Effect of modified levonorgestrel-releasing intrauterine system in human adenomyosis with heavy menstrual bleeding

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Abstract

Aim: The levonorgestrel-releasing intrauterine (LNG-IUS) system is an effective primary treatment for adenomyosis; however, it has high expulsion rates. We aimed to modify the system—allowing affixion to the myometrium—and evaluate the expulsion rate, effectiveness, and side effects in patients with adenomyosis and heavy menstrual bleeding.

Methods: This study included patients with adenomyosis and heavy menstrual bleeding who underwent implantation of: a modified LNG-IUS (experimental group, n = 47); and the original system after gonadotropin-releasing hormone agonist treatment (control group, n = 47), between January 2014 and April 2016.

Results: In the experimental group, two device expulsions occurred 12–18 months postimplantation. In the remaining 45 patients, the system was safely removed after the 60-month validity period, and no extraneous device movement or infection occurred. In the control group, downward displacement and expulsion of the device occurred in eight (17%) patients within 60 months. The 5-year total expulsion rates were 4.3% and 17.0% in the experimental and control groups, respectively (p = 0.045). There were significant changes in the pretreatment severity of dysmenorrhea, menstrual volume, uterine volume (cm3), and hemoglobin level in each group compared with after 1 year (p < 0.01 in all groups). The severity of dysmenorrhea, menstrual volume, uterine volume, and hemoglobin level after 1 year were similar between the two groups (p > 0.05 in all groups).

Conclusions: Use of the modified LNG-IUS is a safe, cost-effective, and simple method for reducing the downward movement and expulsion rate in patients with adenomyosis and heavy menstrual bleeding.

Key words: diffuse adenomyosis, heavy menstrual bleeding, hormone-releasing intrauterine devices, IUD expulsion, levonorgestrel.

Introduction

Adenomyosis is a common gynecological condition that adversely affects patients’ quality of life; its main symptoms are dysmenorrhea, heavy menstrual bleeding (HMB), and an enlarged uterus. Treatment for adenomyosis includes medication, local and systemic hormonal therapies, and surgical intervention. Local hormonal therapies include placement of a levonorgestrel-releasing intrauterine system (LNG-IUS).
that can significantly relieve dysmenorrhea and HMB, as well as preserve fertility. Moreover, systemic side effects are minimal due to the localized delivery and low concentration of LNG in the uterus and blood, respectively. However, its biggest disadvantage is the high downward displacement/expulsion rates (range, 9.1%–37.5%). The 2015 Chinese guidelines and 2020 Chinese Consensus on the use of LNG-IUS indicate that 3–6 gonadotropin-releasing hormone agonist (GnRH-a) injections, administered before LNG-IUS insertion in patients with more diffuse adenomyosis, can reduce the downward displacement or expulsion rate. Nevertheless, some studies found that the downward movement and expulsion rates still reached 13.9% and 14.3%, respectively; therefore, modification of the LNG-IUS is needed to improve its inherent design defects and reduce the device expulsion rate.

The LNG-IUS in this study was modified, allowing affixion to the myometrium and thus maintaining its normal position in the uterus. This modified LNG-IUS was inserted in patients with adenomyosis and HMB. We aimed to investigate its 5-year downward displacement and expulsion rates, side effects, and effectiveness, as well as compare the data with that of the original device.

Methods

Subjects

The experimental group included 47 patients with adenomyosis and HMB who received the modified LNG-IUS at the Department of Obstetrics and Gynecology of Hainan Provincial People’s Hospital between January 2014 and April 2016. Forty-seven patients, who received GnRH-a and the original LNG-IUS, constituted the control group (according to the 2015 Chinese Endometriosis Guidelines, it is recommended that patients with a wide uterine cavity or larger uterus should receive 3–6 GnRH-a injections as pretreatment before placement of the LNG-IUS to reduce downward movement and expulsion rates). All patients were premenopausal women with regular menstrual cycles who had exhibited HMB for at least 18 months. All patients provided written informed consent for device placement. This study was approved by the Ethics Committee of Hainan Provincial People’s Hospital and conforms to the provisions of the Declaration of Helsinki.

