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Treatment of symptomatic adenomyosis with the levonorgestrel-releasing intrauterine system

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Abstract

Objective: To determine the long-term effects of using the levonorgestrel-releasing intrauterine system (LNG-IUS) to treat symptomatic adenomyosis.

Method: A prospective longitudinal study was conducted among 1100 women who received the LNG-IUS at a tertiary teaching hospital in China between December 10, 2006, and December 24, 2014. All participants had symptomatic adenomyosis (visual analogue scale [VAS] ≥7 and/or pictorial blood loss assessment chart [PBAC] score >100) diagnosed by transvaginal sonography. Follow-up was at 3, 6, 12, 24, 36, 48, and 60 months after LNG-IUS placement. The primary outcome was symptom relief. Secondary outcomes included LNG-IUS retention status; changes in uterine volume; serum levels of cancer antigen 125 (CA125); menstruation pattern; and adverse events.

Results: In all, 374 (33.7%) participants completed 60 months of LNG-IUS treatment. The VAS, verbal rating scale, PBAC score, hemoglobin level, uterine volume, and serum CA125 level all showed marked improvements at this time point when compared with baseline ($P<0.05$ for all comparisons). The cumulative retention rate of LNG-IUS was 56.2%. Changes in menstruation pattern at 60 months included amenorrhea (n=97, 25.9%) and shortened periods (n=82, 21.9%). The incidence of adverse events was <10% and not considered notable.

Conclusions: Long-term use of LNG-IUS was effective and acceptable for the treatment of symptomatic adenomyosis.

Registered at clinicaltrials.gov (NCT03027648).

KEYWORDS

Adenomyosis; Adverse events; Dysmenorrhea; Gonadotropin-releasing hormone agonist; Heavy menstrual bleeding; Levonorgestrel-releasing intrauterine system

1 | INTRODUCTION

Adenomyosis occurs when ectopic endometrium invades, implants, and proliferates in the uterine myometrium. The reported prevalence of adenomyosis varies from 5% to 70% owing to differences in diagnostic criteria, sampling methods, and observer bias.[1] Clinical manifestations of this condition include heavy menstrual bleeding (50%), dysmenorrhea (30%), and increased uterus size (60%); however, 35% of all patients with adenomyosis display no obvious symptoms.[2]

Adenomyosis has distinct imaging characteristics by transvaginal sonography (TVS) and magnetic resonance imaging (MRI), including globally enlarged uterus, myometrial anteroposterior asymmetry and interrupted junctional zone. Given its low cost relative to MRI, as well as high reproducibility, TVS is widely used for the diagnosis and follow-up of adenomyosis.[3]

Treatment protocols for adenomyosis include hysterectomy, adenomyomectomy, high-intensity focused ultrasonography, radiofrequency ablation, uterine artery embolization, and various medical

regimens that primarily involve progestin and a gonadotropin-releasing hormone agonist (GnRHa).[4] The levonorgestrel-releasing intrauterine system (LNG-IUS) provides sustained, minimally invasive, and effective symptom relief.[4] This approach also offers a practical option for women requiring fertility sparing management of adenomyosis. Nonetheless, most available studies of this method have considerable limitations, such as short follow-up periods and lack of data regarding LNG-IUS retention. To date, the longest follow-up of LNG-IUS for the treatment of adenomyosis was 36 months.[5]

The aim of the present study was to determine the effects of LNG-IUS on symptomatic adenomyosis and potential influencing factors over a 60-month follow-up period.

2 | MATERIALS AND METHODS

A prospective longitudinal study was conducted among women with symptomatic adenomyosis who received treatment with the LNG-IUS at Peking Union Medical College Hospital (PUMCH), Beijing, China, between December 10, 2006, and December 24, 2014. The present study was approved by the Institutional Review Board of PUMCH and registered at clinicaltrials.gov (NCT03027648). All participants provided consent before enrollment.

