Accepted Manuscript

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PII: S0002-9378(17)30248-X
DOI: 10.1016/j.ajog.2017.02.008
Reference: YMOB 11528


Received Date: 14 October 2016
Revised Date: 7 January 2017
Accepted Date: 6 February 2017


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A randomized controlled study

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The authors report no conflict of interest.

The word count of the abstract: 323

The word count of the main text: 3079

Print Version

Table 1-4

Figure 1, 2A and 2B
Condensation Postoperative maintenance therapy using a levonorgestrel-releasing intrauterine system is not effective for preventing endometrioma recurrence.

Short version of title: Postoperative maintenance therapy for endometriomas
ABSTRACT

BACKGROUND:

According to three randomized trials, levonorgestrel-releasing intrauterine system significantly reduced recurrent endometriosis-related pelvic pain at postoperative year 1. Only a few studies have evaluated the long-term effectiveness of the device for preventing endometrioma recurrence, and the effects of a levonorgestrel-releasing intrauterine system as a maintenance therapy remain unclear.

OBJECTIVES: To evaluate whether a maintenance levonorgestrel-releasing intrauterine system is effective for preventing postoperative endometrioma recurrence.

STUDY DESIGN: From May 2011 through March 2012, a randomized controlled trial including 80 patients with endometriomas undergoing laparoscopic cystectomy followed by six cycles of gonadotropin-releasing hormone agonist treatment was conducted. After surgery, the patients were randomized to groups that did or did not receive a levonorgestrel-releasing intrauterine system (intervention group n=40, vs control group, n=40). The primary outcome was endometrioma recurrence 30 months after surgery. The secondary outcomes included dysmenorrhea, CA125 levels, noncyclic pelvic pain and side effects.

RESULTS: Endometrioma recurrence at 30 months did not significantly differ between the two groups (the intervention group, 10/40, 25% vs the control group
15/40, 37.5%; hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.27-1.33, \( P =0.209 \). The intervention group exhibited a lower dysmenorrhea recurrence rate with an estimated HR of 0.32 (95% CI: 0.12-0.83, \( P =0.019 \)). Over a 30-month follow-up, the intervention group exhibited a greater reduction in dysmenorrhea as assessed with a visual analogue scale (VAS) score (mean±SD 60.8±25.5 vs 38.7±25.9, \( P <0.001 \), 95% CI: [10.7-33.5]), noncyclic pelvic pain VAS score (39.1±10.9 vs 30.1±14.7, \( P =0.014 \), 95% CI: [1.9-16.1]) and CA125 (median [interquartile range] -32.1 [-59.1-14.9] vs -15.6 [-33.0-5.0], \( P =0.001 \)) compared with the control group. The number needed-to-treat benefit (NNT-B) for dysmenorrhea recurrence at 30 months was 5. The number of recurrent cases requiring further surgical or hormone treatment in the intervention group (1/40, 2.5%, 95% CI:-2.3-7.3%) was significantly lower than that in the control group (8/40, 20%, 95% CI: 7.6-32.4%; \( P =0.031 \)).

**CONCLUSION:** Long-term maintenance therapy using a levonorgestrel-releasing intrauterine system is not effective for preventing endometrioma recurrence.

**Key words:** postoperative, maintenance therapy, levonorgestrel-releasing intrauterine system, endometrioma, recurrence

**Level of evidence:** I
INTRODUCTION

Endometriosis is responsible for dysmenorrhea, chronic pelvic pain and infertility, and it affects approximately 10-20% of women of reproductive age.\textsuperscript{1} Seventeen to fifty-five percent of women with endometriosis have an endometrioma, and ovarian endometrioma is usually an advanced disease stage of endometriosis.\textsuperscript{2}

Postoperative medical therapies have been considered to reduce surgical treatment failures.\textsuperscript{3-5} Current postoperative hormonal treatments include gonadotropin-releasing hormone agonists (GnRHas), progestin, and combined oral contraceptives (OC).\textsuperscript{6-9} However, endometriosis-associated pain symptoms usually return after the cessation of postoperative hormonal therapy.\textsuperscript{10} For example, the long-term recurrence rates reported 5 years after therapy with GnRHas are more than 40% for patients with endometrioma.\textsuperscript{11} Thus, maintenance therapy for endometriosis is a reasonable approach for prolonging the recurrence-free period.