Patients were included in the experimental group if they had adenomyosis with HMB, the thickness of the muscle layer of the fundus was ≥12 mm, they expressed a desire to preserve their uterus, and they did not consent to any other medical or surgical interventions. We excluded patients with a thin myometrium, those who could not be followed up, those with contraindications to the LNG-IUS, and those with severe coagulopathy. In addition, those with congenital valvular heart disease; vaginal, cervical, or uterine congenital malformations; known or suspected uterine or cervical malignant tumors; acute pelvic inflammatory disease; or a uterus larger than that of a 12-week-pregnant woman, were excluded.

The inclusion criteria for the control group were adenomyosis with menorrhagia, a uterine cavity depth ≥9 cm, and having received GnRH-a injections before LNG-IUS placement. The duration of GnRH-a administration was about 8–16 weeks, consisting of 2–4 injections at 4-week intervals. The exclusion criteria of the experimental group were also applied to the control group.

Before LNG-IUS implantation, each woman underwent pelvic examination, transvaginal ultrasound, endometrial biopsy, and cervical smears. Two patients (4.3%) had adenomyosis complicated by a submucous myoma (diameter < 30 mm) and were included in the experimental group. Follow-up was performed until March 2021.

Definition of dysmenorrhea and HMB degree

The degree of dysmenorrhea was evaluated using the verbal rating scale (VRS), and scored as follows: 0, no pain; 1, tolerable pain, no disturbance to daily life or sleep; 2, obvious pain that cannot be tolerated (requiring analgesics and sleep disturbance present); and 3, severe pain and cannot be tolerated (requiring analgesics and severe sleep disturbance that may be accompanied by autonomic disorders or passive posture). Menstrual volume was scored using the original pictorial blood assessment chart (PBAC) as previously reported. According to the Higham criteria, a PBAC score > 100 indicates menstrual flow >80 mL, classified as HMB.

LNG-IUS modification and placement method

The structure of the frameless fixed intrauterine device (IUD) (GyneFix; Tianjin Medic Medical Equipment Co., Ltd., Tianjin, China) is shown in Figure 1a. A 1-mm anchoring knot (GyneFix knot) was tied to a polypropylene suture (0 PROLENE® Suture; Johnson &
Johnson Medical Devices, California, USA) using a hemostat. The loop at the tail end of the LNG-IUS’s vertical stem was tied onto the polypropylene suture (2 cm from the anchoring knot), and the cross-arm of the LNG-IUS was removed. The syringe-like plunger of the frameless fixed IUD was hooked onto the anchoring knot; the tail strings were fixed into the notch of the plunger, and an LNG-IUS sleeve—cut to the same length as that of the frameless fixed IUD sleeve—was used to encase the modified LNG-IUS. Toward the end of the menstrual cycle, the anchoring knot was pushed into the fundal muscle layer (to a depth of 1 cm) using a syringe-like plunger; this was performed such that the drug-loaded tubing of the LNG-IUS was suspended in an inverted position within the uterine cavity, with the tail strings extruding 2 cm through the cervical canal. After removing the speculum from the vagina, uterine massage was performed to securely anchor the knot into the muscle layer. Figures 1b–d (utility model patent number: 201822176433.9), and Figure 2 show the original LNG-IUS, a schematic diagram of the modified LNG-IUS anchored to the uterus, and a schematic diagram of the anchoring knot, respectively. After placement, routine oral antibiotics and an anti-inflammatory rectal suppository (Kangfu anti-inflammatory suppository; Sunflower Pharmaceutical Group Co., Ltd., Heilongjiang, China) were administered for 3 and 7 days, respectively, to prevent infection. Regular follow-up B-ultrasounds were performed 1, 3, 6, and 12 months after implantation.

**Statistical analysis**

The effectiveness, expulsion rate, and side effects of the systems were compared between the experimental and control groups. Variables were first subjected to normality tests (one-sample Kolmogorov–Smirnov test). The PBAC score, VRS score, uterine volume, and hemoglobin (HB) level at the baseline and 1-year posttreatment were compared using paired t-tests between the experimental and control groups. Various indicators were compared between the two groups using the independent sample t-test. All data were expressed as mean ± SD. The number of downward movements/expulsions of the LNG-IUS between the two groups was compared using the Chi-squared test. Statistical analysis was performed using SPSS 11.0 software (SPSS Inc., Illinois, USA).