The participants attended PUMCH, which is a tertiary teaching hospital in an urban setting. The inclusion criteria for the present study were age 18–45 years; premenopausal status with regular frequency of menstruation; diagnosis of adenomyosis by TVS; severe dysmenorrhea and/or menorrhagia; endometrial biopsy performed to exclude endometrial hyperplasia, endometrial intraepithelial neoplasia, or carcinoma; uterine size less than 12 weeks of pregnancy by pelvic examination; no previous use of the LNG-IUS; and at least 12 months of follow-up data. Severe dysmenorrhea was defined as a visual analogue scale (VAS) score of at least 7.[6] The VAS is a subjective tool for the self-assessment of pain, with possible scores ranging from 0 (no pain) to 10 (most severe pain).[6] The four-point verbal rating scale (VRS) was used to record dysmenorrhea on a daily basis (0, no pain; 1, mild pain; 2, moderate pain; and 3, severe pain). A monthly score was then generated by totaling the daily VRS scores, which provided outcomes ranging from 0 (no pain) to 96 (maximum pain).[7] Menorrhagia was defined by a pictorial blood loss assessment chart (PBAC) score of greater than 100, as described by Higham et al.[8]

The exclusion criteria were current breast cancer or history of breast cancer; pathologic discoveries of malignancy (e.g. endometrial cancer); any contraindication to the placement of LNG-IUS; and previous surgery for adenomyosis.

Eligible patients were informed of the current research question and outcome measures via published pamphlets and explanations from the researchers (LL and SJ). They consented to participate in the present study only if they understood and accepted the information provided.

Among the first 30 patients enrolled, the mean VAS and PBAC scores at baseline were 7.9 ± 3.7 and 108.2 ± 38.3, respectively. With class I and class II error probabilities (α and β) of 0.05 and 0.10, from baseline to 60 months, at least 117 cases with severe dysmenorrhea were needed to achieve a mean decrease in VAS score of 1, and 125 cases with heavy menstrual bleeding were needed to achieve a mean decrease in PBAC score of 10, respectively. By December 15, 2016, an adequate number of cases for analysis had completed 60 months of treatment.

The LNG-IUS (Mirena; Bayer, Shanghai, China) contained 52 mg of levonorgestrel and was placed on the first to fifth day of menstruation. Before placement, long-acting GnRHa was provided for patients with large uterus size (equivalent to ≥10 weeks of pregnancy) or PBAC scores of greater than 200. The LNG-IUS was placed within 28 days after the last dose of GnRHa. Patients attended follow-up visits at 3, 6, 12, 24, 36, 48, and 60 months after placement of LNG-IUS in outpatient clinics at PUMCH attended by two researchers (LL and J. Leng). The primary and secondary outcomes were recorded prospectively at baseline and each phase of follow-up.

The primary outcome was symptom relief for severe dysmenorrhea (assessed by VAS and VRS) and heavy menstrual bleeding (assessed by PBAC). The secondary outcomes included changes in uterine volume; changes in serum levels of cancer antigen 125 (CA125; with reference <35 kU/L); LNG-IUS retention status (unplanned removal, expulsion, or retention); patient-reported changes in menstruation; and adverse events.

The criteria for diagnosis of adenomyosis by TVS were as previously described.[9,10] Briefly, TVS was performed in two perpendicular planes. Focal areas with poorly defined borders or abnormal echo texture were assessed. When these areas were present, the following criteria were evaluated: heterogeneity; increased or decreased areas of echogenicity; and myometrial cysts.[10] Adenomyosis was confirmed by the presence of at least two of these criteria. Examinations were performed by the experienced and skilled senior sonographer who had in-depth understanding of adenoymosis. Uterine volume was estimated by TVS according to the formula of Yaman et al.[11] During the present study period, several types of scanner were used to perform these examinations, which were not a mandatory part of the protocol.

Changes in menstruation reported by the participants included amenorrhea (lack of menstrual periods for ≥3 months); shortened periods (reduction of ≥2 days vs baseline); and prolonged menstruation (whole cycle ≥42 days). Irregular uterine bleeding was assessed on a daily basis as it is the most frequently reported adverse effect within the first 6 months after LNG-IUS placement.[12] Other self-reported adverse effects included lower abdominal pain; headache; breast swelling; acne; hirsutism; leg swelling; mood changes; ovarian cysts on TVS; body weight increase (≥5 kg/year); and abnormal vaginal discharge.

Measures of LNG-IUS status included ongoing retention; completing 60 months of treatment; unplanned removal of the device; and expulsion of the device. Unplanned removal was defined as removal of the device owing to adverse effects or dissatisfaction with the treatment effects. Expulsion was defined as unintentional loss of the device from the uterus.

