GYNECOLOGY

Mepivacaine instillation for pain reduction during intrauterine device placement in nulliparous women: a double-blinded randomized trial

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BACKGROUND: Fear of pain associated with intrauterine device (IUD) placement has been identified as a significant barrier to the adoption of long-acting reversible contraception, contributing to lower utilization of the most effective reversible contraceptive methods.

OBJECTIVE: To assess whether instillation of intrauterine mepivacaine before IUD placement alleviates pain more effectively than a placebo.

STUDY DESIGN: We conducted a multicenter, double-blind, randomized, placebo-controlled trial involving nulliparous women undergoing IUD placement. An intrauterine instillation of 10 mL of 20 mg/mL mepivacaine or 0.9 mg/mL sodium chloride was administrated through a hydrosonography catheter 2 minutes prior to IUD placement. Pain scores were assessed using a 100 mm visual analog scale (VAS) at prespecified time points. Primary outcome measured the difference in VAS pain scores between the intervention group and the placebo group during IUD placement. Secondary outcomes included VAS pain scores at instillation and 10 minutes after placement, tolerability of the placement pain, as well as acceptability of the analgesia method.

RESULTS: We enrolled 151 participants, with 76 assigned to the mepivacaine group and 75 to the placebo group. The mean VAS pain score during IUD placement showed a difference of 13.3 mm (95% confidence interval (CI) 5.75—20.87; $P<.001$): the mepivacaine group had a mean of 53.9 mm (standard deviation [SD] 22.8), while the placebo group had a mean of 67.2 mm (SD 22.4). After adjusting for each individual provider's impact, the difference in mean pain scores remained statistically significant (12.2 mm 95% CI 4.85—19.62; $P<.001$). A greater proportion of women in the intervention group reported tolerable pain during placement with 70/75 participants (93.3%) compared to 53/66 participants (80.3%) in the placebo group ($P=.021$).

CONCLUSION: The intrauterine instillation of mepivacaine results in statistically significant reduction in pain score among nulliparous women during IUD placement. Although the precise clinical impact of this pain reduction method remains uncertain, the observed reduction in pain score result in a higher proportion of women reporting tolerable pain. This finding and the high acceptance as a pain reduction method thereby suggests clinical relevance. Intrauterine instillation of mepivacaine is a possible strategy to increase IUD utilization, particularly among nulliparous women who are at high risk of unintended pregnancy.

Key words: analgesia, contraception, family planning services, hormone-releasing intrauterine device, intrauterine devices, long-acting reversible contraception, mepivacaine, pain, topical anesthetic, visual analog scale

Introduction

Ensuring access to all effective contraceptive methods is a fundamental pillar of family planning and reproductive health. Long-acting reversible contraception (LARC), such as intrauterine devices (IUDs) and subdermal implants are the most effective reversible contraceptive options available and recommended options for contraception by numerous guidelines.[1] Despite their high effectiveness and high tolerability, LARC methods have lower user rates than less effective short-acting methods, especially among nulliparous women.[2,3] To support reproductive autonomy, contraceptive counseling emphasizing method effectiveness has been proved to aid in informed contraceptive choice.[4] Fear of pain and discomfort associated with IUD placement is a recognized barrier to the uptake of IUDs[5] and nulliparous women report higher pain scores at placement compared to parous women.[6–8] At present, there is no easily accessible highly acceptable pharmacological intervention that has conclusively demonstrated consistent and effective pain reduction during IUD placement.[9–11] While the paracervical block (PCB) can reduce placement related pain, the lack of trained providers limits accessibility and use of the method.[12–14] Additionally, administration of PCB can cause pain.[14,15] This leaves women with limited options for pain relief, potentially driving them to opt for less effective contraceptive methods.[13,16]

In a pilot trial, we compared intrauterine instillation of 10 mg/mL mepivacaine to placebo prior to placement in nulliparous women.[17] This trial indicated that mepivacaine led to a reduction in pain with very little pain experienced during the instillation. However, the effect size did not reach the clinically significant threshold. Still, the intervention group reported a more positive overall placement experience. Building upon this pilot trial, we designed a trial to evaluate the effect of a higher concentration of mepivacaine.