**Results**

**Patients’ baseline characteristics**

Ninety-four women (experimental group: n = 47; control group: n = 47) aged 33–49 years participated in the study. Before treatment, no significant differences...
TABLE 1 Clinical profiles of patients at baseline

|                     | Modified LNG-IUS group (n = 47) | GnRH + original LNG-IUS group (n = 47) | p-value |
|---------------------|----------------------------------|---------------------------------------|---------|
| Age (years)         | 40.9 ± 3.6 (33.0–49.0)           | 41.4 ± 3.2 (35.0–47.0)                | 0.513   |
| BMI (kg/m²)         | 22.1 ± 1.7 (19.2–26.8)           | 22.6 ± 1.4 (20.2–25.1)                | 0.171   |
| Dysmenorrhea VRS score | 2.4 ± 0.9 (0–3)              | 2.5 ± 0.9 (0–3)                      | 0.815   |
| Menstrual volume score (PBAC) | 501.1 ± 202.8 (120–830) | 450.2 ± 210.7 (110–855)            | 0.307   |
| Uterine volume (cm³) | 221.8 ± 76.3 (412.2–79.0)       | 213.0 ± 65.9 (389.2–110.4)            | 0.699   |
| Hemoglobin (g/dL)   | 8.3 ± 1.5 (5.0–10.8)            | 8.8 ± 1.8 (5.4–13.8)                  | 0.157   |
| Uterine cavity depth (cm) | 10.5 ± 1.1 (8.5–13)          | 10.1 ± 1.0 (9–12)                     | 0.110   |

Note: Calculation of uterine volume, cm³ = length × thickness × width × 0.5236. All results are expressed as mean ± SD. and Abbreviations: BMI, body mass index; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial blood assessment chart; VRS, verbal rating scale.

were noted regarding age, body mass index, degree of dysmenorrhea, degree of HMB, uterine volume, HB level, or uterine cavity depth between the groups. All patients had HMB, 63.8% had severe dysmenorrhea, 24.5% had moderate dysmenorrhea, and 11.7% had no or mild dysmenorrhea.

In the experimental group, 48.9% of the patients had been previously treated with the original LNG-IUS; however, they had a history of 1–4 downward movements or expulsions. Subsequently, the modified LNG-IUS was implanted; of these cases, 19 exhibited repeated (≥2) expulsions or downward movements. The longest duration (mean ± SD) that the LNG-IUS remained in the correct intrauterine position was 11.58 ± 6.22 months (range, 3–25 months). In nine of the 19 patients with repeated downward movements or expulsions, the LNG-IUS was manually repositioned under B-ultrasound monitoring. Among those nine patients, five, three, and one underwent position restoration once, twice, and three times, respectively (the shortest time that the device remained in the correct position was 1 week). The uterine cavity depth in the control group was >9 cm, and the LNG-IUS was placed after 2 months; the modified LNG-IUS was also expelled, with excessive menstruation and abdominal pain, 18 months after implantation. The expulsion rate over the 5-year validity period of the device was 4.3%. In the remaining 45 cases, the LNG-IUS was safely removed after the 60-month validity period, with no downward movement or expulsion; no cases of extrauterine device migration were noted. In the control group, there were eight cases of expulsion within the 5-year period, with an expulsion rate of 17.0% (chi-squared = 4.029, p = 0.045; Table 2). No uterine perforation or infection occurred in either group.

### Comparison of indicators between the two groups after 12 months of treatment

The VRS score, PBAC score, uterine volume, and HB level after 12 months of treatment were compared between the two groups. No significant differences

TABLE 2 Comparison of expulsion and downward movement rates between the two groups

|                  | Modified LNG-IUS group (n = 47) | GnRH-a + original LNG-IUS group (n = 47) |
|------------------|----------------------------------|----------------------------------------|
| 6 months         | 0                                | 0                                      |
| 6–12 months      | 1                                | 5                                      |
| 12–24 months     | 1                                | 1                                      |
| 24–36 months     | 0                                | 1                                      |
| 36–60 months     | 0                                | 1                                      |
| Total expulsion rate and downward movement rate at 60 months | 2 (4.3%) | 8 (17.0%) |

Note: Pearson’s chi-square = 4.029, p = 0.045. and Abbreviations: GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system.