The data were analyzed using SPSS version 19.0 (IBM, Armonk, NY, USA). Potential confounders were identified using

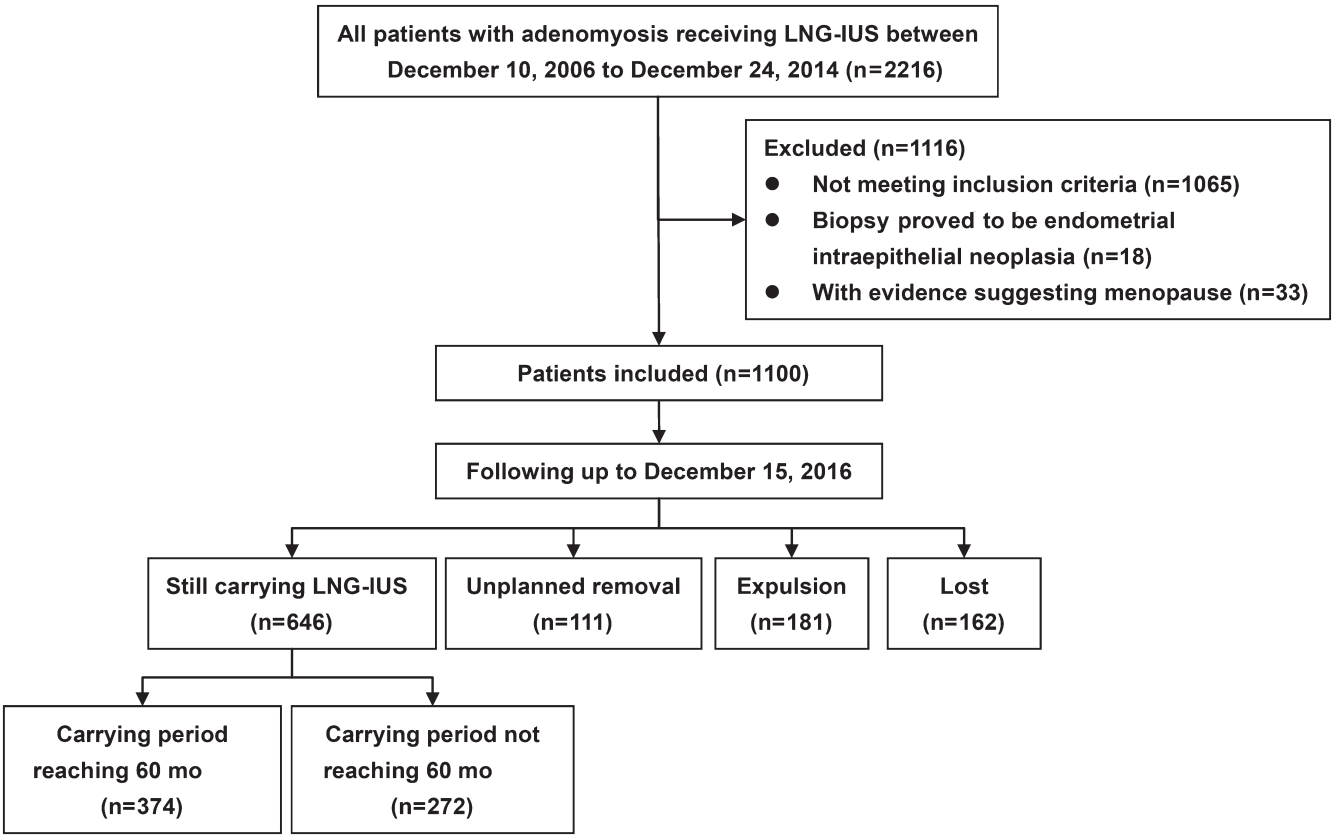

FIGURE 1 Flow diagram of the present study protocol. Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.

the nonparametric κ2 or Fisher exact tests for independent samples and *t* tests for paired samples. Multivariate logistic regression analysis of treatment effects included the following factors: age; adverse events; and changes in VRS, VAS, hemoglobin level, PBAC, CA125 level, and uterine size. Evaluation of the LNG-IUS retention status was performed using survival curve analysis and the Cox hazards model. A *P* value of less than 0.05 was considered to be statistically significant.

