Reproductive Biology and Endocrinology

RESEARCH

Open Access

The role of different LNG-IUS therapies in the management of adenomyosis: a systematic review and meta-analysis

Biyun Zhang[1,2], Jinghua Shi[1,2], Zhiyue Gu[1,2], Yushi Wu[1,2], Xiaoyan Li[1,2], Chenyu Zhang[1,2], Hailan Yan[1,2], Qiutong Li[1,2], Shiqing Lyu[1,2], Yi Dai[1,2] and Jinhua Leng[1,2,3*]

Abstract

Objective To summarize evidence on the efficacy and safety of the levonorgestrel-releasing intrauterine system (LNG-IUS) in managing adenomyosis (AM), both as a monotherapy and in combination with other therapies.

Methods We searched Medical Literature Analysis and Retrieval System On-Line: Medline, The Cochrane Library, Embase, SinoMed, China National Knowledge Infrastructure, and Wanfang from the inception to Aug 12, 2024 for articles using the LNG-IUS both alone and combined with other therapies in patients with AM. The primary outcome included dysmenorrhea, menstrual bleeding, uterine volume, endometrial thickness and quality of life. The secondary outcome was the assessment of adverse events. Data synthesis was conducted using random-effects model with significant heterogeneity ($I^2 > 50\%$), otherwise using fixed-effects model.

Results The final analysis included 28 studies. Compared with etonogestrel, LNG-IUS was more effective in reducing uterine volume and associated with a lower risk of weight gain, but showed no significant difference in reducing dysmenorrhea and endometrial thickness. Comparing LNG-IUS with mifepristone, there was no significant difference in terms of quality of life. The combination of LNG-IUS with Gonadotropin-releasing hormone agonists (GnRH-a) was more effective than LNG-IUS alone, providing benefits in reducing dysmenorrhea (mean deviation, MD: -1.14), menstrual bleeding (MD: -11.94), uterine volume (MD: -30.39), endometrial thickness (MD: -0.89), and adverse events. The combination of LNG-IUS with surgical excision was more effective than surgical excision alone, providing benefits in reducing dysmenorrhea (MD: -1.49), menstrual bleeding (MD: -5.13) at 12 months, reducing uterine volume at 6 (MD: -9.23), 12 (MD: -16.53) and 24 (MD: -27.17) months. The combination of LNG-IUS with focused ultrasound ablation (FUA) was more effective than FUA alone, providing benefits in reducing dysmenorrhea (MD: -0.62), menstrual bleeding (MD: 0.17).

Conclusions This study found no clear evidence to recommend single-drug therapy for improving pain and quality of life in AM management within 12 months. Combining LNG-IUS with GnRH-a is effective in alleviating pain, controlling heavy bleeding, reducing lesion volume, reducing the probability of expulsion and irregular bleeding.

*Correspondence:
Jinhua Leng
lengjenny@vip.sina.com

Full list of author information is available at the end of the article

Postoperative LNG-IUS helps reduce long-term pain and bleeding. In combined FUA, LNG-IUS is effective for managing short-term pain and bleeding.

Trial registration PROSPERO registration number: CRD42024578824.

Keywords Adenomyosis, Efficiency, Safety, LNG-IUS, Treatment

Introduction

Adenomyosis (AM) is a condition characterized by the infiltration of endometrial glands and stroma into the myometrium. The primary clinical manifestations include menorrhagia, dysmenorrhea, and infertility, which can severely impact patients' physical and mental health as well as their overall quality of life [1]. Surgical excision is a common clinical approach for treating this disease. However, it often results in varying degrees of tissue damage and a prolonged recovery period [2]. Consequently, current clinical guidelines recommend the use of non-steroidal anti-inflammatory drugs, oral contraceptives, progesterone, and gonadotropin-releasing hormone agonists (GnRH-a) as standard options for the long-term management of AM. These pharmacological treatments are particularly important for patients desiring to preserve fertility, allowing symptom control without resorting to surgical intervention [3]. The levonorgestrel-releasing intrauterine system (LNG-IUS), has been utilized in clinical settings to manage AM. When placed in the uterine cavity, this system provides a sustained release of progesterone, thereby inhibiting endometrial growth and alleviating symptoms of AM [4]. In recent years, LNG-IUS has gained recognition as an effective treatment for AM, with multiple studies indicating its efficacy in reducing menstrual bleeding, pelvic pain, and other associated symptoms [5–7].

An increasing number of studies have reported the clinical efficacy of the LNG-IUS in the management of AM. LNG-IUS is employed not only as a monotherapy but also in combination with other pharmacological agents to more effectively alleviate patient symptoms. LNG-IUS also follows surgical or interventional procedures to reduce the recurrence rate of AM [8, 9]. However, there is currently no comprehensive research summarizing the optimal treatment strategies for AM patients.

To address this gap, we conducted a systematic review and meta-analysis of the available literature to assess the efficacy and safety of LNG-IUS, both as a monotherapy and in combination with other therapies. The goal is to provide robust, evidence-based data to inform clinical decision-making.

Materials and methods

Study design and search strategy

This study adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews [10]. And the study was retrospectively registered in PROSPERO (CRD42024578824). A comprehensive systematic search was conducted across several databases, including Medical Literature Analysis and Retrieval System On-Line: Medline, The Cochrane Library, Embase, SinoMed, China National Knowledge Infrastructure, and Wanfang with a time-limit ranging from their inception until August 12, 2024 (see Additional file 1).

Eligibility criteria

The inclusion criteria targeted studies involving patients aged 18 and older who were diagnosed with AM, regardless of complications, severity, and diagnostic method, including clinical symptoms, imaging, or pathological diagnosis of a total hysterectomy. The primary focus was on the application of LNG-IUS as a part of conservative therapeutic strategies. The primary outcome was the efficacy of the treatment, which was evaluated based on factors such as the intensity of dysmenorrhea, menstrual blood loss, uterine volume, endometrial thickness, and quality of life. The secondary outcome included the assessment of adverse events. The treatment effect was categorized into three timeframes: up to six months, six months to one year, and beyond one year. This review encompassed a wide range of study types, including randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), and observational studies. However, letters, editorials, case reports, and case series were excluded.

Two independent reviewers screened the search results by examining titles and abstracts. Full-text versions of potentially relevant studies were thoroughly reviewed. Any disagreements were resolved through discussion, with the involvement of a third-party researcher if needed. The entire study selection process was illustrated using a PRISMA flow diagram.

Data extraction

Data extraction was performed independently by two reviewers using a standardized extraction form. Any differences in interpretation were discussed and resolved, again with the aid of a third-party researcher if necessary. Only studies published in English-language journals or Chinese technological publications were considered to assess the efficacy of LNG-IUS in managing AM. Extracted data included details such as study author,

publication year, country, study period, evidence types, intervention categories, comparators, participants' age. Treatment-related details included product name, LNG-IUS placement date, management specifics of the intervention, and treatment duration. Outcomes were pre-specified and included follow-up length and both dichotomous and continuous results.

Data synthesis and analysis

The treatment efficacy of interventions was synthesized from comparative studies. Meta-analyses were conducted using Review Manager (RevMan) 5.3 to calculate pooled treatment effects where data were available. Dichotomous outcomes were reported as risk ratios (RRs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean deviations (MDs) with 95% CIs. A statistically significant difference was indicated when the 95% CI did not include 0 for MDs or 1 for RRs. Forest plots were visually inspected to identify potential statistical heterogeneity. An I^2 estimate greater ≥ 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity. A random-effects model was applied in cases of statistically significant heterogeneity; otherwise, a fixed-effects model was applied.

Quality assessment

For included RCTs, the risk of bias was assessed using the Cochrane risk-of-bias tool [11]. For non-RCTs, qualitative judgments were made in the areas of selection, comparability and exposure/outcome according to the Newcastle-Ottawa Scale (NOS) [12].

Results

Study selection process

After removing duplicates, we obtained 2367 unique references. By reading the title and abstract of the literature, we included 91 articles into the full text index, of which 3 articles could not be found. Finally, 28 comparative studies published in English journals or journals listed in China Technology from 2010 to 2024 were included in the present meta-analysis. Figure 1 shows the PRISMA chart.

Summary of intervention in comparative studies

A total of 28 comparative studies involving 2530 patients, including 9 randomized controlled trials and 19 non-randomized controlled trials, were selected to compare LNG-IUS with alternative treatments in both conservative and postoperative therapeutic protocols (see Additional file 2).

LNG-IUS in conservative therapy

LNG-IUS vs. etonogestrel

In the comparative study of LNG-IUS and etonogestrel, LNG-IUS showed a better effect than etonogestrel in reducing the volume of the uterus, but there was no difference in relieving dysmenorrhea measuring by visual analogue scale (VAS) and reducing the thickness of the endometrium at follow-up points of 6 and 12 months (Figs. 2, 3 and 4). In terms of adverse effects, the incidence of weight gain in LNG-IUS was less, but there was no significant difference in acne or breast tenderness between LNG-IUS and etonogestrel at 12-month follow-up (Fig. 5) [13–16].

LNG-IUS vs. mifepristone

Between LNG-IUS and mifepristone, two studies [17, 18] with a total of 248 patients were analyzed. Five aspects of quality of life were included in the two studies, which were thoughts/desires, arousal, pleasure/orgasm, receptivity/initiation, and abnormal sexual behavior. The forest plots exhibited that no difference in the quality of life was observed between groups at 6-month and 12-month follow-up (Figs. 6 and 7).

Gonadotropin-releasing hormone agonists (GnRH-a) + LNG-IUS vs. LNG-IUS

For patients with AM, compared with LNG-IUS alone, GnRH-a + LNG-IUS had beneficial effects in reducing the intensity of dysmenorrhea within six-month period (Fig. 8) [19–24]. Regarding menstrual blood loss measuring by pictorial blood loss assessment chart (PBAC), six studies [20–25] with three cycles of GnRH-a (Fig. 9) reported a beneficial effect in the GnRH-a + LNG-IUS group at 6-month follow-up. Similar significant benefits were found in terms of reducing uterine volume, endometrial thickness, and adverse effects of expulsion, irregular bleeding and abdominal pain, except breast pain (Figs. 10, 11 and 12) [19–27].