The primary objective for this placebo controlled randomized controlled trial was to establish superiority of 2% mepivacaine for reduction in pain at IUD placement in nulliparous women compared to placebo.

Cite this article as: Envall N, Elgemark K, Kopp Kallner H. Mepivacaine instillation for pain reduction during intrauterine device placement in nulliparous women: a double-blinded randomized trial. Am J Obstet Gynecol 2024;XXX:XX—XX.

0002-9378

https://doi.org/10.1016/j.ajog.2024.05.038

AJOG at a Glance

Why was this study conducted?

The study aimed to assess the efficacy of intrauterine mepivacaine instillation to reduce pain during intrauterine device (IUD) placement compared to placebo.

Key findings

The instillation of mepivacaine significantly reduced pain during IUD placement and increased the tolerability of pain during placement compared to placebo.

What does this add to what is known?

To date, there is no truly effective and well-tolerated method easily accessible for pain reduction at IUD placement. The study findings support the use of intrauterine mepivacaine instillation as an effective and well-tolerated method for reducing pain among nulliparous women. The observed pain reduction suggests potential clinical relevance, offering a promising strategy to enhance the acceptance of IUDs and potentially address one of the known barriers to its utilization.

Method

The study was a multicenter, double-blind, randomized placebo-controlled trial involving nulliparous women aged 18 to 31 who opted for a 52-mg levonorgestrel hormonal IUD for contraception. IUDs were placed on any day of the menstrual cycle, provided that pregnancy could be definitively ruled out. There are 2 hormonal IUDs with a reservoir of 52-mg levonorgestrel available, one featuring a placement tube with a diameter of 4.4 mm and the other with a diameter of 4.8 mm.[18] The study exclusively included participants opting for the device with a 4.4 mm placement tube (Mirena, produced by Bayer AG, Leverkusen, Germany). Additional inclusion criteria were ability to comprehend oral and written information, sign written informed consent in either Swedish or English, a willingness to undergo randomization and to complete study questionnaires and having a confirmed negative pregnancy test. Exclusion criteria were current use of IUD (ie, coming for replacement), prior conization, a known diagnosis of cervical stenosis, body weight below 40 kg, clinical signs of ongoing genital infection, a known uterine abnormality, underlying medical conditions associated with elevated risk of bleeding during IUD placement, unexplained abnormal uterine bleeding, contraindication to local anesthesia, or use of any other method for pain relief (including oral analgesics) prior to placement.

The study was conducted in 12 centers, which included youth clinics, sexual health clinics, and the Danderyd Hospital research center in Stockholm, Sweden. These centers were strategically located in both rural and urban areas. Providers included midwives and gynecologists all well experienced with IUD placement. Women were screened and enrolled during IUD placement appointments by midwives or physicians. All patients received oral and written information and signed informed consent prior to any study procedures. All informed consents were signed by the local investigator.

Demographic information and details about participants' prior pregnancies were collected at inclusion. Participants assessed their current pain level and worst menstrual cramping during a typical menstruation on a 100-mm visual analog scale (VAS), with the zero anchoring point indicating "no pain" and the 100 mm anchoring point indicating "worst pain imaginable." Thereafter, a nurse, nurse-midwife, or physician who was not involved in the IUD placement process randomized the patient by opening opaque sealed envelopes in sequential order and prepared a syringe with either 10 mL of 20-mg/mL mepivacaine or 10 mL of 9-mg/mL sodium chloride (placebo). The randomization was conducted in a 1:1 ratio with permuted blocks of 2 to 4 using a computer-generated randomization sequence created by an independent research midwife and available at www.sealedenvelope.com (seed 22368010835101). All participants, study staff, and physicians performing IUD placements were blinded to the study allocation, ensuring an unbiased administration of the intervention. The randomization key was not disclosed until after collection of all study data and after analysis of the primary outcome. The syringes were indistinguishable in terms of viscosity, color, and odor.

