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Bleeding changes after levonorgestrel 52mg intrauterine system insertion for contraception in women with self-reported heavy menstrual bleeding

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BAC serves on an Advisory Board for Merck & Co. Magee-Womens Research Institute has received funding for contraceptive research from Medicines360, Merck, and Sebela.

DLE serves on scientific advisory boards for FemaSys and Medicines360, is a consultant for ACI Clinical, FemaSys and Merck, and serves as a DSMB chair for a study sponsored by Sebela. The Department of Obstetrics and Gynecology, Washington University in St. Louis, receives contraceptive research funding from Medicines360.

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DTK is a consultant for Sebela Pharmaceuticals, Inc. The Department of Obstetrics and Gynecology, University of Utah, receives contraceptive research funding from Bayer, Cooper Surgical, Medicines360, Merck & Co. and Sebela.

AIO is an employee of Medicines360.

MDC serves on an Advisory Board for Lupin and Merck & Co. and is a consultant for Danco, Estetra, Exeltis, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding from Daré, HRA Pharma, Medicines360, Merck & Co. and Sebela.

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CONDENSATION

Most women with self-reported heavy menstrual bleeding will have a rapid decrease in flow following levonorgestrel 52mg intrauterine system placement.

SHORT TITLE

LNG 52mg IUS treatment of HMB

AJOG AT A GLANCE

Why was the study conducted?

- To evaluate cycle-by-cycle decrease in self-reported heavy menstrual bleeding (HMB) among women initiating levonorgestrel 52mg intrauterine system (IUS) use.

What are the key findings?

- HMB decreases significantly even with the first period after insertion, more than 90% of women no longer have subjective heavy bleeding within 6 months, and amenorrhea rates during the first year are lower than in women without self-reported baseline HMB.

What does this study add to what is already known?

- This study provides a cycle-by-cycle evaluation of bleeding changes, showing how rapidly flow decreases after LNG 52mg IUS insertion in U.S. women with self-reported HMB.

ABSTRACT

Background: The levonorgestrel 52mg intrauterine system (IUS) has proven efficacy for heavy menstrual bleeding (HMB) treatment in clinical trials, but little data exists to demonstrate how rapidly the effects occur and the effects in women with self-reported heavy bleeding as seen commonly in clinical practice.

Objective: Evaluate changes in bleeding patterns in women with self-reported HMB prior to levonorgestrel 52mg IUS insertion.

Study Design: A total of 1,714 women aged 16-45 years old received a levonorgestrel 52mg IUS in a multicenter trial evaluating contraceptive efficacy and safety for up to 10 years. At screening, participants described their baseline menstrual bleeding patterns for the prior 3 months. Participants completed daily diaries with subjective evaluation of bleeding information for the first 2 years. For this analysis, we included women with at least one complete 28-day cycle of IUS use and excluded women using a hormonal or copper intrauterine contraception in the month prior to study enrollment. We evaluated changes in menstrual bleeding and discontinuation for bleeding complaints per 28-day cycle over 26 cycles (2 years) in women who self-reported their baseline pattern as heavy. We also compared rates of amenorrhea, defined as no bleeding or spotting, within the entire study population in women with subjective HMB at baseline compared to those who did not complain of HMB.

Results: Of the 1513 women in this analysis, 150 (9.9%) reported baseline HMB. The majority of women reported no longer experiencing HMB by the end of cycle 1 (112/150, 74.7%) with even higher rates by cycle 2, (124/148, 83.8%). At the end of cycles 6, 13 and 26, 129/140 (92.1%, 95% CI 87.7-96.6%), 114/123 (92.7%, 95% CI 88.1-97.3%) and 100/103 (97.1%, 95% CI 93.8-100%) women reported no HMB, respectively. After cycles 13 and 26, 63/123 (51.2%, 95% CI 42.4-60.1%) and 66/103 (64.1%, 95% CI 54.8-73.3%), respectively, reported their bleeding as amenorrhea or spotting only. A lower proportion of women with baseline self-reported HMB reported amenorrhea as compared to women in the overall study cohort without HMB at the end of 6 cycles (319 [25.5%] vs. 21 [15.0%], p=.005) and 13 cycles (382 [34.4%] vs. 26 [21.1%], p=.003); differences were not significant after 19 cycles (367 [37.2%] vs. 36 [31.0%], p=.022) and 26 cycles (383 [43.5%] vs. 38 [36.9%], p=.21). Only 4 (2.7%) women with baseline HMB discontinued for bleeding complaints (2 for HMB and 2 for irregular bleeding), all within the first year.

