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*Original Article*

# Effects of Leuprorelin combined with Mirena on endocrine function, emotion, quality of life, and endometrial receptivity in patients with adenomyosis

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**Abstract:** Objective: To evaluate the combined effects of Leuprorelin and Mirena on endocrine profiles, emotional well-being, quality of life, and endometrial receptivity (ER) in patients with adenomyosis. Methods: This is a retrospective cohort study involving 144 patients with adenomyosis, in which 81 received Mirena alone and 63 received the combination of Mirena and Leuprorelin. Primary outcomes included menstrual volume, dysmenorrhea, uterine volume, hormone levels, emotional status, quality of life, and ER, assessed via clinical scales and ultrasound. Results: Combination therapy significantly reduced menstrual volume, dysmenorrhea, and uterine volume compared to Mirena alone (all $P < 0.05$). Endocrine hormone levels were notably lower in the combination group ($P < 0.05$). Anxiety improved significantly ($P = 0.012$), with trends toward improved depression outcomes. Psychological health and social quality of life also showed significant improvement ($P < 0.05$). ER was enhanced, with better endometrial characteristics and blood flow ($P < 0.05$). Adverse events were similar between groups. Conclusion: The combination of Leuprorelin and Mirena offers superior efficacy over Mirena alone in managing adenomyosis. This regimen provides enhanced symptom relief, reduces endocrine disruptions, and improves emotional well-being and quality of life without increasing adverse events.

**Keywords:** Adenomyosis, GnRH agonist, Leuprorelin, levonorgestrel-releasing intrauterine device, menstrual bleeding, endometrial receptivity

## Introduction

Adenomyosis is a common gynecological condition characterized by the presence of endometrial tissue within the myometrium, leading to uterine enlargement, chronic pelvic pain, heavy menstrual bleeding, and dysmenorrhea. It not only impairs physical health but also significantly affects emotional well-being and quality of life (QoL) [1, 2]. Although adenomyosis is prevalent, its exact cause remains unclear, and treatment options are limited. Medical treatments typically involve hormonal therapies, such as gonadotropin-releasing hormone (GnRH) agonists like Leuprorelin, oral contraceptives, progestins, or the levonorgestrel-releasing intrauterine device (LNG-IUD, e.g., Mirena), which suppress ovarian function and reduce estrogen levels to alleviate symptoms. Surgical options, including laparoscopic surgery or hysterectomy, may be considered depending on the patient's reproductive plans [3].

Leuprorelin, a GnRH agonist, works by suppressing the pituitary-gonadal system, thereby reducing the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), leading to a low-estrogen state [4, 5]. Estrogen plays a crucial role in adenomyosis, stimulating the growth of both the endometrium and myometrium [6]. However, the low-estrogen state induced by GnRH agonists can cause side effects, which often prompts the addition of other treatments to improve outcomes and manage these effects [7].

The LNG-IUD, or Mirena, is effective in managing heavy menstrual bleeding and dysmenorrhea [8, 9]. It releases a high concentration of

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levonorgestrel locally, inducing decidualization and atrophy of the endometrial tissue, thereby mitigating the proliferative effects of estrogen [1]. This local action is critical for symptom relief in adenomyosis and provides a non-surgical alternative to hysterectomy [10].

While Leuprorelin and Mirena have been studied separately for adenomyosis treatment, their combined effects remain poorly explored. The potential interplay between systemic hormonal suppression and local endometrial effects warrants further investigation [11]. The integration of these therapies may provide a holistic approach, targeting both systemic and local pathways to optimize therapeutic efficacy. This retrospective cohort study aims to explore the combined effects of leuprorelin and Mirena on endocrine profiles, emotional well-being, QoL, and endometrial receptivity (ER) in adenomyosis patients.

## Materials and methods

*Research design and patient selection criteria*

This retrospective cohort study included 144 patients diagnosed with adenomyosis, treated at the First People's Hospital of Jiashan County between January 2022 and December 2023. Among them, 81 received Mirena alone, and 63 received a combination of Mirena and Leuprorelin. Patient data were extracted from the hospital's case management system. The study was approved by the Ethics Review Committee of the hospital, and individual patient consent was waived for this retrospective analysis.

Inclusion criteria: Patients aged ≥ 18 years with progressive dysmenorrhea [12], prolonged menstrual periods, increased menstrual volume, and a dysmenorrhea severity score between 4 and 10 on the Visual Analog Scale (VAS); a diagnosis of adenomyosis confirmed by transvaginal ultrasound (TVS) [2].

Exclusion criteria: Pregnant or lactating women; patients with hepatic, renal, or cardiac dysfunction; severe endocrine disorders, immune diseases, or tumors; abnormal uterine cavity conditions (e.g., intrauterine adhesions, submucosal leiomyomas ≥ 5.0 cm); patients who had received other treatments within the past three months; those with a history of uterine surgery, allergies, hematopoietic dysfunction, or acute/chronic infectious diseases.

*Ultrasound diagnosis and classification of adenomyosis*

All participants underwent baseline TVS between Days 2 and 6 of their menstrual cycle, performed by two experienced radiologists. Adenomyosis was diagnosed based on radiological criteria: (1) an enlarged, globular uterine configuration, (2) asymmetrical thickening of the uterine walls, (3) poorly defined junctional zones, (4) heterogeneous myometrial texture, and (5) sub-endometrial myometrial striations and cysts [13]. If ultrasound findings were inconclusive, a pelvic MRI was used to confirm or rule out adenomyosis [14]. Adenomyosis was classified as focal if distinct regions with adenomyotic features were observed; otherwise, it was classified as diffuse [15].

