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Amenorrhea rates and predictors during 1 year of levonorgestrel 52 mg intrauterine system use☆,☆☆

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Abstract

Objective: The objective was to evaluate amenorrhea patterns and predictors of amenorrhea during the first year after levonorgestrel 52 mg intrauterine system (IUS) placement.

Study design: This cohort analysis includes 1714 nulliparous and parous women who received a Liletta® levonorgestrel 52 mg IUS in a multicenter trial to evaluate efficacy and safety for up to 8 years. Participants maintained a daily diary with bleeding information. We assessed bleeding patterns in 90-day intervals; amenorrhea was defined as no bleeding or spotting in the preceding 90 days. We employed multivariable regression to identify predictors of amenorrhea at 12 months. The predictor analysis only included women not using a levonorgestrel IUS in the month prior to study enrollment.

Results: In the month before enrollment, 148 and 1566 women, respectively, had used and not used a levonorgestrel IUS. Prior users averaged 50±19 months of use before IUS placement; 38.4% of these women reported amenorrhea at 12 months. Amenorrhea rates for non-prior-users at 3, 6, 9 and 12 months were 0.2%, 9.1%, 17.2% and 16.9%, respectively. During the first 12 months, 29 (1.7%) women discontinued for bleeding irregularities; no women discontinued for amenorrhea. The only significant predictor of amenorrhea at 12 months was self-reported baseline duration of menstrual flow of fewer than 7 days vs. 7 or more days (18.2% vs. 5.2%, adjusted odds ratio 3.70 [1.69, 8.07]). We found no relationships between 12-month amenorrhea rates and age, parity, race, body mass index, baseline flow intensity or hormonal contraception use immediately prior to IUS placement.

Conclusions: Amenorrhea rates during the first year of levonorgestrel 52 mg IUS use are similar at 9 and 12 months. Amenorrhea at 12 months is most common among women with shorter baseline duration of menstrual flow.

Implications statement: This information provides more data for clinicians when counseling women about amenorrhea expectations, especially since women seeking a levonorgestrel 52 mg IUS for contraception are different than women desiring treatment for heavy menstrual bleeding. Amenorrhea at 12 months is most common among women with shorter baseline duration of menstrual flow.

Keywords: Contraception; Intrauterine device; Intrauterine system; Levonorgestrel; Liletta; Amenorrhea

1. Introduction

The introduction of the levonorgestrel (LNG) 52 mg intrauterine system (IUS) in Europe in 1990 and the United States in 2000 changed acceptance of intrauterine contraception. Using an intrauterine contraceptive became more appealing due to the potential for less menstrual bleeding and dysmenorrhea with this novel option. For many women, amenorrhea became a desirable effect of using a hormonal contraceptive. The first LNG 52 mg IUS introduced to the market reported a 1-year amenorrhea rate of 20% but lacked information about when amenorrhea occurred during the first year or who becomes amenorrheic [1,2]. The data for the 20% amenorrhea rate were obtained primarily from

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Scandinavian multiparous women, 75% of whom had used intrauterine contraception previously [3].

The significant reduction in overall menstrual bleeding with the LNG 52 mg IUS encouraged further studies which led to its approval for treatment of heavy menstrual bleeding (HMB) [4,5]. Much has been published about decrease in menstrual flow and amenorrhea in women using a LNG 52 mg IUS for HMB [6] but little about changes in women using the product primarily for contraception. Because HMB significantly increases with age and peaks in the perimenopausal period [7], those women who use a LNG IUS primarily for HMB likely differ in age and other characteristics from those who use it primarily for contraception. de Jonge et al. [8] reported predictors of 12-month oligoamenorrhea rates in 141 mostly nonobese women using a LNG 52 mg IUS for contraception (n=98) or HMB (n=52). The investigators reported that women in the contraception group were significantly younger (34 vs. 39 years) and had fewer subjective bleeding abnormalities at baseline (20% vs. 96%). In univariate analyses, duration of menses less than 5 days and absence of HMB at baseline predicted oligoamenorrhea at 12 months.

This report describes amenorrhea rates and predictors over the first year of use among participants in "A Comprehensive Contraceptive Efficacy and Safety Study of an IUS" (ACCESS IUS). This US study of women primarily using the LNG 52 mg IUS for contraception had significant proportions of obese and nulliparous women, which allowed for a broad, generalizable assessment of the characteristics of women who develop amenorrhea [9].

2. Materials and methods

This study represents a secondary analysis of data from the ACCESS IUS multicenter, Phase 3, open-label clinical trial of Liletta® [Medicines360, San Francisco, CA, USA, and Allergan, Irvine, CA, USA; Liletta® is a registered trademark of Odyssea Pharma SPRL (Belgium), an Allergan affiliate]. A central or local Institutional Review Board for each center approved the study. All women signed written informed consent before study participation.

