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Bleeding and spotting with the levonorgestrel 13.5 mg intrauterine system: the impact of insertion timing☆,☆☆,★

Noa'a Shimoni [a,*], Tasmiah Choudhury [a], Alice R. Goldman [b], Michelle Frondelli [a], Ping-Hsin Chen [a]

[a] Rutgers New Jersey Medical School, Department of Family Medicine, 183 South Orange Avenue, E1562, Newark, NJ 07103
[b] Johns Hopkins School of Medicine, 601 North Caroline Street 3171D, Baltimore, MD 21287

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ABSTRACT

Objective: To assess the impact of early versus late menstrual cycle insertion on bleeding/spotting in the 90 days following levonorgestrel (LNG) 13.5 mg intrauterine system (IUS) insertion.
Study design: In this observational study, participants received a LNG 13.5 mg IUS and provided 90 days of bleeding/spotting data by answering the following daily text: "Have you had no flow (0), spotting (1), or bleeding (2) today?" We dichotomized insertion timing as early (days 1–7 from last menstrual period) and late (remainder of menstrual cycle) and compared bleeding/spotting between the two groups in the 90- and 30-day reference periods. We used multivariate regression methods to study associations between cycle day at insertion, parity, historical bleeding, recent hormonal contraceptive use and bleeding/spotting.
Results: In the 90-day dichotomous analysis (n=125), we found no differences in the number of days of bleeding/spotting, bleeding or spotting between the early and late insertion groups. In the 30-day dichotomous analysis (n=131), early insertion was associated with fewer days of bleeding than late insertion (5±3 vs. 7±4 days, p<.01). Recent hormonal contraceptive users experienced fewer days of bleeding than new users (5±4 vs. 7±3 days, p<.01). In the 90- and 30-day regression models, earlier insertion was associated with fewer days of bleeding (p=.02, p=.02). Recent contraceptive use was associated with fewer days of bleeding/spotting (90-day, p=.03) and fewer days of bleeding (30-day, p<.01). Nulliparity was associated with spotting (30-day, p=.04).
Conclusions: Early cycle insertion does not impact 90-day bleeding/spotting. Early cycle insertion and recent hormonal contraceptive use decrease 30-day bleeding.
Implications: The LNG 13.5 mg IUS may be inserted throughout the menstrual cycle with small differences in bleeding patterns in the 30 but not the 90 days following insertion. Shared decision making should determine timing of insertion.

1. Introduction

While the majority of women using a levonorgestrel (LNG) intrauterine system (IUS) express long-term satisfaction and continue to use the LNG-IUS for multiple years, women who remove devices cite bleeding pattern changes as one of the reasons, regardless of LNG dose [1–5].

The LNG 13.5 mg IUS is indicated to prevent pregnancy for up to 3 years. Women report a range of 40–45 days of bleeding/spotting in the first 90-day reference period after LNG 13.5 mg IUS insertion [2,4,6]. Removal rates for bleeding alterations range from 4.2% to 4.7% in the first 12 months, with only a fraction due to decreased bleeding [1,4].

In the past, clinicians preferentially inserted devices during menstruation, and study protocols required the same to ensure that women were not pregnant at device insertion. This practice resulted in a body of bleeding literature based on menstrual insertion. Clinicians now increasingly insert devices throughout the cycle, but we were unable to find any published data that compared bleeding patterns with menstrual insertion to bleeding patterns with later cycle insertion when we conceived this study.

We hypothesized that insertion during menstruation, when the uterine endometrium is thinnest [7], would result in fewer days of bleeding and spotting in users of the LNG 13.5 mg IUS. We also hypothesized that recent hormonal contraceptive use would result in fewer days of bleeding and spotting.

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* Corresponding author. Tel.: +1 973 972 4097.
E-mail address: noaa.shimoni@rutgers.edu (N. Shimoni).

