Efficacy of high-intensity focused ultrasound combined with LNG-IUS for adenomyosis: a systematic review and meta-analysis

Ting-Ting Zhao¹ · Li-Li Pang¹ · Lei-Lei Yang¹ · Ruo-Nan Li¹ · Ling-Xiu Fan¹ · Yi Wen²

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Abstract
Objective To evaluate the efficacy and safety of high-intensity focused ultrasound (HIFU) combined with the levonorgestrel intrauterine system (LNG-IUS) for adenomyosis.

Methods We searched PubMed, Embase, Cochrane Library, Web of Science, CNKI, SinoMed, Wanfang, and VIP databases from their inception to Nov 20, 2021 for relevant articles that compared HIFU combined with LNG-IUS vs. HIFU alone in patients with adenomyosis. RevMan5.4 software was used for the data analysis. The primary outcome was changes in volume of the uterus. Secondary outcomes included visual analog scale (VAS) scores for dysmenorrhea, serum CA125 level, recurrence rate, changes in volume of the adenomyotic lesion, menstrual volume scores, and adverse reactions. Data synthesis was conducted using a random-effects model with significant heterogeneity ($I^2 > 50\%$), and using a fixed-effects model otherwise. This study is registered on the PROSPERO platform (CRD42021295214).

Results The final analysis included 13 studies, with a total of 1861 patients. Results of analysis revealed that there was no significant difference in uterine volume reduction between the HIFU control group and the HIFU/LNG-IUS group at 3 months after procedure (MD:30.63). Compared with the HIFU control group, the HIFU/LNG-IUS group had more pronounced reduction in uterine volume at 6 (MD:29.04) and 12 months (MD:22.10) after procedure. The HIFU/LNG-IUS group has lower VAS scores for dysmenorrhea than the HIFU control group at 3 (MD:1.68), 6 (MD:1.69), and 12 months (MD:1.30) after procedure. Serum CA125 level in the HIFU/LNG-IUS group decreased more significantly than the HIFU control group at 6 (MD:18.34) and 12 months (MD:18.49) after procedure. The recurrence rate in the HIFU/LNG-IUS group was lower than that in the HIFU control group (RR:0.20).

Conclusions Compared to HIFU control group, HIFU/LNG-IUS group for the management of adenomyosis had more advantages in alleviating symptoms and decreasing the volumes of the uterine and adenomyotic lesions. However, since the number of the included studies was too small and some of them were not RCT, this conclusion needs to be referenced with caution.

Keywords HIFU · LNG-IUS · Adenomyosis · Meta-analysis

What does this study add to the clinical work
Adenomyosis is an estrogen-dependent disease, and all conservative surgical treatments cannot avoid postoperative recurrence. The same is true for HIFU treatment. LNG-IUS is currently the only non-oral long-acting therapy to inhibit the growth of adenomyosis. Therefore, the purpose of this study was to evaluate the efficacy and safety of high-intensity focused ultrasound (HIFU) combined with the levonorgestrel intrauterine system (LNG-IUS) for adenomyosis. Provide evidence-based data support for clinical treatment of adenomyosis.
Introduction

Adenomyosis is an estrogen-dependent benign gynecological disease that often occurs in women of childbearing age. The prevalence of adenomyosis ranges from 20 to 25% [1]. Dysmenorrhea, abnormal uterine bleeding and infertility are the main clinical symptoms in patients with adenomyosis [1, 2]. Currently, hysterectomy is still the only radical treatment for adenomyosis [3]. However, it is not suitable for patients who still have fertility requirements or who are unwilling to remove the uterus. To explain the pathogenesis of adenomyosis, many hypotheses have been put forward in recent years. Endometrial implantation and luminal epithelial chemotaxis are two of the most accepted theories [4].

