Bleeding patterns of women with heavy menstrual bleeding or dysmenorrhoea using the levonorgestrel-releasing intrauterine system: results from a real-world observational study in Japan (J-MIRAI)

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ABSTRACT

Purpose: To collect real-world safety and clinical outcome data on the levonorgestrel-releasing intrauterine system (LNG-IUS) for functional/organic heavy menstrual bleeding (HMB) and dysmenorrhoea in Japanese women (J-MIRAI).

Materials and methods: In this prospective, multicentre, single-cohort, open-label, post-authorisation study, we assessed menstrual blood loss after LNG-IUS insertion by changes from baseline in pictorial blood loss assessment chart (PBAC) scores. Scores for the menorrhagia multi-attribute scale (MMAS) were collected for 12 months to assess quality of life.

Results: We included 47 patients with complete PBAC score and patient diary data. The median PBAC score before LNG-IUS insertion was 159.0, which decreased significantly to 6.0 at 12 months post-insertion; for patients with adenomyosis (n = 20), PBAC score decreased from 174.5 pre-insertion to 19.5 at 12 months. The number of patient-reported bleeding days was correlated with PBAC score >5. The proportion of women with prolonged bleeding decreased from 85.7% to 34.6% by the study’s end. Some women reported no bleeding after the first 90-day reference period. The mean MMAS overall score significantly increased from 50.50 before insertion to 88.67 at 12 months.

Conclusions: Japanese women with functional/organic HMB experienced substantial reductions in bleeding symptoms and improvements in quality of life after 12-month use of the LNG-IUS.

Introduction

Heavy menstrual bleeding is generally defined as menstrual blood loss ≥80 mL [1]. However, the Japanese clinical definition is a total menstrual blood loss ≥140 mL per cycle [2]. In clinical practice, this definition is often not strictly applied, and most physicians diagnose heavy menstrual bleeding based on the patient’s subjective perception of her menstrual blood loss [1,3], and the common co-presentation with iron deficiency anaemia [4,5]. Additionally, the 2020 version of the Guideline for Gynecological Practice in Japan states that the cause of heavy menstrual bleeding should be identified based on the abnormal uterine bleeding algorithm of the International Federation of Gynecology and Obstetrics [7]. In Japan, the prevalence of heavy menstrual bleeding was estimated at 19%, and that of dysmenorrhoea was estimated at 50% [8]. Moreover, heavy menstrual bleeding has been reported to interfere with women’s social and professional activities and leads to decreased quality of life (QoL) [1,9,10].

The management of heavy menstrual bleeding depends on several factors, such as underlying conditions (organic [e.g., fibroids or adenomyosis] or functional), treatment preferences, and fertility wishes. Medical therapies include hormonal treatments, of which the levonorgestrel-releasing intrauterine system (LNG-IUS) and combined hormonal contraceptives are the most commonly prescribed [1].

The LNG-IUS contains levonorgestrel 52 mg, with an initial release rate of 20 µg/day (Mirena®, Bayer Yakuhin, Ltd., Osaka, Japan). The LNG-IUS suppresses endometrial growth, including endometrial glandular atrophy, decidualisation, stroma, and vascular changes [11,12] resulting from sustained progesterin release into the uterus, which greatly reduces menstrual blood loss [11,13]. In addition to the indication as a contraceptive (approved in Japan in 2007), Japan approved the LNG-IUS for heavy menstrual bleeding and dysmenorrhoea in 2014 through a public knowledge-based application of drug use. Therefore, there is a lack of data on the safety and effectiveness of the LNG-IUS.
prescribed for Japanese patients with heavy menstrual bleeding and dysmenorrhea. We conducted an observational, multicentre, prospective, single-cohort study (J-MIRAI) to collect real-world safety and clinical outcome data on LNG-IUS use in Japanese patients with heavy menstrual bleeding and/or dysmenorrhea.

In the present report, we focused on the degree of menstrual blood loss and menstrual bleeding patterns based on patient diaries, changes from baseline in the pictorial blood loss assessment chart (PBAC) scores, and changes from baseline in the menorrhagia multi-attribute scale (MMAS) scores after LNG-IUS insertion.

Materials and methods

Study design, patients, treatment, and data collection

This research is based on the J-MIRAI study, an observational, multicentre, single-cohort study conducted in 83 centres in Japan between 2015 and 2019. Women included in J-MIRAI had been diagnosed with heavy menstrual bleeding and/or dysmenorrhea based on the clinician’s judgement, and planned to undergo treatment with the LNG-IUS in accordance with the investigator’s routine treatment. We excluded women who had previously used the LNG-IUS for heavy menstrual bleeding, dysmenorrhea, or contraception. In principle, the LNG-IUS insertion was to be in accordance with the product label in Japan, which specifies that insertion should be performed within 7 days of the onset of menstruation, regardless of bleeding status [14].