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2. Materials and methods

2.1. Participants

We recruited women ages 18–45 interested in the LNG 13.5 mg IUS (Skyla®; Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA) at three sites — Rutgers New Jersey Medical School's Student Health Services, New Jersey Family Practice Center and Planned Parenthood of Central and Greater Northern New Jersey — between April 2016 and May 2017. Eligible participants had regular menstrual cycles (21–35 days), had a working mobile phone and were willing to accept text messages and report daily bleeding for 90 consecutive days. We excluded women with a recent delivery (past 12 weeks), abortion (past 6 weeks), uterine bleeding of unknown etiology, acute liver disease, an abnormal pap awaiting further management or contraindications to IUS use (U.S. Medical Eligibility Criteria categories 3 or 4). Rutgers' Institutional Review Board approved the protocol, and all women signed written informed consent before initiating study participation.

We enrolled women into early and late insertion groups based on their last menstrual period (LMP) at insertion day: early cycle insertion days 1–7 from LMP and late cycle insertion from day 8 through the end of the cycle. We permitted women who used combined or progestin-only contraception in the 12 weeks prior to enrollment into the study provided they had regular menstrual cycles; we defined this group as recent contraceptive users. Same day insertion was standard practice for all sites whenever possible. Enrollment was ongoing in both groups until a group filled; once one group filled, women could only enroll in the remaining group.

2.2. Data collection

We used Research Electronic Data Capture to collect screening, baseline and follow-up questionnaires. Since endometrial thickness correlates with menstrual cycle day, we performed transvaginal ultrasound to measure endometrial thickness at baseline as an alternate measure of cycle day [7]. Coauthor A.G., a radiologist blinded to the participant's LMP, reviewed the ultrasound images.

Following LNG 13.5 mg IUS insertion, participants received the following daily text (at 7:00 p.m.) for 90 days: "Have you had no flow (0), spotting (1), or bleeding (2) today?" A reminder text was sent 1 hour later if no response was received: "A friendly reminder: Have you had no flow (0), spotting (1), or bleeding (2) today?" We instructed participants to define bleeding as menstrual flow requiring sanitary protection and spotting as menstrual flow requiring no sanitary protection or only a panty liner. This definition was chosen for consistency with other studies of the LNG 13.5 mg IUS [2,4,6]. Participants received backup paper diaries and were instructed to complete them if unable to text a response.

Text message surveys were sent, and responses were received in real time by a centralized secure database developed and managed by Mosio, a text messaging software company. Research staff regularly checked the database to identify missing texts and reached out to participants via text, phone or email (per the participant's preference) to complete missing data when texts went unanswered. Participants received compensation every 30 days for submitted data.

2.3. Data analysis

2.3.1. Sample size

We used historical 90-day bleeding data for the LNG 13.5 mg IUS from the Phase II and III studies to calculate sample size; in those studies, women bled/spotted for approximately 40 days [2,4]. To detect a 25% difference in bleeding/spotting in the 90-day reference period following insertion, we used a mean difference of 10 days, a standard deviation of 18.7 days, an α of 0.05 and 80% power. A two-sided test yielded a 1:1 sample size of 55 women in each group. An additional 20% allotted for loss to follow-up resulted in 66 women in each insertion group, for a total sample of 132. We were not aware of any studies on women's perceptions of bleeding to guide our sample size calculations.

2.3.2. Analytic plan

We analyzed three bleeding constructs: combined bleeding/spotting, bleeding only and spotting only. Our primary analysis *a priori* compared bleeding/spotting in the 90-day reference period between the two insertion groups using a Student's *t* test. Our secondary analyses compared bleeding and spotting between the two insertion groups (30-day reference), between parous and nulliparous participants (30- and 90-day reference periods), and between new and recent hormonal contraceptive users (30- and 90-day reference periods). We tested all bleeding and spotting data for normalcy.

