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Overcoming barriers to levonorgestrel-releasing intrauterine system placement: an evaluation of placement of LNG-IUS 8 using the modified EvoInserter® in a majority nulliparous population☆

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Abstract

Objectives: To report placement success rate, and ease and pain associated with placement, of the levonorgestrel-releasing intrauterine system (LNG-IUS) 8 using the modified EvoInserter® placement device.
Study design: This was a pooled analysis using data from three previously reported Phase III studies in nulliparous (83.3%) or parous (16.7%) women aged 12–35 years (*N*=965). LNG-IUS 8 was placed using the modified EvoInserter®. The main outcomes assessed were placement success, ease of placement as reported by healthcare professionals (HCPs), pain at placement as reported by participants, and assessment of the EvoInserter® placement device by HCPs.
Results: LNG-IUS 8 placement using the modified EvoInserter® with an insertion tube diameter of 3.8 mm was successful in 99.5% of subjects. HCPs rated the placement procedure as "easy" in 91.6% of cases. Placement pain was reported as absent by 19.1% of participants, as mild by 39.3%, as moderate by 31.6%, and as severe by 10.0%. Overall 89.2% of HCPs completely agreed that the device was easy to prepare and 85.7% completely agreed that placement of an LNG-IUS was easy/simple with the EvoInserter®. Post hoc exploratory analyses indicated a significant association between ease/pain of placement and patient age and between pain of placement and parity.
Conclusions: The modified EvoInserter® was associated with a high placement success rate, ease of placement, and manageable pain, and was assessed to have a user-friendly design. These findings suggest that the EvoInserter® may remove some concerns among HCPs about difficult placement of LNG-IUSs, thereby encouraging increased uptake of an effective contraceptive.
Implications statement: Results reported in this study further strengthen evidence of the high placement success rate, ease of deployment, and manageable pain associated with the modified EvoInserter® placement device. These findings might reduce concerns among HCPs about placement of LNG-IUSs, meaning uptake of such contraceptives is increased.

Keywords: LNG-IUS; Levonorgestrel; Insertion; EvoInserter; Intrauterine device

1. Introduction

Despite the availability of many hormonal and non-hormonal contraceptive options, the high rate of unintended pregnancy is a global concern [1,2]. Increasing the uptake of long-acting reversible contraception, such as the levonorgestrel-releasing intrauterine system (LNG-IUS), the effectiveness of which is independent of user compliance, could potentially decrease the rate of unintended pregnancy [3,4]. However, healthcare professionals' (HCPs)

☆ Conflicts of interest: Kristina Gemzell-Danielsson serves on advisory boards and has been an invited speaker at scientific meetings for Bayer Pharma AG, MSD/Merck, HRA Pharma, Exelgyn, and Gedeon Richter on an ad hoc basis. Her institution received grants for the Phase II and Phase III clinical trials of LNG-IUS 8 and LNG-IUS 12. Dan Apter's institution received grants from Bayer Pharma AG for the Phase II and Phase III trials of LNG-IUS 8 and LNG-IUS 12. He has also taken part in advisory boards and has been an invited speaker at scientific meetings for Bayer Pharma AG, MSD/Merck, HRA Pharma, and Gedeon Richter on an ad hoc basis. Eeva Lukkari-Lax is an employee of Bayer Oy. Marco Serrani and Katrin Roth are employees of Bayer AG.

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and women's concerns about placement difficulty or pain associated with placement may limit the uptake of intrauterine contraception (IUC) [5,6].

LNG-IUS 8 (levonorgestrel [LNG] total content 13.5 mg, average LNG release rate ~8 μg/24 h over the first year; Jaydess®/Skyla®, Bayer Pharma AG) [7,8] is a lower-dose LNG-IUS with smaller T-body dimensions and narrower insertion tube diameter compared with LNG-IUS 20 (LNG total content 52 mg, average LNG release rate ~20 μg/24 h over the first year; Mirena®, Bayer Pharma AG) [9,10]. This may increase the suitability of LNG-IUSs to a wider range of women, including those who are young and nulliparous [11,12]. An additional LNG-IUS, known as LNG-IUS 12 (LNG total content 19.5 mg, average LNG release rate ~12 μg/24 h over the first year, and the same T-body dimensions as LNG-IUS 8; Kyleena™, Bayer Pharma AG), has also been developed and recently received marketing authorization. Both LNG-IUS 8 and LNG-IUS 12 are placed using an insertion tube with a 3.8 mm diameter. The diameter of the LNG-IUS 20 insertion tube is 4.4 mm. For comparison, the diameter of the insertion tube used with LNG20 (Liletta®, Allergan, Inc.) is 4.8 mm [13].