3 | RESULTS

Flow of participants through the present study is outlined in Figure 1. A total of 1100 eligible patients were included in the analysis, 640 (58.2%) with severe dysmenorrhea and 618 (56.2%) with heavy menstrual bleeding. After a median follow-up of 45 months (range 12–60 months), 272 (24.7%) participants still retained the LNG-IUS and 374 (34.0%) had completed 60 months of treatment.

The characteristics of the 1100 participants are presented in the Supplementary file S1 "Data for Sharing." The median age at LNG-IUS placement was 36 years (range 20–44 years). Most of the participants (n=1064, 96.7%) were Chinese Han and/or citizens of Beijing (n=1082, 98.4%).

Table 1 shows the main measurements of symptom relief after placement of the LNG-IUS. The mean VAS and VRS scores decreased before 48 months of follow-up among the 640 patients with severe dysmenorrhea at baseline ($P<0.05$ for all comparisons). After 48 months, the mean VAS and VRS scores continued to decrease; however, the observed change lacked statistical significance. After 24 months, none of the participants had a VAS score of 7 or higher. For the 230 patients with severe dysmenorrhea at baseline who completed 60 months of treatment, the mean decreases in VAS and VRS scores were 6.9 ± 1.5 (range 2–10) and 43.9 ± 20.5 (range −2 to 89), respectively.

As shown in Table 1, the mean PBAC scores and mean hemoglobin levels improved before 36 months of follow-up among the 618 patients with heavy menstrual bleeding at baseline ($P<0.05$ for all comparisons). After 36 months, the PBAC score and hemoglobin level continued to improve but this change lacked statistical significance. After 24 months, none of the participants had PBAC scores of greater than 100. For the 205 patients with heavy menstrual bleeding at baseline who completed 60 months of treatment, the mean decrease in PBAC score was 90.7 ± 41.0 (range 19–158) and the mean increase in hemoglobin level was 35.1 ± 13.9 g/L (range 13–71 g/L).

The mean uterine volume decreased from baseline among all 1100 participants after 12 months of follow-up ($P<0.05$ for all comparisons; Table 1) and continued to decrease thereafter, although this change was not statistically significant. The mean serum CA125 level decreased at all follow-up phases after 12 months ($P<0.05$ for all comparisons).

In the univariate analysis, relief of severe dysmenorrhea (VAS and VRS scores); relief of heavy menstrual bleeding (PBAC score and

TABLE 1 Outcomes after placement of the levonorgestrel-releasing intrauterine system.[a]

Outcome	Baseline	Follow-up time after placement of LNG-US, mo						
		3	6	12	24	36	48	60
Status of LNG-IUS								
Still carrying	NA	957 (87.0)	874 (79.4)	805 (73.2)	738 (67.1)	605 (60.0)	481 (52.6)	374 (45.1)
Unplanned removal	NA	28 (2.5)	57 (5.2)	69 (6.3)	85 (7.7)	94 (9.3)	102 (11.2)	111 (13.4)
Expulsion	NA	45 (4.1)	71 (6.5)	121 (11.0)	142 (12.9)	160 (15.9)	172 (18.8)	181 (21.9)
Lost	NA	70 (6.4)	98 (8.9)	105 (9.5)	135 (12.3)	149 (14.8)	159 (17.4)	162 (19.6)
Total no. of participants	NA	1100	1100	1100	1100	1008	914	828
Assessment of severe dysmenorrhea								
VAS[b]	8.1 ± 0.9 (n=640)	5.5 ± 2.4 (n=549)	4.6 ± 2.4 (n=502)	3.2 ± 2.1 (n=473)	2.2 ± 2.2 (n=429)	2.0 ± 1.8 (n=398)	1.9 ± 1.4 (n=330)	1.9 ± 1.1 (n=230)
VRS[b]	44.4 ± 20.7 (n=640)	16.4 ± 15.8 (n=514)	9.3 ± 9.0 (n=479)	6.7 ± 6.5 (n=451)	6.0 ± 7.5 (n=362)	5.7 ± 5.2 (n=330)	5.6 ± 4.1 (n=278)	5.6 ± 2.4 (n=176)
Assessment of menorrhagia								
PBAC score[b]	116.9 ± 34.1 (n=618)	93.5 ± 34.8 (n=543)	70.0 ± 33.2 (n=482)	67.3 ± 17.6 (n=434)	63.2 ± 12.7 (n=380)	62.8 ± 13.9 (n=366)	62.8 ± 7.7 (n=312)	61.9 ± 22.3 (n=205)
Hemoglobin level, g/L[b]	93.2 ± 13.9 (n=618)	100.9 ± 21.9 (n=488)	113.7 ± 9.0 (n=397)	115.5 ± 10.0 (n=380)	118.3 ± 6.7 (n=335)	119.1 ± 6.6 (n=305)	120.2 ± 5.9 (n=278)	120.8 ± 6.4 (n=158)
Other assessments								
Uterine volume, cm^{3}[b]	86 ± 53 (n=1100)	85 ± 54 (n=332)	85 ± 50 (n=252)	84 ± 43 (n=230)	81 ± 42 (n=210)	71 ± 45 (n=198)	70 ± 50 (n=164)	69 ± 42 (n=146)
CA125, kU/L)[b]	32.8 ± 19.5 (n=1100)	32.2 ± 13.8 (n=430)	28.4 ± 10.2 (n=421)	28.1 ± 14.3 (n=388)	22.7 ± 9.5 (n=340)	19.4 ± 7.1 (n=305)	16.7 ± 8.1 (n=225)	13.6 ± 4.2 (n=146)