In addition to the group analyses, we used multivariate regression methods to explore if cycle day at insertion, parity, historical bleeding or recent hormonal contraceptive use was associated with bleeding and/or spotting. We coded the dummy variables as follows: nulliparity=0, parity=1, hormonal contraceptive use=0 and new user=1. We defined historical bleeding as the proportion of bleeding and spotting days in the last cycle prior to LNG 13.5 mg IUS insertion, as reported by the participant at baseline. Lastly, we used χ^2 analyses to compare prolonged and frequent bleeding in the 90-day reference period. The World Health Organization's Belsey criteria define prolonged bleeding as bleeding and spotting episodes lasting more than 14 consecutive days and frequent bleeding as more than 5 bleeding and spotting episodes [8]. We used IBM Statistics SPSS (version 24) for analysis.

We included the bleeding data of women who expelled or removed their LNG 13.5 mg IUS prior to study completion whenever possible. Participants who submitted less than 90 days of bleeding data were only included in the 30-day analyses.

2.3.3. Sensitivity analysis

For our primary outcome, we dichotomized early insertion up to 7 days from LMP and late insertion from 8 days on. To better understand bleeding patterns, we also conducted a sensitivity analysis where we dichotomized early insertion up to 14 days from LMP and late insertion from 15 days on. We present this sensitivity analysis with associated bleeding patterns as an online supplement.

3. Results

3.1. Study participants

We enrolled 138 women. After consent, five women declined placement and one requested same-day removal secondary to pain. We excluded their bleeding data from the analyses. Of the 132 women who received the LNG 13.5 mg IUS (65 early, 67 late), 131 women submitted 30 days of bleeding data and 125 women submitted 90 days. Fig. 1 details participant flow, and Table 1 details their characteristics.

Among the 125 women who completed the 90-day study, 8 days of bleeding data were missing of 11,250 possible days (90 days × 125 participants). Given this small number, we did not impute any data and instead treated the data as missing. Participants texted 98% of collected responses, and study staff obtained the remaining 2% of responses by contacting participants directly. None submitted bleeding diaries. All bleeding data were normally distributed, means and medians were similar, and we used parametric analytic methods.

Overall, in the 90-day reference period, women reported 15±9 days of bleeding and 27±13 days of spotting (n=125). In the 30-day reference period, women reported 6±4 days of bleeding and 12±6 days of spotting (n=131). Almost all women bled and spotted more in the first 30 days after device insertion than in the month priorm to insertion (early n=61/64; late n=65/67). Seven women removed their IUS during the course of the study (two in the early insertion group, five in the late), including one who removed the device after 6 weeks because