*Treatment procedure*

All patients received the Mirena intrauterine device (IUD) (52 mg levonorgestrel; HJ2014-0237, Bayer Oy, Finland), placed in the uterine cavity between Days 3 and 7 of their menstrual cycle. A follow-up B-ultrasound confirmed proper placement of the IUD.

For patients in the combination therapy group, Leuprorelin acetate (3.75 mg; H20093852, Shanghai Lizhu Pharmaceutical Co., Ltd., China) was administered subcutaneously from Days 1 to 5 of menstruation, with injections given every 28 days for three consecutive courses. After treatment completion, patients were monitored for six months starting from the first menstrual recovery.

*Menstrual volume assessment*

Menstrual volume was assessed using the Pictorial Blood Loss Assessment Chart before and six months after treatment [16]. The degree of blood staining on each sanitary pad was recorded, with scores assigned based on the extent of blood coverage: ≤ 1/3 (1 point), 1/3 to 3/5 (5 points), and ≥ 3/5 (20 points). A total score > 100 points indicates menstrual blood loss > 80 ml.

*Dysmenorrhea evaluation*

Dysmenorrhea was assessed before and six months after treatment using the Visual Analogue Scale (VAS) to quantify pain. Patients rated their pain during the most recent menstrual cycle from 0 (no pain) to 10 (severe, intol-

erable pain). A Cronbach's alpha of 0.94 confirmed the reliability of the VAS [17].

*Uterine volume calculation*

Uterine volume was measured before and six months after treatment using TVS. The volume was calculated using the geometric formula for a prolate ellipsoid: long diameter × width diameter × anteroposterior diameter × π/6 [18]. Measurements were taken 3 to 7 days after menstruation.

*Blood tests*

Fasting venous blood samples were collected from patients before treatment and on the third day of their last menstrual cycle, six months post-treatment. Serum was separated and analyzed for hemoglobin, FSH, LH, prolactin (PRL), testosterone (T), estradiol (E2), and progesterone (P) using a fully automated biochemical analyzer (TBA-40FR, Toshiba, Japan).

*Emotional status assessment*

Emotional status was assessed before treatment and six months post-treatment using the Self-Rating Depression Scale (SDS) [19] and the Self-Rating Anxiety Scale (SAS) [20]. Higher scores indicate more intense anxiety and depression.

Anxiety was measured using the SAS, which consists of 20 items rated on a 4-point Likert scale (1 = "none or a little of the time", 4 = "most or all of the time"). Scores range from 20 to 80: 25-49 indicates normal to mild anxiety, 50-59 indicates moderate anxiety, and ≥ 60 indicates severe anxiety. Raw scores were converted to index scores by multiplying by 1.25 [20]. The SAS showed strong reliability with a Cronbach's alpha of 0.849 [21].

Depression was assessed using the SDS, which also consists of 20 items on a 4-point scale, with total scores ranging from 20 to 80. Scores of 25-49 indicate normal to mild depression, 50-59 suggest moderate depression, and ≥ 60 indicates severe depression. The raw scores were converted to index scores by multiplying by 1.25 [19]. This method helps track treatment impact on mental health and overall well-being.

*QoL evaluation*

QoL was measured before treatment and six months later using the WHO-QoL BREF. This questionnaire consists of 24 items across four domains: physical health (7 items), psychological well-being (6 items), social relationships (3 items), and environment (8 items). Responses reflect the prior two weeks' experiences.

Each domain score was converted to a scale from 0 to 100 according to the questionnaire manual. A higher total score indicates better QoL. The WHO-QoL BREF showed excellent reliability with a Cronbach's alpha of 0.912 [22].

*Ultrasound measurement of ER*

Ultrasonography was performed using a color Doppler instrument (Voluson730, GE, USA). The ascending branches of the uterine arteries were measured bilaterally in a transverse section of the internal cervix, with a sampling space of 2 mm and an angle < 60° with the blood flow direction. In six stable cardiac cycles, the pulsatility index (PI), early diastolic notch, and end-diastolic blood flow of the uterine arteries were recorded.

Endometrial-subendometrial blood flows refer to the small-vessel branches entering the inner and inferior halos visible on the screen. Endometrial morphology was classified according to Dickey's criteria [23]: Type A (three strong linear echoes in the outer layer and midline, with weak endometrial echoes); Type B (three weak linear echoes, unclear midline); Type C (homogeneous strong echoes without a midline echo).

ER was assessed using the Salle scale [24], which evaluates endometrial thickness, morphology, myometrial structure, PI, early diastolic notch, end-diastolic blood flow, and endometrial-subendometrial blood flows. A score of ≥ 7 mm for endometrial thickness, multilayer morphology, uniform myometrial echogenicity, PI ≤ 3, absence of a diastolic notch, presence of end-diastolic flow, and endometrial blood flow signals each contribute to the ER score. A score of ≤ 13 indicates poor ER, with a maximum possible score of 20.