Abbreviations: CA125, cancer antigen 125; LNG-IUS, levonorgestrel-releasing intrauterine system; NA, not applicable; PBAC, pictorial blood loss assessment chart; VAS, visual analog scale; VRS, verbal rating scale.
[a]Values are given as number (percentage) or mean ± standard deviation, unless indicated otherwise.
[b]Values are given as mean ± standard deviation (number of cases).

TABLE 2 Menstruation patterns and adverse events after placement of the levonorgestrel-releasing intrauterine system.[a,b]

	Follow-up time after placement of LNG-US, mo						
Outcome	**3 (n=957)**	**6 (n=874)**	**12 (n=805)**	**24 (n=738)**	**36 (n=605)**	**48 (n=481)**	**60 (n=374)**
Changes of menstruation patterns	124 (13.0)	175 (20.0)	172 (21.4)	177 (24.0)	175 (28.9)	207 (43.0)	187 (50.0)
Amenorrhea	0 (0.0)	52 (5.9)	56 (7.0)	74 (10.0)	97 (16.0)	106 (22.0)	97 (25.9)
Shortened menstrual periods	29 (3.0)	44 (5.0)	55 (6.8)	66 (8.9)	60 (9.9)	91 (18.9)	82 (21.9)
Other	86 (9.0)	79 (9.0)	61 (7.6)	37 (5.0)	18 (3.0)	10 (2.1)	11 (2.9)
Irregular bleeding	413 (43.2)	385 (44.1)	193 (24.0)	81 (11.0)	30 (5.0)	19 (4.0)	11 (2.9)
Other adverse events	191 (20.0)	114 (13.0)	177 (22.0)	96 (13.0)	54 (8.9)	53 (11.0)	30 (8.0)
Headache	11 (1.1)	5 (0.6)	7 (0.9)	5 (0.7)	2 (0.3)	5 (1.0)	1 (0.3)
Breast swelling	14 (1.5)	6 (0.7)	11 (1.4)	15 (2.0)	7 (1.2)	6 (1.2)	2 (0.5)
Acne	30 (3.1)	8 (0.9)	9 (1.1)	12 (1.6)	3 (0.5)	3 (0.6)	3 (0.8)
Hirsutism	6 (0.6)	5 (0.6)	7 (0.9)	7 (0.9)	5 (0.8)	7 (1.5)	4 (1.1)
Leg swelling	6 (0.6)	3 (0.3)	5 (0.6)	2 (0.3)	2 (0.3)	2 (0.4)	2 (0.5)
Lower abdominal pain	88 (9.2)	44 (5.0)	36 (4.5)	11 (1.5)	5 (0.8)	2 (0.4)	0 (0.0)
Mood changes	6 (0.6)	7 (0.8)	12 (1.5)	5 (0.7)	2 (0.3)	2 (0.4)	0 (0.0)
Formation of ovarian cyst	16 (1.7)	24 (2.7)	11 (1.4)	8 (1.1)	7 (1.2)	1 (0.2)	3 (0.8)
Body weight increase ≥5 kg/y	0 (0.0)	0 (0.0)	62 (7.7)	24 (3.3)	18 (3.0)	24 (5.0)	15 (4.0)
Abnormal vaginal discharge	14 (1.5)	12 (1.4)	17 (2.1)	7 (0.9)	3 (0.5)	2 (0.4)	0 (0.0)

Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Values are given as number (percentage).
[b]All outcomes were self-reported by the participants.

hemoglobin level); changes in uterine volume; and serum CA125 level showed no statistically significant relationship with age or any clinical factors at baseline or with any changes in menstruation or onset of adverse events at each phase of follow-up.