The observation period was 12 months from the date of insertion, and hospital visits were scheduled as follows: 1 month prior to insertion, day of insertion, and 1, 3, 6, and 12 months post-insertion.

The J-MIRAI study was designed as a post-authorisation safety study in compliance with Japanese Good Post-marketing Study Practice guidelines. The study was registered in ClinicalTrials.gov under the identifier NCT02475356. The institutional review board or ethics committee of each participating centre approved the protocol of the study. Patients provided written informed consent before any study procedures took place. Patients recorded data on subjective symptoms in daily diaries and were required to take these diaries to each study visit.

Study endpoints

The study endpoints were menstrual blood loss assessment after LNG-IUS insertion based on changes from baseline (before insertion) in PBAC score (menorrhagia is defined as a PBAC score ⩾100) [15] and number of bleeding days based on patient diaries, menstrual bleeding patterns based on the World Health Organization (WHO) Belsey criteria [Supplementary Table 1] [16], correlation between the number of bleeding days (from patient diaries) and PBAC score, and changes from baseline (before insertion) in MMAS score (0–100, with lower scores indicating greater severity) after LNG-IUS insertion using the Japanese version of the MMAS [17]. Data for the PBAC were only available from two participating hospitals in this study.

Statistical analysis

The main aspects of the statistical analysis were as follows. The target sample size was 600 patients, and we included all patients with confirmed LNG-IUS insertion in the safety analysis set. The clinical outcomes analysis set included all patients in the safety analysis set who were using the LNG-IUS for the first time for treatment of heavy menstrual bleeding or dysmenorrhea. We calculated frequencies for categorical variables and summary statistics for continuous variables, and described the absolute value and the amount of change after LNG-IUS insertion for continuous variables where applicable. We investigated correlations between the number of bleeding days by severity (no bleeding, spotting, mild, ordinary, or severe) based on patient diaries and PBAC score ⩾1 and ⩾5 using Pearson’s correlation coefficient. Tests were two-sided with a significance level of 5%. We used the Wilcoxon test for comparisons with baseline values. Missing data were not imputed, and the statistical analysis was conducted using SAS version 9.4 (Windows version, SAS Institute Inc., Cary, NC, USA).

Results

Of the 600 patients registered, we excluded five patients for whom we were unable to collect clinical report forms. Of the remaining 595 patients, we collected 250 diaries, representing a diary collection rate of 42.0%. Regarding the PBAC, only two participating centres collected these data, representing 88 patients. Of these, 48 patients completed the questionnaires, reflecting a response rate of 54.5% (Figure 1).

Menstrual blood loss assessment based on changes in PBAC score after LNG-IUS insertion and patient diaries

Although we collected PBAC data from 48 patients, one patient submitted an incomplete questionnaire; thus, we included the background characteristics of the 47 patients with complete data in the PBAC score analysis (Table 1). Most patients had both heavy menstrual bleeding and dysmenorrhea (70.2%): 19.1% and 10.6% of patients had heavy menstrual bleeding only and dysmenorrhea only, respectively. Common underlying conditions were adenomyosis (42.6%), endometrial hyperplasia (19.1%), and functional heavy menstrual bleeding (14.9%). Before insertion, over 60% of patients had PBAC scores ⩾100, and during the month in which the LNG-IUS was inserted, 53.2% had PBAC scores <100.

Overall, the median PBAC score (Q1, Q3) before LNG-IUS insertion was 159.0 (65.0, 242.0), and it decreased from 1 month after insertion. At 12 months post-insertion, it had significantly decreased to 6.0 (0, 28.0) (Wilcoxon test, p < 0.0001) (Figure 2(a)). Among patients with adenomyosis, the median PBAC score (Q1, Q3) before LNG-IUS insertion was 174.5 (71.0, 478.0), and decreased from 2 months after insertion until the end of the study. At 12 months after insertion, the median PBAC score had decreased to 19.5 (0, 78.0) (Wilcoxon test, p < 0.05) (Figure 2(b)). Supplementary Table 2 shows the change in median PBAC scores after LNG-IUS insertion for patients with underlying conditions. The median (Q1, Q3) PBAC scores before
insertion and at 12 months post-insertion, respectively, of patients with functional heavy menstrual bleeding were 81.0 (10.0, 123.0) and 6.0 (0, 14.0); of patients with uterine fibroid, 355.5 (149.5, 545.0) and 64.5 (0, 129.0); and of those with endometriosis, 170.0 (86.0, 344.0) and 9.0 (0, 129.0).

