



Original Research Article

Real-world outcomes of the levonorgestrel-releasing intrauterine system for heavy menstrual bleeding or dysmenorrhea in Japanese patients: A prospective observational study (J-MIRAI) ☆☆☆★★★

Tasuku Harada^{a,*}, Ikuko Ota^b, Jo Kitawaki^c, Mikio Momoeda^d, Nagamasa Maeda^e, Shigeo Akira^f, Mikiko Umeyama^g, Toshiyuki Sunaya^h, Kazufumi Hiranoⁱ

^a Department of Obstetrics and Gynecology, Tottori University Faculty of Medicine, Tottori 683-8503, Japan

^b Department of Gynecology, Kurashiki Heisei Hospital, Okayama 710-0826, Japan

^c Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan

^d Department of Integrated Women's Health, St. Luke's International Hospital, Tokyo 104-8560, Japan

^e Department of Obstetrics and Gynecology, Kochi Medical School, Kochi 783-8505, Japan

^f Department of Obstetrics and Gynecology, Nippon Medical School, Tokyo 113-8603, Japan

^g Medical Affairs Women's Health & Established Products, Bayer Yakuhin, Ltd., Osaka 530-0001, Japan

^h Statistics & Data Insights, Data Sciences & Analytics, Research & Development Japan, Bayer Yakuhin, Ltd., Osaka 530-0001, Japan

ⁱ PMS, Pharmacovigilance Monitoring & Governance, Bayer Yakuhin, Ltd., Osaka 530-0001, Japan

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ABSTRACT

Objectives: We collected real-world data on the safety and clinical outcomes of the levonorgestrel-releasing intrauterine system (LNG-IUS) for heavy menstrual bleeding and dysmenorrhea.

Study Design: This was a prospective, multicenter, single-cohort, open-label, post-authorization 12-month follow-up study of Japanese patients initiating the LNG-IUS for heavy menstrual bleeding and/or dysmenorrhea. The primary endpoint was the safety profile based on adverse events and adverse drug reactions (ADRs), including expulsions and abnormal bleeding, within 12 months of LNG-IUS insertion. Secondary endpoints included changes from baseline in menstrual blood loss based on bleeding days and dysmenorrhea graded on a visual analog scale (VAS).

Results: Of the 595 patients included, many had underlying conditions such as adenomyosis (39.5%), uterine leiomyoma (30.8%), or endometriosis (12.9%). The incidences of ADRs and serious ADRs were 59.7% and 0.3%, respectively. Frequently reported ADRs were metrorrhagia (48.9%), procedural pain (14.1%), and ovarian cyst (6.2%). The cumulative incidence of expulsions at 12 months was 8.7%. Risk factors for expulsion were obesity (body mass index ≥ 25 kg/m²), adenomyosis, and uterine cavity length ≥ 8 cm. The median [interquartile range] VAS score for dysmenorrhea improved from 46.5 [13.0–68.0] at insertion to 1.0 [0.0–13.0] at 12 months, and improvements were also observed in chronic pelvic pain and painful defecation.

Conclusions: The LNG-IUS safely and effectively reduced dysmenorrhea, chronic pelvic pain, and painful defecation. Risk factors for expulsion suggest that patients with underlying organic disease should be monitored carefully when using the LNG-IUS.

Implications: The LNG-IUS is an effective treatment for secondary dysmenorrhea with organic disease, and for the reduction of chronic pelvic pain; however, physicians should be aware of the increased risk of expulsion in patients with organic conditions.

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☆☆ **Data Statement:** The data that support the findings of this study are available from the corresponding author, Tasuku Harada, upon reasonable request.

* **Author Contributions:** Tasuku Harada, Ikuko Ota, Jo Kitawaki, Mikio Momoeda, Nagamasa Maeda, Shigeo Akira, Mikiko Umeyama, Toshiyuki Sunaya, and Kazufumi

Hirano participated in the study conception and design. Mikiko Umeyama, Toshiyuki Sunaya, and Kazufumi Hirano collected and/or assembled the data. Tasuku Harada, Ikuko Ota, Jo Kitawaki, Mikio Momoeda, Nagamasa Maeda, Shigeo Akira, Mikiko Umeyama, Toshiyuki Sunaya, and Kazufumi Hirano did the data analysis and interpretation. Tasuku Harada, Ikuko Ota, Jo Kitawaki, Mikio Momoeda, Nagamasa Maeda, Shigeo Akira, Mikiko Umeyama, Toshiyuki Sunaya, and Kazufumi Hirano