The original EvoInserter® placement device was investigated during clinical trials of LNG-IUS 8 and has subsequently been modified in response to feedback from HCPs who identified development opportunities. In particular, they recommended reducing the number of preparatory steps. Key features of the modified EvoInserter® include simplified loading and a more ergonomic design than the previous model. For instance, the threads are located inside the placement device handle, eliminating the need for direct handling and the risk of accidental entanglement during placement. The device is preloaded in the correct position and the arms are loaded into the device through a simple one-step technique. There is a centimeter scale on both sides of the EvoInserter®, meaning the scale is now visible even when placement is performed in a woman with a retroverted uterus. Whilst the placement procedure fundamentally remains unchanged, the EvoInserter® now allows placement with one hand. In addition, the device cannot now be reloaded should it be released prematurely. The EvoInserter® will be used for the placement of LNG-IUS 8, LNG-IUS 12, and LNG-IUS 20.

Here, we present pooled data relating to ease of placement and pain with placement of LNG-IUS 8 using the modified EvoInserter® device in three previously reported Phase III studies [11,12,14]. These data should also be transferable to LNG-IUS 12, given that both devices have the same T-body dimensions and insertion tube diameter.

2. Material and methods

2.1. Study design

Methodologies for the three Phase III studies have been reported previously. In brief, Study 1 was an open-label, randomized study comparing treatment satisfaction of LNG-IUS 8 with that of the 30 μg ethinyl estradiol/3 mg drospirenone combined oral contraceptive in women aged 18–29 years [12]. Study 2 was an open-label, randomized study comparing discontinuation rates at 12 months of LNG-IUS 8 with the etonogestrel subdermal implant in women aged 18–35 years [11]. Study 3 was a single-arm study of LNG-IUS 8 in postmenarcheal adolescents aged 12–17 years, assessing the incidence of treatment-emergent adverse events over 12 months [14]. Overall, 83% of participants evaluated in this pooled analysis and 88% of those evaluated for pain at/ease of placement were nulliparous. In each case, the appropriate Independent Ethics Committee or Institutional Review Board reviewed and approved the study protocol, and all three studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all participants before study entry.

Participants were required to have had a normal or clinically insignificant cervical smear ≤6 months before screening and to have regular menstrual cycles (21–35 days). Participants were excluded if they had had a vaginal delivery, cesarean section, or abortion ≤6 weeks before screening. In all three studies, LNG-IUS 8 was placed using the EvoInserter® placement device. LNG-IUS 8, which has a 28×30 mm T-frame, was placed during the first 7 days of the participant's menstrual cycle. At the investigator's discretion the cervical canal was dilated to facilitate placement. Additionally, either local anesthesia (e.g., paracervical blockade) or systemic painkillers (e.g., oral nonsteroidal anti-inflammatory drugs) were permitted, to minimize participant discomfort during placement. A maximum of two placement attempts were permitted per participant.

2.2. Study outcomes and assessments

Secondary outcomes in the three studies included placement success and reasons for failure, ease of placement (HCPs assessed placement as "easy," "slightly difficult," or "very difficult"), and pain at placement (participants assessed pain as "none," "mild," "moderate," or "severe," based on their own perceptions of what these terms meant). Information on when, during the placement procedure, women were asked to rate their pain is not available. Ease of/pain at placement was not assessed in Study 2.

In Study 1 [12], additional secondary outcomes were assessed using an investigator questionnaire. After each successful LNG-IUS 8 placement, HCPs completed the questionnaire to assess their level of agreement with statements regarding use of the EvoInserter® during placement, and to evaluate the features and design of the EvoInserter® using a 5-point Likert-type scale ("completely agree," "somewhat agree," "neutral," "somewhat disagree," or "completely disagree"). HCPs assessed ease of preparation of the EvoInserter®, ease of placement, control of

placement, correct deployment, and removal thread qualities, and rated the features of the EvoInserter®.

2.3. Statistical analyses

All variables were analyzed by descriptive statistics. The full analysis set (FAS) comprised all participants enrolled in Study 1, 2, or 3 for whom at least one LNG-IUS 8 placement attempt was made, regardless of success. Where the same outcome was reported across more than one study, data have been pooled. Therefore, data were pooled from Studies 1, 2, and 3 for placement success and reasons for failure, and from Studies 1 and 3 for ease of/pain at placement. Subgroup analyses were performed to evaluate the effect of age and parity on ease of/pain at LNG-IUS 8 placement, and associations between these factors were assessed using Fisher's exact test (in case of small numbers) or the Chi-square test. Stratified Cochran-Mantel-Haenszel tests (general association statistic) were used to assess the association of ease of placement and pain at placement, and the association of prophylactic analgesics and pain at placement, both adjusted for age group and parity. All analyses are exploratory and reported p-values should not be interpreted in a confirmatory manner.