The health-care provider placed the IUD according to a standardized protocol. The patient was positioned in the lithotomy position, and a self-holding vaginal speculum was introduced. Participants received the assigned study treatment through a 1.6 mm thin sterile hydrosonography catheter (Probimed, Neuilly-en-Thelle, France). After a 2-minute interval, a single tooth tenaculum was applied to the cervix to straighten the uterus, and the length to the fundus was measured using a uterine sound. Subsequently, the IUD was placed into the uterus in accordance with the manufacturer's instruction.

The effectiveness of the intervention for pain reduction was measured as pain scores on VAS, where the participant with a pencil marked the perceived pain score with a vertical line over a printed paper showing the 100-mm VAS. These were recorded at baseline (prior to the examination) and momentarily after intrauterine instillation, IUD placement, and at 10 minutes following speculum removal. At each time point of the procedure, the participants also categorized their perception of pain tolerability as yes/no. Also, 10 minutes following speculum removal, the participants rated their overall placement procedure experience as either "easier than expected," "as expected," or "worse than expected" and if they required additional pain relief (yes/no). Additionally, as a measure of acceptability, participants expressed their willingness to recommend the pain relief method to a friend (yes/no) and indicated whether they would choose to have an IUD placed

again, considering their experience at this placement (yes/no).

Safety evaluation involved monitoring adverse events including allergic reaction, vasovagal reactions, failed placements, and side effects in each group from the first study visit until the end of the trial.

Study data were collected and managed using REDCap (Research Electronic Data Capture) hosted by Karolinska Institutet.[19,20] Data analysis was conducted using IBM SPSS Statistics version 28.0, following an intention-to-treat (ITT) approach and per the protocol (PP), with a significance level set at *P* values less than .05.

To compare VAS pain scores between study arms, a student's *t* test was employed, due to the normal distribution of the data. In addition, the intervention effect was analyzed using a generalized linear mixed model which included the provider as a random effect, as specified in the study protocol. Missing data are presented as missing without imputation. A sensitivity analysis, using the Student's *t* test, was performed within the mepivacaine group to compare mean VAS pain scores among participants receiving the intrauterine instillation according to protocol and those with uncertain position of the cathether tip.

The sample size was determined based on findings from our preceding pilot study that evaluated placement pain after treatment with 10 mL of 10-mg/mL mepivacaine.[17] In the control group, the mean pain score was 63 mm with a standard deviation (SD) of 22 mm. We deemed a 20% reduction in mean VAS pain scores in our intervention group as a clinically significant difference. This corresponds to an absolute reduction of 13 mm, aligning with previous studies on the clinically relevant reduction of VAS for acute pain.[21,22] To detect this difference with 90% power at a significance level of 0.05, each group required 71 participants. To accommodate for anticipated failed placements, we aimed to enroll 75 patients in each arm.