Throughout the post-insertion period, the number of patients in whom the total PBAC score increased by 50% compared with before insertion was 10 patients at 3 months, six patients at 6 months, five patients at 9 months, and two patients at 12 months. There was an increase (from 7.3% at 3 months post-insertion to 38.5% at 12 months post-insertion) in the proportion of patients in whom the total PBAC score decreased by 100%; a 100% reduction indicates that the monthly PBAC score dropped to zero at a given timepoint (i.e., 3, 6, 9, or 12 months) (Figure 3). One of the 10 patients with a PBAC score increase by 50% at 3 months post-insertion experienced anaemia as an adverse event.

Based on patient diaries, the proportion of women with a high number of bleeding days (≥22 days/month) decreased throughout the post-insertion period, and the proportion of women with a low number of bleeding days (≤7 days/month) increased progressively over time (Figure 4).

Changes in menstrual bleeding patterns according to WHO Belsey criteria

Using 90-day reference periods, we evaluated menstrual bleeding patterns and found that 85.7%, 64.1%, 39.5%, and 34.6% of women had prolonged bleeding during the first, second, third, and fourth 90-day reference periods. Thus, there was a gradual and progressive decrease in the proportion of women with prolonged bleeding throughout the 12-month post-insertion period, with a decrease of 51.1% at the end of the study. We observed the largest decrease in the proportion of women with prolonged bleeding between the second and third 90-day reference periods, with a decrease of 24.6%. The proportion of women with infrequent bleeding increased throughout the post-insertion period from 2.4% in the first reference period to 5.1%, 15.8%, and 26.9% in the second, third, and fourth reference periods, respectively, and finally to 24.5% by the end of the study. Generally, there was also a slight increase in the proportion of women with regular and frequent bleeding. Finally, 2.6%, 5.3%, and 3.9% of women reported no bleeding at all in the second, third, and fourth 90-day periods, respectively.

Correlation between number of menstrual bleeding days and PBAC scores

For the correlation between the number of bleeding days by severity (spotting, mild, ordinary, or severe) based on patient diaries and PBAC score ≥1, the Pearson’s correlation coefficients were 0.353 (n = 42) at 1 month, 0.331 (n = 41) at 3 months, and 0.458 (n = 40) at 6 months after
insertion (Supplementary Table 3), suggesting weak correlations at each timepoint. For the correlation between the number of bleeding days by severity (mild, ordinary, or severe) and PBAC score ≥5, the Pearson’s correlation coefficients were 0.571 (n = 42) at 1 month, 0.499 (n = 41) at 3 months, and 0.536 (n = 40) at 6 months after insertion.
Changes in MMAS after LNG-IUS insertion

The MMAS overall score before LNG-IUS insertion (mean ± standard deviation [SD]) was 50.50 ± 22.90, and those at 3 and 12 months post-insertion were 84.41 ± 18.43 and 88.67 ± 14.46, respectively. The significant increases in MMAS score and each of its domains began at 3 months and were maintained until 12 months (Wilcoxon test, \( p < 0.0001 \) each) (Table 2).

Supplementary Table 4 shows the MMAS score changes over time by underlying cause (i.e., functional heavy menstrual bleeding, uterine fibroid, and adenomyosis). MMAS overall scores and scores for each domain significantly and progressively increased over time in patients with functional heavy menstrual bleeding, adenomyosis, or uterine fibroid.

Discussion

This research used data from the J-MIRAI post-authorisation safety study, which collected real-world data on the safety and clinical outcomes of the LNG-IUS for Japanese women.
with heavy menstrual bleeding and/or dysmenorrhoea. The present report focuses on the changes in menstrual blood loss and bleeding patterns after LNG-IUS insertion. Although there are several methods for assessing the degree of menstrual blood loss, including the alkaline haematin technique, self-recording of menstrual status and use of menstrual products (i.e., by patient diaries), and the PBAC, objective assessment is generally difficult to conduct outside of clinical trials, and the PBAC is not widely used in clinical practice outside of clinical research [18]. In our study, which was observational and conducted under real-world clinical conditions, only 2 of the 83 study sites were able to cooperate in the collection of PBAC data; this limited the potential pool of patients with PBAC data to 88, of whom 48 provided the requested data.