Table 1 also outlines the retention status of LNG-IUS during follow-up. Excluding the lost cases without known carrying status, the cumulative retention rates ranged from 805 of 995 (80.9%) participants at 12 months to 374 of 666 (56.2%) at 60 months. In all 828 cases at 60 months, there were 111 (13.4%), 181 (21.8%), and 162 (19.6%) cases of unplanned removal, expulsion, and loss to follow-up. Retention status displayed no statistically significant relationship with any of the epidemiologic or clinical factors at baseline or with any changes in menstruation or the onset adverse events at each phase of follow-up, except for pretreatment with GnRHa (P=0.001).

Among the 111 patients with unplanned removal of LNG-IUS, the reported causes included changes in menstruation or onset of adverse events (n=98, 88.3%); dissatisfaction with the treatment effects (n=58, 52.2%); and unspecified reasons (n=11, 9.9%).

For the group with expulsion of the LNG-IUS (n=181), 55 (30.4%) participants selected to undergo replacement of this device. By contrast, 106 (58.6%) participants selected another therapy or observation, whereas 20 (11.0%) made no specific choice.

Menstruation pattern and adverse events are listed in Table 2. At 60 months of follow-up, amenorrhea (97/374, 25.9%) and shortened menstrual periods (82/374, 21.9%) were the most common patterns of menstruation. Irregular bleeding decreased from 385 of 874 (44.0%) participants at 6 months to 11 of 374 (2.9%) participants at 60 months. Other adverse events decreased from 177 of 805 (22.0%) participants at 12 months to 30 of 374 (8.0%) participants at 60 months.

In all 666 with known carrying status, 252 (37.8%) patients were followed-up for at least 6 months after unplanned LNG-IUS removal, LNG-IUS expulsion, or completing 60 months of treatment. Except for 45 (17.8%) patients who underwent hysterectomy, most cases of amenorrhea (57/66, 86.4%), lower abdominal pain (45/50, 90.0%), and irregular bleeding (98/99, 99.0%) had disappeared. Three (0.4%) patients did not resume menstruation and the results of sex-hormone testing suggested the onset of menopause.

A total of 378 (34.4%) participants accepted GnRHa pretreatment before LNG-IUS placement. The GnRHa regimens included leuprorelin (n=178, 47.1%), triptorelin (n=107, 28.3%), and goserelin (n=93, 24.6%). The median injection times of GnRHa was 3 (range 1–5). Compared with the patients not using GnRHa, those who accepted GnRHa pretreatment had similar epidemiologic and clinical characteristics at baseline. However, differences were seen at baseline for the pretreatment versus no pretreatment groups with regard to mean PBAC score (126.1 vs 115.3; P<0.001); mean VAS score (5.9 vs 5.5; P=0.017); and mean uterine volume (89.1 vs 82.8 mL; P=0.016). At each phase of follow-up, there were no statistically significant

between-group differences in any of the variables assessed. For patients with and without GnRHa pretreatment, the 60-month cumulative retention rates were 178 of 280 (63.6%) and 196 of 386 (50.6%; *P*=0.001). After adjustment of PBAC scores, VAS scores, and uterine volume at baseline, pretreatment with GnRHa remained an independent factor for retention of LNG-IUS (hazard ratio 0.6, 95% confidence interval 0.4–0.8; *P*<0.001). The category of GnRHa regimen did not influence the effect of pretreatment (*P*=0.357).

4 | DISCUSSION

The present study found that use of the LNG-IUS for treatment of patients with adenomyosis achieved rapid and persistent relief of pain and/or heavy bleeding. This observation was in agreement with a previous report.[13] The effects observed in the present study were not altered by changes in menstruation pattern or the onset of adverse events during follow-up. In addition, the 60-month cumulative LNG-IUS retention rate (56.2%) was similar to the 36-month rate reported by Lockhat et al.[14] The retention rate was 45.2% if case lost to follow-up were included.