### Downward movement or expulsion

Among the 47 patients in the experimental group, two experienced device expulsion associated with menstrual blood loss, abdominal pain, and a sudden increase in menstruation at 12 and 18 months after LNG-IUS implantation, respectively. One of the two patients received four GnRH-a injections, the original LNG-IUS was entirely discharged after two placements. Then the modified LNG-IUS was inserted; however, this was also expelled 12 months later, with abdominal pain and menstrual bleeding. In another case, the original LNG-IUS was expelled after 2 months; the modified LNG-IUS was also expelled, with excessive menstruation and abdominal pain, 18 months after implantation. The expulsion rate over the 5-year validity period of the device was 4.3%. In the remaining 45 cases, the LNG-IUS was safely removed after the 60-month validity period, with no downward movement or expulsion; no cases of extrauterine device migration were noted. In the control group, there were eight cases of expulsion within the 5-year period, with an expulsion rate of 17.0% (chi-squared = 4.029, p = 0.045; Table 2). No uterine perforation or infection occurred in either group.
were observed in these parameters 1 year after LNG-IUS placement ($p > 0.05$ in all groups; Table 3).

**Comparison of indicators before and after treatment in each group**

The VRS score, PBAC score, uterine volume, and HB level in the experimental and control groups before treatment and 1 year after placement are shown in Table 4. In both groups, significant differences were noted in all parameters between pretreatment and 1 year after placement (all $p < 0.01$).

**Intraoperative placement of the modified LNG-IUS in the experimental group**

All 47 patients in the experimental group reported lower abdominal pain and discomfort within 1–5 days postimplantation of the modified LNG-IUS. They received oral anti-inflammatory drugs and a rectal anti-inflammatory suppository, and their symptoms disappeared within 5 days. In four patients, the gynecologist felt that the uterine muscles were loose and had no resistance when the anchor knot was implanted. In these cases, implantation was unsuccessful during the first attempt; the anchor knot was removed when the needle was inserted and exited the needle pusher. A second attempt was made by slightly adjusting the injection angle, leading to successful anchoring. In two of these four cases, the modified LNG-IUS was expelled with menstrual blood, abdominal pain, and suddenly increased menstruation after 12 and 18 months, respectively.

In three of the 47 cases in the experimental group, transient abdominal pain and increased vaginal bleeding occurred a few months after inserting the modified LNG-IUS; B-ultrasound was performed the day after bleeding, which confirmed the correct position of the modified fixed LNG-IUS. The symptoms resolved spontaneously in all these cases.

**LNG-IUS removal in the experimental group**

In 45 of the 47 patients in the experimental group, the modified LNG-IUS remained correctly positioned in the uterus 60 months after placement. The modified IUS was completely removed in all patients by pulling out the tail string, without residue or breakage.

**Medical expenses**

GnRH-a injections were not required in the experimental group, the control group required 2–4 injections before LNG-IUS placement. The cost was therefore significantly reduced in the experimental group ($p < 0.01$). During the study, the pretreatment cost in the experimental group was $0, whereas the pretreatment cost in the control group (injection of GnRH-a) was $684.8 \pm 145.5$ ($484$–$968$).

**TABLE 3** Comparison of VRS, PBAC, uterine volume, and hemoglobin between the two groups after 12 months of treatment

| Indicator                                      | Modified LNG-IUS group (n = 46)       | GnRH-a + original LNG-IUS group (n = 42) | $p$-value |
|------------------------------------------------|--------------------------------------|-----------------------------------------|-----------|
| VRS                                           | 0.07 ± 0.26 (0–1)                    | 0.07 ± 0.26 (0–1)                       | 0.238     |
| PBAC                                          | 23.7 ± 15.6 (0–60)                   | 23.7 ± 15.6 (0–60)                      | 0.843     |
| Uterine volume (cm$^3$)                       | 180.3 ± 64.7 (296.8–80.2)            | 178.3 ± 64.7 (296.8–80.2)               | 0.499     |
| HB (g/dL)                                      | 12.7 ± 1.1 (10.1–15.2)               | 12.7 ± 1.1 (10.1–15.2)                  | 0.561     |

Note: All results are expressed as mean ± SD. and Abbreviations: HB, hemoglobin; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial blood assessment chart; VRS, verbal rating scale.