*Ultrasound assessment of adenomyosis-specific features*

To assess treatment effects on adenomyosis-specific structural changes, the following parameters were evaluated before and six months after treatment: (1) Myometrial thickness asymmetry: Measured at the fundus, body, and cervix using TVS. The average asymmetry was calculated for each patient. (2) Uterine artery doppler parameters: Resistance index (RI) and PI were evaluated using color Doppler ultrasonography, with measurements taken bilaterally and mean values used for analysis. (3) Elastography scores: Shear wave elastography (SWE) was performed to assess myometrial stiffness, with higher shear wave velocity indicating increased tissue stiffness.

*Serum biomarker measurement*

Serum biomarkers associated with adenomyosis were analyzed at baseline and six months post-treatment. Blood samples were collected after an overnight fast, centrifuged at 3,000 rpm for 10 minutes, and stored at -80°C. Cancer antigen 125 (CA125) levels were quantified using an ELISA kit (DCA125, R&D Systems, USA). Vascular endothelial growth factor (VEGF) levels were measured using an ELISA kit (ab100656, Abcam, UK). Interleukin-6 (IL-6) concentrations were determined using an ELISA kit (BMS213, Thermo Fisher Scientific, USA). All assays were performed in duplicate, and the average value was used for statistical analysis. Quality control samples were included in each batch to ensure accuracy.

*Statistical analysis*

Continuous variables were expressed as mean ± standard deviation (SD), and between-group comparisons were analyzed using t-tests (for normally distributed data with homogeneous variance) or nonparametric tests (for non-normally distributed data or data with heterogeneous variance). Categorical variables were presented as frequencies and percentages, and group comparisons were conducted using the chi-square test (for large samples with expected frequencies ≥ 5) or Fisher's exact test (for small samples with expected frequencies < 5). A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS version 28.0 (SPSS Inc., Chicago, IL, USA).

## Results

*Comparison of baseline characteristics*

The mean age, BMI, and disease duration were similar between the Mirena and combination groups, with no significant differences (all P > 0.05). Additionally, there were no significant differences in the incidence of hypertension, diabetes, smoking or drinking history, and other baseline characteristics such as abortion history, previous surgeries, or menstrual cycle length (all P > 0.05). The groups were well-matched, ensuring a fair comparison of outcomes. See **Table 1**.

*Comparison of menstrual volume and hemoglobin levels*

Both groups showed a significant reduction in menstrual volume and an increase in hemoglobin levels after treatment. The combination group demonstrated a greater reduction in menstrual volume (P < 0.001) and a more significant increase in hemoglobin levels (P = 0.030) compared to the Mirena group. See **Figure 1**.

*Comparison of dysmenorrhea scores*

Both groups showed improvement (both P < 0.05). The combination group showed a significantly greater reduction in dysmenorrhea scores post-treatment (P = 0.002) compared to Mirena alone. Both groups experienced a reduction, but the combination group had a more pronounced improvement. See **Table 2**.

*Comparison of uterine volume reduction*

Both groups showed a reduction in uterine volume (both P < 0.05), but the combination resulted in a significantly greater decrease (P = 0.024) compared to Mirena alone. See **Table 3**.

*Comparison of endocrine hormone levels*

Significant reductions in FSH, LH, PRL, E2, P, and T levels were observed in both groups (all P < 0.05). The combination group showed more pronounced reductions, particularly in FSH, LH, and testosterone levels (all P < 0.05), suggest-

**Table 1.** Comparison of demographic and basic data between the two groups

| Parameters | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Age (years) | 35.56 ± 4.12 | 35.99 ± 4.08 | 0.630 | 0.530 |
| BMI (kg/m$^2$) | 23.91 ± 3.92 | 23.51 ± 4.12 | 0.595 | 0.553 |
| Disease course (years) | 3.52 ± 1.94 | 3.55 ± 1.91 | 0.102 | 0.919 |
| Hypertension | 12 (14.81%) | 13 (20.63%) | 0.837 | 0.360 |
| Diabetes | 9 (11.11%) | 5 (7.94%) | 0.407 | 0.524 |
| Drinking history | 4 (4.94%) | 5 (7.94%) | 0.152 | 0.696 |
| Smoking history | 6 (7.41%) | 6 (9.52%) | 0.208 | 0.649 |
| Etiology | | | 4.341 | 0.362 |
| Male factor | 1 (1.23%) | 3 (4.76%) | | |
| Tubal | 13 (16.05%) | 11 (17.46%) | | |
| Endometriosis | 27 (33.33%) | 13 (20.63%) | | |
| Anovulation | 2 (2.47%) | 1 (1.59%) | | |
| Mixed/Unexplained/Other | 38 (46.91%) | 35 (55.56%) | | |
| Adenomyotic lesions | | | 0.330 | 0.566 |
| Diffuse | 61 (75.31%) | 50 (79.37%) | | |
| Focal | 20 (24.69%) | 13 (20.63%) | | |
| Previous abortion | 22 (27.16%) | 19 (30.16%) | 0.156 | 0.692 |
| Previous ovarian surgery | 19 (23.46%) | 13 (20.63%) | 0.163 | 0.686 |
| History of delivery | 16 (19.75%) | 15 (23.81%) | 0.345 | 0.557 |
| History of pregnancy | 49 (60.49%) | 41 (65.08%) | 0.318 | 0.573 |
| Menstrual cycle (d) | 35.31 ± 3.04 | 35.14 ± 3.83 | 0.299 | 0.765 |

BMI: body mass index.

ing that Leuprorelin enhances the effect of Mirena in reducing endocrine hormones. See **Table 4**.