Conclusions: Most women who self-report HMB experience significant improvement quickly after levonorgestrel 52mg IUS insertion. Discontinuation for bleeding complaints among women with baseline HMB is very low.

KEY WORDS

Heavy menstrual bleeding, menorrhagia, Intrauterine device, Intrauterine system, Liletta, Amenorrhea

Introduction

Normal menstrual blood loss (MBL) ranges between 20 and 60 mL/cycle. Heavy menstrual bleeding (HMB), formerly referred to as menorrhagia, is excessive blood loss that occurs alone or in combination with other symptoms and has a negative impact on a woman's physical, social, emotional, and material quality of life (1). Although studies for agency approval typically define HMB as MBL ≥80 mL per cycle, only about half of women who complain of HMB meet these criteria (1,2).

Approximately 30% of women are affected by HMB during their reproductive years, resulting in increased health costs (3). A variety of functional, structural, and non-structural conditions can cause HMB, including adenomyosis, leiomyomas, and coagulopathies as well as iatrogenic causes. In many women, the underlying cause of HMB is unknown and is referred to as functional HMB (4).

In the early 1990s, the levonorgestrel 52mg intrauterine system (IUS) emerged as an option for medical management of HMB. While oral progestins have variable effects, combined oral contraceptives, non-steroidal anti-inflammatory drugs and antifibrinolytics can reduce MBL by 40-50% within a few cycles of treatment, a levonorgestrel 52mg IUS can decrease measured MBL by 71% within 6 months and up to 94% after 1 year (5,6). Additionally, the levonorgestrel 52mg IUS provides greater improvement in women's assessment of the effect of HMB on their daily routine and

psychological and physical well-being compared to usual medical treatment (1,7-9).

Although data from clinical trials evaluate outcomes in women with a quantifiable level of blood loss per cycle, clinical guidelines recognize that the diagnosis should be based on subjective measures rather than the objective measure of MBL because HMB has a major impact on a woman's quality of life, (10). No prospective study has reported the impact of a levonorgestrel 52mg IUS in U.S. women with "real-life" HMB. This report describes bleeding changes and outcomes over the first two years of levonorgestrel 52mg IUS use among participants in a Phase 3 contraceptive trial who self-reported baseline HMB.

Materials and Methods

This secondary analysis includes data from the ACCESS IUS (A Comprehensive Contraceptive Efficacy and Safety Study of an IUS) multicenter, open-label trial of Liletta® (Medicines360, San Francisco, CA and Allergan, Irvine, CA; Liletta® is a registered trademark of Odyssea Pharma SPRL [Belgium], an Allergan affiliate). The methods of the primary study have been reported previously (11). Briefly, investigators at 29 sites in the United States enrolled healthy nulliparous and parous women aged 16-45 years (inclusive) who desired a hormonal intrauterine system (IUS) for contraception from December 2009 to April 2013. Entry criteria included regular menstrual cycles every 21-35 days with a typical cycle length

variation of no more than five days and no abnormality of the uterus resulting in distortion of the cavity incompatible with insertion. A local or central Institutional Review Board approved the study for each site. Each woman signed written informed consent before study participation.

At screening, investigators asked participants to describe their baseline and worst menstrual bleeding patterns for the prior 3 months as light, normal or heavy flow. We defined self-reported HMB as a response of heavy flow for both questions. Follow-up during the first year included visits at one, three, six and 12 months, and a telephone contact at month nine. Participants completed a daily paper diary to indicate the greatest amount of bleeding that day as none, spotting, light flow, normal flow, or heavy flow based on their subjective impression. Details of diary instructions and completion have been previously published (12). We only included qualifying cycles for bleeding-related calculations, defined as 23 or more days of reporting, and did not impute any missing data.