The levonorgestrel-releasing intrauterine system (Mirena, Bayer Ag, Turku, Finland) is a suitable medical device for maintenance therapy because it directly delivers 20 $\mu$g/day of levonorgestrel into the uterine cavity over its 5-year lifespan.\textsuperscript{12} According to three randomized trials, the device significantly reduced recurrent endometriosis-related pelvic pain at postoperative year 1.\textsuperscript{4-6, 13} One retrospective study showed that the device provided symptom control for laparoscopically
confirmed endometriosis throughout the 3-year study period. Few studies have evaluated the long-term effectiveness of the device for preventing endometrioma recurrence.\textsuperscript{15, 16} and the effects of levonorgestrel-releasing intrauterine system maintenance therapy remain unclear.

The objective of our study was to examine the efficacy of postoperative levonorgestrel-releasing intrauterine system maintenance therapy for preventing endometrioma recurrence.

**Materials and Methods**

The study was designed as a prospective, randomized, controlled clinical trial (RCT) to examine the effects of maintenance levonorgestrel-releasing intrauterine system therapy on postoperative endometrioma recurrence. The participants were recruited from a tertiary medical center in Northern Taiwan from May 1, 2011 through March 31, 2012. The study protocol was approved by the Institutional Review Board, Taipei Veterans General Hospital, Taiwan, R.O.C. (VGHIRB: 97-04-03). This trial was registered with clinicaltrials.gov, www.clinicaltrials.gov, (NCT01125488).

Informed consent was obtained from all patients.

The sample size was calculated using a formula to compare two proportions. Based on an alpha=0.05, a power= 0.80, recurrent endometriomas proportions of 0.30 for the control group\textsuperscript{11} and 0.05 for the intervention group,\textsuperscript{15} equal sizes for both
groups and a two-tailed test, the sample size required for each group was 39.

Women with dysmenorrhea and sonographic diagnosis of endometrioma who were scheduled for elective laparoscopic ovarian cystectomy surgery were included in the study. The patients selected for screening were the consecutive patients of one study surgeon (Y.J.C.) who required laparoscopic cystectomy during the study period. The inclusion criterion was moderate and severe symptomatic endometriosis (stages 3 and 4) according to the revised American Society for Reproductive Medicine (ASRM) classification, with a chocolate-containing cyst observed during laparoscopic surgery. The exclusion criteria included the desire to become pregnant within 30 months, age <20 years or >43 years, the inability to undergo conservative surgery, any hormonal therapy within the 3 months preceding surgery, a history of previous surgery for endometriosis, the use of GnRHas, a clinical history of pelvic inflammatory disease, uterine and adnexal pathologies other than endometrioma (e.g., adenomyosis, leiomyoma, other ovarian pathologies), and other contraindications for the use of the levonorgestrel-releasing intrauterine system.\(^6\)

Laparoscopy was performed under general anesthesia using the four-puncture technique. The severity of endometriosis was evaluated using the ASRM classification of endometriosis, and staging was performed intraoperatively by two experienced surgeons (Y.J.C. and H.W.T.) who were involved in the operations.
Computer-generated random numbers in sequentially sealed opaque envelopes were used to randomly allocate the patients into either the control group (n = 40) or the intervention group (n = 40). All the subjects underwent laparoscopic ovarian cystectomy and received postoperative GnRHa injections every 4 weeks for 6 months (Figure 1). The operations were performed using only mechanical instruments and electrosurgery. Adhesions were dissected and the ovaries were completely mobilized. The endometriomas were evacuated and excised using countertraction applied to the pseudocapsule and the normal ovarian tissue. Bleeding was stopped with the limited application of a bipolar current. Remaining fragments of the ovarian endometrioma wall were fulgurated using electrocauterization. After the laparoscopic cystectomy was completed and before anesthesia was reversed, the patients were allocated to either group. For those in the intervention group, a levonorgestrel-releasing intrauterine system was inserted into the uterine cavity by the surgeon while the patient was still unconscious under general anesthesia. Specimens were submitted for histopathological evaluation to confirm the presence of endometriosis in all patients. Within 3 days after surgery for endometriosis, GnRHa was administered. The patients in both groups received GnRHa in 3.75 mg leuprolelin acetate i.m. (Enantone; Takeda IMC Ltd., Japan) once every 4 weeks for 6 doses. The contraception method for the control group was condoms and periodic
abstinence.