1. Introduction

Heavy menstrual bleeding and dysmenorrhea are common menstrual symptoms that can dramatically reduce quality of life and hinder activities of daily living and work productivity [1–3]. In a large-scale Japanese survey, 74% of respondents complained of menstrual symptoms; of these, 50% reported dysmenorrhea, and 19% reported heavy menstrual bleeding [4]. However, many patients with heavy menstrual bleeding and dysmenorrhea in Japan are not receiving the recommended treatments [5].

The levonorgestrel-releasing intrauterine system (LNG-IUS; levonorgestrel 52 mg; Mirena®, Bayer, Germany) exhibits a local intrauterine progestogenic effect [6], exerts a greater contraceptive effect than oral contraceptives [7], and reduces menstrual blood loss volume [8] and dysmenorrhea [9] to a similar extent. British practice guidelines specify the LNG-IUS as first-line therapy for heavy menstrual bleeding [10], and the LNG-IUS is recommended for dysmenorrhea in both European [11] and Japanese [5] guidelines. Although the LNG-IUS is approved for dysmenorrhea in some countries, no studies exist on primary dysmenorrhea [12].

Japan approved the LNG-IUS as a contraceptive in 2007 and as treatment for heavy menstrual bleeding/dysmenorrhea in 2014. Because these label extensions were approved based on data from non-Japanese clinical trials [13], there is limited information on LNG-IUS use in Japanese patients for these indications. This observational study (J-MIRAI), funded by Bayer Yakuhin, aimed to confirm the efficacy and safety of the LNG-IUS for heavy menstrual bleeding/dysmenorrhea by collecting real-world data in Japan. We previously reported J-MIRAI results clarifying the effect of the LNG-IUS on bleeding symptoms [14] and quality of life [15]. The present paper focuses on pain outcomes and risk factors for expulsion.

2. Methods

2.1. Study design

We conducted a prospective, multicenter, single-cohort study in 83 Japanese centers between 2015 and 2019 (enrollment period: June 2015–May 2017; ClinicalTrials.gov: NCT02475356). Patient enrollment was handled via fax by participating centers in which patients consented to use of the LNG-IUS. The physician at each center assessed patient eligibility (based on a diagnosis of secondary menorrhagia or secondary dysmenorrhea) and recorded conditions including uterine leiomyoma, adenomyosis, and endometriosis prior to enrollment and according to standard diagnostic criteria in the Japanese guidelines [5]. The observation period was for 12 months post-insertion, which was performed following the

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* Corresponding author: Tasuku Harada, Department of Obstetrics and Gynecology, Tottori University Faculty of Medicine, 86 Nishi-cho, Yonago-shi, Tottori 683-8503, Japan, Tel: +81-85938-6641, Fax: +81-85938-6649

E-mail address: tasuku@med.tottori-u.ac.jp (T. Harada).

Japanese product label [16]. Patients could refuse further participation in the study at any time and without providing any reason. We recorded discontinuations due to adverse events (AEs) and insufficient effectiveness; patients were considered lost to follow-up if they did not attend scheduled outpatient visits or contact the hospital for 6 months.

The institutional review board at each center approved the study, which was compliant with Japanese Good Post-marketing Study Practice guidelines, which mandate the surveillance of pharmaceuticals under real-world use after approval [17]. All participants provided written informed consent before study participation.

2.1.1. Participants

We included patients aged ≥ 20 years with heavy menstrual bleeding and/or dysmenorrhea. All patients with confirmed LNG-IUS insertion were included in the safety analysis set, and patients using the LNG-IUS for contraception only, or those who had previously used the LNG-IUS, were excluded from the effectiveness analysis set.

2.1.2. Study visits

Outpatient visits occurred 1 month before insertion, on the day of insertion, and 1, 3, 6, and 12 months post-insertion. At the first visit, we obtained informed consent, collected patient background data, and conducted physical and ultrasound examinations.