Post-surgical excision therapy

LNG-IUS vs. expected treatment

Regarding the intensity of dysmenorrhea and menstrual blood loss, inconsistent results were observed. Compared with the expected, a beneficial effect was observed in the surgical excision + LNG-IUS at 12-month follow-up, but not at 6-month follow-up. (Figs 13 and 14) [28–31].

As for uterine volume, four studies [28–30, 32] showed a statistically significant reduction in uterine volume in the surgical excision + LNG-IUS treatment group compared with the surgical excision only group at the 6-month, 12-month and 24-month follow-up (Fig. 15).

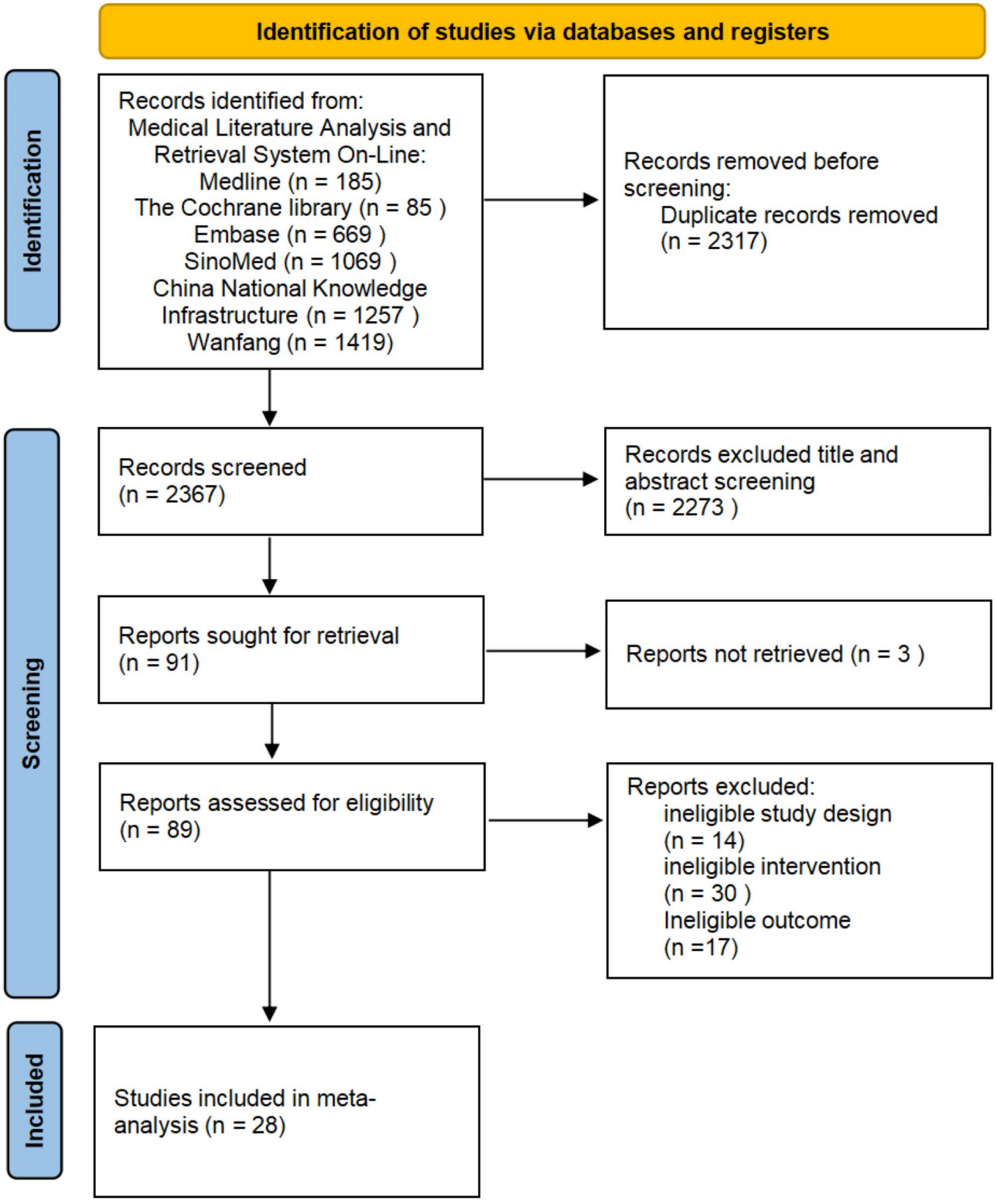

Fig. 1 PRISMA 2020 flowchart representing the study selection process

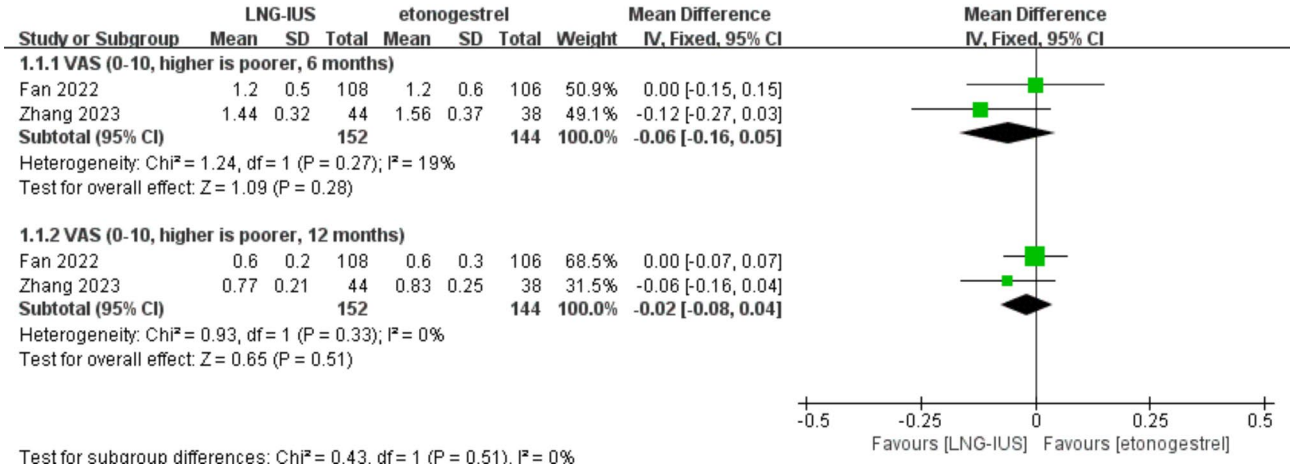

Fig. 2 Forest plot of the pain score after LNG-IUS insertion or etonogestrel subcutaneous implantation

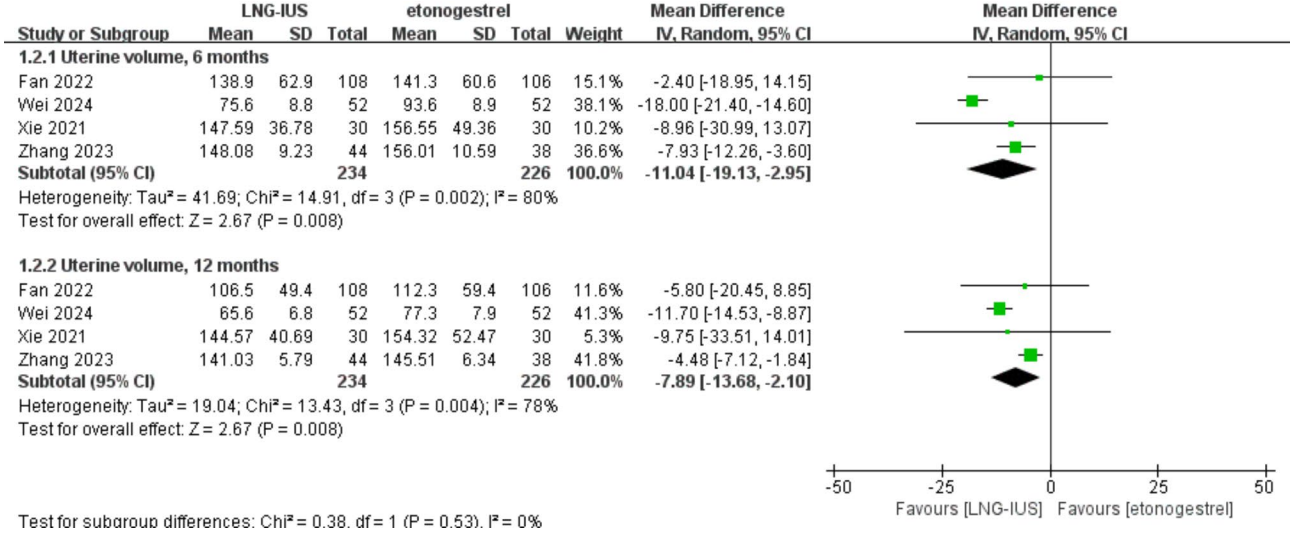

Fig. 3 Forest plot of the uterus volume after LNG-IUS insertion or etonogestrel subcutaneous implantation