*Comparison of anxiety scores*

Before treatment, anxiety scores (assessed by the SAS) showed no significant difference between the Mirena group (41.15 ± 3.24) and the combination group (39.67 ± 3.75) (P = 0.239). However, after treatment, both groups showed improvements in anxiety, with a more significant reduction in the combination group (t = 2.539, P = 0.012). While both groups improved in depression scores (SDS), the difference was not statistically significant (P = 0.058). See **Figure 2**.

*Comparison of QoL scores*

Both groups experienced improvements in physical health, psychological health, social relationships, and environment post-treatment. However, the combination group showed more pronounced improvements, especially in psychological and social domains. The overall QoL score was significantly higher in the combination group (279.24 ± 49.23) compared to the Mirena group (259.76 ± 50.52) (t = 2.321, P = 0.022). See **Table 5**.

*Comparison of ER*

The combination group showed significantly better ER than the Mirena group, with thinner endometrial thickness (8.23 ± 1.19 mm vs. 9.21 ± 2.32 mm, P = 0.001) and higher prevalence of Type A endometrium during ovulation (36.51% vs. 20.99%, P = 0.039). Additionally, markers of uterine vascular function, including the PI and diastolic notch prevalence, were significantly improved in the combination group (all P < 0.05), highlighting the superior ER achieved with the addition of Leuprorelin. See **Table 6**.

*Comparison of imaging outcomes*

Ultrasound imaging revealed that the combination therapy led to more significant improvements in myometrial thickness asymmetry (2.75 ± 1.22 mm vs. 3.42 ± 1.78 mm, P =

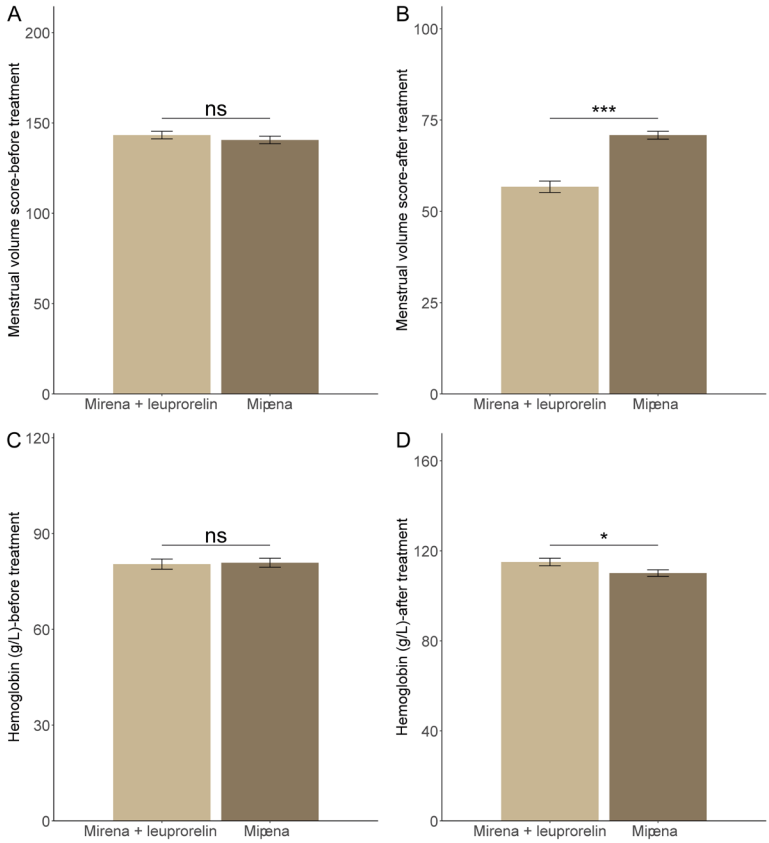


**Figure 1.** Comparison of menstrual volume between the two groups. A: Menstrual volume score before treatment; B: Menstrual volume score after treatment; C: Hemoglobin before treatment; D: Hemoglobin after treatment. ns: no significant difference, *P < 0.05, ***P < 0.001.

0.009) and uterine artery Doppler parameters. The combination group also showed better results in elastography scores (t = 2.015, P = 0.046). These findings suggest that Mirena combined with Leuprorelin leads to better structural normalization of the myometrium and improved tissue uniformity compared to Mirena alone. See **Figure 3**.

**Figure 3** shows typical ultrasound images of adenomyosis before and after treatment between the groups. Pre-treatment images (**Figure 3A** and **3C**) reveal thickened, irregular myometrium with heterogeneous echogenicity in both groups, consistent with diffuse adenomyosis (both P < 0.05). Post-treatment images (**Figure 3B** and **3D**) indicate reduced myometrial thickness asymmetry and improved tissue uniformity, with more significant improvements observed in the combination therapy group (both P < 0.05).

Quantitative data in **Table 7** support these findings, demonstrating that compared to the Mirena-only group, the combination group achieved statistically significant post-treatment improvements in multiple key imaging metrics related to adenomyosis (all P < 0.05).

