulliparous women was sufficient to detect a difference of 14 mm in VAS score while that of parous women could detect a difference of 10 mm. We failed to enroll our expected sample size due to poor follow-up for interval IUD placement following first-trimester uterine aspiration, underscoring the desirability of immediate postabortion placement of an IUD [13].

Nulliparous women in our study reported approximately twice as much pain with IUD insertion compared to multiparous women (approximately 60 mm versus 30 mm). Parous women who have not had a vaginal delivery appear to report similar pain to nulliparous women as opposed to parous women who have a prior vaginal delivery. These pain levels with IUD insertion are consistent with results from recent European and U.S. studies of other pain control interventions. A Swedish study evaluating misoprostol for IUD insertion among nulliparous women reported pain scores of 65–70 mm on a 100-mm VAS [18]. A Dutch

Table 1
Baseline characteristics

	Ibuprofen N=101	Placebo N=101	p*
Age (median, range)	27 (18–41)	26 (18–44)	.5
Gravidity			.98
1	24	22	
2	18	17	
3	19	24	
4	17	18	
5	11	8	
≥6	12	12	
Parity			.69
0	37	36	
1	24	27	
2	25	19	
≥3	15	19	
Race			.60
White	59	58	
Black	26	20	
Hispanic	11	13	
Asian	1	3	
Other	4	7	
Education			.72
Some high school	1	3	
High school graduate	36	32	
Some college	41	49	
College graduate	20	15	
Graduate school	2	1	
Other	1	1	
Medical insurance			.31
No	36	43	
Yes (Medicaid or Private)	65	58	
IUD type chosen			.12
LNG-IUS	85	76	
Copper T380A IUD	16	25	

* χ^2, or Student *t* test as appropriate.

Table 2
Pain scores in women having IUD placement

	Median		p*	Mean	
	Ibuprofen mm (range)	Placebo mm (range)		Ibuprofen mm (±S.D.)	Placebo mm (±S.D.)
All subjects	*n*=101	*n*=101		*n*=101	*n*=101
Speculum	**7** (0–93)	**11** (0–81)	.14	**15.2** (±19.7)	**18.0** (±20.6)
IUD insertion	**38** (0–100)	**41.5** (0–100)	.5	**40.8** (±27.4)	**43.4** (±25.9)
Nulliparous	*n*=37	*n*=36			
Speculum	**8** (0–72)	**13** (0–81)	.11	**16.2** (±20.6)	**22.5** (±24.5)
IUD insertion	**59** (0–97)	**60** (0–100)	.60	**52.8** (±24.6)	**56.4** (±26.3)
Parous	*n*=64	*n*=65			
Speculum	**6** (0–93)	**11** (0–77)	.51	**14.63** (±19.4)	**15.68** (±17.9)
IUD insertion	**29** (1–100)	**34** (1–96)	.34	**33.7** (±26.6)	**36.3** (±22.9)

* Wilcoxon rank-sum test used for analyses, as data not normally distributed. Mean (±S.D.) presented for comparison.

study evaluating misoprostol with IUD insertion reported mean pain scores of 54–59 mm in nulliparous and 26–33 mm in multiparous women [19]. A U.S. study evaluating intracervical lidocaine for IUD insertion among 200 women reported mean pain scores of 61–62 mm in nulliparous and 43–48 mm in multiparous women [20]. Previous studies demonstrate similar pain scores between American nulligravid and nulliparous women who have had previous early pregnancies, as in our study [21,22]. In contrast, pain levels with IUD insertion reported by Chilean women are comparably low for both groups {mean pain score on a 100-mm VAS of 28 mm [95% confidence interval (CI) 20–35 mm] for the nulliparous group and 20 mm (95% CI 18–21 mm) for the multiparous group} [7]. Accordingly, it appears that women in Chile experience less pain overall with IUD insertion compared to U.S. or European women.