2.2. Study endpoints

In accordance with guidelines for post-authorization safety studies, the primary endpoint was safety, based on AEs and adverse drug reactions (ADRs, which were AEs for which a causal relationship to the LNG-IUS could not be ruled out), including expulsions (partial and complete, diagnosed by clinical symptoms and/or ultrasound) and abnormal bleeding (physicians' subjective judgement), within 12 months of LNG-IUS insertion. Physicians recorded details about device insertion, including the need for cervical dilators and use of anesthesia, and noted (in the clinical report form) patient-reported pain while wearing the device. Secondary endpoints included dysmenorrhea, chronic pelvic pain, and painful defecation graded on a visual analog scale (VAS).

2.3. Data collection

Patients recorded data on subjective symptoms in paper diaries. Patients provided VAS scores for dysmenorrhea, chronic pelvic pain, dyspareunia, and defecation pain before LNG-IUS insertion and at 1, 3, 6, and 12 months post-insertion. At each time point, patients recorded their most recent severe pain.

At each visit, the investigator recorded the data (e.g., gynecological examinations, including any imaging exams that were performed at the attending physician's discretion, such as uterine ultrasonography or magnetic resonance imaging; endometrial thickness in adenomyosis patients; and laboratory tests) in a clinical report form. We collected imaging data, if available, for 1 month prior to insertion, and 3, 6, and 12 months post-insertion. Medical history, concomitant diseases, and AEs were coded using the Japanese Medical Dictionary for Regulatory Activities v22.1.

2.4. Additional analyses

Based on the safety data, we analyzed risk factors for LNG-IUS expulsion, and because uterine leiomyoma is a risk factor for expulsion, in a *post hoc* analysis, we assessed leiomyoma size at baseline and evaluated changes before and 1, 3, 6, and 12 months after LNG-IUS insertion. Leiomyoma size was assessed by transvaginal

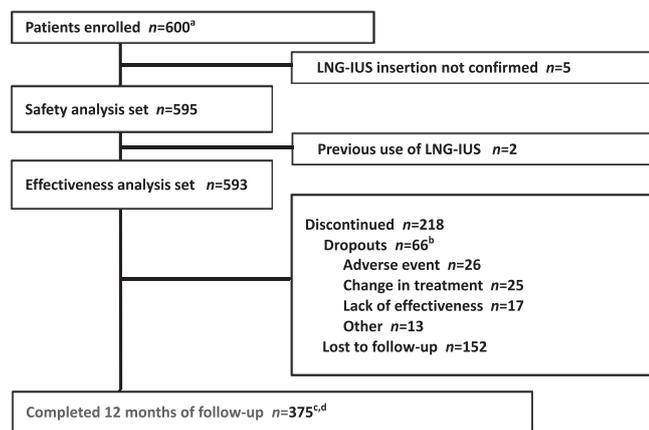


Fig. 1. Disposition of patients treated with the LNG-IUS in Japan from 2015 to 2019.

^aDoctors at each institution confirmed that the patient met the eligibility criteria. Patients who provided written informed consent to participate in the study were registered at the enrollment center by fax.

^bPatients may have had multiple reasons for dropping out.

^cIncludes 29 cases of expulsion with successful re-insertion.

^d250 patient diaries were collected (250/595; 42.0%), 249 of which had full data for bleeding days, 170 of which had full data for the visual analog scale, and 72 of which had full data for the Menstrual Distress Questionnaire.

LNG-IUS, levonorgestrel-releasing intrauterine system.

ultrasonography in most facilities, with magnetic resonance imaging used at a few centers. The assessment was performed by the attending physician or a technician, depending on the policies of each participating center. The change from baseline of the maximum uterine leiomyoma size after 12 months was aggregated. The cut-off value for change in uterine leiomyoma size was set to 20% for clinical reasons.

2.5. Statistical analysis

The target number of patients was 600 for a 95% probability to detect at least one major ADR (e.g., pelvic inflammatory disease) with an incidence of 0.5%. The safety analysis set included all enrolled patients with confirmed LNG-IUS insertion. The effectiveness analysis set included patients in the safety analysis set who used the LNG-IUS for the first time for treatment of heavy menstrual bleeding/dysmenorrhea.