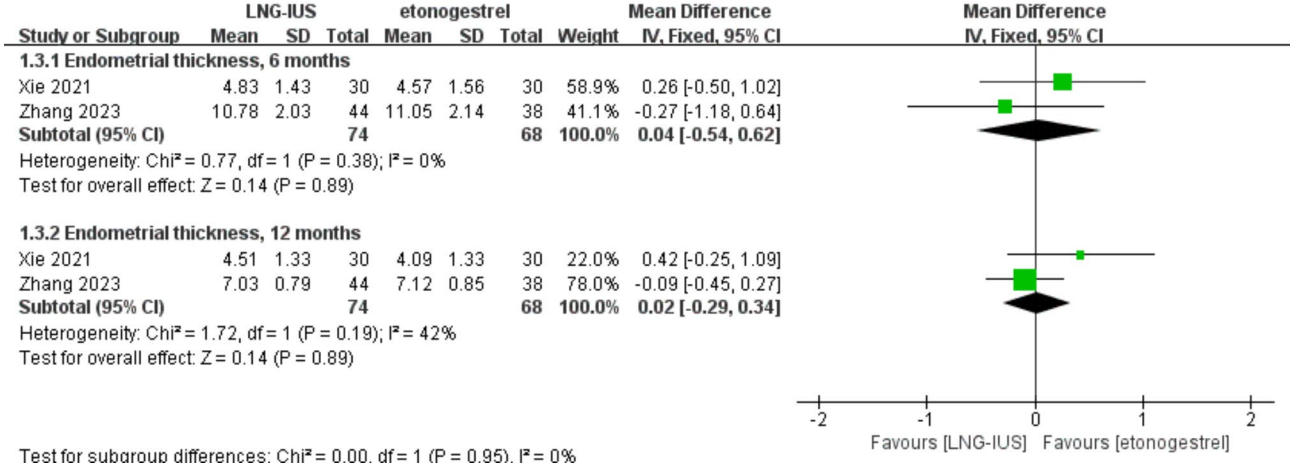

Fig. 4 Forest plot of the endometrial thickness after LNG-IUS insertion or etonogestrel subcutaneous implantation

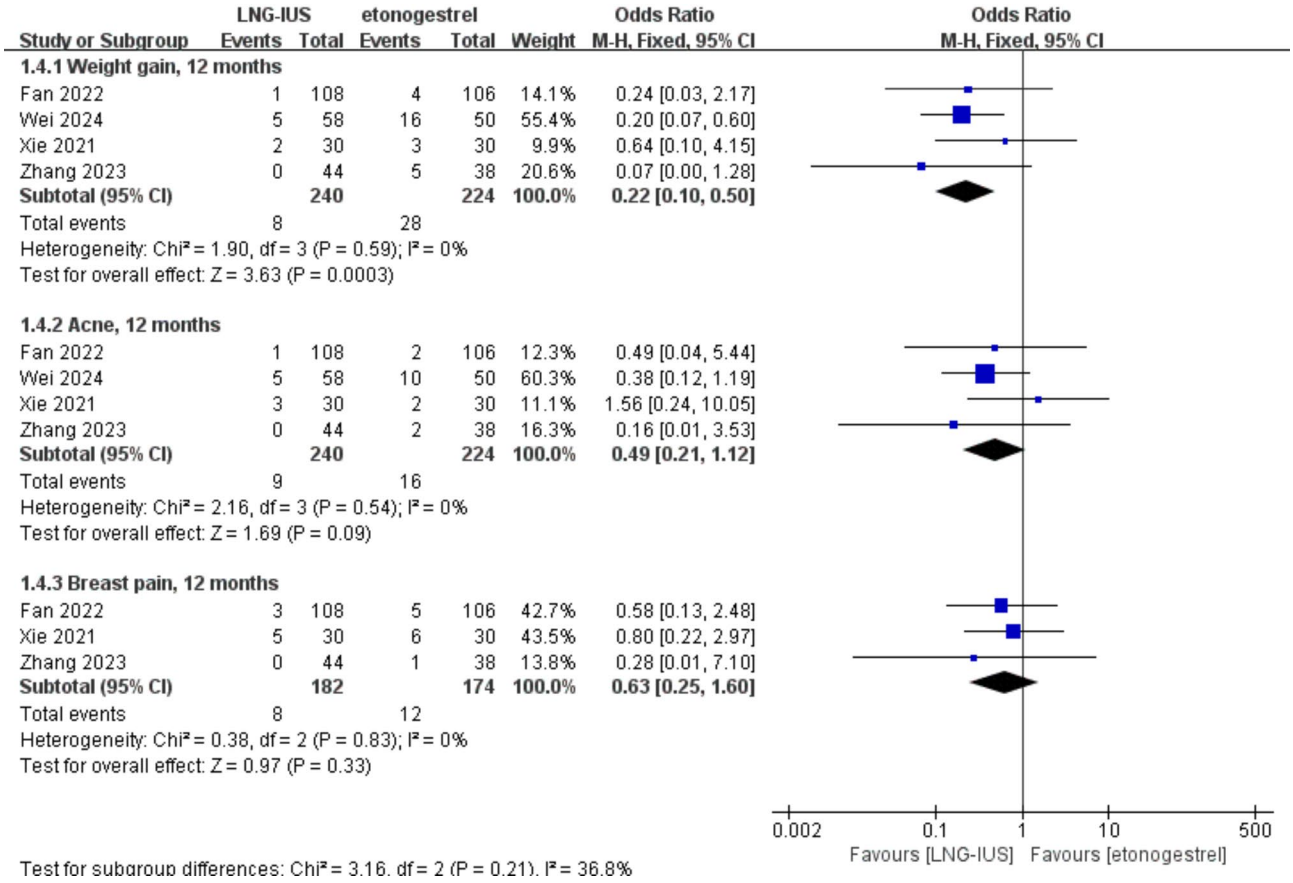

Fig. 5 Forest plot of the adverse effects after LNG-IUS insertion or etonogestrel subcutaneous implantation

Post-focused ultrasound ablation (FUA) therapy

LNG-IUS vs. expected treatment

In terms of the intensity of dysmenorrhea, a significant benefit for FUA + LNG-IUS group at 6-month and 12-month follow-up (Fig. 16) [33–38].

Another two studies [39, 40] showed better efficacy in reducing pain in the FUA + LNG-IUS than in the FUA group at 12-month follow-up (Fig. 17). Regarding menstrual blood loss, a statistically significant benefit was observed in the FUA + LNG-IUS group at 6 months in two studies [33, 38]. But at 12-month follow-up, the other meta-analysis of two studies reported no statistically significant difference in menstrual blood loss reduction between FUA + LNG-IUS and FUA alone groups (Fig. 18).

Risk of bias assessment and quality of judgment

The summary of the risk of bias assessment can be found in Additional file 3. Furthermore, the quality of judgement is summarized in Additional file 4.

Discussion

When comparing LNG-IUS to mifepristone, there was no significant difference observed in terms of quality of life. Compared with etonogestrel, LNG-IUS had a better effect on reducing the size of the uterus and less incidence of weight gain, but there was no difference in reducing pain and reducing the thickness of the endometrium. In terms of follow-up time, the comparative study of monotherapy was mostly 6–12 months. Data over a longer period of time is lacking to determine whether LNG-IUS differs from other monotherapy treatments.

The most frequently compared treatments were the combination of GnRH-a with LNG-IUS versus LNG-IUS alone. The meta-analysis indicated that the combination of LNG-IUS with GnRH-a was more effective, providing statistically significant benefits in reducing dysmenorrhea, menstrual volume, uterine volume, and endometrial thickness. Additionally, preconditioning with GnRH-a prior to the insertion of LNG-IUS was associated with a reduced likelihood of device expulsion, irregular vaginal bleeding and abdominal pain. This outcome may be attributed to the reduction in uterine volume achieved by GnRH-a, which mitigates the risk of LNG-IUS expulsion, particularly in patients with uterine enlargement due to

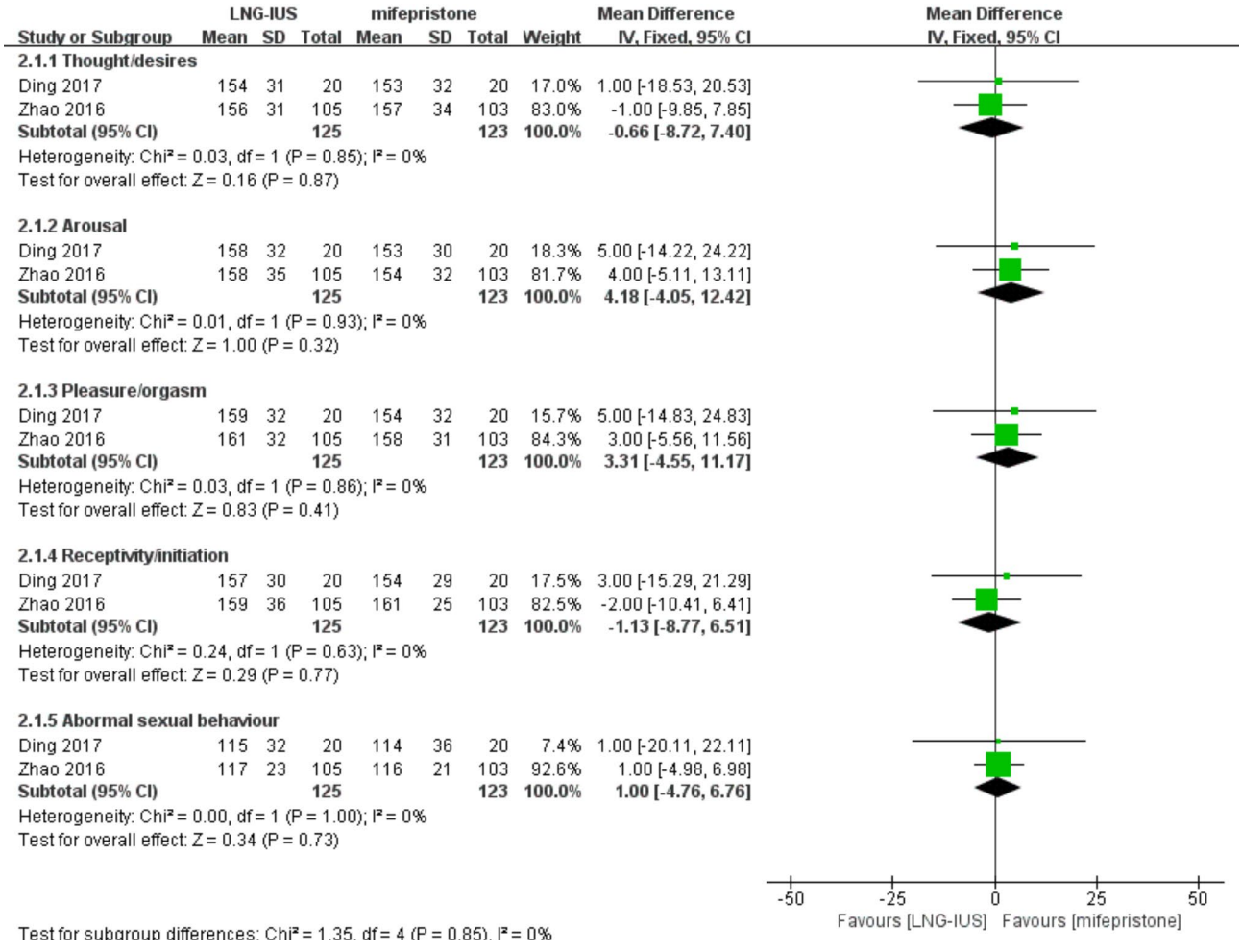

Fig. 6 Forest plot of the quality of life after LNG-IUS insertion or mifepristone treatment at 6-month follow-up

AM [41]. LNG-IUS releases progesterone into the uterine cavity, resulting in a high local concentration of levonorgestrel. This downregulates the expression of estrogen and progesterone receptors, rendering the endometrium less responsive to circulating estradiol, thereby inhibiting endometrial hyperplasia and reducing menstrual bleeding [42]. While GnRH-a suppresses the secretion of LH and FSH from the pituitary gland, leading to decreased production of estrogen and progesterone [43]. Therefore, GnRH-a preconditioning is recommended for patients with an enlarged uterus or a history of LNG-IUS expulsion.