The mechanism of action of HIFU is that cause high-intensity ultrasound energy to act on target tissues and ablating the lesion [5]. Finally, the purpose of effectively preserving uterine function while ablating the lesions can be achieved. With the advantages of shorter hospital stay, rapid recovery, significant alleviation of symptoms and fewer complications, HIFU has been widely used in clinical practice and can be used as a reliable alternative to hysterectomy. However, adenomyosis is an estrogen-dependent disease, all conservative treatments have need face the problem of recurrence or poor efficacy after treatment. The same is true for HIFU therapy [6]. Thus, effectively preventing the recurrence of adenomyosis after HIFU and maintaining durable long-term effects of treatment is an urgent problem needed to solve. As an intrauterine device, LNG-IUS acts on the uterus and can inhibit the growth of residual lesions after HIFU for a long time, thereby maintaining the curative effect of HIFU and preventing recurrence, has attracted more attention [7, 8].

This study aimed to compare the differences between HIFU combined with LNG-IUS and HIFU treatment alone in treating adenomyosis and improving prognosis. Therefore, we carried out a systematic review and meta-analysis of the existing literature to provide evidence-based data to support the clinical application of HIFU combined with LNG-IUS in the treatment of adenomyosis.

Methods

Search strategy

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, and was registered on the PROSPERO platform (CRD42021295214). PubMed, Embase, Cochrane Library, Web of Science, CNKI, SinoMed, Wanfang, and VIP databases were performed to search relevant studies published from their inception to Nov 20, 2021. The search terms were as follows: ((Adenomyos*[MeSH Terms]) AND (“High-Intensity Focused Ultrasound Ablation” [Mesh]) OR (HIFU)) AND (((“Levonorgestrel” [Mesh]) OR (LNG-IUS)) OR (Mirena)).

Selection criteria

Inclusion criteria: (1) studies comparing the efficacy of HIFU combined with LNG-IUS vs. HIFU alone in the management of adenomyosis; (2) studies object: the age of the patients must older than 18 years; women with adenomyosis diagnosed by ultrasound or magnetic resonance imaging (MRI); (3) outcome indicator: the primary outcome was changes in volume of the uterine. Secondary outcomes included visual analog scale (VAS) scores for dysmenorrhea, serum CA125 level, recurrence rate, changes in adenomyotic lesion volume, menstrual volume scores, and adverse reactions.

Exclusion criteria: (1) studies for which the original text was not available; (2) animal experiments, case reports, reviews, conference abstracts, guidance or comments, and conference proceedings.

Data extraction

Two authors (TT Z and LL P) independently extracted data from included studies. Extracted data were cross-checked and any discrepancies were resolved through consensus discussion. Below is the data we got from the research: first author, publication year, title, study design, random sequence generation, sample size, BMI, average age, and imaging diagnostic methods.

Quality assessment

Quality evaluation of the included studies was assessed using the Risk of Bias Assessment Tool recommended by the Cochrane Collaboration. The specific contents include: performance bias, selection bias, attrition bias, detection bias, reporting bias, and other bias. Each item had three options: “Yes” (indicating low risk of bias), “No” (indicating high risk of bias), and “Unclear” (indicating that the article did not provide sufficient information for bias assessment).

Statistical analysis

Continuous variables are expressed as mean difference (MD), discontinuous variables are expressed as risk ratios (RR), and corresponding interval estimates are expressed as
95% confidence interval (CI). \( P < 0.05 \) indicates a significant difference. Heterogeneity analysis was performed for the included studies, with \( P < 0.1 \) and \( I^2 > 50\% \) indicating high heterogeneity. Sensitivity analysis was performed to determine the source of heterogeneity. If heterogeneity decreased after sensitivity analysis, the fixed-effects model was used for meta-analysis; otherwise, the random-effects model was applied. If the data could not be combined, descriptive analysis was performed.

**Results**

**Literature search results**

A total of 168 articles were retrieved, and 25 articles were excluded as duplicates. After browsing the titles and abstracts of the articles, 130 articles were excluded for various reasons. Thirteen studies with data for 1861 patients were finally included in the present meta-analysis. The literature screening process is shown in Fig. 1.