We calculated frequencies for categorical variables, and summary statistics (mean, standard deviation, range, median, and quartiles [Q]) for continuous variables. When applicable, we described the absolute value and the amount of change from baseline for continuous variables. We also conducted subgroup analyses (by purpose of LNG-IUS use and underlying condition) where necessary. Additional details are provided in the **Supplementary Methods**. We conducted the statistical analyses using SAS v9.4 (Windows version, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Of the 600 patients included, 595 patients met the safety analysis set criteria (Fig. 1); we excluded five patients whose clinical report forms confirming LNG-IUS insertion were unavailable. Two patients who had previously used LNG-IUS were excluded from the effectiveness analysis set (n=593). A total of 375 patients completed the study; the most common reason for discontinuation was loss to follow-up (152 patients). In total, 66 patients dropped out of the study for documented reasons; mainly, AEs, switching treat-

Table 1

Baseline demographics of patients in Japan receiving the LNG-IUS for treatment of heavy menstrual bleeding and/or dysmenorrhea between 2015 and 2019 (n = 595)

Age, years (median [Q1–Q3]) (n = 593)	42.0 (38.0–45.0)
BMI, kg/m ² (median [Q1–Q3]) (n = 503)	21.2 (19.6–23.7)
Childbirth history ^a	
Nullipara	30 (5.0)
Vaginal delivery	405 (68.1)
Caesarean section	89 (15.0)
Uterine cavity length, cm (median [Q1–Q3]) (n = 558)	7.3 (7.0–8.0)
Main indication for use of LNG-IUS ^a	
Heavy menstrual bleeding	469 (78.8)
Primary heavy menstrual bleeding	133 (28.4)
Secondary heavy menstrual bleeding ^b	336 (71.6)
Dysmenorrhea	377 (63.4)
Primary dysmenorrhea	118 (31.3)
Secondary dysmenorrhea ^b	259 (68.7)
History of gynecological surgery ^a	
None	406 (68.2)
Endometriosis	46 (24.7)
Uterine leiomyoma	37 (19.9)
Adenomyosis	6 (3.2)
Other	114 (61.3)
History of medication in the year prior to enrollment ^a	
None	328 (55.1)
Combined estrogen progestin agent (CHC)	107 (40.4)
Progestin-only agent	51 (19.5)
GnRH agonist	52 (19.6)
Estrogen-only agent	4 (1.5)
Danazol	1 (0.3)
Other	90 (34.0)

Data are n (%) unless otherwise indicated.

BMI, body mass index; CHC, combined hormonal contraceptive; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; Q, quartile.

^a Multiple selections are possible.

^b Includes adenomyosis, uterine leiomyoma, and endometriosis.

ments, lack of effectiveness, and “other” in 26, 25, 17, and 13 patients, respectively (Supplementary Table 1).

The median age was 42.0 years and median body mass index (BMI) was 21.2 kg/m² (Table 1). Within the safety analysis set, 235/595 (39.5%), 183/595 (30.8%), and 77/595 (12.9%) patients had adenomyosis, uterine leiomyomas, or endometriosis as underlying conditions, respectively (Supplementary Table 2). The LNG-IUS was indicated for secondary heavy menstrual bleeding (i.e., menorrhagia due to adenomyosis, uterine leiomyomas, endometriosis, or endometrial hyperplasia) in 336/469 (71.6%) and primary heavy menstrual bleeding in 133/469 (28.4%) patients. In 259/377 (68.7%) and 118/377 (31.3%) patients, LNG-IUS indications were secondary and primary dysmenorrhea, respectively. Among patients in our study with moderate or severe chronic pelvic pain prior to insertion of the LNG-IUS, 10/49 (20.4%) were diagnosed with endometriosis, whereas 7/21 (33.3%) with moderate or severe defecation pain had endometriosis.

3.2. Safety

The incidence of AEs was 63.2% (376 patients), and that of serious AEs was 0.5% (three patients, four events), including one event each of uterine leiomyoma, pelvic inflammatory disease, and ovarian cyst and ruptured ovarian cyst, which occurred in the same patient. The investigator judged the uterine leiomyoma to be unrelated to the LNG-IUS and the patient continued to use the device. The patient with pelvic inflammatory disease experienced pelvic inflammation approximately 12 weeks after insertion and was hospitalized and given antibiotics. Symptoms improved 1 week after onset, but the LNG-IUS was discontinued due to other AEs (non-

Table 2

Risk factors for LNG-IUS expulsion among patients in Japan treated with the LNG-IUS for heavy menstrual bleeding and/or dysmenorrhea between 2015 and 2019