Factors that determine the treatment effects of LNG-IUS are unclear. In the present study, neither epidemiologic nor clinical factors at the baseline or during follow-up had an impact on symptom relief. A previous study found that GnRHa markedly reduced uterine volumes.[15] Furthermore, uterine volumes were related to LNG-IUS expulsion rates.[16,17] Reduced lymphangiogenesis might be one mechanism by which LNG-IUS reduces adenomyosis-related symptoms.[4] In the present study, pretreatment with GnRHa did not improve treatment results but it did reduce LNG-IUS expulsion by 40%. Expulsion of LNG-IUS wastes healthcare resources and increases anxiety among patients; therefore, it seems reasonable to pretreat selected patients with GnRHa to help control the symptoms of heavy menstrual bleeding. That said, the adverse effects of GnRHa (e.g. menopausal symptoms and risk of osteoporosis) should be addressed by prevention or treatment, as appropriate. The cost–benefit profile of GnRHa pretreatment also requires evaluation.

The primary concerns of patients already using LNG-IUS to manage adenomyosis—as well as those contemplating such intervention—are focused on the adverse effects and safety of both hormonal and nonhormonal contraceptive methods; however, few data are available regarding the benefits that these methods offer beyond contraception.[18] Adverse events associated with LNG-IUS reflect both the local and systemic effects of progestin, which are probably the main drivers of unplanned LNG-IUS removal by patients and their dissatisfaction with the device in previous reports,[10] as well as in the present study. However, the current findings suggested that there were no statistically significant differences between the changes in menstruation or adverse events reported by patients before unplanned removals of LNG-IUS. Individualized and detailed patient education might therefore reduce rates of unplanned removal.

Several points must be clarified regarding the design of the present study. Patients who had previously undergone surgery for adenomyosis were excluded, which would have markedly interfered with the assessment of symptom relief.[19,20] Well-designed comparative studies are urgently needed to examine the effects arising from LNG-IUS interventions combined with uterine-sparing operations. For patients with unplanned removal or expulsion of LNG-IUS, detailed follow-up about symptom relief and further treatment plans will be imperative for future studies.

The present study used TVS as a diagnostic tool for adenomyosis for several reasons. First, when compared with MRI, TVS is convenient for use in outpatient clinics and is of low cost, which is extremely important among low-resource countries (e.g. China) and for patient compliance and follow-up. Second, despite some controversy questioning the accuracy of TVS,[21] the use of TVS as a diagnostic tool for adenomyosis has the advantage of universal agreement and criteria.[22] Third, TVS is comparable to MRI with regard to diagnostic accuracy.[23]

The present study design did not incorporate other tools for evaluating adenomyosis (e.g. MRI or histopathology), which might have given rise to misdiagnosis. Additional analysis is needed to clarify the role of diagnostic methods in clinical trials of adenomyosis, which had a more specific description in the consensus opinion from the Morphological Uterus Sonographic Assessment group.[22] The terms and definitions described in the consensus could form the basis for prospective studies to predict the risk of different myometrial pathologies (adenomyosis included), based on their ultrasound appearance, and thus should be relevant for the clinician in daily practice and for clinical research.[22] Furthermore, the present study did not consider economics or quality of life. Although most LNG-IUS placement and follow-up was performed in outpatient clinics, the direct and indirect costs of LNG-IUS treatment and managing adverse events demand serious consideration. Some investigators have noted problems with quality of life during LNG-IUS treatment,[24,25] which should be assessed in future controlled studies.

In conclusion, use of LNG-IUS for up to 60 months proved effective and tolerable for relieving dysmenorrhea and heavy menstrual bleeding caused by adenomyosis. Pretreatment with GnRHa markedly reduced LNG-IUS expulsion. However, symptom relief was not related to any epidemiologic or clinical factors at baseline or to any changes in menstruation pattern or adverse events at each phase of follow-up.

AUTHOR CONTRIBUTIONS

LL and J Leng contributed to the acquisition, analysis, and interpretation of the data, as well as revising the manuscript critically for important intellectual content. All authors contributed to the study conception, study design, and writing the manuscript. All authors provided final approval for the submitted manuscript and agreed to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA SHARING STATEMENT

The data for all patients enrolled in the present study can be accessed by all interested parties as Supplementary file S1 "Data for sharing".

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The diagnostic criteria of adenomyosis by ultrasound.

Data S1. Data of all patients for sharing.