At 12 months post-insertion, the PBAC score significantly decreased compared with before insertion ($p < 0.0001$). Throughout the 12-month post-insertion period, there was an increase in the proportion of women with a lower PBAC score compared with before insertion, and women reported fewer bleeding days throughout the study.

Changes in bleeding patterns also indicated that the proportion of women with prolonged bleeding had decreased markedly by the end of the observation period.

We found a correlation between the number of bleeding days and the PBAC score, which was stronger with PBAC scores $\geq 5$ than scores $\geq 1$. This suggests that both the PBAC questionnaire and patient diary were correctly filled in. Thus, both indicators may be used to accurately examine the amount of bleeding and the number of bleeding days.

Although a small number of patients had increased PBAC scores, the decrease in menstrual blood loss by PBAC score after insertion of the LNG-IUS was similar to that in international studies [13,19]. A pooled analysis of studies on women without structural pelvic pathology using the LNG-IUS solely for heavy menstrual bleeding concluded that bleeding patterns in these women were similar to those observed in women using the LNG-IUS for contraception but that women with heavy menstrual bleeding may experience more days of bleeding and spotting during their first year of treatment [20].

![Figure 5. Change in bleeding patterns according to the World Health Organization Belsey criteria after LNG-IUS insertion by 90-day reference period. LNG-IUS: levonorgestrel-releasing intrauterine system.](image)

| Observational period (four 90-day reference periods) | 1st 90 days | 2nd 90 days | 3rd 90 days | 4th 90 days |
|-----------------------------------------------------|-------------|-------------|-------------|-------------|
| (N = 42)                                             | (N = 39)    | (N = 38)    | (N = 26)    |
| Proportion of women by bleeding pattern (%)          |             |             |             |
| Regular bleeding                                    |      |      |      |      |
| Irregular bleeding                                  |      |      |      |      |
| Infrequent bleeding                                 |      |      |      |      |
| Frequent bleeding                                   |      |      |      |      |
| Prolonged bleeding                                  |      |      |      |      |
| No bleeding                                         |      |      |      |      |

**Figure 5.** Change in bleeding patterns according to the World Health Organization Belsey criteria after LNG-IUS insertion by 90-day reference period. LNG-IUS: levonorgestrel-releasing intrauterine system.

**Table 2.** Changes over time in MMAS overall scores and domains for patients with heavy menstrual bleeding.

|                      | Before insertion | After 3 months | After 12 months | Wilcoxon test |
|----------------------|------------------|----------------|-----------------|---------------|
| n                    | 131              | 130            | 116             |               |
| Mean (SD)            | 50.50 (22.90)    | 84.41 (18.43)  | 88.67 (14.46)   |               |
| Practical difficulties| 133              | 132            | 119             |               |
| Mean (SD)            | 4.96 (4.83)      | 11.71 (3.67)   | 12.52 (2.94)    |               |
| Social life          | 131              | 132            | 123             |               |
| Mean (SD)            | 6.43 (2.52)      | 9.22 (1.82)    | 9.54 (1.23)     |               |
| Psychological well-being | 132         | 132            | 122             |               |
| Mean (SD)            | 8.12 (3.63)      | 11.92 (3.04)   | 12.35 (2.93)    |               |
| Physical health      | 132              | 132            | 121             |               |
| Mean (SD)            | 6.23 (5.98)      | 14.49 (6.89)   | 15.58 (6.47)    |               |
| Work routine         | 132              | 132            | 121             |               |
| Mean (SD)            | 9.25 (5.23)      | 15.96 (3.33)   | 16.52 (3.08)    |               |
| Family life          | 132              | 133            | 121             |               |
| Mean (SD)            | 15.51 (6.53)     | 21.11 (3.98)   | 21.59 (3.29)    |               |

*Before insertion vs. after 3 months.*

*Before insertion vs. after 12 months.*

MMAS: menorrhagia multi-attribute scale; SD: standard deviation.
Regarding the change in bleeding patterns according to the WHO Belsey criteria [16], there was a gradual and progressive reduction in the proportion of women with prolonged bleeding, which was most notable between the second and third 90-day reference periods and was reduced by 51.1% by the fourth 90-day reference period. Compared with the first reference period, in which none of the women reported no bleeding, the proportion of women without any bleeding increased in the second, third, and fourth reference periods. Similar findings were reported by Jensen et al. in a study of bleeding patterns among women without structural pelvic pathologies using the LNG-IUS for heavy menstrual bleeding [20].