The methods of the primary study have been reported previously [9]. Briefly, investigators at 29 clinical sites in the United States enrolled healthy, nonpregnant, sexually active, nulliparous and parous women aged 16–45 years (inclusive) who desired a hormonal IUS for contraception from December 2009 to April 2013. Participants were required to have regular menstrual cycles every 21–35 days with a typical cycle length variation of no more than 5 days. Those currently using hormonal contraception had a typical history of such cycles prior to their most recent hormonal contraception initiation. Women recently using progestin injectable contraception could not enter the study if they received an injection within the preceding 9 months, or 6 months for women who had two spontaneous regular menstrual cycles (required minimum of three menses). After subjects completed screening and enrollment (IUS placement), follow-up during the first year included visits at 1, 3, 6 and 12 months and a telephone contact at month 9.

Subjects completed a daily paper diary to indicate the greatest amount of bleeding that day as none, spotting, light flow, normal flow or heavy flow. The study staff instructed the subject to record the intensity of spotting/bleeding based on her subjective impression of the heaviest flow for that day. The subject brought the diary to each visit during which the study staff reviewed the diary for completion. Any subject who did not bring a diary completed an office recall diary. The study staff instructed the subject to bring in the original diary at her earliest convenience or to her next scheduled visit, and this original diary replaced the office recall diary. We considered any missing data for a particular diary day as having no reported bleeding.

This secondary data analysis includes only those women with successful IUS placement. We compared outcomes in women who had and had not used a LNG IUS in the month prior to enrollment. We did not ask women using a LNG IUS prior to study enrollment if they were experiencing amenorrhea. We evaluated bleeding patterns in 90-day intervals, defining amenorrhea as no bleeding or spotting in the preceding 90 days. We assessed the proportion of women who had amenorrhea at 6 and 9 months who were still amenorrheic at 12 months. We used Fisher's Exact Test for comparisons of proportions. Our multivariable binary regression used key participant characteristics to identify predictors of amenorrhea at 12 months, specifically parity, body mass index (BMI), race, age, use of hormonal contraception in the month preceding enrollment, and reporting heavy or prolonged menstrual flow when not using hormonal contraceptives. We excluded women who used an LNG IUS in the month prior to enrollment from predictor analyses; only the LNG 52 mg IUS was available in the United States during participant recruitment. We used SAS® 9.3 (Cary, NC, USA), with a p value of .05 considered statistically significant.

3. Results

Of the 1751 women enrolled, 1714 (97.9%) had successful placement and are included in the study analyses. Participant characteristics of the 148 (8.5%) women using a LNG 52 mg IUS in the month before enrollment and the 1566 (91.5%) women who were not are presented in Table 1. We had data on duration of LNG 52 mg IUS use for 144 (97.3%) of prior users, which averaged 50.4±18.7 months. Overall, the most commonly used contraceptive methods during the month prior to study enrollment were male condoms (n=600, 35.0%) and combined oral contraceptives (n=496, 28.9%).

Amenorrhea rates at 3, 6, 9 and 12 months of LNG 52 mg IUS use are presented in Table 2. During the first 12 months,

Table 1
Demographics and contraceptive method at enrollment for women in a phase 3 study of a LNG 52 mg IUS

Characteristic	Women using a LNG 52 mg IUS prior to enrollment *n*=148	Women not using a LNG 52 mg IUS prior to enrollment *n*=1566
Age (years)	28.8±3.7	27.0±5.6
<25	16 (13.4)	605 (38.6)
25–30	59 (49.6)	577 (36.8)
31 and older	44 (37.0)	384 (24.5)
Ethnicity		
Hispanic or Latina	24 (20.2)	222 (14.2)
Race[a]		
American Indian or Alaska Native	2 (1.7)	19 (1.2)
Asian	3 (2.5)	63 (4.0)
Black or African American	9 (7.6)	214 (13.7)
Native Hawaiian or other Pacific Islander	1 (0.8)	5 (0.3)
White	97 (81.5)	1219 (78.0)
Multiracial	7 (5.9)	42 (2.7)
BMI (kg/m^2)[a]	27.0±7.0	26.9±6.7
Obese (≥30.0)	36 (30.5)	391 (25.0)
Partner status		
Lives with partner	83 (69.7%)	898 (57.3)
Parity		
Nulliparous	42 (35.3)	941 (60.1)
Marital status		
Never married	61 (51.3)	1015 (64.8)
Married	43 (36.1)	419 (26.8)
Divorced	13 (10.9)	104 (6.6)
Separated	2 (1.7)	26 (1.7)
Widowed	0	2 (0.1)
Contraception used during the month before enrollment		
CHC		643 (41.1%)
POP		35 (2.2%)
Copper IUD		30 (1.9%)
Hormonal implant		9 (0.6%)
Nonhormonal/ non-IUD method		692 (44.2%)
None		157 (10.0%)

Data are presented as *n* (%) or mean±standard deviation.
CHC=combined hormonal contraceptive; POP=progestin-only pill.
[a] Data missing for four participants (race) and three participants (BMI).