All studies included in this review involved the administration of GnRH-a were three cycles. One study [44] utilized a sustained release of GnRH-a before LNG-IUS insertion, demonstrating similar results in alleviating dysmenorrhea, reducing menstrual volume, and improving hemoglobin and CA125 levels without increasing adverse reactions. However, the number of GnRH-a cycles may influence the outcomes. GnRH-a exerts a moderate inhibitory effect on the pituitary-ovarian axis, reducing estrogen release. Long-term use can decrease the sensitivity of the hypothalamic-pituitary pathway, leading to reduced secretion of pituitary gonadotropins [45]. One study [46] reported that after six cycles of GnRH-a, 54 patients developed symptoms such as hot flashes and restlessness, which resolved spontaneously two weeks post-treatment cessation. Therefore, further comparative studies are necessary to determine the optimal dosage, formulation, and treatment duration for GnRH-a to balance symptom management and side effect reduction.

In the context of post-surgical excision therapy, the combination of surgical excision with LNG-IUS has demonstrated superior efficacy in preventing recurrence compared to surgical excision alone. This is particularly evident in the long-term reduction of uterine size. Over extended follow-up periods, such as three years, the combination therapy has shown increasing success in controlling symptoms and reducing the recurrence of AM [47]. This may be related to the lesion cannot be fully identified or completely excised during surgery. Without additional intervention post-surgery, long-term estrogen

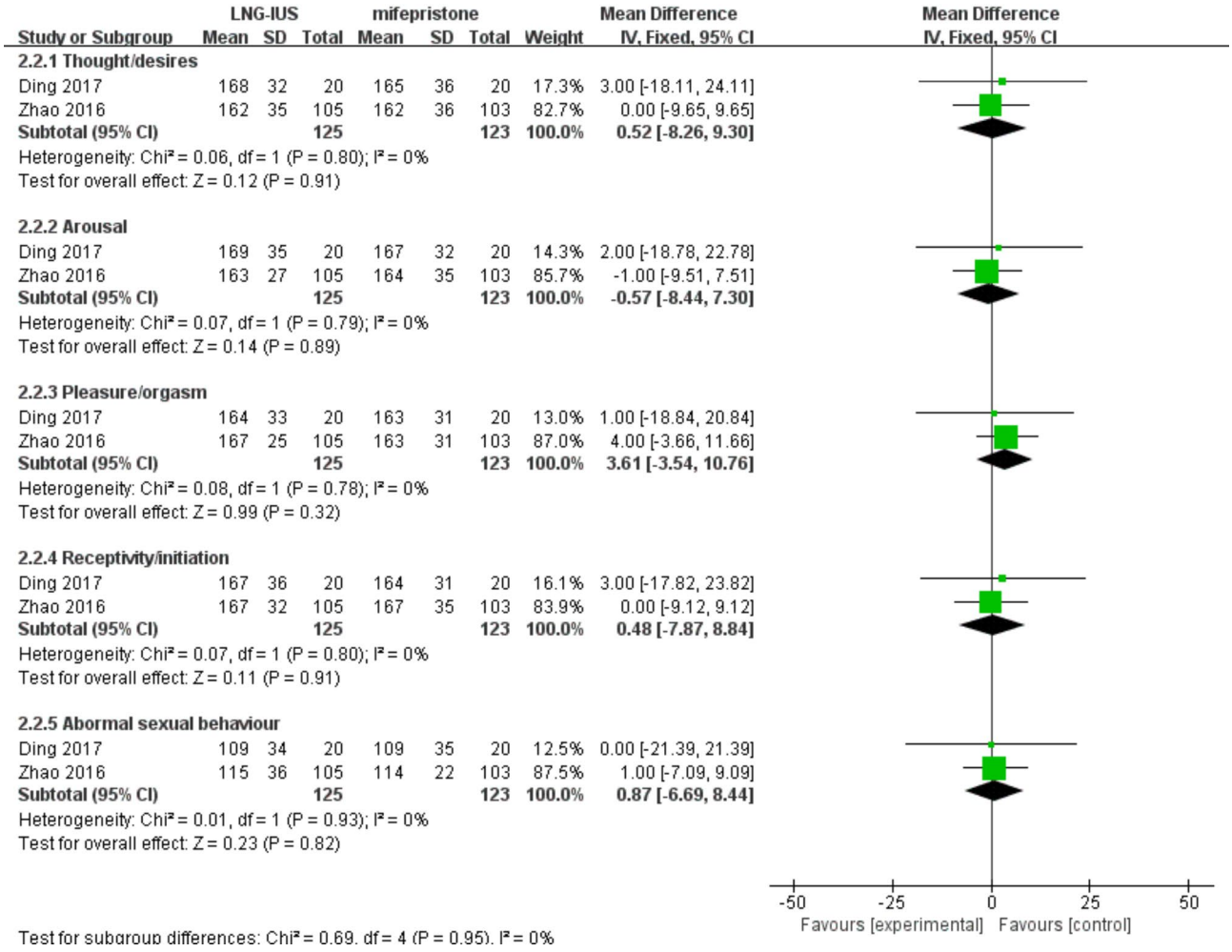

Fig. 7 Forest plot of the quality of life after LNG-IUS insertion or mifepristone treatment at 12-month follow-up