The collected baseline information included age, parity, body mass index (calculated as weight (kg)/ [height (m)]^2), endometriosis stage according to the revised American Society for Reproductive Medicine (ASRM) classification, and the severity of pelvic pain, including dysmenorrhea and noncyclic pelvic pain. Transvaginal ultrasonography demonstrating ovarian endometrioma and the CA-125 levels in the follicular phase were obtained to confirm the diagnosis. Dysmenorrhea and noncyclic pelvic pain were measured using a linear VAS. In the present study, dysmenorrhea was defined as pelvic pain associated with any vaginal bleeding episode including cyclic and erratic bleeding. The VAS consisted of a nongraduated 100-mm line ranging from “no pain” to “pain that is as bad as it could be”. The score was measured using a ruler with a minimum measuring unit of 1 mm.

The follow-up visits occurred 1, 3, 6, 12, 15, 18, 21, 24, 27 and 30 months after treatment. The patients met with a gynecologist (B.S.H. or Y.H.C.) who performed a clinical examination and transvaginal ultrasonography and provided treatment as indicated. The research nurse recorded the data regarding the dysmenorrhea VAS score, the noncyclic pelvic pain VAS score and the predefined checklist of side effects. This step was undertaken to maintain the single-blind status, i.e., the assessing nurse and outcome assessor were blinded to study allocation. The
surgeons and participants were not blinded to study allocation.

The primary outcome was endometrioma recurrence assessed with sonography 1, 3, 6, 12, 15, 18, 21, 24, 27 and 30 months after treatment. The secondary outcomes were the severity of the dysmenorrhea, the CA125 level, noncyclic pelvic pain and side effects 30 months after surgery.

Endometrioma recurrence which was defined via the ultrasound identification of a round mass with a thick wall, a minimum diameter of 3 cm, regular margins and homogeneously low-echogenic fluid content with scattered internal echoes, without papillary projection and with absent or poor vascularization of capsule, and septa.21

The use of LNG-IUS does not fully inhibit ovulation. If an ultrasound scan suggested evidence of recurrence, sonography was repeated after 2 months to confirm the diagnosis of endometrioma recurrence.9, 22 If a woman presented an apparent endometrioma on several scans that resolved on subsequent scans, she was not considered to have an endometrioma. If a patient had two ovarian endometriomas (each <3 cm in diameter), recurrence was recorded when the sum of the diameters was at least 3 cm. Because some studies defined the size of endometrioma recurrence as 2 cm, we also analyzed endometrioma recurrence was defined via the ultrasound identification of a round mass with a thick wall, a minimum diameter of 2 cm.22

Dysmenorrhea recurrence was defined as a pain score greater than 50 mm after 3
months of postoperative pain relief. The statistical analysis was performed with SPSS (version 21; IBM Inc., Armonk, NY, US). Descriptive statistics are presented as the medians (interquartile ranges), means ± standard deviations or numbers with percentages. The chi-square test or Fisher’s exact test were performed to evaluate the discrete variables. For continuous variables, we used Student’s t test. All continuous variables were tested for normality with the Shapiro-Wilk’s method. For variables that were not normally distributed, non-parametric statistical tests were used. The data were compared using Mann-Whitney U tests for continuous data, Wilcoxon signed rank tests were used for paired continuous data. The Kaplan-Meier method was used to calculate the cumulative probability that women would present with recurrent, dysmenorrhea or ovarian endometriomas. The HRs for recurrence were assessed with Cox proportional hazard models. The analyses of the efficacy outcomes were based on intent-to-treat analyses, whereas side effects were analyzed using per-protocol analyses. A two-tailed $P<0.05$ was considered significant.

Results

A flow chart of study participant selection is provided in Figure 1. Eighty-eight patients satisfied the eligibility criteria, but 3 declined to participate in the trial and 5
did not meet the inclusion criteria. The 5 patients did not show moderate and severe
endometriosis or did not present a chocolate cyst during laparoscopic surgery.
Histopathological tissue samples confirming the diagnoses of endometrioma were
available in all 80 cases. The remaining 80 patients underwent randomization into the
intervention group (n=40) or the control group (n=40) in the intention-to-treat
analysis.