All analyses only included women who had successful IUS insertion, were not using any intrauterine contraception in the month prior to insertion, attended at least one follow-up visit, and had at least one qualifying cycle of diary data. We compared demographic characteristics, bleeding patterns and discontinuation rates among women with and without self-reported HMB at baseline. We evaluated bleeding patterns and discontinuation rates in 28-day intervals (“cycles”) and defined amenorrhea as no bleeding or spotting during the cycle. We used Fisher’s exact test for comparisons of proportions.

We used SAS® 9.3 (Cary, NC) with a p-value of .05 considered statistically significant.

Results

Of the 1714 women who enrolled and had successful placement, 1691 women completed at least one 28-day cycle of follow-up. We excluded 178 women who had been using intrauterine contraception in the month prior to enrollment. Of the 1513 women in the analysis population, 150 (9.9%) self-reported HMB during the 3 months prior to enrollment. We present participant characteristics in Table 1; of note, women with baseline HMB were more likely to be African-American.

Changes in bleeding patterns are presented in Figure 1. By the 28th day of levonorgestrel 52mg IUS use, 112 (74.7%, 95% CI 67.7-81.6%) women reported the absence of subjectively heavy bleeding. By the end of cycle 2, 124 (83.8%, 95% CI 77.8-89.7%) of the 148 women that started the cycle reported no HMB. At the end of cycles 6, 13 and 26, 129/140 (92.1%, 95% CI 87.7-96.6%), 114/123 (92.7%, 95% CI 88.1-97.3%) and 100/103 (97.1%, 95% CI 93.8-100%) women reported no HMB, respectively. After cycles 13 and 26, 63/123 (51.2%, 95% CI 42.4-60.1%) and 66/103 (64.1%, 95% CI 54.8-73.3%), respectively, reported their bleeding as amenorrhea or spotting only. Amenorrhea rates are reported in Table 2. Of note, women who self-report baseline HMB had significantly lower amenorrhea rates than the remainder

of the levonorgestrel 52mg IUS user population, but only during the first 13 cycles of IUS use.

Women with baseline HMB did not discontinue IUS use more or less frequently than those women who did not report subjective baseline HMB (Table 3). Only 4 (2.7%) women with baseline HMB discontinued for bleeding complaints (2 for HMB and 2 for irregular bleeding), all within the first year. These rates did not differ from the discontinuation rates for bleeding complaints in the remainder of the study population (Table 3). The reasons for discontinuation did not differ between women with and without subjective baseline HMB (Table 4).

Comment

Principal Findings

We found that women with self-reported HMB have a very rapid and dramatic decrease in flow following levonorgestrel 52mg IUS insertion. Three-fourths of women report no HMB after just one cycle. During the first year of use, women with self-reported HMB report significantly lower amenorrhea rates compared to women not reporting HMB. Amenorrhea rates in the 6th and 13th cycle of levonorgestrel 52 mg IUS use are 60-70% higher in women without subjective HMB (Table 2).

Results

These findings represent women's subjective views of their bleeding patterns, which differ from studies in which women are enrolled to test a

treatment for HMB for regulatory approval. These HMB treatment studies require blood loss quantification to ensure a baseline MBL ≥80 mL per cycle. Although the studies for regulatory approval measure changes in blood loss, they do not describe how quickly blood flow decreases in each of the first few months, as was shown in our current study. The two available levonorgestrel 52mg IUS products are approved in various countries throughout the world as a treatment for HMB based on such studies (4,7). A multicenter, single-blind randomized trial in Eastern Europe compared the two available levonorgestrel 52mg IUS products in patients with HMB utilizing a pictorial blood loss chart to assess MBL and demonstrated equal decreases in MBL and increases in ferritin and hemoglobin (4), resulting in European Medicines Agency approval of Levosert® (Liletta) in Europe. In the U.S., only Mirena® (Bayer Healthcare, Whippany, NJ) is currently approved for HMB treatment in women desiring an IUS for contraception. In the trial for Food and Drug Administration approval, 642 of 807 (79.6%) women failed screening, typically because of blood loss that did not meet the 80 mL per cycle criterion (7). Thus, it is possible that most women with self-reported HMB do not have the degree of MBL evaluated in studies for regulatory approval. Although many women who self-report HMB in the general population may not have MBL ≥80 mL per cycle, these women still recognize subjectively significant bleeding reduction.