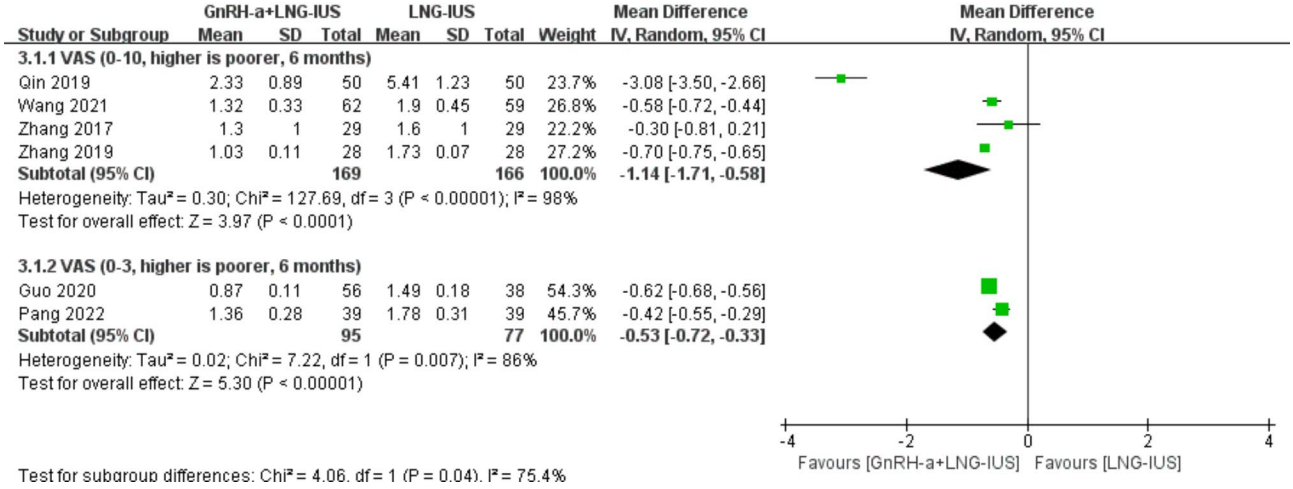

Fig. 8 Forest plot of the pain score after GnRH-a + LNG-IUS or LNG-IUS only

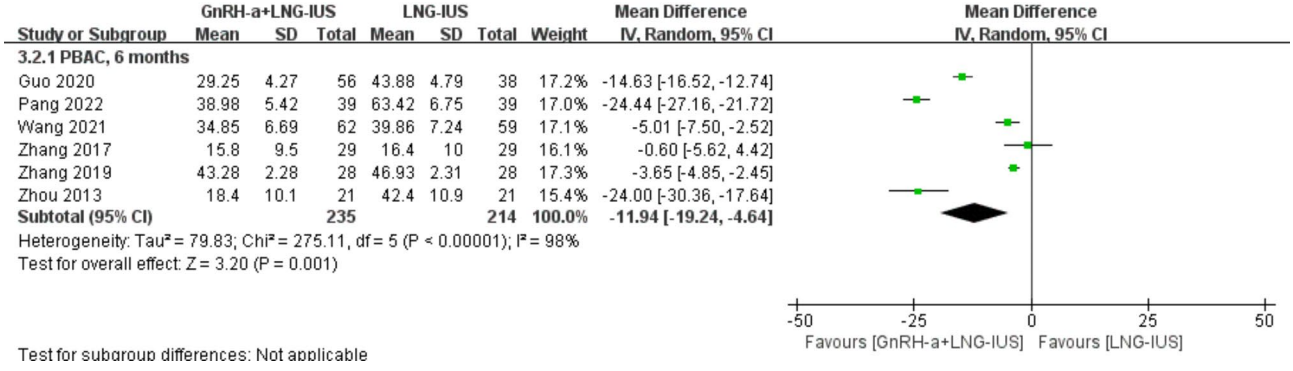

Fig. 9 Forest plot of the PBAC after GnRH-a + LNG-IUS or LNG-IUS only

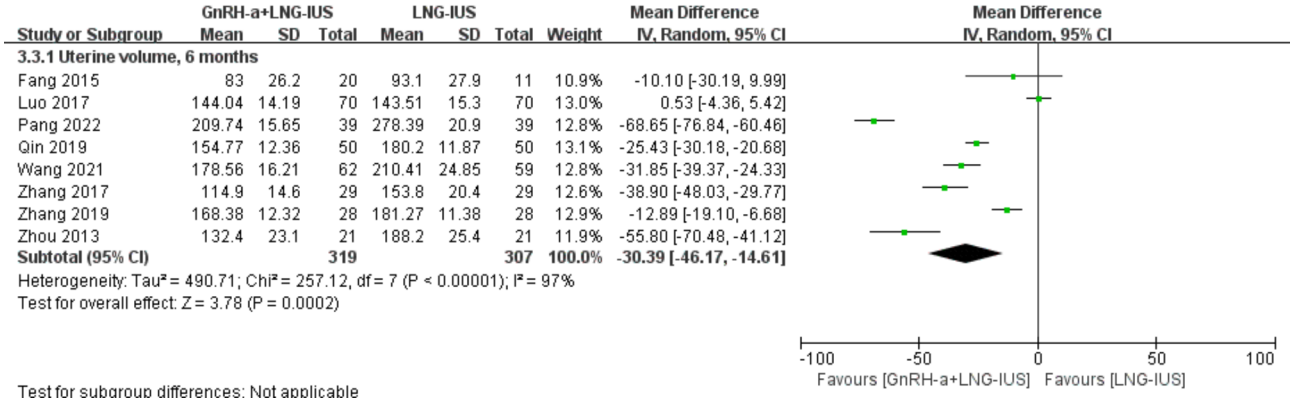

Fig. 10 Forest plot of the uterine volume after GnRH-a + LNG-IUS or LNG-IUS only

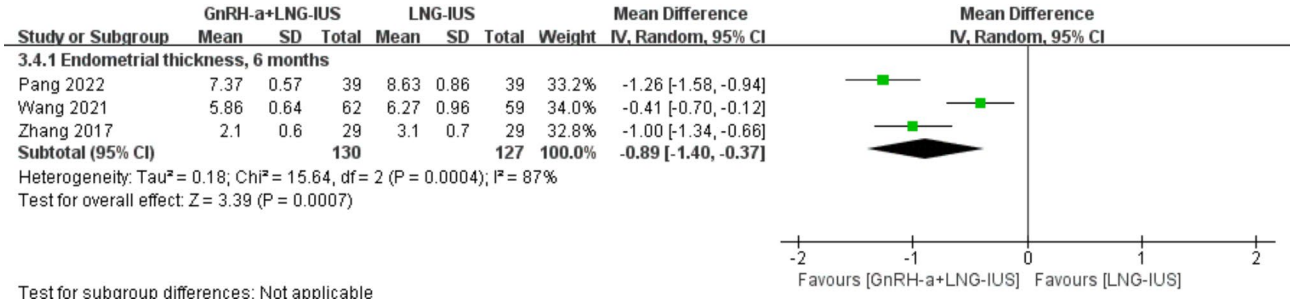

Fig. 11 Forest plot of the endometrial thickness after GnRH-a + LNG-IUS or LNG-IUS only

stimulation and repeated endometrial shedding may lead to recurrence or progression of the condition [48]. Therefore, the post-operative application of LNG-IUS is advised to achieve more favorable outcomes.

With advancements in image-guided technology, FUA has emerged as a novel surgical approach for the treatment of AM in recent years [49]. Utilizing real-time ultrasound or MRI monitoring, FUA precisely determines the size of the lesion and surrounding tissue, enabling the application of high-intensity ultrasound energy to ablate the targeted tissue [50]. This meta-analysis incorporated seven studies to evaluate the outcomes associated with the use of LNG-IUS following FUA treatment. The findings indicate that the application of LNG-IUS after FUA significantly control over patients' pain. However, at the 12-month follow-up point, combination therapy did not show a significant advantage in reducing menstrual blood loss.

Regarding the use of additional medications post-FUA, Fang et al. [9] found that GnRH-a combined with FUA was significantly more effective in alleviating dysmenorrhea, reducing uterine volume, and decreasing blood loss after 12 months. Conversely, Zhu et al. [38] compared the effects of mifepristone following FUA and observed differences in the rate of uterine volume reduction and dysmenorrhea scores within 12 months, though no significant differences were noted after 24 months of follow-up.

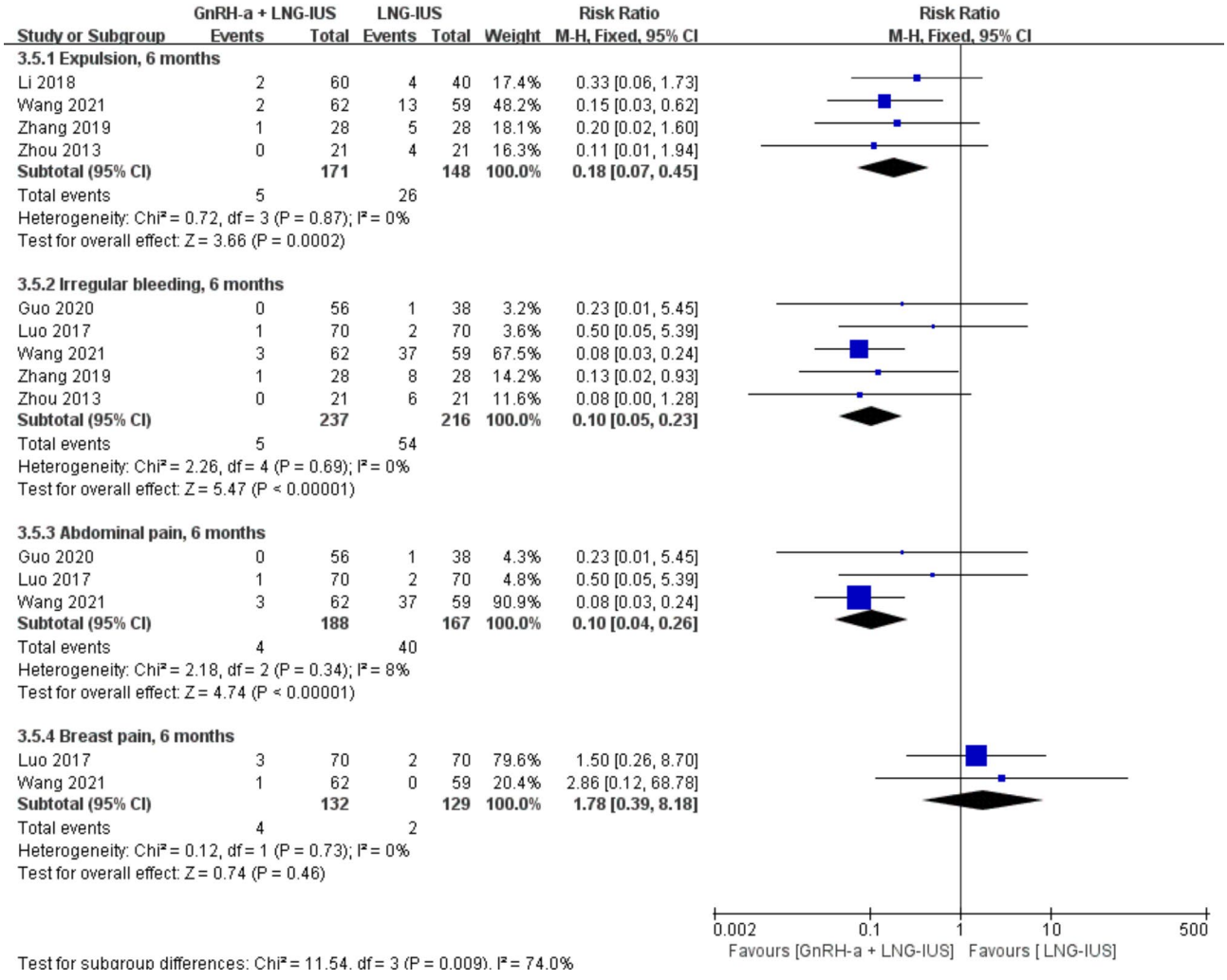

Fig. 12 Forest plot of the adverse effects after GnRH-a + LNG-IUS or LNG-IUS only

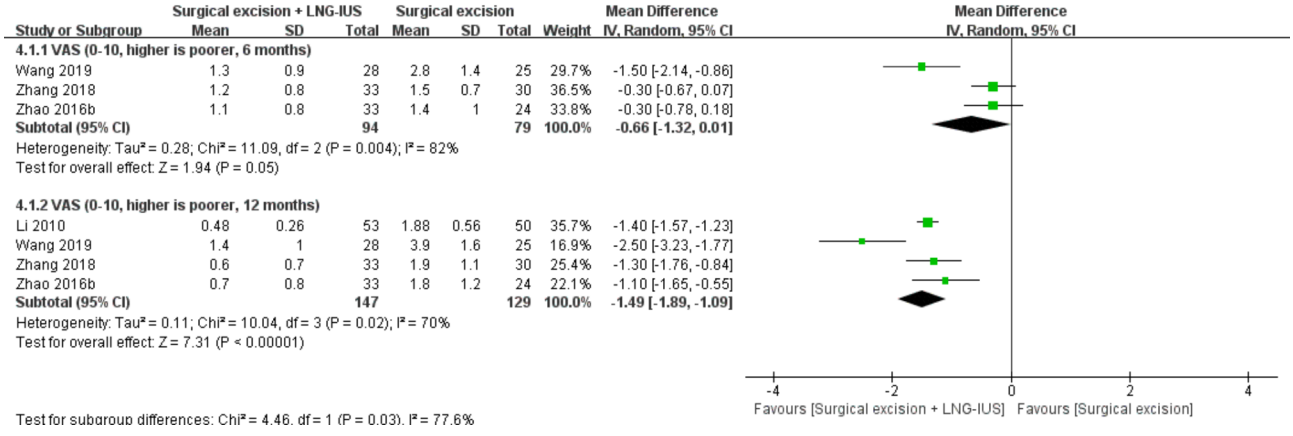

Fig. 13 Forest plot of the pain score points after surgical excision + LNG-IUS insertion or surgical excision only