*Comparison of serum biomarker levels between groups*

Both groups showed reductions in CA125, VEGF, and IL-6 post-treatment, but the combination group had significantly greater reductions (all P < 0.001). See **Table 8**.

*Comparison of adverse events between groups*

No significant differences were observed in the incidence of adverse events between the two groups. Vaginal spotting, amenorrhea, breast tenderness and low estrogen were reported in similar proportions across both groups, with no statistically significant differences (P > 0.05). See **Table 9**.

## Discussion

The endocrine system plays a pivotal role in the pathophysiology of adenomyosis [25]. Our results indicate that combining Leuprorelin, a GnRH agonist, with the Mirena IUD, which releases levonorgestrel, significantly reduces key hormones such as FSH, LH, and E2. Leuprorelin downregulates the pituitary-gonadal axis, thereby decreasing the secretion of FSH and LH [26, 27]. The resulting reduction in ovarian steroidogenesis leads to decreased production of E2, a hormone known to drive the proliferative phase of the menstrual cycle and contribute to the pathogenesis of adenomyosis [28, 29]. This mechanism efficiently induces a hypoestrogenic state, further complemented by the local effects of levonorgestrel released

**Table 2.** Comparison of dysmenorrhea score between the two groups

| Parameters | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|
| Before treatment | 6.41 ± 1.07 | 6.41 ± 0.95 | 0.017 | 0.986 |
| After treatment | 3.81 ± 1.04 | 3.12 ± 1.42 | 3.229 | 0.002 |

**Table 3.** Comparison of Uterine volume ($cm^3$) between the two groups

| Parameters | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|
| Before treatment | 82.42 ± 13.12 | 82.03 ± 13.42 | 0.175 | 0.861 |
| After treatment | 79.38 ± 14.08 | 74.12 ± 13.28 | 2.281 | 0.024 |

**Table 4.** Comparison of endocrine hormone levels between the two groups

| Parameters | | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|---|
| FSH (IU/L) | Before treatment | 8.47 ± 4.04 | 8.42 ± 3.74 | 0.082 | 0.935 |
| | After treatment | 5.84 ± 2.15 | 5.03 ± 2.31 | 2.187 | 0.030 |
| LH (IU/L) | Before treatment | 5.45 ± 2.43 | 5.72 ± 2.83 | 0.616 | 0.539 |
| | After treatment | 3.82 ± 1.13 | 3.15 ± 1.26 | 3.341 | 0.001 |
| PRL (ng/mL) | Before treatment | 25.38 ± 3.42 | 25.15 ± 3.26 | 0.411 | 0.682 |
| | After treatment | 21.96 ± 2.29 | 21.14 ± 2.58 | 2.008 | 0.047 |
| E2 (pg/mL) | Before treatment | 230.18 ± 80.09 | 233.03 ± 83.23 | 0.209 | 0.835 |
| | After treatment | 85.26 ± 10.38 | 81.64 ± 10.16 | 2.095 | 0.038 |
| P (ng/mL) | Before treatment | 5.28 ± 1.34 | 5.39 ± 1.26 | 0.504 | 0.615 |
| | After treatment | 1.49 ± 0.35 | 1.26 ± 0.43 | 3.548 | < 0.001 |
| T (ng/dL) | Before treatment | 28.15 ± 3.59 | 28.26 ± 3.14 | 0.199 | 0.842 |
| | After treatment | 22.36 ± 4.69 | 20.24 ± 4.13 | 2.839 | 0.005 |

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL: prolactin; E2: estradiol; P: progesterone; T: testosterone.

by the Mirena IUD. Levonorgestrel acts primarily on the endometrium, promoting decidualization and atrophy, counteracting estrogen's proliferative effects, and potentially modulating the molecular pathways involved in the establishment and progression of adenomyotic lesions [30]. This combination therapy targets both systemic and local hormonal modulation, significantly contributing to symptom relief and disease control, as observed in our findings.

Dysmenorrhea is a cardinal symptom of adenomyosis, severely impacting patients' QoL [31, 32]. Our study revealed that the combination of Leuprorelin and Mirena resulted in a more pronounced reduction in dysmenorrhea scores compared to Mirena alone. This effect is likely due to the synergy between the two treatments. Leuprorelin suppresses ovarian function systemically, while the levonorgestrel-releasing IUD induces local endometrial atrophy [5]. The reduction in menstrual flow leads to improved hemoglobin levels, further supporting the efficacy of this combination for symptoms like menorrhagia. Additionally, the levonorgestrel IUD may reduce prostaglandin production locally. Since prostaglandins play a key role in dysmenorrhea, this reduction likely contributes to pain relief, suggesting the IUD has an analgesic effect [33]. These mechanisms likely explain the superior management of pain and menstrual disorders observed in the combination therapy group.