The baseline characteristics of the population are provided in Table 1. The two
groups were comparable in terms of age, obstetric history, weight, body mass index,
largest endometrioma diameter, hemoglobin (Hgb), CA125, dysmenorrhea pain,
ASRM stage, and endometrioma laterality. All patients have the symptom of
dysmenorrhea. The number of ultrasounds women underwent did not differ
significantly between the two groups (intervention group vs control group, 9.2 ±1.2 vs
9.3 ±1.1, \( P=0.701 \)).

There was no significant difference in the rates of endometrioma recurrence at 30
months between the two groups. Additionally, neither the largest diameters of the
recurrent endometriomas nor the rates of bilateral recurrence differed significantly
between the two groups. The distributions of the locations of the recurrent
endometriomas (i.e., ipsilateral or contralateral to the original endometrioma) did not
differ between the two groups (Table 2). In terms of endometrioma recurrence
(size > 3 cm), endometrioma recurrence at 30 months did not significantly differ between the two groups (the intervention group, 10/40, 25% vs the control group 15/40, 37.5%; hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.27-1.33, \( P =0.209\); Figure 2A). In terms of endometrioma recurrence (size >2 cm), endometrioma recurrence at 30 months did not significantly differ between the two groups (the intervention group, 13/40, 32.5% vs the control group 17/40, 42.5%; hazard ratio [HR]: 0.68, 95% confidence interval [CI]: 0.33-1.40, \( P =0.295\); Supplemental Figure 1). A survival analysis using the Kaplan–Meier method revealed a significantly longer duration to dysmenorrhea recurrence in the intervention group (Figure 2B). Analgesic requirements were significantly higher in the control group (intervention vs control group, 17.5 % vs 45 %, \( P =0.008\)).

At 30 months after surgery, the VAS score for dysmenorrhea and noncyclic pelvic pain exhibited greater reductions in the intervention group than in the control group. At 30 months, the intervention group exhibited significantly lower dysmenorrhea and noncyclic pelvic pain VAS scores than the control group (Table 3). At 30 months, the CA125 level exhibited greater reductions in the intervention group than in the control group (Table 3). The side effects of the medical treatments are presented in Table 4. Twenty-nine of the 40 patients (72.5%) in the intervention group and 18 of the 40 (45%) in the control group reported one or more
side effects and this difference was likely related to the levonorgestrel-releasing intrauterine system treatment ($P=0.012$). The rate of irregular menstrual bleeding was significantly higher in the intervention group ($27.5\%$ vs $5\%$, $P=0.006$). Amenorrhea was also more common in the intervention group than in the control group ($15\%$ vs $0\%$, $P=0.026$).

The number needed-to-treat benefit (NNT-B) for dysmenorrhea recurrence was 5. The number of recurrent cases requiring further treatment in the intervention group ($1/40, 2.5\%$) was significantly lower than that in the control group ($8/40, 20\%$; $P=0.031$). For the endometrioma recurrence cases in the control group, we offered reoperation or hormone treatment including oral contraceptive pills, gestrinone or a levonorgestrel-releasing intrauterine system. For endometrioma recurrence in the intervention group, we offered reoperation, oral contraceptive pills, or gestrinone. Finally, one endometrioma recurrence case in the intervention group required reoperation. Eight recurrence cases in the control group required further treatment: three required reoperations, and five were further treated with oral contraceptive pills ($n=2$), gestrinone ($n=2$), or levonorgestrel-releasing intrauterine system ($n=1$).

**Comment**

The pathogenesis of recurrent endometrioma is not fully understood. There may be various factors that lead to the recurrence of endometrioma: the regrowth of
residual lesions, ovulation and de novo lesion due to retrograde menstruation.\textsuperscript{23}

According to literature review, the definition of endometrioma recurrence size as cyst more than 2 or 3 cm, so we analyzed the endometrioma recurrence using both definitions. Postoperative maintenance levonorgestrel-releasing intrauterine system therapy did not result in a longer duration until endometrioma recurrence than GnRHa alone in both definitions. Although the device decreases endometrial proliferation by increasing apoptosis and inducing endometrial atrophy, these effects decrease the amount of retrograde menstrual reflux.\textsuperscript{15, 24} We also found that postoperative maintenance LNG-IUS therapy demonstrated significantly longer durations of dysmenorrhea recurrence-free survival than GnRHa alone. Furthermore, postoperative maintenance LNG-IUS therapy significantly decreased the number of patients who required further treatment for recurrent disease compared with the control condition. However, the device could not inhibit ovulation or the regrowth of residual lesions.