FUA induces coagulative necrosis in the treated area, blocks blood supply to the lesion, and inhibits its progression. Over time, the necrotic fibroid tissue is typically absorbed by the body's metabolic processes [51]. Therefore, as these necrotic areas are resorbed, the long-term effectiveness of FUA combined with LNG-IUS therapy may not surpass that of monotherapy. Moreover, the ongoing debate regarding the long-term efficacy of

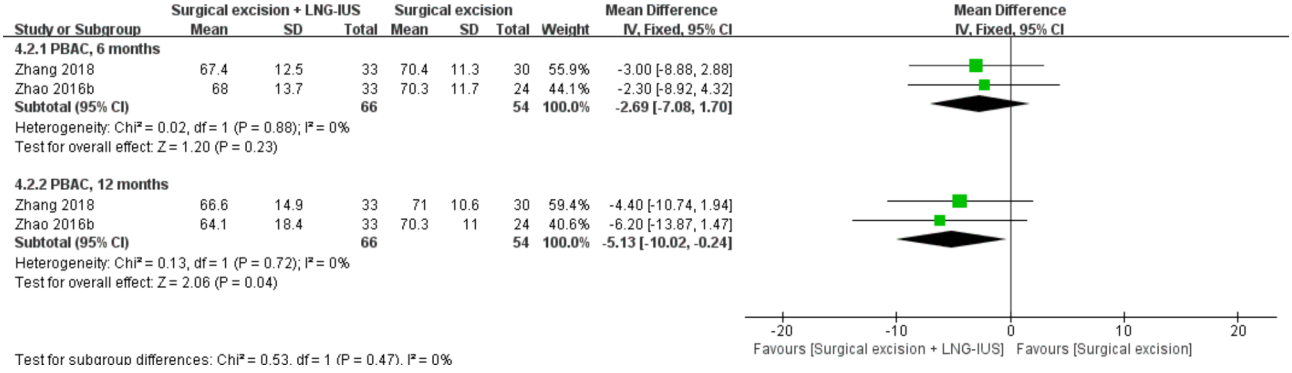

Fig. 14 Forest plot of the PBAC after surgical excision + LNG-IUS or surgical excision only

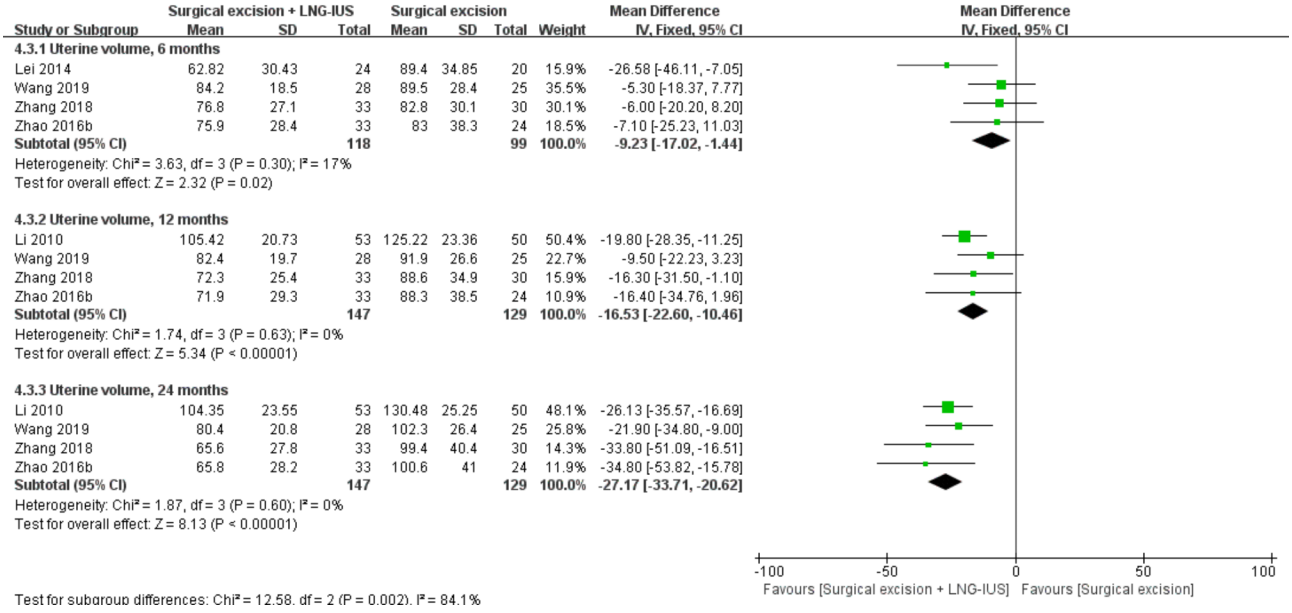

Fig. 15 Forest plot of the uterine volume after surgical excision + LNG-IUS or surgical excision only

combination therapy could be influenced by the specific effects of FUA.

FUA presents certain limitations. Specifically, there may be regions that cannot be effectively ablated during the procedure. In cases where the AM lesion is located deep within the posterior wall of the uterus, the ultrasound may lack sufficient penetration depth to completely ablate the lesion. This limitation is notable given that the posterior uterine wall is often the most severely affected area in patients with AM. One study [52] reported a markedly higher efficacy of FUA in patients with AM located in the anterior uterine wall compared to those with lesions in the posterior wall. Consequently, the use of LNG-IUS following FUA is recommended to mitigate the risk of AM recurrence.

It is important to note that most follow-up periods in this systematic review and meta-analysis were limited to 6 and 12 months. Currently, a cohort study with a 5-year follow-up of patients with adenomyosis who received LNG-IUS treatment has demonstrated that LNG-IUS significantly reduces uterine volume and improves menstrual patterns in patients [53]. Further research with longer follow-up durations is warranted to more comprehensively assess the long-term efficacy and safety of LNG-IUS therapy relative to other treatments. Additionally, emerging evidence suggests that LNG-IUS may improve sustained pregnancy rates, clinical pregnancy outcomes, and implantation rates in patients with AM [54]. Therefore, it may be necessary to pay attention to the fertility of patients. More research is needed to further evaluate not only the relief of symptoms, but also the fertility of patients.

Conclusion

In conclusion, this study shows that for single-drug therapy aimed at improving pain and quality of life, current evidence does not support a definitive recommendation for a preferred treatment within 12 months. In the

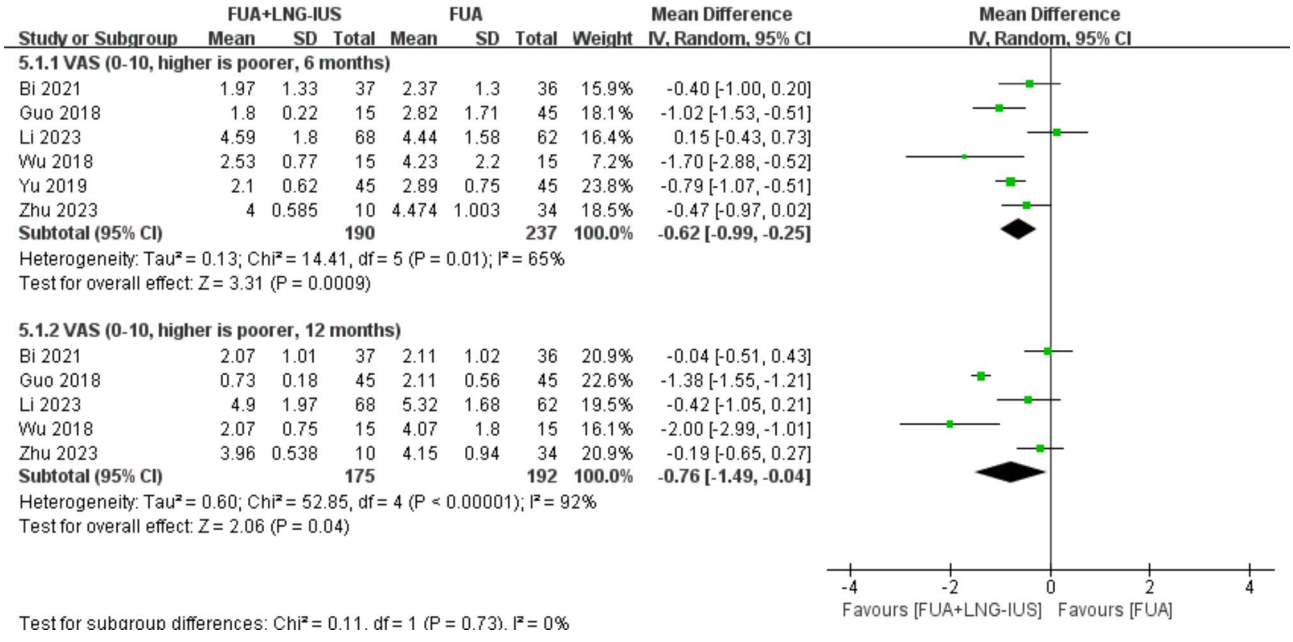

Fig. 16 Forest plot of the change in the pain score after FUA + LNG-IUS or FUA only