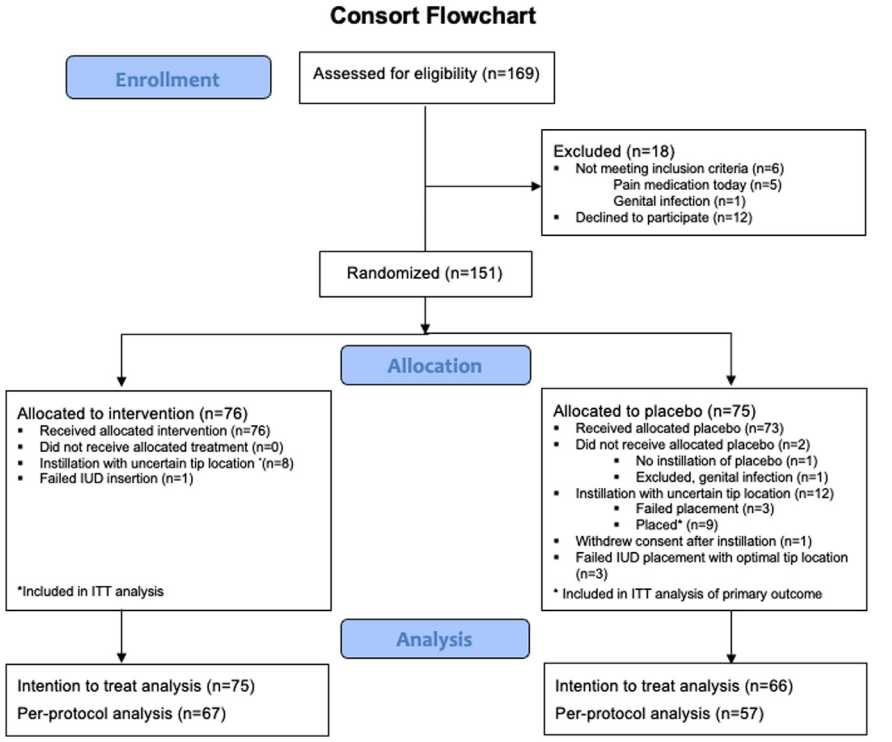
The methodology has been previously described in the pilot trial.[17] Approval was obtained from the Medical Product Agency (EudraCT-no 2020-002271-36) and The Swedish Ethical Review Authority (permit number 2021-00618, with amendments for including new study centers 2021-03087, 2021-04411). No changes were made to the protocol after submission.

Results

We enrolled and randomly assigned 151 women between May 2021 and August 2023, whereof 76 women were allocated to the intervention group and 75 to the placebo group. A total of 8 placements failed, with 1/76 (1.3%) occurring in the intervention group and 7/75 (9.6%) in the placebo group, whereof one did not receive the study drug due to a protocol violation and was therefore excluded from further analysis. Consequently, 6 of the failed placements in the placebo group were considered in the calculations of failed placements (6/72, 8.3%; *P*=.058). In the placebo group, 3 women were excluded post-randomization (Figure). Among the participants, 20 women (8 in the intervention group and 12 in the placebo group), did not receive allocated treatment exactly according to study protocol due to challenges in passing the internal cervical os with the hydrosonography catheter. However, these women received the study drug although the position of the tip of the catheter was uncertain. This resulted in a total of 141 and 124 participants being included in the ITT and PP analyses, respectively (Figure). Demographic characteristics showed no significant differences between groups (Table 1). The mean VAS pain score during the most intense period of cramping during menstruation was 50.7 mm (SD 27.1) for the mepivacaine group and 55.1 mm (SD 25.3) for the placebo group (*P*=.31). Group difference in VAS pain score at different placement procedures is detailed in Table 2.

In the ITT analysis, mean VAS pain score during IUD placement was lower in the mepivacaine group (53.9 mm, SD 22.8) compared to the placebo group

FIGURE
CONSORT 2010 flow diagram



CONSORT, Consolidated Standards of Reporting Trials; *ITT*, intention-to-treat; *IUD*, intrauterine device.

TABLE 1
Baseline characteristics

Characteristic	Mepivacaine n=76	Placebo n=75
Age		
Mean (SD)	20.7 (2.3)	21.5 (3.2)
Reproductive history		
Previous Pregnancy	3 (3.9)	4 (5.3)
Previous Medical Abortion	3 (3.9)	4 (5.3)
Previous Surgical Abortion	0 (0.0)	1 (1.3)
Previous Spontaneous Abortion	1 (1.3)	2 (2.7)
Menstruation information		
Last MP[a] (d) n=113 Mean (SD)	15.0 (11.5)[b]	12.6 (10.8)[c]
Amenorrhea[d]	18 (23.7)	19 (25.7)
Uncertain Last MP	0 (0.0)	1 (1.3)
VAS worst menstrual pain, Mean (SD)	50.7 (27.1)[e]	55.1 (25.3)[e]
Previous IUD use	3 (3.9)[f]	4 (5.3)[f]

Baseline characteristics of participants opting for IUD for contraception.