3. Results

3.1. Participant disposition and baseline characteristics

Participant disposition for the three studies is shown in Fig. 1. Of the 971 participants randomized/allocated to receive LNG-IUS 8, 965 had at least one placement attempt and were included in the FAS. Baseline characteristics of the FAS are shown in Table 1.

Table 1
Baseline characteristics (full analysis set*).

Variable	LNG-IUS 8 (*N*=965)
Mean age, years (range)	21.8 (12–35)
Mean BMI, kg/m^2 (range)	23.2 (15.3–46.0)
Nulliparous, *n* (%)	804 (83.3)
Contraceptive method at screening, *n* (%)	
Oral hormonal contraception	506 (52.4)
Barrier method	256 (26.5)
Vaginal hormonal contraception	46 (4.8)
LNG-IUS	14 (1.5)
Implant	7 (0.7)
Transdermal hormonal contraception	8 (0.8)
IUD	6 (0.6)
None	122 (12.6)

BMI: body mass index; IUD: intrauterine device; LNG-IUS: levonorgestrel intrauterine system.
* Full analysis set including participants who experienced at least one placement attempt.

3.2. Placement success

There were 978 LNG-IUS 8 placement attempts in 965 participants. Overall, placement was successful in 99.5% of participants (960/965) after a maximum of two placement attempts. Placement was successful at first attempt in 98.2% (948/965) of participants. A second attempt at placement was successfully completed for 12/13 participants (92.3%). A

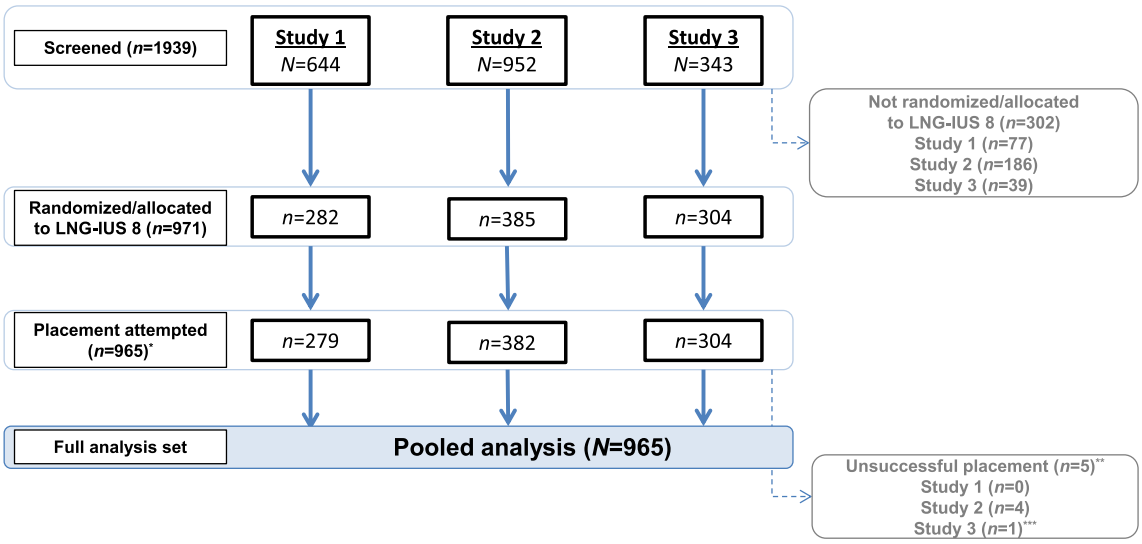

Fig. 1. Participant disposition in the three studies [11,12,14]. *Six participants who were randomized/allocated to LNG-IUS 8, three participants from Study 1 (one protocol violation and two withdrawals of consent) and three participants from Study 2 (one protocol violation and two withdrawals of consent) did not have a placement attempt. **Reasons for failure on the first attempt were: IUS came out immediately after placement (*n*=3); cervix was too tight for placement (*n*=1); position of the uterus (*n*=1); pain (*n*=2); and other reasons (*n*=10). The reason for failure on the second attempt in one woman was due to being unable to pass the IUS through the internal orifice of the cervix. ***The 51 participants listed as discontinuing by Gemzell-Danielsson et al. [14] comprise 50 participants listed under "premature discontinuation" and one participant who had an "unsuccessful placement".LNG-IUS: levonorgestrel-releasing intrauterine system.

second attempt at placement was not undertaken in four participants; reasons for not undertaking a second placement were not available.