Few studies have evaluated the long-term effectiveness of the device for preventing endometrioma recurrence. Wong et al. demonstrated that both LNG-IUS (n=15) and depot medroxyprogesterone acetate (MPA; n=15) administered for 3 years after laparoscopic ovarian cystectomy or oophorectomy can inhibit symptom recurrence.\textsuperscript{16} However, because this RCT study also included oophorectomy cases, it
was difficult to isolate the long term effects of LNG-IUS for endometrioma recurrence prevention. Furthermore, a high dropout rate was noted in the study only 20 participants continued throughout the follow-up period. In one cohort study comparing the efficacy of LNG-IUD and OC for preventing endometrioma recurrence after laparoscopic conservative surgery, Cho et al. concluded that the postoperative use of an LNG-IUS seemed to be as effective as OC for preventing endometrioma recurrence.\(^{15}\) However, the efficacy of LNG-IUS for preventing long-term endometrioma recurrence after conservative surgery is questionable because of a lack of well-designed RCT.

There are three possible reasons that maintenance levonorgestrel-releasing intrauterine system therapy did not inhibit endometrioma recurrence. First, the women who were treated with the device might have had a higher risk of ovarian cyst formation.\(^{25}\) These device induced ovarian cysts might have been misdiagnosed as endometriomas. Second, it has been reported that ovulation is not suppressed in women who are treated with a levonorgestrel-releasing intrauterine system.\(^{23}\) Conventional therapies for ovulation suppression, such as GnRHa, are provided not only to suppress estrogen production but also to inhibit ovulation. Although a levonorgestrel-releasing intrauterine system might induce anovulation in 71–85% of menstrual cycles in the first 3 months after insertion, the ovulation rate increases to
more than 50% thereafter. Third, the device cannot suppress the regrowth of residual endometrioma lesions. Conservative surgery is occasionally insufficient to completely remove the endometrioma lesion; therefore, lesions frequently redevelop postoperatively. A maintenance levonorgestrel-releasing intrauterine system is not effective for preventing the endometrioma recurrence after laparoscopic cystectomy. Hence, long-term OC regimens are recommended to preventing endometrioma recurrence.

There are 2 reasons for GnRHa and LNG-IUS given simultaneously. First, up to one in five LNG-IUS devices can be expelled from the uterine cavity after insertion. The greatest risk of this is during the first 6 weeks post-insertion. The rate of expulsion is higher in nulliparous women. Combined GnRHa and LNG-IUS treatment reduced the device expulsion rate. Second, postoperative medical therapies have been considered to reduce surgical treatment failures. If there is no postoperative adjuvant GnRHa therapy in control group, the dropout rate will be higher in the control group. In order to examine the long term efficacy of postoperative maintenance LNG-IUS for preventing endometrioma recurrence, so GnRHa and LNG-IUS are given simultaneously in intervention group.

The most common side effect of LNG-IUS is our study was unscheduled vaginal bleeding. Patterns included irregular secretory endometrium, a lack of proliferation,
suppressed proliferation, and increases in the number of veins and the number of dilated veins at the endometrial/myometrial junction. The variety of histologic findings further supports the difficulty of clearly identifying the etiology and determining an effective treatment approach. The second most common side effect was amenorrhea. This is likely due to the strong endometrial suppression provoked by high local LNG concentrations within the endometrial cavity leading to atrophy of the glandular epithelium. There are some limitations to the present study. First, although the prevention of endometrioma recurrence is the ultimate goal of treatment, it is impossible to fully evaluate this therapeutic effect with any intervention because recurrent lesions are evaluated using ultrasonography rather than laparoscopy with histological confirmation. Second, double blinding was not performed in our study. A true double-blind study would be quite difficult to perform. Although the investigator tried to mask the patients in the intervention group, most of the patients in the intervention group (92.6%) correctly guessed which group they were in because the levonorgestrel-releasing intrauterine system causes various types of abnormal uterine bleeding. Therefore, the present study was not a double-blind study. Consequently, some bias in favor of the treatment group may have been introduced. Third, a major confounder of this study is that some of the secondary outcomes (for example dysmenorrhea) may have been period-related rather than endometriosis
related. Fourth, the numbers of cases and adverse events were small and the study was not sufficiently powered to assess the side effects. Fifth, to avoid possible confounding factors, it is reasonable to apply strict inclusion criteria to maintain clinical homogeneity. However, a large number of exclusion criteria would have limited the population of patients who could have been included in this study (i.e., the exclusion of those with prior surgery, preoperative hormone therapy use, etc. would have excluded many patients who are seen in a typical endometriosis practice). The recurrence rate in intervention group was higher than the expected recurrence. The possible reason is that endometrioma size in our study is larger than those of previous study (55.9±20.3 mm vs 42±21mm). Compare to the Chao et al retrospective study, we exactly evaluated the endometrioma recurrence by regular sonography follow-up. Thus, a larger RCT or a nationwide population-based cohort study is needed to assess the real practical situation. Sixth, although the follow-up period was described as 30 months in our study, maybe the true follow up period is 24 months. As all of the patients received GnRHa for at least 6 month, no recurrence was detected during the first 6 month.