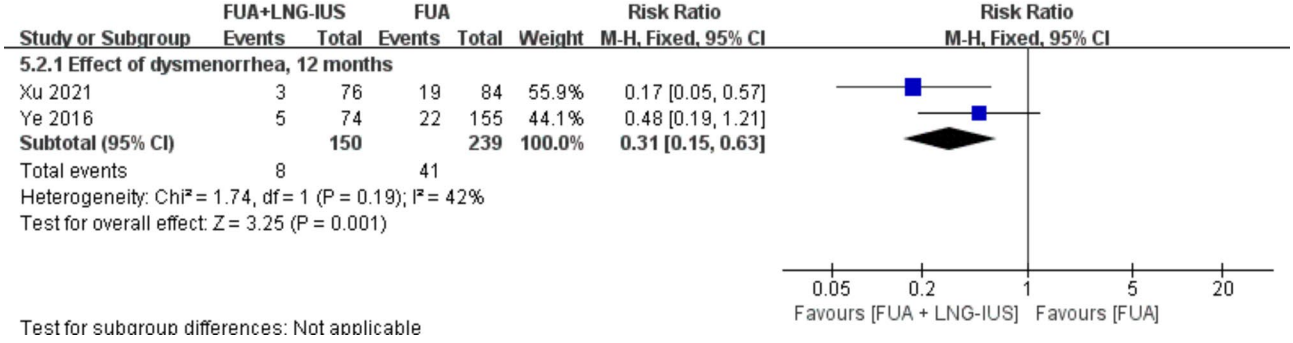

Fig. 17 Forest plot of the effect of dysmenorrhea after FUA + LNG-IUS or FUA only

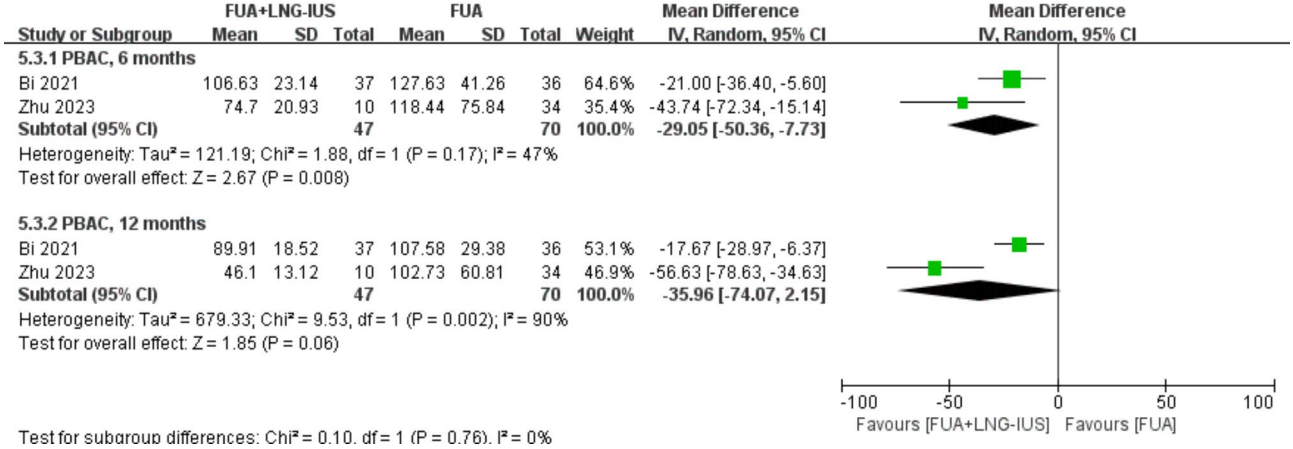

Fig. 18 Forest plot of the change in the PBAC after FUA + LNG-IUS or FUA only

management of moderate to severe AM, LNG-IUS combined with GnRH-a is recommended, as this approach has demonstrated significant efficacy in reducing lesion volume, alleviating pain, controlling heavy menstrual bleeding, inducing endometrial atrophy, reducing the probability of expulsion, and mitigating irregular bleeding. Regarding surgical interventions, the addition of postoperative LNG-IUS offers benefits in reducing long-term pain and menstrual bleeding, so we speculated that younger patients or those experiencing significant pain and bleeding might benefit from this combined therapy with LNG-IUS. Additionally, in the context of combined FUA, LNG-IUS has shown advantages in managing short-term pain and menstrual bleeding. It is advised that patients presenting with severe symptoms receive LNG-IUS as soon as possible following the intervention. However, more research with high quality is needed to further evaluate the effect and safety in more than 12 months.

Abbreviations

AM	Adenomyosis
GnRH-a	Gonadotropin-releasing hormone agonists
LNG-IUS	Levonorgestrel-releasing intrauterine system
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
RevMan	Review Manager
RRs	Risk ratios
Cis	Confidence intervals
MDs	Mean differences
NOS	Newcastle-Ottawa Scale
VAS	Visual analogue scale
PBAC	Pictorial blood loss assessment chart
FUA	Focused ultrasound ablation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01349-4.

Supplementary Material 1: Search strategy

Supplementary Material 2: Characteristics of studies

Supplementary Material 3: Risk of bias assessment of RCTs

Supplementary Material 4: Quality judgement of non-RCTs

Acknowledgements
Not applicable.

Author contributions
YD and JL contributed to the study conception and design. BZ and JS performed the literature search and study selection, BZ, XL, YW, HY, ZG and CZ performed the data extraction. BZ, JS, XL, QL, SL and YW performed the data summary. BZ, JL, JS and CZ prepared and wrote the manuscript. All authors were finally approval of manuscript.

Funding
This work was supported by the National Key R&D Program of China (2022YFC2704000), the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-085), and the National Natural Science Foundation of China (86071628).

Data availability
The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[2]National Clinical Research Center for Obstetric & Gynecologic Diseases, Beijing, China
[3]Shuaifuyuan No. 1, Dongcheng District, Beijing, China

Received: 25 September 2024 / Accepted: 24 January 2025
Published online: 13 February 2025

References

1. Leng J. Chinese experts' consensus on diagnosis and treatment of adenomyosis. Chin J Obstet Gynecol. 2020;55:376–83. https://doi.org/10.3760/cma.j.cn112141-20200228-00150.
2. Xiong F, Li W, Rao X. Comparison of hysteroscopic electrotomy and curettagein the treatment of abnormal uterine bleeding caused byendometrial polyps. Contemp Med. 2021;27:88–90.
3. Chinese Obstetricians and Gynecologists Association; Cooperative Group of Endometriosis, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Guideline for the diagnosis and treatment of endometriosis (third edition). Chin J Obstet Gynecol. 2021;56:812–24. https://doi.org/10.3760/cma.j.cn112141-20211018-00603.
4. Gemzell-Danielsson K, Kubba A, Caetano C, Faustmann T, Lukkari-Lax E, Heikinheimo O. Thirty years of mirena: a story of innovation and change in women's healthcare. Acta Obstet Gynecol Scand. 2021;100:614–8. https://doi.org/10.1111/aogs.14110.
5. Dason ES, Chan C, Sobel M. Diagnosis and treatment of adenomyosis. CMAJ: Can Med Association J = J de L'Association Medicale Canadienne. 2021;193:E242. https://doi.org/10.1016/j.jogc.2023.04.008.
6. Kho KA, Chen JS, Halvorson LM. Diagnosis, evaluation, and treatment of adenomyosis. JAMA. 2021;326:177–8. https://doi.org/10.1001/jama.2020.26436.
7. Schrager S, Yogendran L, Marquez CM, Sadowski EA. Adenomyosis: diagnosis and management. Am Family Phys. 2022;105:33–8.
8. Li Q, Yuan M, Li N, Zhen Q, Chen C, Wang G. The efficacy of medical treatment for adenomyosis after adenomyomectomy. J Obstet Gynaecol Res. 2020;46:2092–9. https://doi.org/10.1111/jog.14376.
9. Fang H, Hong C, Gong X. Effects of Levonorgestrel combined with GnRH-a drug-assisted focused Ultrasound ablation on PI3K/PTEN signaling pathway in Adenomyosis. Clin Exp Obstet Gynecol. 2023;50. https://doi.org/10.31083/j.ceog5012269.
10. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, et al. PRISMA Extension for scoping reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–73. https://doi.org/10.7326/M18-0850.
11. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical Res ed). 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.
12. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford 2000.