Clinical features	Univariate analysis	Multivariate analysis adjusted	Multivariate analysis stepwise
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Expulsion			
BMI: ≥ 25 / < 25 kg/m ²	3.25 (1.71–6.19)	2.43 (1.20–4.89)	2.74 (1.38–5.46)
Adenomyosis: yes / no	2.23 (1.26–3.92)	2.34 (1.19–4.59)	2.34 (1.22–4.51)
Uterine cavity length: ≥ 8 / < 8 cm	3.08 (1.71–5.55)	3.08 (1.54–6.16)	3.44 (1.77–6.70)
Uterine leiomyoma: yes / no	2.09 (1.19–3.68)	1.32 (0.64–2.69)	
Age: ≥ 41 / < 41 years	1.86 (1.00–3.46)	1.93 (0.89–4.16)	

Multivariate analysis using logistic regression model was adjusted by BMI, presence of adenomyosis, uterine cavity length, presence of uterine leiomyomas, and age. BMI, presence of adenomyosis, and uterine cavity length were significant by a stepwise method with a significance level of 5%.

BMI, body mass index; CI, confidence interval; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio.

serious irregular uterine bleeding and pain). The patient with the ovarian cyst had the cyst before device insertion, but enlargement of the cyst was observed approximately 4 weeks post-insertion. The patient experienced severe abdominal pain approximately 5 months later and discontinued use as she elected to undergo a total hysterectomy.

The incidence of ADRs was 59.7% (355 patients) (Supplementary Table 3). Frequently reported ADRs were metrorrhagia 48.9%, procedural pain 14.1%, ovarian cyst 6.2%, pain 4.2%, lower abdominal pain 3.0%, and abdominal pain 2.7%. The incidence of serious ADRs was 0.3% (two patients, three events), which included the above-mentioned serious AEs of pelvic inflammatory disease, ovarian cyst and ruptured ovarian cyst, judged as related to the LNG-IUS.

3.2.1. Evaluation of LNG-IUS insertion and pain

A total of 71.1% of devices were inserted without additional procedures such as anesthesia or cervical dilators. Cervical dilators were needed in 23.7% of patients, and use of local anesthesia was documented in 0.7%. Investigators rated the insertion as “easy” in 94.8% of patients. Pain at insertion was reported in 20.3% of patients, some cases of which included abdominal pain or pain not related to the insertion procedure itself.

3.3. Clinical outcomes

Dysmenorrhea for all patients with available VAS data at 12 months ($n=117$) was reduced at 12 months (median [Q1–Q3] VAS score 1.0 [0.0–13.0]; Wilcoxon test, $p < 0.0001$) from 1 month post-insertion of the LNG-IUS compared with baseline (median VAS score 46.5 [13.0–68.0]) (Fig. 2A, Supplementary Table 4). Dysmenorrhea was also reduced in patients with primary heavy menstrual bleeding, primary dysmenorrhea, endometriosis, uterine leiomyoma, and adenomyosis from 1 month post-insertion of the LNG-IUS compared with baseline (Fig. 2B, Supplementary Table 4). Among patients with severe chronic pelvic pain before insertion (VAS score 70–100), a reduction in pain was observed (Fig. 3A), from a median VAS score of 75.5 (73.0–78.0) before insertion to 3.0 (0.0–14.0) at 12 months post-insertion. The median chronic pelvic pain VAS score of patients with endometriosis decreased from 19.5 (0.5–65.5) before insertion to 5.0 (0.0–14.0) at 12 months. Patients with defecation pain presented decreases in defecation pain at 1, 3, 6, and 12 months post-insertion (Fig. 3B, Supplementary Table 5). Patients with dyspareunia also presented decreases in dyspareunia at 1, 3, and 12 months post-insertion (Supplementary Table 5).

3.4. Additional analyses

3.4.1. Expulsion risk

The univariate and multivariate analyses examining risk factors for LNG-IUS expulsion are shown in Table 2. The cumulative incidence of LNG-IUS expulsions at 12 months after insertion was 8.7%. Risk

factors for expulsion were BMI ≥ 25 kg/m² (odds ratio [OR]: 2.43), adenomyosis (OR: 2.34), and uterine cavity length ≥ 8 cm (OR: 3.08).