The present findings are supported by a recent meta-analysis of seven clinical trials and cohort studies of the LNG-IUS in women with regular menses. The meta-analysis showed that the greatest decreases in menstrual bleeding and spotting occurred during the 3 to 6 months after insertion [21]. Another recent study reported that over 90% of women with self-reported heavy menstrual bleeding no longer reported heavy menstrual bleeding within 6 months of treatment [22]. Although direct comparisons with other IUs are not possible, the present findings are in accordance with those reported for another 52-mg LNG-IUS [23]. Significant increases in the MMAS overall scores and each of its domains, as well as by the underlying causes (i.e., functional heavy menstrual bleeding, uterine fibroid, and adenomyosis), were observed as early as 3 months after LNG-IUS insertion. These increases in the MMAS scores suggested improvements in health-related QoL over time. Our findings are consistent with previous reports of women with heavy menstrual bleeding treated with the 52-mg LNG-IUS [24,25].

The limitations of this study are as follows. The J-MIRAI study did not include a control group, and there was a high risk of selection bias. Additionally, the sample size was relatively small, and it decreased progressively up to the 12-month follow-up. PBAC results were only available for a small number of patients, as this metric is not widely used to evaluate menorrhagia in Japanese medical institutions. Finally, our study was limited to Japanese women, and as such, generalisation to other ethnic groups should be made with caution.

In conclusion, the LNG-IUS ameliorated bleeding symptoms in Japanese women with functional/organic heavy menstrual bleeding in the clinical setting. According to the MMAS score, improvement in QoL was demonstrated in patients with organic/functional heavy menstrual bleeding. Our results support the continued use of the LNG-IUS in this patient group.

Acknowledgements
All authors thank the people who were involved in this study, including participating women as well as the investigators at all institutions. The analysis was performed by EPS Corporation. The data collection was supported by AC Medical Inc. Noriko Takahashi supported the statistical analyses and interpreted the results of the menorrhagia multi-attribute scale. Finally, the authors thank Keyra Martinez Dunn, MD, of Edanz, for providing medical writing support, which was funded by Bayer Yakuhin, Ltd. through EMC K.K. in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Author contributions
Jo Kitawaki, Shigeo Akira, Tasuku Harada, Nagamasa Maeda, Mikio Momoeda, Ikuko Ota, Taku Murakami, Toshiyuki Sunaya, and Kazufumi Hirano participated in the study conception and design. Tasuku Murakami, Toshiyuki Sunaya, and Kazufumi Hirano collected and/or assembled the data. Jo Kitawaki, Shigeo Akira, Tasuku Harada, Nagamasa Maeda, Mikio Momoeda, Ikuko Ota, Tasuku Murakami, Toshiyuki Sunaya, and Kazufumi Hirano did the data analysis and interpretation. Jo Kitawaki, Shigeo Akira, Tasuku Harada, Nagamasa Maeda, Mikio Momoeda, Ikuko Ota, Taku Murakami, Toshiyuki Sunaya, and Kazufumi Hirano wrote and revised the manuscript. All authors made the final decision to submit the article for publication.

Disclosure statement
Jo Kitawaki received personal fees from Bayer Yakuhin, Ltd., Mochida Pharmaceutical Co., Ltd., and ASKA Pharmaceutical Co., Ltd., a grant from Nichimo Biotics, has a patent of materials related to the treatment of endometriosis, and is a member of the Proper Use Advisory Committee for Mirena. Shigeo Akira received personal fees from Bayer Yakuhin, Ltd., and is a member of the Proper Use Advisory Committee for Mirena. Tasuku Harada received personal fees from Bayer Yakuhin, Ltd., and is a member of the Proper Use Advisory Committee for Mirena. Nagamasa Maeda received personal fees from Bayer Yakuhin, Ltd., and is a member of the Proper Use Advisory Committee for Mirena. Mikio Momoeda received personal fees from Bayer Yakuhin, Ltd., and is a member of the Proper Use Advisory Committee for Mirena. Ikuko Ota received personal fees from Bayer Yakuhin, Ltd., and personal fees from Mochida Pharmaceutical Co., Ltd., and ASKA Pharmaceutical Co., Ltd., unrelated to the submitted work. Taku Murakami, Toshiyuki Sunaya, and Kazufumi Hirano are employees of Bayer Yakuhin, Ltd.

Funding
This work was supported by Bayer Yakuhin, Ltd., Osaka, Japan, which actively participated in the study design and managed all operational aspects of the study, including monitoring data collection, statistical analyses, and writing of the report.

Data availability statement
The data that support the findings of this study are available from the corresponding author, Jo Kitawaki, upon reasonable request.

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