Beyond physiological effects, adenomyosis significantly impacts emotional well-being and QoL [34]. The study found significant improvements in anxiety levels among patients receiving the combination treatment, with trends toward improved depression scores. These observations highlight the psychological aspect of chronic gynecological disorders, demonstrat-

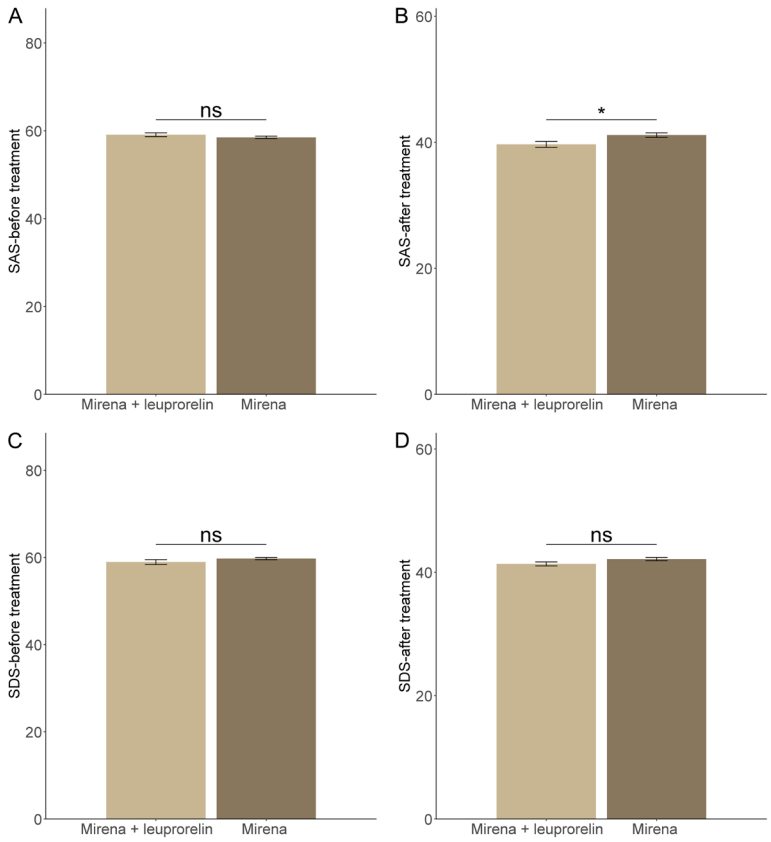


**Figure 2.** Comparison of emotion status between the two groups. A: SAS before treatment; B: SAS after treatment; C: SDS before treatment; D: SDS after treatment. ns: no significant difference, *P < 0.05. SAS: self-rating anxiety scale; SDS: self-rating depression scale.

ing that relief from physical symptoms can also improve emotional health. This correlation emphasizes the importance of addressing both physical and mental health in treatment plans. The continuous endocrine modulation provided by prolonged administration of GnRH analogs like Leuprorelin, which are known to influence neurotransmitters such as β-endorphins and potentially modulate mood, may contribute to these improvements [35]. Moreover, the combination treatment alleviates distressing symptoms like pain and abnormal uterine bleeding, likely reducing anxiety and enhancing the overall psychological state. The observed improvements in QoL across various domains, including physical health, psychological well-being, and social relationships, are likely a result of both direct health benefits and improved emotional status due to effective symptom control.

A key finding in this study was that combination therapy significantly improved ER, a crucial factor for adenomyosis patients seeking pregnancy. The therapy led to changes in hormone levels and structural improvements, which enhanced blood flow in the endometrial and subendometrial regions. It also improved the endometrial structure, which is beneficial for treatment. Levonorgestrel works locally to improve the endometrial environment, supporting implantation by modulating angiogenesis and reducing inflammation. Meanwhile, Leuprorelin exerts systemic effects by lowering estrogen levels, which may induce structural changes that enhance ER [36, 37]. Improved Salle scale scores in the combination therapy group further support these findings, highlighting the critical role of this combined approach in promoting favorable conditions for implantation and pregnancy outcomes.

Our study also demonstrated significant improvements in imaging features. Specifically, the combination group showed less asymmetry in myometrial thickness and improved uterine artery Doppler parameters, including lower RI and PI. These findings suggest that this therapy may modulate local tissue stiffness and vascular resistance. Earlier research supports this, as GnRH agonists have been shown to reduce myometrial edema and inflammation, while levonorgestrel suppresses abnormal angiogenesis [38]. Enhanced elastography scores also support the idea that combination therapy promotes structural normalization of the myometrium, which could contribute to symptom relief and long-term disease control.

Additionally, serum biomarkers CA125, VEGF, and IL-6 showed marked reductions, highlighting the anti-inflammatory and anti-angiogenic effects of the combination therapy. CA125, a well-established marker of adenomyosis activity, decreased more in the combination group than with Mirena alone. This aligns with findings that GnRH agonists inhibit ovarian ste-

**Table 5.** Comparison of QoL between the two groups

| Parameters | Time | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|---|
| Physical health | Before treatment | 55.97 ± 16.12 | 54.35 ± 19.67 | 0.542 | 0.589 |
| | After treatment | 67.09 ± 17.78 | 70.94 ± 13.83 | 1.461 | 0.146 |
| Psychological health | Before treatment | 55.79 ± 12.67 | 56.26 ± 15.67 | 0.195 | 0.845 |
| | After treatment | 66.06 ± 11.62 | 71.15 ± 15.37 | 2.185 | 0.031 |
| Social relationships | Before treatment | 56.29 ± 20.57 | 55.26 ± 19.77 | 0.302 | 0.763 |
| | After treatment | 66.68 ± 21.29 | 72.97 ± 13.63 | 2.153 | 0.033 |
| Environment | Before treatment | 58.94 ± 14.49 | 60.09 ± 19.81 | 0.389 | 0.698 |
| | After treatment | 63.92 ± 12.02 | 64.18 ± 16.42 | 0.104 | 0.917 |
| Overall | Before treatment | 238.26 ± 50.14 | 240.97 ± 61.02 | 0.293 | 0.770 |
| | After treatment | 259.76 ± 50.52 | 279.24 ± 49.23 | 2.321 | 0.022 |

QoL: quality of life.