3.3. Ease of placement

Pooled data on ease of placement using the EvoInserter® were available from Studies 1 and 3 (*n*=582). HCPs rated placement as "easy" in 91.6% (*n*=533) of participants, "slightly difficult" in 7.7% (*n*=45) of participants, and "very difficult" in 0.7% (*n*=4) of participants (Table 2). Data on ease of placement by age and parity subgroups are also presented (Table 2). Exploratory analyses indicated a significant association between the ease of placement and age, but not parity, although the nature of this association is unclear (Table 2). More HCPs rated placement as "easy" in women aged <18 years and 26−35 years compared with women aged 18−25 years.

3.4. Pain at placement

Among the 965 participants, local anesthesia, including paracervical blockade, was given in 213 (22.1%) before the procedure, two (0.2%) when the procedure proved difficult, and one (0.1%) when the procedure proved difficult and painful; this woman received a paracervical block in addition to other forms of local anesthesia at different time points. Analgesics were administered to 354 participants (36.7%) before the procedure, two participants (0.2%) when placement proved difficult, and 42 participants (4.4%) when they experienced pain.

Pooled data on pain at placement were available for 582 participants with a successful placement in Studies 1 and 3. Overall, 19.1% (*n*=111) of participants reported no pain, 39.3% (*n*=229) reported mild pain, 31.6% (*n*=184) reported moderate pain, and 10.0% (*n*=58) reported severe pain during the placement procedure. Data on pain on placement by age and parity are presented in Table 2. Exploratory analyses indicated significant associations connecting participants' evaluation of pain during placement, age and parity; the nature of this association is not entirely clear (Table 2). More parous women reported "no" pain and fewer parous women reported either moderate or severe pain compared with nulliparous women. More women aged 26−35 years reported "no" pain as well as fewer women reporting "moderate" or "severe" pain compared with women aged either <18 years or 18−26 years.

3.5. Association between ease of placement and pain on placement

Additional post hoc exploratory analyses indicated a significant association (p<.0001) between the investigator's evaluation of ease of placement and the women's evaluation of pain on placement. Placements considered by HCPs to be easier were generally less painful for women. This association was maintained even when adjusting for age and parity.

3.6. Association between prophylactic analgesia and pain on placement

In these additional post hoc exploratory analyses, a significant association (p=.0262) was also observed between administration of prophylactic analgesia and women's evaluation of pain on placement. Women generally evaluated their pain to be lower when prophylactic medication was not given, compared with when it was given. This association was maintained even when adjusting for age and parity.

3.7. Investigators' evaluation of the EvoInserter®

In Study 1, HCPs viewed the EvoInserter® favorably in terms of ease of preparation, ease of placement, being in

Table 2
Ease of LNG-IUS 8 placement rated by HCPs and pain of LNG-IUS 8 placement rated by participants [12,14].

n (%)	All	Age, years				Parity		
		<18	18–25	26–35	p-value	Nulliparous	Parous	p-value
Total	582	301 (51.7)	193 (33.2)	88 (15.1)		512 (88.0)	70 (12.0)	
Placement rating (HCP assessment)								
Easy	533 (91.6)	284 (94.4)	168 (87.0)	81 (92.0)		466 (91.0)	67 (95.7)	
Slightly difficult	45 (7.7)	14 (4.7)	24 (12.4)	7 (8.0)	p=.02*	42 (8.2)	3 (4.3)	p=.61†
Very difficult	4 (0.7)	3 (1.0)	1 (0.5)	0 (0.0)		4 (0.8)	0 (0.0)	
Pain rating (participant assessment)								
None	111 (19.1)	62 (20.6)	28 (14.5)	21 (23.9)		82 (16.0)	29 (41.4)	
Mild	229 (39.3)	104 (34.6)	80 (41.5)	45 (51.1)	p=.02*	197 (38.5)	32 (45.7)	p<.01
Moderate	184 (31.6)	103 (34.2)	64 (33.2)	17 (19.3)		176 (34.4)	8 (11.4)	
Severe	58 (10.0)	32 (10.6)	21 (10.9)	5 (5.7)		57 (11.1)	1 (1.4)	

HCP: healthcare professional; LNG-IUS: levonorgestrel-releasing intrauterine system.

* p-Value calculated using chi-square test. p-Values indicate an association between the relevant age/parity and investigators'/participants' rating of the placement procedure.