**TABLE 4** Comparison of VRS, PBAC, uterine volume, and HB level before and after treatment in each group

| Indicator                                      | Modified LNG-IUS group | GnRH-a + original LNG-IUS group |
|------------------------------------------------|------------------------|---------------------------------|
| Before treatment                               | 1 year after treatment | $p$-value                      |
| VRS                                           | 2.4 ± 0.9              | 0.15 ± 0.36                     | <0.001   |
| PBAC                                          | 501.1 ± 202.8          | 23.0 ± 15.0                     | <0.001   |
| Uterine volume (cm$^3$)                       | 221.8 ± 76.3           | 184.8 ± 69.2                    | <0.001   |
| HB (g/dL)                                      | 8.3 ± 1.5              | 12.8 ± 1.1                      | <0.001   |

Note: All results are expressed as mean ± SD. and Abbreviations: GnRH, gonadotropin-releasing hormone; HB, hemoglobin; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial blood assessment chart; VRS, verbal rating scale.
Discussion

In this study, all patients in the experimental group were successfully implanted with a modified LNG-IUS, which was safely removed in 95.7% of the patients after 60 months of use. Compared with the original LNG-IUS, the modified LNG-IUS demonstrated significantly reduced downward movement and expulsion rates, without obvious complications; it had a satisfactory effect on the patients with adenomyosis and HMB. Although the LNG-IUS was expelled after implantation in two cases, no uterine perforation or infection occurred; however, in these two cases, the uterine retention time significantly exceeded the intrauterine time of the original LNG-IUS used in their initial treatment. Notably, 48.9% of patients in the experimental group had previously experienced downward movement or expulsion of the original LNG-IUS—as well as symptom recurrence (HMB and dysmenorrhea)—after initially receiving standard treatment following Chinese guidelines. Among 19 of the 23 patients with repeated downward movement or expulsions, nine patients received an upward push to restore the LNG-IUS to its correct position in the uterine fundus under B-ultrasound monitoring; still, this approach was not completely successful or completely failed. No patients in the experimental group were treated with GnRH-a; thus, significantly reducing the medical cost. Our study is the first to demonstrate successful, continued use of the modified LNG-IUS after repeated downward movements or expulsions.

Ber and Seidman9 used alligator pliers to restore the LNG-IUS position in 18 women who experienced downward movement of the device, confirmed using ultrasound. Placement restoration was successful immediately in 17 of the 18 cases. Of these, the device moved downward again within 2 months in three cases, with 14 remaining in their normal position 6 months after restoration; the success rate of restoration was 78.0%. Kuzel et al.10 evaluated the effectiveness of symptom relief with hysteroscopic restoration of symptoms associated with downward displacement of the LNG-IUS position; they found that 110 of 113 patients had a correct IUS position 6 months after restoration. In these studies, high success rates were only indicative of short-term performance (up to 6 months after repositioning), whereas device retention rates 1, 2, 3, and 5 years after repositioning were not reported. None of the approaches used addressed the two main causes of LNG-IUS downward movement and expulsion, a large uterine cavity and the “scouring effect” of HMB.2 Notably, the implantation and fixation method can effectively address both issues.11

Intrauterine LNG delivery with a frameless fiber system was studied by Wildemeersch et al.12 in a review including 304 contraceptive patients. Achieving satisfactory results, there were three cases of expulsion, three cases of downward movement, and two cases of uterine perforation (attributed to novice and rough placement). Moreover, they only included 21 patients with adenomyosis and 32 patients with menorrhagia, respectively. Our study enrolled adenomyosis patients with a thick myometrium, while anchored nodules were implanted under B-ultrasound monitoring; thus, the possibility of perforation during the procedure was eliminated. Moreover, the circular tail of the improved system was expanded, and the diameter of the cartridge was 3 mm. Theoretically, the probability of late uterine rejection and perforation would be lower than that of the Gyne IUD, which has a thin, straight structure.

Zhang and Liu13 passed the polyethylene thread through the LNG silica gel stick (which was originally to be embedded under the skin for contraception) and anchored it to the myometrium in the same way. Although satisfactory results were achieved, the diameter of the embedding silica gel stick was 2 mm, limiting the thickness of the polyethylene thread and hardness of the anchoring knot, and thereby increasing the difficulty of firm anchoring. Furthermore, that device is valid for only 2 years. In our study, a 0.0 polypropylene wire with a thicker diameter was selected to allow for a higher anchoring success rate. The histopathological structure of the muscle layer in patients with adenomyosis is inconsistent with the physiological structure of the myometrium in the rest of the population; therefore, the success rate of anchoring in patients with adenomyosis is unknown. This study revealed that patients with adenomyosis had a significantly higher expulsion rate of the device than contraceptive women in the study by Wildemeersch et al.12 (4.3% vs. 1.9% [6/304]). To our knowledge, this IUD study included the largest number of patients with adenomyosis and HMB to date.