**Table 6.** Comparison of ER between the two groups

| Parameters | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Endometrial thickness on ovulation day (mm) | 9.21 ± 2.32 | 8.23 ± 1.19 | 3.301 | 0.001 |
| Type A endometrium in ovulation | 17 (20.99%) | 23 (36.51%) | 4.255 | 0.039 |
| Uneven myometrial structure | 20 (24.69%) | 7 (11.11%) | 4.290 | 0.038 |
| Pulsatility index of uterine artery > 3 | 16 (19.75%) | 5 (7.94%) | 3.972 | 0.046 |
| Diastolic notch or deficiency of end diastolic blood flow | 10 (12.35%) | 1 (1.59%) | 4.389 | 0.036 |
| Endometrial-subendometrial blood flow (counts of vessels) | 8.49 ± 3.71 | 10.18 ± 3.34 | 2.834 | 0.005 |
| Salle score | 14.41 ± 3.02 | 16.27 ± 2.63 | 3.887 | < 0.001 |

ER: endometrial receptivity; Salle score: a scoring system for assessing endometrial receptivity.

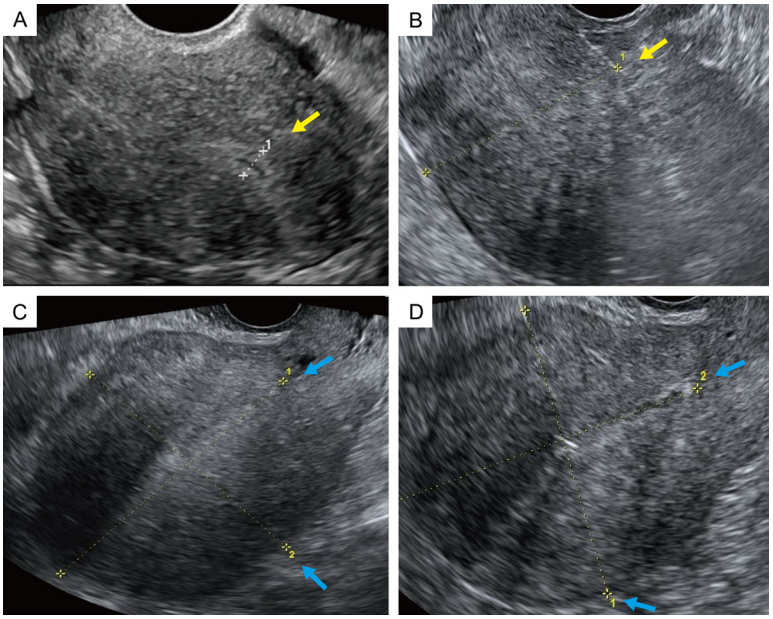


**Figure 3.** Comparison of typical ultrasound images of adenomyosis between the two groups. Arrows indicate the location of the lesions. A: Mirena group before treatment; B: Mirena group after treatment; C: Mirena combined with Leuprorelin group before treatment; D: Mirena combined with Leuprorelin group after treatment.

roidogenesis and reduce peritoneal fluid levels of this marker [33]. The reduction in VEGF levels is particularly noteworthy, as adenomyosis often involves vascular overgrowth. Lower VEGF levels may limit lesion progression. Similarly, the decrease in IL-6, a pro-inflammatory cytokine, suggests that the combination therapy modulates the inflammatory milieu of the myometrium, potentially alleviating pain and improving ER [25, 39].

Compared to previous studies, our findings further support the efficacy of GnRH agonists like leuprolide acetate in reducing hormone levels and alleviating symptoms in adenomyosis patients. For exam-

**Table 7.** Comparison of Imaging features between the two groups

| Parameters | Time | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|---|
| Myometrial thickness asymmetry (mm) | Before treatment | 4.14 ± 1.82 | 4.26 ± 1.80 | 0.393 | 0.695 |
| | After treatment | 3.42 ± 1.78 | 2.75 ± 1.22 | 2.648 | 0.009 |
| Uterine artery RI | Before treatment | 0.74 ± 0.16 | 0.75 ± 0.15 | 0.542 | 0.588 |
| | After treatment | 0.70 ± 0.14 | 0.64 ± 0.12 | 2.393 | 0.018 |
| Uterine artery PI | Before treatment | 1.82 ± 0.35 | 1.85 ± 0.34 | 0.446 | 0.656 |
| | After treatment | 1.70 ± 0.30 | 1.55 ± 0.28 | 2.987 | 0.003 |
| Elastography score | Before treatment | 9.92 ± 2.61 | 10.31 ± 2.43 | 0.933 | 0.353 |
| | After treatment | 9.25 ± 2.34 | 8.49 ± 2.17 | 2.015 | 0.046 |

RI: resistance index; PI: pulsatility index.