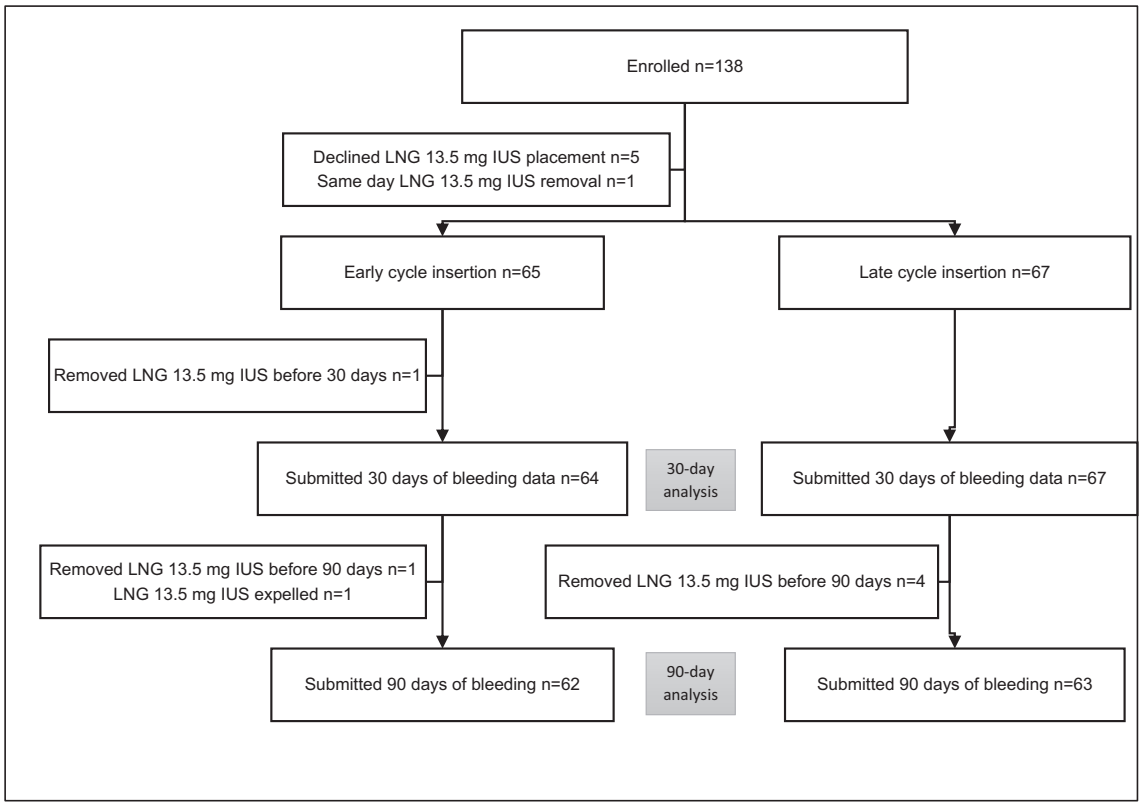

Fig. 1. Study participant flow from enrollment to data analysis (two arms: early cycle insertion from days 1–7 of LMP and late cycle insertion from days 8 on).

of spotting. One woman expelled the IUS 75 days after insertion. No pregnancies occurred during the study.

3.2. Bleeding and spotting in the 90- and 30-day reference periods following insertion: dichotomous analyses

We found no differences in bleeding/spotting, bleeding or spotting between the early and late insertion groups in the 90-day reference period. Table 2 details the dichotomous analyses. The only variable associated with bleeding pattern changes in the 90-day reference was recent hormonal contraceptive use. Women who recently used hormonal contraceptives reported fewer days of bleeding/spotting in the 90 days following insertion (39±16 vs. 45±16, p=.04).

Several bleeding pattern differences were notable in the 30-day reference period. Women in the early insertion group bled fewer days than those in the late insertion group (5±3 vs. 7±4 days, p<.01). Recent hormonal contraceptive users also bled fewer days (5±4 vs. 7±3 days, p<.01), and parous women spotted fewer days (10±5 vs. 12±6, p<.05). Women in the early insertion group trended towards more days of spotting (13±6 vs. 11±5, p=.06). Over the 90-day study, 40% and 77% of women reported prolonged and frequent bleeding, with no differences between the early and late insertion groups (data not shown).

Table 1
Characteristics of participants who received a LNG 13.5 mg intrauterine system and submitted a minimum of 30 days of bleeding data

Variable	All participants *N*=131	Early cycle insertion *n*=64	Late cycle insertion *n*=67	p-value
Age (years)	27±6	26±6	28±7	.15
Past pregnancy status				
Nulliparous	103 (79%)	53 (83%)	50 (75%)	.29
Parous	28 (21%)	11 (17%)	17 (25%)	
Recent hormonal contraception use				
New users	78 (60%)	39 (61%)	39 (58%)	.86
Recent users	53 (40%)	25 (39%)	28 (42%)	
Combined oral contraceptives	44	23	21	
Norelgestromin/EE patch	1	0	1	
Etonorgestrel/EE ring	5	1	4	
LNG-IUS	3	1	2	
Endometrial thickness (mm)[a]	5.3±3	4.3±3	6.2±3	<.001

Early cycle insertion includes days 1-7 from LMP and late cycle insertion includes the remainder of the menstrual cycle. Age and endometrial thickness data represent mean ± standard deviation; past pregnancy status and recent hormonal contraception use represent n (%); specific contraceptives used are presented as n. EE ethinyl estradiol.