29 [1.7%, 95% confidence interval (CI) 1.1%–2.3%] LNG 52 mg IUS users discontinued for bleeding complaints including one (0.7%, 95% CI 0%–2.0%) woman who had been using a LNG IUS at enrollment compared to 28 (1.8%, 95% CI 1.1%–2.4%) women who had not been using a LNG IUS (p=.51). No women discontinued for amenorrhea. Among women who had not been using a LNG IUS at enrollment, continued LNG 52 mg IUS use through 12 months, and reported amenorrhea at 6 and 9 months, 58/135 (43.0%, 95% CI 34.6%–51.3%) and 133/241 (55.2%, 95% CI 48.9%–61.5%), respectively, remained amenorrheic at 12 months.

Predictors of amenorrhea at 12 months for new IUS users are presented in Table 3. The only significant predictor was self-reported baseline duration of menstrual flow of fewer than 7 days vs. 7 or more days [18.2% vs. 5.2%, adjusted odds ratio (aOR) 3.70 (1.69–8.07)]. We found no relationships in 12-month amenorrhea rates for age, parity, race, BMI, baseline flow intensity or use of hormonal contraception immediately prior to LNG IUS placement. When duration of menstrual flow is removed from the model, none of the other factors become significant. Further evaluation of this relationship of 12-month amenorrhea rates and baseline duration of menstrual flow demonstrates that when typical duration is less than 7 days, fewer days of bleeding predict a higher likelihood of amenorrhea at 12 months of LNG 52 mg IUS use (Table 4).

4. Discussion

Among women who entered the study not using a LNG IUS, we found a slightly lower 1-year amenorrhea rate than the 20% amenorrhea rate commonly cited for the LNG 52 mg IUS based on the original product label [2]. The 1-year amenorrhea rate of 18.6% for the entire ACCESS IUS cohort, which included women who had been using a LNG IUS in the month prior to enrollment, corroborates the historic rate. Small studies (200 or fewer subjects) have reported varying rates of 11% to 26% [10–12]. Most importantly, our findings demonstrate that the rate among new LNG 52 mg IUS users varies by participant characteristic from 13% to 19% and is most dependent on the number of days of menstrual bleeding reported at baseline. One-year amenorrhea rates are 20% or slightly higher for women who typically have menses lasting 4 days or less as compared to only 5% for women with menses typically lasting 7 days or more.

Predictors of amenorrhea in women using the LNG 52 mg IUS primarily for contraception have not been categorically evaluated until recently. Mejia and colleagues [13] recently published their findings on amenorrhea rates and predictors from the CHOICE study, which enrolled 9256 women from 2007 to 2011, including 3317 LNG 52 mg IUS users of whom 3025 continued use for 1 year. The primary outcome, amenorrhea at 12 months, was defined as no bleeding or spotting for the prior 6 months as reported during a phone interview (no daily menstrual diary). The investigators documented a 1-year amenorrhea rate of 15.4%, with women self-reporting heavy bleeding at baseline being less likely to report amenorrhea at 12 months than those who reported moderate bleeding (aOR 0.36; 95% CI 0.16–0.69). These findings are concordant with key findings from our current analysis which found that the amenorrhea rate is slightly lower than the 20% rate reported historically and that baseline bleeding characteristics are important predictors of who develops amenorrhea. However, the study by Mejia and colleagues [13] has important limitations. First, data for 1223

Table 2
Amenorrhea rates over the first year of LNG 52 mg IUS use

Duration of use	Total *N*=1714	Women using a LNG IUS prior to enrollment *n*=148	Women not using a LNG IUS prior to enrollment *n*=1566
3 months	0.4% (0.1%–0.7%) (7/1700)	2.7% (0.1%–5.4%) (4/147)	0.2% (0%–0.4%) (3/1553)
6 months	11.3% (9.7%–12.8%) (183/1621	33.8% (26.0%–41.6%) (48/142)	9.1% (7.7%–10.6%) 135/1479
9 months	18.7% (16.8%–20.7%) (289/1542)	34.5% (26.6%%–42.4%) (48/139)	17.2% (15.2%–19.2%) 241/1403
12 months	18.6% (16.6%–20.6%) (269/1448)	34.8% (26.8%–42.9%) (47/135)	16.9% (14.9%–18.9%) 222/1313

Amenorrhea is defined as no bleeding or spotting for 3 preceding months.
Data are presented as %, 95% CI.
Denominators reflect the number of women who completed LNG IUS use for that duration.

women were missing, leaving only 1802 women (59.6% of the cohort of women who completed 1 year of follow-up) for the analysis. Second, they included a small percentage (2%–3%) of LNG IUS and injectable contraception users who may have altered their prediction model and biased the results in the direction of higher amenorrhea rates. Most importantly, they relied on telephone interviews and recall, whereas our current analysis uses prospectively collected daily diary data. Therefore, we believe that our findings are likely more accurate in defining new user amenorrhea rates and predictors.