† p-Value calculated using Fisher's exact test. p-Values indicate an association between the relevant age/parity and investigators'/participants' rating of the placement procedure.

control of the placement, and correct deployment (Supplementary Table 1).

4. Discussion

This pooled analysis confirms the utility of the EvoInserter® in the placement of LNG-IUS 8. The placement failure rate of 0.5% in our analysis compares favorably with those reported in several studies of intrauterine device (IUD) placement (0–2.5%) [15–20]. However, failure rates with traditional placement methods in community practice may be higher than those observed in randomized studies (19.6% in nulliparous women and 13.6% in parous women) [21].

The high placement success rates reported in our analysis may be as a result of the modified placement procedure, along with the smaller diameter of the placement tube. It may also be due to the high levels of experience of HCPs typically involved in clinical trials [21]. Our findings demonstrate that placement of an LNG-IUS using the EvoInserter® is appropriate for most women, including young women. This is not insignificant given that younger women have a higher rate of unintended pregnancy than older women [3,22–24] and HCPs are less likely to recommend IUC as a contraceptive to these women [25,26].

There are conflicting data on the effectiveness of prophylactic medication to manage pain associated with IUC placement [27,28]. Nevertheless, fear of pain during placement may cause women to avoid using IUC [28] and anticipation of pain appears to significantly increase the perception of pain [29]. In our analysis, the association of pain prophylaxis and increased pain may be a result of bias, i.e., analgesics may be more often prescribed for women that the HCP assumes will have a lower tolerance to placement-related pain. These findings emphasize the need for pre-procedure counseling and "verbal anesthesia" during the placement procedure [30].

The EvoInserter® was developed to decrease the number of preparatory steps compared with earlier devices. In the current analysis, over 90% of HCPs using the EvoInserter® with LNG-IUS 8 reported that placement was "easy." Our data support the findings of a Phase II, randomized study of 738 parous or nulliparous participants aged 21–40 years, in which HCPs rated placement of LNG-IUS 8 or LNG-IUS 12 using a device with the same diameter as the EvoInserter® (i.e., 3.8 mm) as "easy" in 94% of cases. This was compared with 86% for LNG-IUS 20 using a 4.8 mm diameter inserter, with cervical dilation being used more frequently in the LNG-IUS 20 group [31]. Furthermore, 72% of participants reported either "no pain" or "mild pain" on placement of LNG-IUS 8 or LNG-IUS 12, compared with 58% in the LNG-IUS 20 group. The authors concluded that the significantly easier and less painful placement of LNG-IUS 8 and LNG-IUS 12 compared with LNG-IUS 20 was likely due to the smaller placement tube diameter (3.8 mm versus 4.8 mm). It must be noted that the placement device used with LNG-IUS 20 in that study was the previous model, which is no longer used. LNG-IUS 20 is now placed using the EvoInserter® with a placement tube diameter of 4.4 mm [10,32]. Pivotal Phase III trial results of LNG-IUS 8 and LNG-IUS 12 stratified by age and parity have also been published [33,34]. Although most HCPs (89.6%) rated placement as "easy" in that study, a slightly higher proportion of HCPs (91.6%) rated placement as "easy" in our analysis which included more nulliparous participants. Furthermore, more nulliparous participants reported "no pain" and fewer participants reported "severe pain" in our analysis than in the pivotal Phase III study (16.0% vs. 6.1% and 11.1% vs. 15.5%, respectively).

The main limitation of the current analysis is that the analysis of pooled data from the three studies was retrospective. In addition, ease of placement and pain data were available for only two of the studies, and data for HCP evaluation of the EvoInserter® was from one study only. Although the studies allowed for pain management and cervical dilation, this was at the discretion of the individual investigators, and was applied neither systematically nor randomly. Therefore, it is not possible to draw conclusions regarding ease of placement and perceived pain associated with placement in terms of dilation and/or pain medication.

In conclusion, this pooled analysis of three Phase III studies of nulliparous (83.3%) and parous (16.7%) participants aged 12–35 years shows that LNG-IUS 8 placement using the EvoInserter® was successful in 99.5% of participants after a maximum of two placement attempts. These data, therefore, suggest that when using the EvoInserter®, both LNG-IUS 8 and LNG-IUS 12 are suitable for nulliparous women and that the EvoInserter® may remove some concerns among HCPs about difficult placement of IUC; this may translate into less fear of difficult and painful placements on the part of potential users, ultimately encouraging greater uptake of this effective, long-acting, reversible contraceptive method.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.contraception.2017.08.004.

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