[a] One outlier >5 SD from the mean was excluded.

Table 2
Mean number of bleeding and/or spotting days in the 90- and 30-day reference periods after LNG 13.5 mg intrauterine system insertion, analyzed by insertion timing, parity, and recent hormonal contraceptive use

	Bleeding/spotting	Bleeding	Spotting
90-day reference period			
All (N=125)	42±16	15±9	27±13
Insertion timing[a]			
Early (n=62)	42±16	14±7	28±14
Late (n=63)	43±17	16±10	26±13
p-value	.79	.14	.51
Parity			
Nulliparous (n=100)	42±16	14±9	28±13
Parous (n=25)	43±17	18±10	24±13
p-value	.93	.10	.16
Recent hormonal contraceptive use[b]			
Yes (n=52)	39±16	13±10	25±12
No (n=73)	45±16	16±8	29±14
p-value	.04	.08	.17
30-day reference period			
All (N=131)	18±7	6±4	12±6
Insertion timing[a]			
Early (n=64)	18±7	5±3	13±6
Late (n=67)	18±6	7±4	11±5
p-value	.86	.009	.06
Parity			
Nulliparous (n=103)	18±7	6±4	12±6
Parous (n=28)	17±7	7±4	10±5
p-value	.38	.16	<.05
Recent hormonal contraceptive use[b]			
Yes (n=53)	17±7	5±4	12±6
No (n=78)	18±6	7±3	12±5
p-value	.23	.002	.57

Data presented as mean ± standard.
[a] Early cycle insertion includes days 1-7 of LMP and late cycle insertion includes the remainder of the cycle.
[b] Recent hormonal contraceptives used in the cycle immediately prior to insertion include combined oral contraceptives, norelgestromin/ethinyl estradiol patch, etonorgestrel/ethinyl estradiol ring, and LNG-IUSs.

We conducted an additional analysis that excluded the three recent IUS users. Early insertion and recent contraceptive use were still associated with fewer days of bleeding in the 30-day reference period (5±3 vs. 7±4, p<.01; 5±3 vs. 7±3, p=.001); nulliparity was no longer associated with spotting in the 30-day reference period (12±6 vs. 10±5, p=.11), and recent contraceptive use was no longer associated with bleeding/spotting in the 90-day reference period (39±16 vs. 45±16, p=.06).

3.3. Bleeding and spotting in the 90- and 30-day reference periods following insertion: multivariate regression analyses

We conducted six multivariate linear regression analyses to explore the association of bleeding/spotting, bleeding and spotting with cycle day, age, parity, recent contraceptive use and historical bleeding in the 90- and 30-day reference periods. In the 90-day models, insertion earlier in the cycle was associated with fewer days of bleeding [coefficient=0.2, 95% confidence interval (CI)=0 to .3, p=.02], and recent contraceptive use was associated with fewer days of bleeding and spotting (coefficient=6.6, 95% CI=.8 to 12.4, p=.03). In the 30-day reference period, insertion earlier in the cycle and recent hormonal contraceptive use were associated with fewer days of bleeding (coefficient=0.1, 95% CI=0 to .1; p=.02; coefficient=2.0, CI=.8 to 3.3, p=.002); nulliparity was associated with spotting (coefficient=−3.0, 95% CI=−5.8 to −.2, p=.04).

4. Discussion

4.1. Early and late insertion

In our study, early cycle LNG 13.5 mg IUS insertion was associated with fewer days of bleeding in the 30 days following insertion. This difference subsided with time and by 90 days the excess bleeding in the late insertion group was marginal. We expected this pattern; namely, that the LNG would quickly decidualize the already thin early cycle endometrial stroma and result in fewer days of bleeding [9]. Early insertion did not impact bleeding/spotting possibly because bleeding and spotting trended in opposite directions and canceled each other out.