3.4.2. Leiomyoma diameter and ultrasonography findings

Changes in largest leiomyoma diameter at 12 months are shown in Supplementary Table 6. The largest mean (standard deviation) diameter of ovarian cyst changed from 2.9 ± 1.6 cm ($n = 35$) before insertion to 3.3 ± 1.6 cm ($n = 12$) at 12 months post-insertion. Mean (standard deviation) endometrial thickness of adenomyosis was 7.7 ± 6.8 mm before insertion ($n = 152$) and 3.3 ± 2.2 mm ($n = 61$) at 12 months post-insertion.

4. Discussion

To our knowledge, this is the first large-scale, observational study reporting safety and clinical outcomes of the LNG-IUS for real-world treatment of heavy menstrual bleeding and dysmenorrhea in Japan. The safety data and clinical outcomes were consistent with those previously reported [18–20].

A previous study of a similar LNG-IUS device reported a 1-year cumulative expulsion rate of only 2.9% [21]; other research has found higher rates: 4.9% (after 6 cycles) [20], and 6.3% (after 1 year) [22]. Furthermore, a Korean study reported an overall 1-year cumulative expulsion rate of 7.9% (similar to that of our study, 8.7%), and the rate was significantly higher in patients with underlying disease such as uterine leiomyoma (14.5%) [23]. The differences in expulsion rates among studies is likely related to the characteristics of the study populations; studies in which patients use the LNG-IUS purely for contraceptive purposes are likely to report lower expulsion rates because they may exclude patients with underlying organic disease such as adenomyosis and uterine leiomyoma.

Obesity, dysmenorrhea, heavy menstrual bleeding, adenomyosis, and uterine leiomyoma are associated with higher risk of expulsion [23–26]. In this study, we used a BMI cut-off of 25 kg/m², which is classified as obese in Japan [27]. Differences in body composition between East Asians and other races have been found on a population level, as Asians typically have a higher body fat percentage than Caucasians with the same BMI [28]. Therefore, we consider the threshold of obesity in our study to be appropriate with respect to comparing expulsion risk with studies conducted in Western countries with a higher cut-off. A study conducted in the US found that the 36-month expulsion rate was higher in women with a BMI ≥ 30 kg/m² compared with non-obese women (hazard ratio=1.27, 95% confidence interval 1.02–1.60) [22]. Our data were consistent with this finding, showing that Japanese women with a BMI ≥ 25 kg/m² face higher risk of expulsion than non-obese women. Although an association of increased uterine cavity length with increased risk of LNG-IUS expulsion was reported among patients with abnormal uterine bleeding [29], this