Data are n (%) unless otherwise indicated.

IUD, intrauterine device; *MP*, menstrual period; *SD*, standard deviation; *VAS*, visual analog scale.

[a] First day of last menstrual period.; [b] n=58.; [c] n=54.; [d] Amenorrhea due to current hormonal contraception.; [e] *P* value=.31 analyzed with Independent *t* test.; [f] *P* value=.72 analyzed with Fisher's exact test.

(67.2 mm, SD 22.4) with an absolute difference of 13.3 mm (95% CI 5.75−20.87; *P*<.001). In the generalized linear mixed model introducing provider as a random effect, the intervention effect demonstrated a mean reduction in VAS pain score of 12.2 mm, with 55.2 mm (SD 26.5) in the intervention group vs 67.4 mm (SD 25.6) in the control group (95% CI 4.85−19.62; *P*<.001). In the PP analysis, the mean pain scores, after adjusting for the individual provider, were 54.5 mm (SD 26.7 mm), in the mepivacaine group and 66.8 mm (SD 25.8) in the placebo group, resulting in a mean pain reduction of 12.3 mm (*P*<.001). In a sensitivity analysis within the mepivacaine group, the mean VAS pain score at IUD placement was 53.8 mm and 55.3 mm among participants with successful instillation and uncertain location of the catheter tip, respectively (*P*=.86).

TABLE 2
Mean VAS pain score in mm at placement procedures by group allocation, intention to treat, and per protocol

Placement procedure	Mepivacaine	Placebo	*P* value[a]
Baseline pain (n=150)[b,c]	1.70 (3.9)	1.41 (4.0)	.65
Intention to treat (total N=141)	(n=75)	(n=66)	
Instillation of study drug or placebo[d,e]	23.6 (21.3)	27.7 (24.9)	.28
IUD placement	53.9 (22.8)	67.2 (22.4)	<.001
IUD placement adjusted for provider	55.2 (26.5)	67.4 (25.6)	<.001[f]
10 min after placement	37.3 (24.2)	42.4 (25.7)	.23
Per protocol (total N=124)	(n=67)	(n=57)	
Instillation of study drug or placebo	25.3 (21.9)	30.5 (24.0)	.21
IUD placement	53.8 (23.3)	67.0 (22.6)	.002
IUD placement adjusted for provider	55.2 (26.5)	67.4 (25.6)	<.001[f]
10 min after placement	37.1 (24.0)	42.2 (26.3)	.24

Data are presented as mean (standard deviation), unless otherwise indicated.

ITT, intention-to-treat; *IUD*, intrauterine device; *VAS*, visual analog scale.

[a] Student's *t* test unless stated otherwise; [b] Mepivacaine n=76; [c] Placebo n=74; [d] Mepivacaine n=76; [e] Placebo n=73; [f] Generalized linear mixed models.

At 10 minutes after placement, neither VAS pain scores (37.3 mm, SD 24.2 vs 42.4 mm, SD 25.7 mm; *P*=.23) nor the need for additional pain medication (53/75, 70.7% vs 49/66, 74.2%; *P*=.64) differed between the mepivacaine and placebo group.

No serious adverse effects associated with mepivacaine instillation were identified, and there were no cases of uterine perforation observed in either group. In the mepivacaine group, 98.7% (75/76) of the participants found the pain at instillation to be tolerable, compared to 97.3% (71/73) in the placebo group (*P*=.54). A higher proportion of participants in the mepivacaine group (57/74, 77.0%) compared to the placebo group (39/64, 60.9%) would recommend intrauterine instillation for pain relief to a friend (*P*=.04). During IUD placement, 93.3% (70/74) of the participants in the mepivacaine group reported the pain as tolerable compared to 80.3% (53/66) in the placebo group (*P*=.02). Detailed information on participant acceptability is presented in Table 3.