4.2. Recent hormonal contraceptive use

Participants who switched from another hormonal method to the LNG 13.5 mg IUS experienced fewer days of bleeding in the 30-day reference period and fewer days of bleeding/spotting in the 90-day reference period. Women in this group had used a progestin-only or a combined estrogen/progestin method prior to insertion and appeared to benefit from an inhibited endometrium as well. Gemzell-Danielsson and colleagues documented a similar effect in women who received a second consecutive LNG 52 mg IUS. Women in their study experienced a fraction of bleeding or spotting with the second device than they had with their first [10].

When we excluded the three recent IUS users from our analyses, the stronger associations (decreased bleeding with early insertion and recent contraceptive use, 30-day) remained strong, and the weaker associations (decreased bleeding/spotting with recent contraceptive use, 90-day and decreased spotting with parity, 30-day) lost statistical significance likely because of the smaller numbers and reduced power.

4.3. Parity

Our study highlights bleeding patterns in nulliparous women with the LNG 13.5 mg IUS. While the total number of bleeding/spotting days in our study was similar to previous LNG 13.5 mg IUS phase 2 and 3 trials [2,4,6], women in our study consistently reported fewer days of bleeding and more days of spotting than in previous studies. Our participants were predominantly nulliparous (79%) compared with other LNG 13.5 mg IUS studies where 6%, 22% and 39% of participants were nulliparous [2,4,6]. If nulliparous women spot more and bleed less as the 30-day analyses suggest, our larger proportion of nulliparous women may explain the bleeding and spotting differences between the studies. Other population demographic differences may also play a role in bleeding and spotting differences.

None of our other parity analyses achieved statistical significance, although nulliparous women consistently trended towards more spotting and less bleeding in both the 30- and 90-day reference periods. This highlights how the large proportion of nulliparous women is a limitation in our nulliparity/parity comparisons. Since only 21% of women in our study were parous, we may have had inadequate power to compare bleeding between parous and nulliparous women. If a difference in bleeding or spotting exists, a study with a larger proportion of parous women should be better able to detect it. It is possible that a parous or larger uterus translates into a larger surface area, which might contribute to more bleeding in this group.

Seventy-seven percent of women in our study reported frequent bleeding in the 90-day reference period following LNG 13.5 mg IUS insertion (as defined by Belsey), significantly higher than the 26% reported by Schreiber and colleagues in a large prospective study of the LNG 52 mg IUS [11]. More parous than nulliparous women in our study experienced frequent bleeding (92% vs. 73%, p=.06), in contrast to Schreiber where more nulliparous women experienced frequent bleeding than parous women in the 90 days following insertion (29% vs. 23%, p=.01). The reasons for these opposing patterns are unclear, but the different level of LNG in the two devices likely plays a role.

4.4. Questions raised and clinical implications

Our study raised several questions. Our results repeatedly showed opposing trends in bleeding and spotting, suggesting that bleeding and spotting may have different underlying mechanisms and are not merely a continuum. We did not expect this finding and recognize that we know little about women's attitudes towards bleeding versus spotting. Is either one individually associated with dissatisfaction, is it both, or is it the unscheduled nature of the bleeding? We do not know, nor do we know the impact of insertion timing on bleeding/spotting with an IUS that releases more LNG. Other demographic variables not collected in this study such as body mass index may also influence bleeding patterns.

In this study, we demonstrate that early cycle LNG 13.5 mg IUS insertion decreases bleeding in the 30 days following insertion when compared with late cycle insertion, but not in the 90-day reference period. The difference in the number of bleeding days is small, and a delay in LNG 13.5 mg IUS insertion may increase the risk of unintended pregnancy and the inconvenience of returning to the office for device placement. In cases where devices are immediately available and patients are ready for insertion, the slight decrease in bleeding must be balanced against the convenience of same-day insertion and sooner contraceptive effectiveness. Shared decision making after appropriate counseling should inform timing of LNG 13.5 mg IUS insertion for each patient individually.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.02.004.

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