Whereas first-line treatment for HMB includes the levonorgestrel 52mg IUS (13,14), currently available lower dose levonorgestrel IUS products have

not demonstrated efficacy for HMB treatment. When flow patterns are evaluated in young women using a levonorgestrel IUS, more women using lower dose products experience prolonged or heavy flow as compared to a 52mg product (15).

Clinical Implications

This information is important for counseling women with self-reported HMB about the expected outcome when using the levonorgestrel 52mg IUS for therapeutic purposes to decrease subjectively heavy menstrual flow. Although much has been published about the decrease in menstrual flow in women using a levonorgestrel 52mg IUS for HMB (16), little is known about the effects in women with HMB using the product primarily for contraception. Because HMB significantly increases with age (17), women who use a LNG IUS primarily for HMB likely differ in age and other characteristics from those who use it primarily for contraception. Studies evaluating HMB treatment with the levonorgestrel 52mg IUS for agency approval in the United States and Europe had an average age of 38 years (4,7) whereas women in the ACCESS IUS contraceptive trial with self-reported HMB had an average age of 27.5 years.

Strengths and Limitations

A strength of this study is the findings in a diverse population of women and daily collection of flow in a diary. Even with this diversity, we are not powered to adequately evaluate potential racial differences in amenorrhea rates or rare outcomes such as discontinuation for bleeding

concerns among women with self-reported baseline HMB. A weakness is that the outcomes represent the strictest definitions of bleeding; for example, one day of spotting would count as non-amenorrheic. Accordingly, to understand the true decrease in bleeding, the rates of amenorrhea or spotting rather than amenorrhea alone provide more realistic information for counseling patients. At one year and beyond, approximately 50%-60% of women will report amenorrhea or spotting, with about two-thirds of this pattern as spotting.

Research Implications

The number of women in racial subgroups when evaluating amenorrhea and discontinuation due to bleeding complaints is too low to discriminate these outcomes, especially the rare outcome of discontinuation for a bleeding complaint in women with self-reported HMB. Very large population-based studies could address these issues.

Conclusions

These findings demonstrate the expected outcomes within young women with self-reported heavy bleeding using the levonorgestrel 52mg IUS for contraception. A potential benefit of levonorgestrel 52mg IUS use by women choosing this method for contraception is the significant decrease in flow. Clinicians can use the information provided in this report to better counsel women based on their baseline subjective bleeding pattern.

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360Table 1. Demographics at enrollment for women with and without pre-study
361self-reported HMB* in a phase 3 study of a levonorgestrel 52mg IUS
362(N=1513)

Characteristic	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value
Age (years)	27.5 ± 5.8	26.8 ± 5.5	.17
≥36	13 (8.7%)	96 (7.0%)	.50
Ethnicity			.22
Hispanic or Latina	26 (17.3%)	186 (13.6%)	
Race			.007
White	99 (66.0%)	1079 (79.2%)	
Black or African American	36 (24.0%)	168 (12.3%)	
Asian	8 (5.3%)	55 (4.0%)	
Multiracial	4 (2.7%)	36 (2.6%)	
American Indian or Alaska Native	3 (2.0%)	16 (1.2%)	
Native Hawaiian or Other Pacific Islander	0	5 (0.4%)	
Data missing	0	4 (0.3%)	
Body Mass Index (kg/m^2)	28.6 ± 7.2	26.7 ± 6.6	.001
Obese (≥30.0)	47 (31.3%)	328 (24.1%)	.06
Parity			
Nulliparous	84 (56.0%)	839 (61.6%)	.19
Marital Status			.58
Never married	93 (62.0%)	896 (65.7%)	
Married	41 (27.3%)	358 (26.3%)	
Divorced	14 (9.3%)	85 (6.2%)	
Separated	2 (1.3%)	22 (1.6%)	
Widowed	0	2 (0.1%)	

363

364* based on self-report of menstrual bleeding patterns for the 3 months prior
365to screening