Discussion

Principal findings

In this double-blind, randomized, placebo-controlled trial, intrauterine instillation of mepivacaine resulted in a statistically significant reduction of mean VAS pain at IUD placement of 12.2 mm from mean 67.4 mm (SD 25.2) in the control group to 55.2 mm (SD 27.8) in the intervention group (*P*<.001)

TABLE 3
Acceptability of IUD placement by group allocation

Overall experience	Mepivacaine (n=74)	Placebo (n=64)	*P* value[a]
Placement pain tolerable n(%)[b,c]	70 (93.3)	53 (80.3)	.02
Easier than expected	30 (40.5)	16 (25.0)	.04
As expected	25 (33.8)	19 (29.7)	
Worse than expected	19 (25.7)	29 (45.3)	
Would choose IUD for contraception again	64 (86.5)	44 (68.8)	.01
Would recommend the method for pain relief	57 (77.0)	39 (60.9)	.04

IUD, intrauterine device.

[a] Chi-square test; [b] Mepivacaine n=75; [c] Placebo n=66.

when adjusted for provider. The unadjusted difference was 13.3 mm.

Results in context of what is known

Nulliparous women experience more pain at IUD placement [6–8,23] and therefore comparison to studies with a mixed parity population is difficult. According to a Cochrane review, certain preparations of lidocaine reduce pain related to IUD placement.[9] Studies have investigated the effect of topical local anesthesia with lidocaine or lidocaine/prilocaine and found an effect on pain levels during IUD placement. However, these studies involved women with mixed parity or parous women.[15,24–27]

Although pain is often stated as a concern prior to placement, previous studies show that a majority of nulliparous women report pain as mild to moderate.[28–30] Although we did not categorize pain as mild, moderate, or severe, our study findings likely align with these observations, as 74.3% in the mepivacaine group and 54.5% in the placebo group rated the placement experience to be either easier than or as expected.

In our previous pilot trial with instillation of 10 mL of 1% mepivacaine, we demonstrated a nonsignificant reduction in placement pain.[17] Nevertheless, the instillation process in itself was highly tolerable. In this study we used a higher concentration which led to statistically significantly lower pain scores with maintained high tolerability.

Another instillation method that has demonstrated pain reduction involved the use of 4% lidocaine gel applied to the cervix and instilled into the uterine cavity. In this study, approximately 36% in the lidocaine group reported strong/very strong discomfort at instillation.[31] For a method of pain relief to be considered acceptable, it must not induce more discomfort than the actual procedure it aims to alleviate. In contrast, close to all participants in our intervention group (98.7%) reported pain as tolerable confirmed by mean VAS at 23.6 mm at instillation of mepivacaine.

Clinical implications

While our study employed a clinical significance threshold of 13 mm based on studies on the validation of important changes in pain severity,[21,22] the fact that other studies have chosen a benchmark of 17 mm, as suggested in a comprehensive review,[32] raises concerns about the clinical significance of our findings. In our generalized linear mixed model introducing provider as random effect, the difference in pain scores was 12.2 mm, whereas the unadjusted difference was 13.3 mm, which may represent a setting closer to "real-life," where not only experienced providers place IUDs. The exact clinically significant pain reduction during IUD placement remains unknown. We argue that the pain reduction in our study is clinically important as a greater proportion of women in our intervention group, compared to the placebo group, reported tolerable pain during placement and to a higher extent rated the placement as easier than expected and expressed a willingness to choose IUD as contraception again.

Research implications

The close to significant higher failure rate in the placebo group could indicate that mepivacine is associated with a lower rate of failed placements. This suggests a field for potential research as successful placements are crucial for women to receive their desired method of contraception. Moreover, difficult placements may be associated with increased pain. Interventions that lower placement failures are rare. A previous trial involving self-administered vaginal lidocaine gel demonstrated a significant decrease in the need for cervical dilation before IUD placement.[33] Further studies are required to explore whether local anesthetics, such as mepivacaine, have a direct impact on cervical dilation and placement failure rates.

