ELSEVIER

Contraception xx (2017) xxx – xxx

Contraception

Original research article

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

Philip D. Darney[a], Gretchen S. Stuart[b], Michael A. Thomas[c], Carrie Cwiak[d], Andrea Olariu[e], Mitchell D. Creinin[f,*]

[a]University of California, San Francisco, San Francisco, CA, USA
[b]University of North Carolina School of Medicine, Chapel Hill, NC, USA
[c]University of Cincinnati, Cincinnati, OH, USA
[d]Emory University, Atlanta, GA, USA
[e]Medicines360, San Francisco, CA, USA
[f]University of California, Davis, Sacramento, CA, USA

Received 13 June 2017; revised 6 October 2017; accepted 9 October 2017

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

☆ Clinical trial registration: Clinicaltrials.gov NCT00995150.

☆☆ Presented in part as an oral abstract at the North American Forum on Family Planning, November 13–15, 2015, Chicago, IL, USA.

* Corresponding author. Tel.: +1 916 734 6670.
E-mail address: mdcreinin@ucdavis.edu (M.D. Creinin).

https://doi.org/10.1016/j.contraception.2017.10.005
0010-7824/

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,