13. Fan L, Duan R, Fu Y. Effect of etonogesterone implant and levonorgestrel intrauterine system for treating patients with adenomyosis. Chin J Family Plann. 2022;30:279–83. https://doi.org/10.3969/j.issn.1004-8189.2022.02.007.
14. Zhang L, Wang X. Influence of etonogestrel implant on improvement of pain relief and life quality in patients with adenomyosis. Chin J Clin Obstet Gynecol. 2023;24:487–9.
15. Xie B, Liu Y,Huang Y, Lu C. Analysis on clinical effect of etonogestrel subdermal implant in treatment of adeno-myosis. Maternal Child Health Care China. 2021;36:1708–11.
16. Wei A, Tang X, Yang W, Zhou J, Zhu W, Pan S. Efficacy of etonogestrel subcutaneous implants versus the levonorgestrel-releasing intrauterine system in the conservative treatment of adenomyosis. Open Med (Poland). 2024;19. https://doi.org/10.1515/med-2024-0914.
17. Ding H, Han Y. Impact on the sexual function of patients of three treatments for adenomyosis. Chin J Hum Sexuality. 2017;26:48–51. https://doi.org/10.3969/j.issn.1672-1993.2017.08.015.
18. Zhao D, Zhang Y. Effects of different treatment methods on the quality of sexual life and marital life of patients with adenomy-osis. Chin J Hum Sexuality. 2016;25:43–6. https://doi.org/10.3969/j.issn.1672-1993.2016.06.014.
19. Qin W, Liao J. Effects of Triptorelin acetate injection combined with levonorgestrel-releasing intra-uterine Systemon Uterine Hemodynamics,ovarian function and safety in patients with adenomyosis of Uterus. Evaluation Anal drug-use Hosp China. 2019;19:546–8. https://doi.org/10.14009/j.issn.1672-2124.2019.05.010.
20. Wang L, Tang C. Influence of GnRH-αcombined with levonorgestrel intrauterine device system for treating women with adenomyosis on their pain symptoms, serum MMPs level, and recurrence rate. Chin J Family Plann. 2021;29:266–270274. https://doi.org/10.3969/j.issn.1004-8189.2021.02.014.
21. Zhang Y. Application effect of GnRHa before placing levonorgestrel releasingintrauterine system on severe dysmenorrheaand menstrual volume plus adenomyosis. Anhui Med Pharm J. 2017;21:1311–3. https://doi.org/10.3969/j.issn.1009-6469.2017.07.039.
22. Zhang D, Guo H, Qiu H. Effects of GnRH-α combined with mirena and serum recurrence related indicators in patients with adeno▪myosis. J Practical Med. 2019;35:84–7. https://doi.org/10.3969/j.issn.1006-5725.2019.01.018.
23. Guo M, Deng Z, Xu H. Clinical study of Mirena combined with gonadotropin-releasing hormone agonist inthe treatment of adenomyosis. J Guangxi Med Univ. 2020;37:506–9. https://doi.org/10.16190/j.cnki.45-1211/r.2020.03.031.
24. Pang H, Chen J, Ruan Y. Clinical efficacy of GnRH-a combined with a levonorgestrel-releasing intrauterine system (Mirena) in patients with adenomyosis and its effects on ovarian function, CA125, CA153 and CEA expression. Chin J Prim Med Pharm. 2022;29:825–9. https://doi.org/10.3760/cma.j.issn.1008-6706.2022.06.006.
25. Zhou Y, Wu X, Dong Q, Huang M. GnRH-a combined with levonorgestrel-releasing Intrauterine System in the treatment of large uterine adenomyosis. Chin J Minim Invasive Surg. 2013;13:1002–4.
26. Fang F, Liu S, Wang X, Lin X. Classified conservative treatment for adenomyosis:a preliminary observation. Shanghai Med J. 2015;38:239–44.
27. Li Q, Ding Y, Zhang X-Y, Feng W-W, Hua K-Q. Drug therapy for adenomyosis: a prospective, nonrandomized, parallel-controlled study. J Int Med Res. 2018;46:1855–65. https://doi.org/10.1177/0300060517752997.
28. Wang X, Han X. Comparative study on treatment of adenomyosis with Adenomyotomy combined with Mirenaor GnRH-a. J Med Res. 2019;48:148–51.
29. Zhang C, Deng S. The effect observation of postoperative use of levonorgestrel slow releasing system in the vagina on adeno-myosis patients after laparoscopic uterus wedge resection. Chin J Hum Sexuality. 2018;27:106–8. https://doi.org/10.3969/j.issn.1672-1993.2018.04.033.
30. ZhaoR, Wang L, Gu Y, Chen Y, Wei T, Wu N, Wang S. The efficacy of laparoscopic cytoreductive surgery with levonorgestrel releasing intra uterine system for the treatment of adenomyosis. Chin J Clin Obstet Gynecol. 2016;17:24–7. https://doi.org/10.13390/j.issn.1672-1861.2016.01.008.
31. Li D, Xu Y, Shou J, Lin F, Zhang M, Shen Q. Observation of 53 cases of pain of adenomyosis treated with laparoscopic adenomyomectomy combined with the levonorgestrel releasing intra uterine system. Chin J Crit Care Medicine(Electronic Edition). 2010;3:331–4. https://doi.org/10.3877/cma.j.issn.1674-6880.2010.05.011.
32. Lei Q, Gong C, Li L, Xi F. Clinical analysis of uterine function reserved major uterinewall resection combined with mirena for severe adenomyosis. China J Mod Med. 2014;24:82–4.
33. Bi X, Ma J. The comprehensive application of conservative treatment for adenomyosis. J Chin Physician. 2021;23. https://doi.org/10.3760/cma.j.cn431274-20200504-00553.
34. Guo Q, Xu F, Ding Z, Li P, Wang X, Gao B. High intensity focused ultrasound treatment of adenomyosis: a comparative study. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2018;35:505–9. https://doi.org/10.1080/02656736.2018.1509238.
35. Li X, Zhang Y, Chen J, Fang C. Efficacy of high intensity focused Ultrasound combined with GnRH-a and LNG-IUS in the treatment of Adenomyoma. J Clin Res. 2023;40:168–72. https://doi.org/10.3969/j.issn.1671-7171.2023.02.003.
36. Wu Z, Pan Z, Lv X, Du Y, Jing M. Clinical observation of high-intensity focused ultrasound combined with levonorgestrel intrauterine sustained-release system in the treatment of adenomyosis. Shandong Med J. 2018;58:65–7. https://doi.org/10.3969/j.issn.1002-266X.2018.03.020.
37. Yu L, Xu L. Effect of high intensity focused ultrasound combined with levonorgestrel releasing intrauterine system on serum CA 125, EMAb, hemoglobin and ovarian function in patients with adenomyosis. Chin J Family Plann Gynecotokology. 2019;11:33–6. https://doi.org/10.3969/j.issn.1674-4020.2019.04.10.
38. Zhu H, Ma Q, Dong G, Yang L, Li Y, Song S, Mu Y. Clinical evaluation of high-intensity focused ultrasound ablation combined with mifepristone and levonorgestrel-releasing intrauterine system to treat symptomatic adenomyosis. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2023;40:2161641. https://doi.org/10.1080/02656736.2022.2161641.
39. Xu Y, Zhou Z, Wang H, Shao L, Liu G. High-intensity focused Ultrasound Combined with Gonadotropin-releasing hormone agonist or levonorgestrel-releasing Intrauterine System in treating dysmenorrhea of severe adenomyosis. J Comput Assist Tomogr. 2021;45:224–31. https://doi.org/10.1097/RCT.0000000000001138.
40. Ye M, Deng X, Zhu X, Xue M. Clinical study of high intensity focused ultrasound ablation combined with GnRH-a and LNG-IUS for the treatment of adenomyosis. Chin J Obstet Gynecol. 2016;51:643–9. https://doi.org/10.3760/cma.j.issn.0529-567x.2016.09.002.
41. Yan H, Peng L. Gonadotropin-releasing hormone agonist combined with levonorgestrel intrauterine sustained-release system in treatment of adenomyosis. China Med Eng. 2020;28:33–5. https://doi.org/10.19338/j.issn.1672-2019.2020.05.009.
42. Dhamangaonkar PC, Anuradha K, Saxena A. Levonorgestrel intrauterine system (Mirena): an emerging tool for conservative treatment of abnormal uterine bleeding. J Mid-life Health. 2015;6:26–30. https://doi.org/10.4103/0976-7800.153615.
43. Capezzuoli T, Rossi M, La Torre F, Vannuccini S, Petraglia F. Hormonal drugs for the treatment of endometriosis. Curr Opin Pharmacol. 2022;67:102311. https://doi.org/10.1016/j.coph.2022.102311.
44. Luo Y, Li Q, Mai Y, Li X, Zhang M. Clinical Observation of Goserelin in the treatment of Adenomyosis complicated with severe Dysmenorrhea before placing Levonorgestrel Intrauterine System. China Pharm. 2017;28:3671–4. https://doi.org/10.6039/j.issn.1001-0408.2017.26.20.
45. McArdle CA, Franklin J, Green L, Hislop JN. Signalling, cycling and desensitisation of gonadotrophin-releasing hormone receptors. J Endocrinol. 2002;173. https://doi.org/10.1677/joe.0.1730001.
46. Zhao Y. Observation of the effect of GnRH-a combined with LNG-IUS in the treatment of adenomyosis. Maternal Child Health Care China. 2017;32:1194–6. https://doi.org/10.7620/zgfybj.j.issn.1001-4411.2017.06.27.
47. Jiang J, Pan Y, Yu J, Zhang Y, Yang Y, Xu H, Sun F. Laparoscopic adenomyomectomy combined with levonorgestrel-releasing intrauterine system is effective for long-term management of adenomyosis. BMC Womens Health. 2024;24:28. https://doi.org/10.1186/s12905-023-02795-1.
48. Haiyan S, Lin W, Shuhua H, Wang W. High-intensity focused ultrasound (HIFU) combined with gonadotropin-releasing hormone analogs (GnRHa) and levonorgestrel-releasing intrauterine system (LNG-IUS) for adenomyosis: a case series with long-term follow up. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2019;36:1179–85. https://doi.org/10.1080/02656736.2019.1679892.
49. Dai Y, Liu L, Yu G, Peng Y, Chen N, Gao J, Shi Q, Jin P. Evaluation of the therapeutic efficacy of high-intensity focused ultrasound ablation combined with different drugs in the treatment of adenomyosis. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2024;41:2384471. https://doi.org/10.1080/02656736.2024.2384471.
50. Liu L, Wang T, Lei B. Image-guided thermal ablation in the management of symptomatic adenomyosis: a systematic review and meta-analysis. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2021;38:948–62. https://doi.org/10.1080/02656736.2021.1939443.

51. Li J-J, Chung JPW, Wang S, Li T-C, Duan H. The investigation and management of adenomyosis in women who wish to improve or preserve fertility. Biomed Res Int. 2018;2018:6832685. https://doi.org/10.1155/2018.
52. Gong C, Yang B, Shi Y, Liu Z, Wan L, Zhang H, Jiang D, Zhang L. Factors influencing the ablative efficiency of high intensity focused ultrasound (HIFU) treatment for adenomyosis: a retrospective study. Int J Hyperthermia: Official J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2016;32:496–503. https://doi.org/10.3109/02656736.2016.1149232.
53. Magalhaes J, Ferreira-Filho ES, Soares-Junior JM, Baracat EC. Uterine volume, menstrual patterns, and contraceptive outcomes in users of the levonorgestrel-releasing intrauterine system: a cohort study with a five-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2022;276:56–62. https://doi.org/10.1016/j.ejogrb.2022.06.029.
54. Liang Z, Yin M, Ma M, Wang Y, Kuang Y. Effect of pretreatment with a levonorgestrel-releasing intrauterine system on IVF and vitrified-warmed embryo transfer outcomes in women with adenomyosis. Reprod Biomed Online. 2019;39:111–8. https://doi.org/10.1016/j.rbmo.2019.03.101.

Publisher's note