**Study characteristics**

The final analysis included 13 studies (10–22), with a total of 1861 patients: 1131 receiving HIFU alone (HIFU control group) and 730 receiving HIFU plus LNG-IUS (HIFU/LNG-IUS group). Four were retrospective studies (12,17,21–22), one was a prospective clinical controlled trial (11), and eight were randomized controlled trials (10,13–16,18–20). Of the 13 studies, five used MRI for imaging diagnosis of adenomyosis, three used vaginal ultrasound for diagnosis, and five used two diagnostic methods: vaginal ultrasound and MRI. Basic information regarding the included studies is shown in Table 1.

**Quality assessment**

The quality assessment of a single study is shown in Fig. 2. Among the 13 included studies, there were eight randomized controlled trials: four used the random number table method for grouping, one group was formed according to the odd or even number of the entry order, and three mentioned but did not specifically describe the randomization method. None of the studies described methods of random allocation hiding or blinding. The specific risk-bias analysis is presented in Fig. 3.

**Outcome measures**

**Changes in uterine volume**

In the present review, seven studies reported the changes in uterine volume after HIFU [9, 13, 14, 17–20] (519 cases). The overall effect estimates showed that the HIFU/LNG-IUS group had higher uterine volume reduction than the HIFU control group at 6 (MD 29.04, 95% CI 2.68–55.41, \( P = 0.03, I^2 = 99\% \)) and 12 months after procedure (MD 22.10, 95% CI 8.58–35.63, \( P = 0.001, I^2 = 91\% \)). However, the results of analysis revealed that there was no significant difference in the changes of uterine volume between the two groups at 3 months after procedure (MD 30.63, 95% CI 4.74–66.00, \( P = 0.09, I^2 = 97\% \); Fig. 4).

**VAS scores for dysmenorrhea**

Ten studies [9, 10, 12–15, 17–20] (706 cases) reported changes in the VAS scores for postoperative dysmenorrhea between the HIFU/LNG-IUS group and the HIFU control group. Results of analysis revealed that there was no significant difference in the VAS scores of dysmenorrhea between the two groups at 1 month after procedure (MD 0.56, 95% CI 0.08–1.19, \( P = 0.09, I^2 = 0\% \)). However, the VAS scores for dysmenorrhea in the HIFU/LNG-IUS group were lower than the HIFU control group at 3 (MD 1.68, 95% CI 0.93–2.42, \( P < 0.0001, I^2 = 67\% \)), 6 (MD 1.69, 95% CI 0.58–2.81, \( P = 0.003, I^2 = 96\% \)), and 12 months after procedure (MD 1.30, 95% CI 0.70–1.90, \( P < 0.0001, I^2 = 73\% \); Fig. 5). Since the heterogeneity was too high, we reduced the heterogeneity by sequentially removing each study. When the Wang 2015 at 3 months after procedure, Sun 2019, Huang 2019, and Wu 2018 at 6 months after procedure, and S Jiang 2021 and Wu 2018 at 12 months after procedure were removed, the heterogeneity is reduced. The results after sensitivity analysis showed that the VAS scores for dysmenorrhea in the HIFU/LNG-IUS group were lower than the HIFU control group at 3 (MD 1.98, 95% CI 1.36–2.61, \( P < 0.00001, I^2 = 22\% \)), 6 (MD 0.99, 95% CI 0.63–1.34, \( P < 0.00001, I^2 = 0\% \)), and 12 months after procedure (MD 1.43, 95% CI 1.05–1.81, \( P < 0.00001, I^2 = 0\% \); Fig. 6).

**Serum CA125 levels**

Four articles [12, 13, 16, 20] (274 cases) reported changes in serum CA125 levels after procedure. Meta-analysis results showed that the HIFU/LNG-IUS group was superior to the HIFU control group in reducing serum CA125 levels at 6 (MD 18.34, 95% CI 8.57–28.11, \( P = 0.0002, I^2 = 0\% \)) and
Fig. 1 Flowchart of article selection for systematic reviews
12 months after procedure (MD 18.49, 95% CI 9.50–27.47, \( P = 0.00001 \), \( I^2 = 0\% \); Fig. 7).