Strengths and limitations

This study possesses several strengths, including a randomized double-blinded study design and the ITT analysis. In addition, the multicenter design with multiple providers reflects a real-life setting, and exclusion of current IUD users opting for replacement and those who had used any other type of medication for pain reduction prior to placement limit the number of potential confounding factors. Furthermore, we deliberately focused on a group of nulliparous women aged 18 to 31, exclusively placing the levonorgestrel-IUD 52 mg (4.4 mm inserter tube diameter). The targeted inclusion criteria contribute to reducing the risk of bias and enhance the internal validity of our study. Another notable strength is the pain assessment method where participants were provided with a paper-printed VAS during the procedure, enabling them to mark their VAS scores immediately at each step of the placement process. This methodology was chosen to contribute to more

accurate and immediate pain measures with a minimum of recall bias.

A limitation of the study is that certain factors that could potentially influence pain during the placement procedure, such as anticipated pain and patient anxiety and the ease of placement, were not systematically assessed.[34,35] However, we recorded worst period cramping, a factor known to be associated with increased pain at IUD placement[36] and found no difference in menstrual cramping scores between groups. Furthermore, our evaluation focused exclusively on 1 type of IUD (LNG-IUS 52 mg, 4.4 mm) which may limit the generalizability of our finding to other IUD types with different placement tube sizes.

Only experienced providers participated in the study. Consequently, our findings may not be generalizable to settings with less experienced providers necessitating further research to evaluate the pain relief method's applicability and effectiveness in diverse clinical settings.

Conclusion

Intrauterine instillation of 2% mepivacaine results in reduction of pain at IUD placement, increases the proportion of women who experience tolerable pain, and is a highly accepted method among nulliparous women. These results suggest practical relevance and clinical significance to reduce procedural pain during placement of an IUD. Intrauterine instillation of mepivacaine is a possible strategy to reduce barriers to IUD uptake and promote reproductive autonomy among nulliparous women.■

Acknowledgments

The authors would like to acknowledge associate professor Linda Vixner, Dalarna University for her input during the planning of the study and the professional medical statisticians Yunzhang Wang and Fredrik Johansson, Danderyd Hospital, for technical support in analyses. The authors would also like to thank the participating clinics and the local investigators for their help in enrollment of participants and data collection.

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Received Jan. 26, 2024; revised May 1, 2024; accepted May 19, 2024.

Clinical trials registration

Date of registration: 2021 March 04.

Date of initial participant enrollment: 2021 May 17.

Clinical trial identification number: Eudra CT no: 2020-002271-36.

URL of the registration site: https://eudract.ema.europa.eu/index.html.

N.E. has received personal fees from Bayer for educational activities and honorarium from Medsphere Corp USA for expert opinions on long-acting reversible contraception, outside the submitted work. H.K.K. has received honoraria for consultancy work and lectures from Abbvie, Actavis, Bayer, Exeltis, Gedeon Richter, Natural Cycles, Nordic Pharma, Merck, Mithra, Teva, Organon, Ferring, Consilient Health and providing expert opinion for Bayer, Evolan, Gedeon Richter, Exeltis, Merck, Teva, TV4 och Natural Cycles, Dynamic Code, Ellen, Estercare, Pharmiva, Gedea, Gesynta, Essity, and Preglife; is an investigator in trials sponsored by Bayer, MSD, Mithra, Ethicon, Azanta/Norgine, Gedeon Richter, Gedea, planned study for Organon, Pharmiva, and Takeda. None of the above mentioned entities have had any influence on study design, interpretation of results, or manuscript writing. K.E. reports no conflict of interest.

The study was financed by the The Swedish Research Council, grant # 2020-00653. The funding sources were not involved in study design, in the collection, analysis or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Data sharing: The full pseudonymized dataset as well as study protocol will be made available upon request from the corresponding author and be shared with the requester in.sav format (for use in SPSS) from date of submission until 2029 December 31.

Preliminary results presented at Reproductive Health Conference 2023, The Swedish Association of Midwives, Karlstad, Sweden, Oct. 3—4, 2023.

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