The only predictor of pain that remained significant in our study with multivariable analysis was parity. In Chilean women, older age, nulliparity, nonlactation and less time since delivery (3 versus 6 months) were associated with higher levels of insertional pain. Additionally, time since last menses was associated with pain, with women 6–10 days since the start of last menses reporting significantly less mean pain (10 mm) than women less than 6 days or more than 10 days since last menses (18–19 mm). U.S. and European studies evaluating IUD placement pain also demonstrate that parity and time since delivery are associated with pain. However, age, IUD-type and history of dysmenorrhea have shown conflicting results.

Our study did not address pain in the hours after placement. Although it is possible that some women who use ibuprofen or another NSAID before IUD placement may have decreased pain at in the hours following the procedure, these women could also use pain medicine as needed, removing a provision that all women take ibuprofen in advance of the procedure.

Strengths of our study are its power to evaluate effects for both nulliparous and multiparous women, the use of both devices approved in the U.S. during the study period and its double-blind, randomized design. In addition, the maximal dose of ibuprofen was evaluated. Limitations include that pain in the time period following IUD insertion was not evaluated. Also, we evaluated only one time point (30–45 min) for drug absorption. We picked this point because time to pain relief after ingesting ibuprofen has been reported to be in this range [23,24] and to reflect a realistic interval for administration in an office setting. However, it may require as much as 2 h for ibuprofen to reach maximal effective blood levels [25].

The IUDs used in this trial were the only two available at the time. Products recently introduced include a new IUD (LNG 13.5 mg IUS; Skyla, Bayer Healthcare) with a smaller insertion diameter, as well as a new inserter for the LNG 52 mg IUS with a slightly smaller diameter (4.25 mm). Smaller inserters may reduce discomfort but it is not likely that these will alter our conclusion of a lack of benefit of ibuprofen.

Women choosing an IUD for contraception have the highest continuation and satisfaction rates compared to other contraceptive methods [26]. In recent years, IUD use has risen predominately among parous women [27], and as our study confirmed low pain levels with IUD insertion among parous women, likely no additional pain intervention is necessary for this group. However, reducing pain with IUD insertion among nulliparous women may increase the acceptability of this highly effective contraceptive method for this group. NSAIDs, intracervical lidocaine [28], nitric oxide donors [21,22] and misoprostol [29] have all been studied, but none have been shown to be effective. Given the important public health need to reduce barriers to IUD utilization overall, further investigations should concentrate on alternate strategies to reduce pain and improve satisfaction with IUD insertion among nulliparous women.

Acknowledgments

These data were presented in part as a poster abstract at Reproductive Health 2010, the Annual Meeting of the Association of Reproductive Health Professionals and Society of Family Planning, Hollywood, CA. This study was funded by an anonymous foundation. Duramed Pharmaceuticals donated Paragard® for the study. Statistical support was provided from the Oregon Clinical and Translational Research Institute, grant number UL1 RR024140 01 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. We thank Hong Li, M.P.H., M.S., and Zunqiu Chen, M.S., for statistical support.