**Recurrence rates**

A total of four studies [10, 11, 15, 20] (564 cases) compared recurrence rates at 1 year postoperatively between the two

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**Table 1** Characteristics of included studies

| References | Study design | Random sequence generation | Study group | Control group | Sample size (n) | Age (years) | Last follow-up time (months) | Diagnostic imaging | BMI (Kg/M²) |
|------------|--------------|----------------------------|-------------|---------------|----------------|-------------|-------------------------------|-------------------|------------|
| Wang et al. [5] | Randomized control trial | Odd and even grouping | HIFU + M | HIFU | 20/20 | 36.0 ± 5.7/36.8 ± 6.1 | 6 | MRI | NA |
| Guo et al. [6] | Prospective | NA | HIFU + M | HIFU | 15/45 | 39.33 ± 4.30/42.42 ± 5.09 | 12 | TVUS/MRI | NA |
| Ye MZ et al. [7] | Retrospective | NA | HIFU + M | HIFU | 102/229 | 40.7 ± 5.0 | 12 | MRI | NA |
| Wu et al. [8] | Randomized control trial | NA | HIFU + M | HIFU | 15/15 | 41.92 ± 3.86/41.92 ± 6.63 | 12 | TVUS/MRI | NA |
| Yu et al. [9] | Randomized control trial | Random number table | HIFU + M | HIFU | 45/45 | 37.18 ± 3.60/37.09 ± 3.65 | 6 | TVUS | 23.04 ± 1.87/23.11 ± 1.84 |
| Sun [10] | Randomized control trial | NA | HIFU + M | HIFU | 44/44 | 45.1 ± 2.4/37.1 ± 2.4 | 6 | TVUS | NA |
| Han et al. [11] | Randomized control trial | NA | HIFU + M | HIFU | 50/50 | 41.84 ± 5.01 | 12 | TVUS/MRI | NA |
| Xu et al. [12] | Retrospective | NA | HIFU + M | HIFU | 33/48 | 42.1 ± 4.5/43.6 ± 5.1 | 12 | MRI | 22.6 ± 2.3/23.1 ± 2.9 |
| Huang et al. [13] | Randomized control trial | Random number table | HIFU + M | HIFU | 31/31 | 36.52 ± 1.66/36.46 ± 1.62 | 6 | TVUS/MRI | NA |
| Jiang et al. [14] | Randomized control trial | Random number table | HIFU + M | HIFU | 40/40 | 37.67 ± 4.13/38.25 ± 3.62 | 12 | MRI | 23.03 ± 1.49/23.04 ± 1.56 |
| Yang et al. [15] | Randomized control trial | Random number table | HIFU + M | HIFU | 43/43 | 37.48 ± 5.41/37.55 ± 5.39 | 12 | MRI | NA |
| Bi (17) | Retrospective | NA | HIFU + M | HIFU | 37/36 | 40.4 ± 4.9/40.1 ± 4.7 | 12 | TVUS | NA |
| Li et al. [17] | Retrospective | NA | HIFU + M | HIFU | 255/485 | 40.6 ± 5.5 | 36 | TVUS/MRI | 22.6 ± 3.0 |

HIFU, high-intensity focused ultrasound; M, levonorgestrel-releasing intrauterine system; TVUS, transvaginal ultrasound; MRI, magnetic resonance imaging; NA, not applicable
Fig. 2 Review of authors’ judgments on risk of bias terms for each included study

Fig. 3 Review of authors’ judgments on risk of bias items, expressed as a percentage of all included studies

Fig. 4 Meta-analysis of changes in uterine volume between the two groups
groups. The meta-analysis results showed that the HIFU/LNG-IUS group had a lower recurrence rate than the HIFU control group (RR 0.20, 95% CI 0.09–0.46, \( P = 0.0002 \), \( I^2 = 0\% \); Fig. 8).

### Changes in adenomyotic lesion volume

Four studies [10, 13, 15, 16] (331 cases) reported changes in adenomyotic lesion volume after procedure. Yu et al. studied changes in adenomyotic lesion volume of patients at 6 months after procedure and found that the HIFU/LNG-IUS group exhibited a greater reduction in adenomyotic lesion volume, and there was a significant difference compared with the HIFU control group (\( P < 0.001 \)) [13]. Guo et al. reported that the adenomyosis lesion volume reduction rate in the HIFU/LNG-IUS group was higher than that in the HIFU control group at 1, 6, and 12 months after procedure (\( P < 0.05 \)) [10]. Similarly, Han et al. and Xu et al. found that the adenomyosis lesion volume reduction rate in the HIFU/LNG-US group was higher than that in the HIFU control group at 12 months after procedure (\( P < 0.05 \)) [15, 16].