Use of the LNG-IUS is the first-line treatment for adenomyosis, recommended by guidelines in many countries.6,14–17 Since most patients with adenomyosis have a larger uterine cavity and menorrhagia than women without this condition, and the LNG-IUS only has a single model size, a high downward movement
and expulsion rate is inevitable. Lang et al.\textsuperscript{6} proposed that to decrease the downward movement and expulsion rate in cases with obvious uterine enlargement, GnRH-a can be administered for 3–6 months to reduce the uterine volume before LNG-IUS insertion. Li et al.\textsuperscript{1} demonstrated that after GnRH-a application, the expulsion rate reduced to 13.9%. In our study, the expulsion rate was 4.3%. A significant reduction in uterine volume was observed during GnRH-a application; however, the efficacy of GnRH-a disappeared after 3 months. Previous studies demonstrated that even after LNG-IUS placement, the uterine volume would still rebound to restore original size\textsuperscript{18,19}; therefore, the cause of downward movement or expulsion persists, and the routine use of GnRH-a is neither satisfactory nor cost-effective.

In this study, a frameless, fixed IUD was used as a template to modify the LNG-IUS. The GyneFix IUD is currently the most widely used intrauterine contraceptive device worldwide and is particularly suitable for women with a large uterine cavity or relaxation of the cervix. Its main advantage is the low downward movement/expulsion rate of 1.29% over 5 years, and it has been used in China for over 20 years.\textsuperscript{20} In this study, only the ineffective T-stent in the LNG-IUS was removed; the main longitudinal axis (sustained-release cartridge) was retained and remained functional. After modification, the cross-arm was removed, and the remaining longitudinal axis and tail circle could be monitored under B-ultrasound and radiography. The satisfactory effectiveness proves that this modification did not destroy its stability or function.; moreover, the enrolled patients with adenomyosis had a thicker (>12 mm) than usual myometrium. The placement was performed under B-ultrasound monitoring, and the possibility of uterine perforation was negligible.

In this study, two patients experienced LNG-IUS expulsion—with sudden abdominal pain and HMB—12 and 18 months postimplantation, respectively. During implantation, their myometrium felt loose and lacked resistance. In these cases, the anchor knot was removed when the needle was inserted, and exited the pusher during the first attempt; this was corrected during the second attempt. Phenomenon was likely due to individual uterine differences in the density of the smooth muscle fibers, the degree of microhematoma and microcystic cavities of ectopic endometrial glands, and differences in mesenchymal nodules in the muscle layers among patients with adenomyosis,\textsuperscript{21} which can hamper anchoring of the knot within the loose muscle layer. These factors, along with contraction of the myometrium, may cause device expulsion after 12–18 months.

The main limitation of this study was the small number of cases; further studies with more patients are required to validate these results. In addition, when the first anchoring procedure had failed, the NO.0 PROLENE was immediately replaced with a thicker thread to create the anchor knot; whether the second anchoring procedure would reduce the drop-off rate requires further investigation. In addition, all operations in this study were aseptic procedures, as the need to remove the LNG-IUS from the sleeves may increase the risk of infection. We therefore adopted dual infection prevention measures (oral and anal plugging) in each subject, as caution requires less intervention.

In conclusion, modifying the LNG-IUS and fixing it to the myometrium of patients with adenomyosis and HMB—particularly those who experienced repeated downward movements or expulsions with standard LNG-IUS treatment—was found to be a safe, effective, and simple mode of treatment.

Acknowledgments

The authors thank Xiaofang Chen for performing the statistical analyses in this study, Ying Liu for the consultation services provided, Yang Yang for recruiting patients to be included in this study, and Yong Zhou for typesetting the pictures for this article. No specific funding was received for this research. We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of Interest

None declared.

Author Contributions

Conception and design: Hong Yang. Acquisition of data: Hong Yang, ShengTan Wang, and XiaoYan Fu. Analysis and Interpretation of data: Hong Yang, ShengTan Wang, and XiaoYan Fu. Drafting of the manuscript: Hong Yang and ShengTan Wang. Critical revision of the manuscript for important intellectual content: Hong Yang, ShengTan Wang, XiaoYan Fu, and HuMin Gong. Statistical analysis and Administrative technical or material support: RuiHong Lan.
Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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