366Data are presented as n (%) or mean ± standard deviation
367HMB=heavy menstrual bleeding; IUS=intrauterine system

Table 2. Amenorrhea rates over 2 years (26 cycles) of levonorgestrel 52mg IUS use among women with and without self-reported baseline HMB* (N=1513)

Cycles of use	Women with baseline HMB n=150		Women without baseline HMB n=1363		p-value†
	Number entering cycle	Amenorrhea rate	Number entering cycle	Amenorrhea rate	
6	140	21 (15.0%, 9.1-20.9%)	1251	319 (25.5%, 23.1-27.9%)	.005
13	123	26 (21.1%, 13.9-28.4%)	1112	382 (34.4%, 31.6-37.1%)	.003
19	116	36 (31.0%, 22.6-39.5%)	987	367 (37.2%, 34.2-40.2%)	.22
26	103	38 (36.9%, 27.6-46.2%)	880	383 (43.5%, 40.2-46.8%)	.21

Data are presented as n (%, 95% confidence interval).
HMB=heavy menstrual bleeding; IUS = intrauterine system
* based on self-report of menstrual bleeding patterns for the 3 months prior to screening
† Fisher exact test

Table 3. Cumulative discontinuation rates over 2 years (26 cycles) of levonorgestrel 52mg IUS use among women with and without self-reported baseline HMB* (N=1513)

Cycles of use	Discontinuation overall			Discontinuation for bleeding complaint		
	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value†	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value†
3	5 (3.3%, 0.5-6.2%)	50 (3.7%, 2.7-4.7%)	1.0	0	2 (0.1%, 0.0-0.3%)	1.0
6	9 (6.0%, 2.2-9.8%)	108 (7.9%, 6.5-9.4%)	.52	0	6 (0.4%, 0.1-0.8%)	1.0
9	17 (11.3%, 6.3-16.4%)	163 (12.0%, 10.2-13.7%)	.89	1 (0.7%, 0.0-2.0%)	8 (0.6%, 0.2-1.0%)	.61
13	26 (17.3%, 11.3-23.4%)	246 (18.0%, 16.0-20.1%)	.91	3 (2.0%, 0.0-4.2%)	13 (1.0%, 0.4-1.5%)	.21
19	32 (21.3%, 14.8-27.9%)	364 (26.7%, 24.4-29.1%)	.17	4 (2.7%, 0.1-5.2%)	22 (1.6%, 0.9-2.3%)	.32
26	42 (28.0%, 20.8-35.2%)	454 (33.3%, 30.8-35.8%)	.20	4 (2.7%, 0.1-5.2%)	26 (1.9%, 1.2-2.6%)	.53

Data are presented as n (%, 95% confidence interval).
HMB=heavy menstrual bleeding; IUS = intrauterine system
* based on self-report of menstrual bleeding patterns for the 3 months prior to screening
† Fisher exact test

Table 4. Reasons for discontinuation over 2 years (26 cycles) of levonorgestrel 52mg IUS use among women with and without self-reported baseline HMB* (N=1513)

Reason for discontinuation	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value†
Adverse event (not including expulsion or bleeding complaint)	12 (5.3%)	136 (8.1%)	.56
Lost to follow-up/withdrew consent	8 (5.3%)	126 (9.2%)	.13
Expulsion	7 (4.7%)	39 (2.9%)	.21
Desires pregnancy	5 (3.3%)	43 (3.2%)	.81
Bleeding complaint	4 (2.7%)	26 (1.9%)	.53
Subject relocation	3 (2.0%)	28 (2.8%)	1.0
Other	3 (2.0%)	56 (4.1%)	.27

Data are presented as n (%).

HMB=heavy menstrual bleeding; IUS = intrauterine system

* based on self-report of menstrual bleeding patterns for the 3 months prior to screening

† Fisher exact test

Figure Legend

Figure 1.

Title:

Flow patterns after levonorgestrel 52mg IUS insertion in women with self-reported baseline HMB*

Footer:

* Number of women with HMB at baseline is 150; proportion for each cycle is calculated based on the number of women using the levonorgestrel 52mg IUS during that cycle.

HMB=heavy menstrual bleeding; IUS=intrauterine system