### Menstrual volume

Five studies [10, 14, 18, 20, 21] (1041 cases) reported changes in menstrual volume after procedure. Li et al. [21] found that for the problem of increased menstrual flow, at 6 months after procedure, the effective rate of the HIFU control group was 53.5%, and the effective rate of the HIFU/
### Fig. 6
Sensitivity analysis of visual analogue scale (VAS) scores for dysmenorrhea in the two groups

| Study or Subgroup | HIFU+LNG-IUS | HIFU | Mean Difference | Mean Difference |
|-------------------|-------------|------|-----------------|-----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| 2.1.1 after 1 month |      |     |       |      |     |       |                   |                   |
| Qing Guo 2016     | 5.2  | 2.32| 15    | 4.97| 2.02| 45    | 0.04 [0.00, 0.08]  |                   |
| Yimei Huang 2021  | 2.74| 1.71| 31    | 2.14| 1.86| 31    | 0.60 [0.49, 0.70]  |                   |
| Ziyu Wu 2018      | 2.78| 1.7 | 15    | 2.01| 1.86| 15    | 0.77 [-0.18, 0.72] |                   |
| Subtotal (95% CI) | 91   | 15.3| 61    |     |     |       |                   |                   |

Heterogeneity: $\tau^2 = 0.00, \text{ Chi}^2 = 0.35, \text{ df} = 2 (P = 0.84); P = 0$

Test for overall effect: $Z = 1.71 (P = 0.09)$

### Fig. 7
Meta-analysis of serum CA-125 levels in the two groups

| Study or Subgroup | HIFU+LNG-IUS | HIFU | Mean Difference | Mean Difference |
|-------------------|-------------|------|-----------------|-----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| 3.1.1 after 6 months |      |     |       |      |     |       |                   |                   |
| Lixia Yu 2019     | 67.48| 25.76| 45    | 49.34| 26.22| 45    | 37.9% [18.14, 57.29] |                   |
| Xiaodi Bi 2021    | 147.25| 52.86| 37    | 128.83| 66.77| 37    | 57.9% [19.42, 96.40] |                   |
| Ziyu Wu 2018      | 56.28| 47.9 | 15    | 34.63| 74.87| 15    | 22.2% [21.65, 43.33] |                   |
| Subtotal (95% CI) | 97   | 45.8|       |     |     |       |                   |                   |

Heterogeneity: $\text{Chi}^2 = 0.02, \text{ df} = 2 (P = 0.99); P = 0$

Test for overall effect: $Z = 3.68 (P = 0.0002)$

### Fig. 7 Meta-analysis of serum CA-125 levels in the two groups
LNG-IUS group was 96.1%. In addition, at 12 months postoperatively, the effective rate of the HIFU/LNG-IUS group was 88.6%, while the effective rate of HIFU group was 48.5%. Bi et al. and Jiang et al. used the Pictorial Blood Loss Assessment Chart (PBAC) to assess postoperative menstruation, and the results showed that the HIFU/LNG-IUS group was superior to HIFU control group in improving postoperative menstrual volume (P < 0.05) [18, 20]. The study by Guo and Sun et al. also came to the same conclusion (P < 0.05) [10, 14].

Occurrence of adverse reactions

Among the 13 included articles, eight [9–11, 15–17, 20, 21] reported adverse reactions after HIFU. However, the types of adverse reactions reported were not completely consistent. Some studies did not provide specific data regarding adverse reactions in the HIFU/LNG-IUS group or the HIFU control group, which is not conducive to comparisons between the groups. Therefore, we summarized and counted all the adverse reactions and the number of cases in these 8 studies. The main adverse reactions after surgery are as follows: leucorrhea or bleeding, abdominal or sacrococcygeal pain, amenorrhea, LNG-IUS ectopic, or shedding. The Society of Interventional Radiology Clinical Practice Guidelines classify adverse reactions as follows: A: No treatment required, no adverse consequences; B: Simple treatment and observation required, no adverse consequences; C: Hospitalization necessary within 48 h; D: Significant treatment, higher levels of care, and more than 48 h of hospital stay [22]. See Table 2 for details.