**Table 8.** Comparison of Serum biomarkers between the two groups

| Parameters | Time | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | t | P |
|---|---|---|---|---|---|
| CA125 (U/mL) | Before treatment | 44.36 ± 11.75 | 45.63 ± 12.33 | 0.628 | 0.531 |
| | After treatment | 35.24 ± 10.15 | 28.92 ± 9.87 | 3.749 | < 0.001 |
| VEGF (pg/mL) | Before treatment | 120.47 ± 25.76 | 122.15 ± 26.96 | 0.381 | 0.704 |
| | After treatment | 98.35 ± 20.16 | 85.69 ± 18.47 | 3.877 | < 0.001 |
| IL-6 (pg/mL) | Before treatment | 15.28 ± 4.33 | 15.82 ± 4.65 | 0.723 | 0.471 |
| | After treatment | 11.51 ± 3.87 | 9.25 ± 2.98 | 3.959 | < 0.001 |

CA125: cancer antigen 125; VEGF: vascular endothelial growth factor; IL-6: interleukin-6.

**Table 9.** Comparison of adverse events between the two groups

| Parameters | Mirena group (n = 81) | Mirena combined with Leuprorelin group (n = 63) | $\chi^2$ | P |
|---|---|---|---|---|
| Vaginal spotting | 12 (14.81%) | 5 (7.94%) | 1.610 | 0.204 |
| Amenorrhea | 16 (19.75%) | 15 (23.81%) | 0.345 | 0.557 |
| Breast tenderness | 2 (2.47%) | 0 (0.00%) | 0.290 | 0.590 |
| Low estrogen | 4 (4.94%) | 6 (9.52%) | 0.553 | 0.457 |

ple, Clark et al. (2015) demonstrated that GnRH agonists effectively reduce dysmenorrhea and improve QoL [40]. However, our study shows that adding leuprolide acetate to Mirena (a levonorgestrel-releasing intrauterine device) not only enhances symptom relief but also improves ER. Dinehart et al. (2020) similarly noted that local hormonal regulation through the LNG-IUD induces endometrial atrophy and decidualization, thus enhancing treatment efficacy [41]. The combination of systemic and local hormonal regulation is crucial for optimizing adenomyosis management. Furthermore, significant improvements in imaging features, including better myometrial symmetry, reduced uterine artery RI, and decreased serum markers (CA125, VEGF, IL-6), highlight the anti-inflammatory and anti-angiogenic effects of combination therapy. These findings are in line with Brunelli et al. (2023), who reported reduced vascular resistance and myometrial normalization with combination therapy [42]. The decline in CA125 and VEGF levels confirms the role of GnRH agonists and LNG-IUD in suppressing inflammation and angiogenesis. Enhanced ER likely results from systemic hypoestrogenism and local progesterone modulation, as indicated by Munro et al. [43]. Together, these mechanisms emphasize the clinical value of combining systemic and local hormonal therapies for comprehensive adenomyosis management.

The innovation of our study lies in its comprehensive evaluation. We assessed the combined effects of leuprorelin and Mirena across multiple dimensions of health in adenomyosis patients. Previous studies have primarily focused on symptom relief and uterine volume reduction. Our study, however, extends beyond these outcomes by evaluating changes in endocrine profiles, emotional well-being, QoL, and ER. Our findings demonstrate that combination therapy improves menstrual volume, dysmenorrhea, and uterine volume more effectively than Mirena alone. It also leads to more substantial reductions in endocrine hormone levels, enhanced emotional health, improved QoL, and better ER. By integrating systemic hormonal suppression with local endometrial modulation, this approach offers a holistic strategy that addresses both symptomatic relief and reproductive potential, optimizing therapeutic efficacy while minimizing adverse events.

While the combined therapy showed significant efficacy, it is important to consider potential adverse events. The addition of Leuprorelin did not increase adverse events such as vaginal spotting or amenorrhea. These side effects are common concerns in adenomyosis patients undergoing hormonal treatment [39]. This favorable safety profile supports the clinical use of the combination therapy. However, further long-term studies are needed to better understand its long-term implications.

Despite these promising findings, our study has several limitations. The sample size was relatively small, limiting the generalizability of the results. Additionally, the study duration was insufficient to assess long-term outcomes and potential side effects of the combination therapy. We also focused on specific endocrine, emotional, and QoL parameters, but did not explore all possible biological mechanisms that could contribute to the observed therapeutic effects. Furthermore, we did not include a placebo group, and since patients knew they were receiving treatment, their expectations may have influenced reported outcomes. Future research should include larger trials with placebo-controlled groups and extended follow-up periods to validate and expand upon our findings.

In conclusion, the combination of leuprorelin and Mirena effectively manages adenomyosis symptoms, with actions that complement each other through systemic hormonal suppression and local endometrial modulation. This combination not only provides effective symptom relief but also positively impacts patients' psychosocial well-being. These findings underscore the benefits of combining hormonal therapies in adenomyosis treatment and suggest further investigation into the underlying molecular mechanisms. They highlight the importance of personalized medicine in addressing complex gynecological disorders and emphasize the potential for an integrated approach to improve clinical outcomes and enhance QoL for patients. Further research is needed to assess the long-term effects of this treatment combination and its impact on fertility outcomes, which could help develop more comprehensive management protocols for adenomyosis.

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## Disclosure of conflict of interest

None.

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