The 1-year amenorrhea rates with a LNG 52 mg IUS are notably higher than those reported with lower-dose LNG IUS products. The amenorrhea rates at 1 year with products containing 13.5 mg and 19.5 mg of LNG are 6% and 12.7%, respectively [14,15]. It is unclear whether or not some women enrolled in these studies recently used a LNG IUS. In our study, no women discontinued the LNG 52 mg IUS during the first year for amenorrhea, suggesting that amenorrhea is not an undesirable effect for many US women.

The strengths of this study include prospective data collection from a large and diverse cohort representative of the US female population based on recent census data [8] and use of amenorrhea as a primary outcome. Amenorrhea represents a well-defined objective outcome, whereas less bleeding is more subjective. Still, amenorrhea is not the only pattern of decreased flow women experience with LNG 52 mg IUS use. Most women who are not amenorrheic experience light bleeding or spotting, a pattern considered favorable by LNG 52 mg IUS users [10,11].

For clinicians, this information is important to provide more accurate counseling around amenorrhea expectations. Of note, the 17% 1-year population amenorrhea rate in women naive to the LNG 52 mg IUS is achieved by 9 months. Amenorrhea at 12 months in new LNG 52 mg IUS users is most common among women with shorter baseline duration of menstrual flow. We did not investigate overall bleeding patterns, including decrease in flow, of women who report baseline flow of 7 days or more and would not dissuade these women from using a LNG 52 mg IUS.

Table 3
Univariate and multivariable predictors of amenorrhea at 12 months in women initiating LNG 52 mg IUS (*n*=1313)[a]

Classification		Number of subjects	Amenorrhea at 12 months	p value	aOR
Parity	Nulliparous	822	150 (18.3%)	.10	1.10 (0.77–1.57)
	Parous	491	72 (14.7%)		referent
Race[a]	White	1066	190 (17.8%)	.09	1.31 (0.87–1.99)
	Nonwhite	243	32 (13.2%)		referent
BMI (kg/m^2)[b]	<30.0	995	168 (16.9%)	.93	0.90 (0.63–1.27)
	≥30.0	316	54 (17.1%)		referent
Age (years)	<30	927	167 (18.0%)	.11	1.26 (0.87–1.82)
	≥30	386	55 (14.3%)		referent
Menstrual flow[c]	Not heavy	1169	206 (17.6%)	.06	1.33 (0.76–2.33)
	Heavy	144	16 (11.1%)		referent
Duration of menstrual flow[c]	<7 days	134	215 (18.2%)	<.001	3.70 (1.69–8.07)
	7 or more days	1179	7 (5.2%)		referent
Hormonal contraception use in the month prior to enrollment	Yes	674	126 (18.7%)	.08	1.12 (0.83–1.52)
	No	639	96 (15.0%)		referent

Amenorrhea is defined as no bleeding or spotting for 3 preceding months (months 9–12).
[a] Only includes women not using an LNG IUS prior to enrollment and with 12 months of follow-up.
[b] Data missing for four participants (race) and two participants (BMI).
[c] Subjective history when not using hormonal contraceptives.

Table 4
Comparison of 12-month amenorrhea rates based on baseline duration of menstrual flow in a single study population of women initiating LNG 52 mg IUS (n=1313)[a]

Baseline duration of menstrual flow[b]	Number	Amenorrhea at 12 months	Baseline duration of menstrual flow[b]	Number	Amenorrhea at 12 months	p value
2 or less days	92	18 (19.6%)	3 or more days	1221	181 (14.8%)	.228
3 or less days	212	47 (22.2%)	4 or more days	1101	175 (15.9%)	.026
4 or less days	554	112 (20.2%)	5 or more days	759	110 (14.5%)	.007
5 or less days	1029	191 (18.6%)	6 or more days	284	31 (10.9%)	.002
6 or less days	1179	215 (18.2%)	7 or more days	134	7 (5.2%)	<.001

Amenorrhea is defined as no bleeding or spotting for 3 preceding months (months 9–12).
[a] Only includes women not using an LNG IUS prior to enrollment and with 12 months of follow-up.
[b] Self-reported at the study screening visit.

Overall, our findings promote a better understanding of the development of amenorrhea in women choosing a LNG 52 mg IUS for contraception.

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