Discussion

This study is the first systematic review and meta-analysis of HIFU combined with LNG-IUS in the treatment of adenomyosis. Results of this meta-analysis of 1861 patients showed that HIFU combined with LNG-IUS was more effective in relieving symptoms and decreasing the volumes of the uterine compared with HIFU alone in the treatment of adenomyosis.

At present, hysterectomy is still the only curative treatment for adenomyosis, but it is not suitable for patients who wish to remain their fertility. As early as 2008, the American College of Obstetricians and Gynecologists (ACOG) pointed out a variety of alternative treatments for hysterectomy [23]. For adenomyosis patients who want to preserve uterus, the current treatment has gradually changed to a comprehensive treatment mode based on HIFU, lesions resection and other conservative surgery. A number of studies have shown that HIFU treatment of adenomyosis has the advantages of less trauma, higher safety, less adverse effects on pregnancy, and

Table 2 Adverse reactions in patients after treatment

| Complication                        | Total | SIR Grade |
|-------------------------------------|-------|-----------|
| HIFU                                |       |           |
| Irregular vaginal bleeding          | 9     | A         |
| Fever                               | 21    | A         |
| Pain in the lower abdomen           | 872   | A         |
| Sacrococcygeal pain                 | 334   | A         |
| Vaginal drainage and bleeding       | 82    | A         |
| Intestinal fistula                  | 1     | D         |
| Paresthesias in the lower extremities | 3   | A         |
| Lower limb pain                    | 9     | B         |
| Dyskinesia of lower limbs           | 1     | B         |
| Urine retention                     | 1     | B         |
| Bowel perforation                   | 1     | D         |
| LNG-IUS                             |       |           |
| Irregular vaginal bleeding          | 84    | A         |
| Mild lower abdominal pain           | 23    | A         |
| Moderate abdominal pain             | 5     | A         |
| Sacrococcygeal pain                 | 11    | A         |
| Vaginal drainage and bleeding       | 4     | A         |
| LNG-IUSectopic or shedding          | 30    | B         |
| amenorrhea                          | 18    | A         |

HIFU, high-intensity focused ultrasound; M, levonorgestrel-releasing intrauterine system; SIR, Society of Interventional Radiology clinical practice guidelines.
cheaper price compared with traditional surgery. In China, HIFU has been widely used for adenomyosis, and has been recommended as an interventional therapy by Chinese Expert Consensus on diagnosis and Treatment of Adenomyosis.

However, as with other surgical methods that preserve the uterus, HIFU also faces the risk of postoperative recurrence. Therefore, there is an urgent need for a treatment that can maintain the efficacy of HIFU and prevent the recurrence of adenomyosis. All non-surgical treatments for adenomyosis, including LNG-IUS, GnRH-a, oral contraceptives, and herbs, can be used to prevent recurrence of adenomyosis after HIFU. Among these, the combined of LNG-IUS or GnRH-a after HIFU has more widely used in clinical practice, and has achieved good curative effect. We conducted a meta-analysis and systematic review of existing research investigating the treatment of adenomyosis after HIFU combined with GnRH-a. The study shows that HIFU combined with GnRH-a has greater efficacy in relieving symptoms and preventing recurrence compared with HIFU alone in the treatment of adenomyosis. The use of GnRH-a has the disadvantage of causing menopause-like side effects and recurrence of symptoms after cessation of this treatment. Therefore, it is not suitable as long-term maintenance treatment after HIFU.