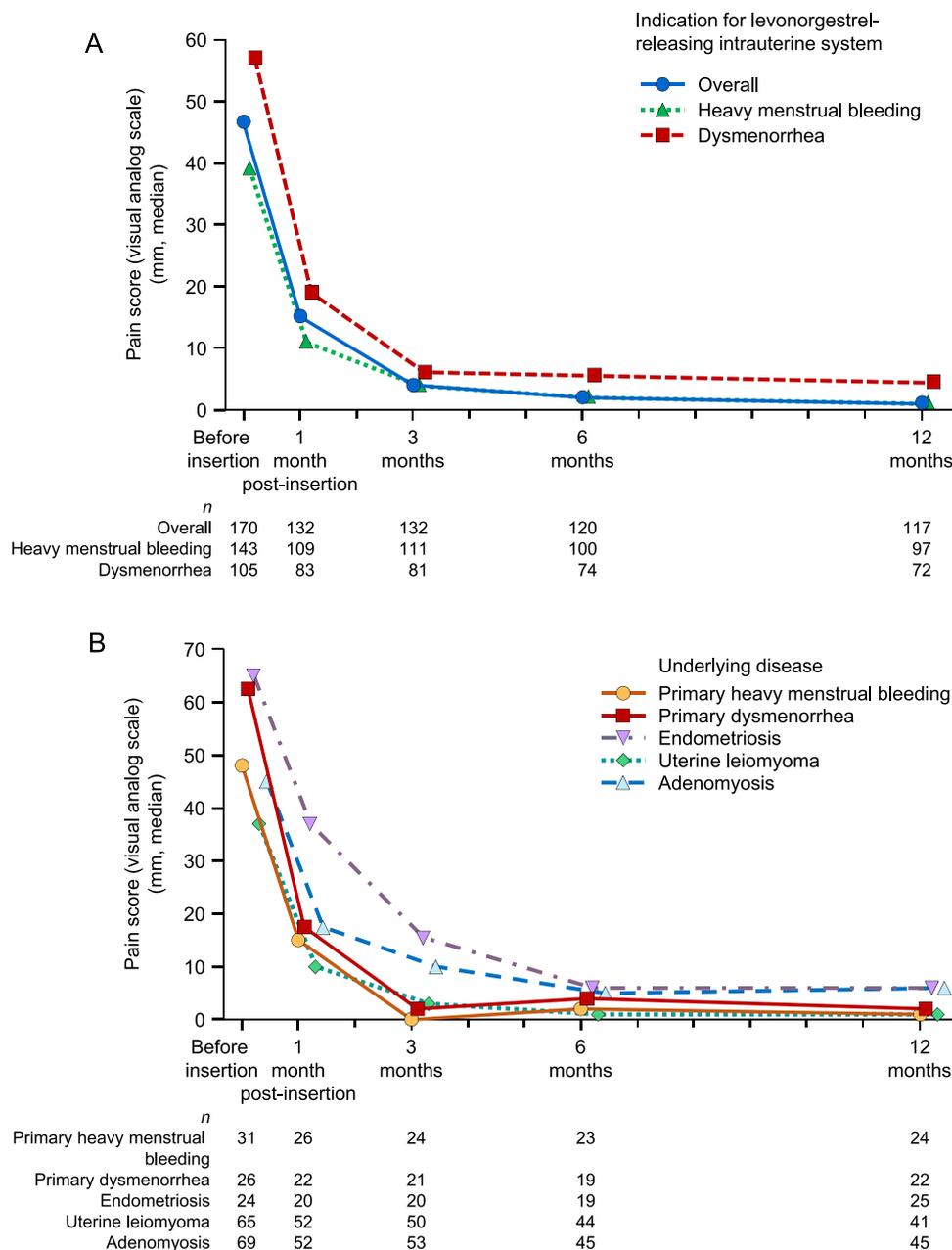


Fig. 2. Change in visual analog scale score (latest menstrual pain) experienced by patients with heavy menstrual bleeding and/or dysmenorrhea during 12-month treatment with the levonorgestrel-releasing intrauterine system in Japan between 2015 and 2019 (A) according to the indication for the levonorgestrel-releasing intrauterine system, and (B) by the underlying disease.

association was not confirmed in patients using an intrauterine device or the LNG-IUS for contraception [30]. Some guidelines recommend that only patients with a uterine depth of 6–10 cm should be considered appropriate candidates for intrauterine devices [31]. In our study, we found a higher risk of expulsion for uterine length ≥ 8 cm; however, it should be noted that the uterine cavity may have been larger in patients with adenomyosis or uterine leiomyomas. A previous study of adenomyosis patients reported that uterine size was large in the treatment discontinuation group including expulsion [32]. Taken together, these results suggest that uterine cavity length is a useful index for patients with heavy menstrual bleeding and dysmenorrhea at higher expulsion risk. Furthermore, patients at high risk of expulsion should be counseled about the risks prior to insertion, and be carefully monitored at follow-up visits.

Patients in this real-world study showed improvements in menstrual, defecation, and chronic pelvic pain, as well as dyspareunia, suggesting a wide range of pain-improvement effects. Dyspareunia and defecation pain are characteristic symptoms of endometriosis, and a recent systematic review revealed that nearly 50% of patients with chronic pelvic pain have endometriosis [33]. Patients with defecation pain have lower quality of life [34]; however, reports of the effects of the LNG-IUS on defecation pain are scarce.

Study limitations include the lack of control group, high risk of selection bias, high rate of loss to follow-up, and low response rates for certain items. Nevertheless, we did not observe any unexpected safety issues in the real-world use of the LNG-IUS in Japanese patients with heavy menstrual bleeding and dysmenorrhea. The strengths of our study included the large sample size, prospective design, and the similar workup for all patients. Our results clearly demonstrate the safety and effectiveness of the LNG-