References

[1] Finer L, Henshaw S. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health 2006;38:90–6.
[2] Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012;366:1998–2007.
[3] Peipert JF, Madden T, Allsworth JE, Secura GM. Preventing unintended pregnancies by providing no-cost contraception. Obstet Gynecol 2012;120:1–7.
[4] Weston MF, Martins SL, Neustadt AB, Gilliam ML. Factors influencing uptake of intrauterine devices among postpartum adolescents: a qualitative study. Am J Obstet Gynecol 2012;206:40.
[5] Asker C, Stokes-Lampard H, Beavan J, Wilson S. What is it about intrauterine devices that women find unacceptable? Factors that make women non-users: a qualitative study. J Fam Plann Reprod Health Care 2006;32:89–94.
[6] Allen RH, Bartz D, Grimes DA, Hubacher D, O'Brien P. Interventions for pain with intrauterine device insertion. Cochrane Database Syst Rev 2009, http://dx.doi.org/10.1002/14651858.CD007373.pub2.
[7] Hubacher D, Reyes V, Lillo S, Zepeda A, Chen P, Croxatto H. Pain from copper intrauterine device insertion: randomized trial of prophylactic ibuprofen. Am J Obstet Gynecol 2006;195:1272–7.
[8] Church L, Oliver L, Dobie S, Madigan D, Ellsworth A. Analgesia for colposcopy: double-masked, randomized comparison of ibuprofen and benzocaine gel. Obstet Gynecol 2001;97:5–0.
[9] Dogan E, Celiloglu M, Sarihan E, Demir A. Anesthetic effect of intrauterine lidocaine plus naproxen sodium in endometrial biopsy. Obstet Gynecol 2004;103:347–51.
[10] Poomtavorn Y, Phupong V. Prospective randomized, double-blinded, placebo-controlled trial of preoperative rofecoxib for pain relief in uterine curettage. Arch Gynecol Obstet 2005;273:115–8.
[11] Suprapto K, Reed S. Naproxen sodium for pain relief in first-trimester abortion. Am J Obstet Gynecol 1984;150:1000–1.
[12] Siddle NC, Young O, Sledmere CM, Reading AE, Whitehead MI. Br J O A controlled trial of naproxen sodium for relief of pain associated with Vabra suction curettage. Obstet Gynaecol 1983;90:864–9.
[13] Bednarek PH, Creinin MD, Reeves MF, Cwiak CA, Espey E, Jensen JT. Immediate versus delayed IUD insertion after first trimester uterine aspiration. N Engl J Med 2011;364:2208–17.
[14] Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996;27:485–9.
[15] Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205–7.
[16] Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38:633–8.
[17] Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5:1086–90.
[18] Saav I, Aronsson A, Marions L, Stephansson O, Gemzell-Danielsson K. Cervical priming with sublingual misoprostol prior to insertion of an intrauterine device in nulliparous women: a randomized controlled trial. Hum Reprod 2007;22:2647–52.
[19] Dijkhuizen K, Dekker OM, Holleboom CAG, de Groot CJ, Hellebrekers BW, van Roosmalen GJ, et al. Vaginal misoprostol prior to insertion of an intrauterine device: an RCT. Hum Reprod 2011;26:323–9.
[20] Maguire K, Davis A, Rosario Tejeda L, Westhoff C. Intracervical lidocaine gel for intrauterine device insertion: a randomized trial. Contraception 2012;86:214–9.
[21] Bednarek PH, Micks EA, Edelman AB, Li H, Jensen JT. The effect of nitroprusside on IUD insertion experience in nulliparous women: a pilot study. Contraception 2013;87:421–5.
[22] Micks EM, Jensen JT, Bednarek PH. The effect of nitroglycerin on the IUD in nulliparous women: a pilot study. Contraception 2014;90:60–5.
[23] Fricke JR, Halladay SC, Francisco CA. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. Curr Ther Res 1993;54:619–27.
[24] Li H, Mandema J, Wada R, Jayawardena S, Desjardins P, Doyle G, et al. Modeling the onset and offset of dental pain relief by ibuprofen. J Clin Pharmacol 2012;52:89–01.
[25] Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet 1998;34:101–54.
[26] O'Neil-Callahan M, Peipert JF, Zhao Q, Madden T, Secura G. Twenty-four-month continuation of reversible contraception. Obstet Gynecol 2013;122:1083–91.
[27] Finer LB, Jerman J, Kavanaugh ML. Changes in use of long-acting contraceptive methods in the United States, 2007–2009. Fertil Steril 2012;98:893–7.
[28] McNicholas CP, Madden T, Zhao Q, Secura G, Allsworth JE, Peipert JF. Cervical lidocaine for IUD insertional pain: a randomized controlled trial. Am J Obstet Gynecol 2012;207:384e1–6.
[29] Edelman AB, Schaefer E, Olson A, Van Houten L, Bednarek P, Leclair C, et al. Effects of prophylactic misoprostol administration prior to intrauterine device insertion in nulliparous women. Contraception 2011;84:234–9.