LNG-IUS is a long-acting hormone-releasing uterine device, which can locally release a small amount of LNG to act on the endometrium for a long time. To achieve the purpose of inhibiting the growth of residual lesions after HIFU, further reducing the volume of uterine and adenomyosis lesions, and relieving symptoms. Compared with GnRH-a, LNG-IUS treatment is milder and more durable. At present, there is only one model of LNG-IUS, so for patients with adenomyosis with larger uterine volume, the shedding rate is higher. The reduction of uterine volume and recovery of uterine cavity morphology after HIFU ablation of the lesion effectively reduced the rate of LNG-IUS dislodgement. The simultaneous application of HIFU and LNG-IUS can effectively make up for the deficiency of each other’s treatment. To achieve long-term effective management of adenomyosis symptoms, improve the quality of life of patients and the purpose of prevention and recurrence. This study further confirmed the efficacy and safety of the combined regimen.

Menorrhagia often leads to anemia; therefore, hemoglobin is an important indicator for assessing the severity of adenomyosis in clinical practice. Three studies’ results showed that HIFU/LNG-IUS group improved hemoglobin levels better than HIFU control group in patients with adenomyosis (P < 0.05).

Dysmenorrhea and menorrhagia are the main symptoms of adenomyosis and often lead to a decrease in the quality of life of patients with adenomyosis. A study by Wu et al. demonstrated that the UFS-QOL score of the HIFU/LNG-IUS group was improved more significantly at 1, 3, 6, and 12 months after procedure compared with HIFU control group (P < 0.05). As an intrauterine contraceptive device, LNG-IUS is suitable for patients with adenomyosis without short-term fertility requirements. Therefore, there are few reports on pregnancy in the HIFU/LNG-IUS group. Guo et al. performed follow-up for 6 months and found that no pregnancy was reported in the HIFU/LNG-IUS group. Li et al. followed up 1982 patients for 5 years, of whom 50 were pregnant, but did not report the pregnancy outcome and the pregnant patients belonged to the HIFU/LNG-IUS group or the HIFU control group. However, it is very necessary to follow up the pregnancy status of patients after HIFU combined with LNG-IUS treatment. It can help physicians provide more prescient advice to patients with adenomyosis who have no reproductive needs temporary. The effect of the combined treatment on postoperative pregnancy in patients with adenomyosis needs to be verified by long-term, large-sample clinical research.

We acknowledge the systematic review and meta-analysis has some limitations. First, this systematic review included a total of 13 studies, of which only eight were randomized controlled trials, and none of the studies described methods of random allocation hiding or blinding, with a selection bias. Second, information on the outcomes was incomplete and the sample sizes of some studies were small. Third, the measurement units of the included studies are inconsistent. For instance, some studies did not report the specific size of the patient’s uterine volume before surgery but, instead, replaced it with the reduction rates of the uterine. In the measurement of menstrual volume, not every study used the PBAC menstrual blood loss chart to indicate menstrual volume, which is not beneficial for subsequent data analysis. Fourth, the effective duration of LNG-IUS is 5 years; however, not all of the studies reported the follow-up results of patients for 5 years after the procedure. Therefore, it is difficult to analyze the long-term efficacy of HIFU combined with LNG-IUS in the treatment of adenomyosis. Future, we look forward to more large-scale, multicenter, high-quality clinical studies to support our conclusions.

Conclusions

Results of the meta-analysis revealed that compared with HIFU alone, HIFU with LNG-IUS for the treatment of adenomyosis had more advantages in improving symptoms and preventing recurrence. According to the characteristics of HIFU combined with LNG-IUS treatment, we believe that it is more suitable for women who need contraception. However, since the number of the included studies was too
small and some of them were not RCT, this conclusion needs to be referenced with caution.

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Author contributions T-TZ developed the search strategy and completed the manuscript writing. R-NL and L-XF completed the electronic search and selected appropriate literature. L-LY and T-TZ extracted the information of the selected studies. T-TZ was responsible for data analysis using RevMan 5.4 software. YW advised on the data analysis and was responsible for correspondence. All authors carefully checked and approved the final manuscript.

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Data availability The original literature provided for the study is featured in the article. For more detailed information, the corresponding author may be contacted directly.

Declarations

Conflict of interest The authors declared that the research was conducted in the absence of any commercial or financial relationships.

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