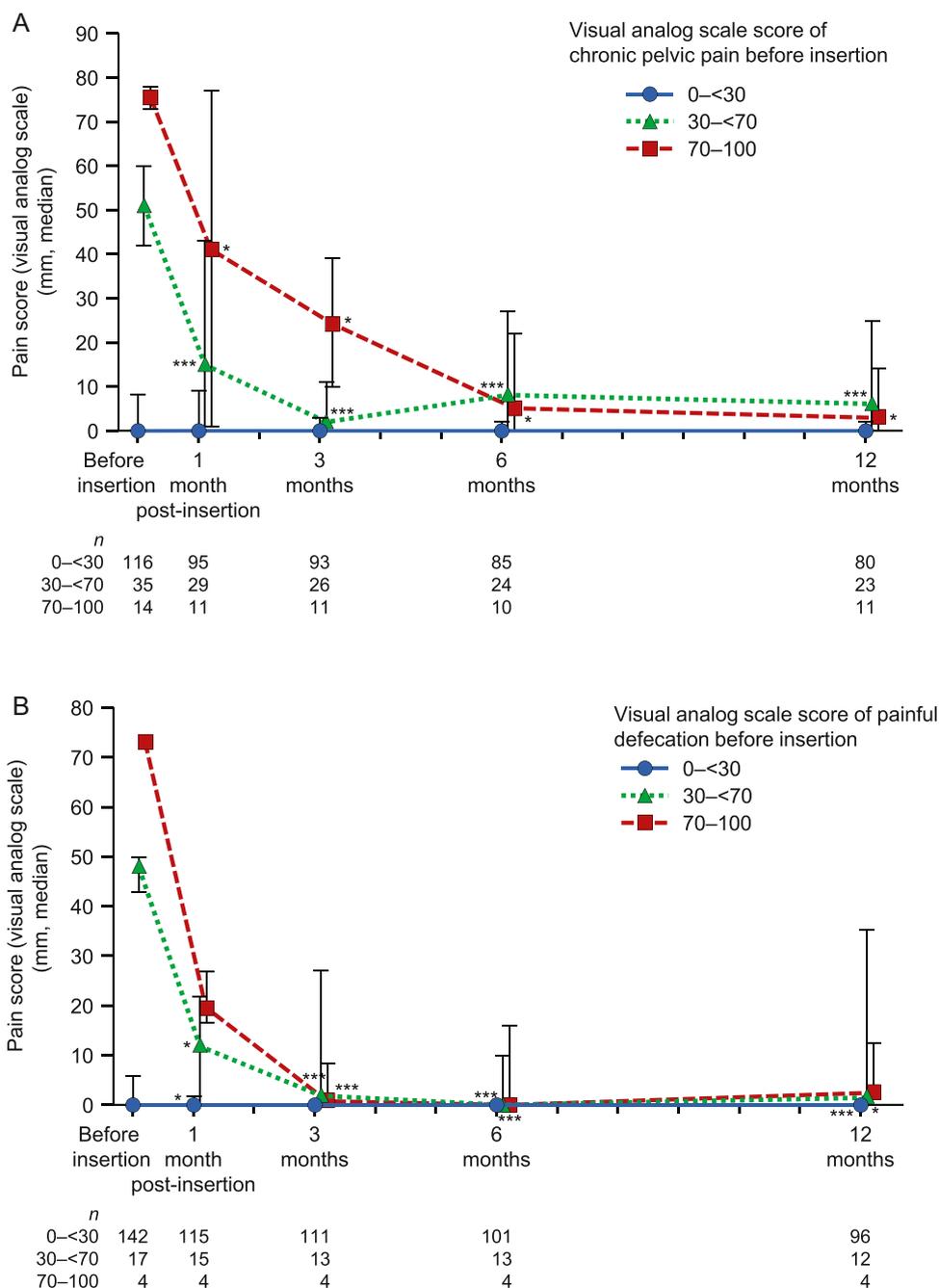


Fig. 3. Change in visual analog scale score experienced by patients with heavy menstrual bleeding and/or dysmenorrhea during 12-month treatment with the levonorgestrel-releasing intrauterine system in Japan between 2015 and 2019 by (A) patients who reported chronic pelvic pain, and (B) patients who reported painful defecation. Patients are grouped by baseline pain scores (before device insertion). Data are shown as median with interquartile range.

p* < 0.05, **p* < 0.001; Wilcoxon test, vs before insertion.

IUS for heavy menstrual bleeding and dysmenorrhea, particularly primary dysmenorrhea.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.contraception.2022.08.006](https://doi.org/10.1016/j.contraception.2022.08.006).

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