In conclusion, the use of a maintenance levonorgestrel-releasing intrauterine system is not effective for preventing the endometrioma recurrence after laparoscopic cystectomy surgery.
ACKNOWLEDGMENTS

This work was supported in part by the Ministry of Science and Technology (NSC 100-2314-B-075-008, NSC 101-2314-B-075-028-MY3, MOST 104-2314-B-075-022 and MOST 104-2314-B-075-058 for YJC), Taipei Veterans General Hospital (VGH-104C-042, and VGH-104-EA-0012 for YJC), Yen-Tjing-Ling Medical Foundation (CI – 104 – 15 for YJC) and Szu-Yuan Research Foundation of Internal Medicine. We thank Miss Pin-Yu Lin and the research nurse Shu Yun Huang (Taipei Veterans General Hospital) for filing the documents for this study.

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Figure legends

FIGURE 1. Flow chart of the randomization and group allocation.

FIGURE 2. Post-laparoscopic recurrence analyses using Kaplan–Meier tests to assess the differences in endometrioma (A) and dysmenorrhea (B) recurrence between the intervention and control groups. The HRs for recurrence were assessed with Cox proportional hazard models.

SUPPLEMENTAL FIGURE 1. Post-laparoscopic recurrence analyses using Kaplan–Meier tests to assess the differences in endometrioma recurrence (cyst size > 2 cm) between the intervention and control groups. The HRs for recurrence were assessed with Cox proportional hazard models.
**TABLE 1. Baseline characteristics of the control and intervention groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group (n=40)</th>
<th>Intervention Group (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>32.9±5.8</td>
<td>35.0±6.2</td>
</tr>
<tr>
<td>Gravida †</td>
<td>0 (0-3)</td>
<td>0 (0-8)</td>
</tr>
<tr>
<td>Parity †</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.1±3.2</td>
<td>158.5±4.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.5±7.0</td>
<td>56.5±8.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5±2.7</td>
<td>22.6±3.5</td>
</tr>
<tr>
<td>ASRM score</td>
<td>50.4±22.9</td>
<td>58.4±21.7</td>
</tr>
<tr>
<td>Stage III</td>
<td>16 (40%)</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>24 (60%)</td>
<td>31 (77.5%)</td>
</tr>
<tr>
<td>Largest diameter endometrioma (mm)</td>
<td>57.8±22.3</td>
<td>55.9±20.3</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.2±1.3</td>
<td>12.3±1.3</td>
</tr>
<tr>
<td>CA125 (U/ml) †</td>
<td>47.7 (23.9-86.7)</td>
<td>45.9 (26.7-66.8)</td>
</tr>
<tr>
<td>Dysmenorrhea VAS (mm)</td>
<td>78.5 ±14.4</td>
<td>82.7±14.1</td>
</tr>
<tr>
<td>Endometrioma side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>13 (32.5%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Right</td>
<td>12 (30.0%)</td>
<td>10 (25.0%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>15 (37.5%)</td>
<td>15 (37.5%)</td>
</tr>
</tbody>
</table>

NA, not applicable; BMI, body mass index; ASRM, American Society for Reproductive Medicine; Hb, hemoglobin; VAS, visual analog score.

* Mean difference or risk difference

The data are presented as the means ± standard deviations or the n (%) unless otherwise specified.

† Median (interquartile range)

The data were compared using Student’s t test or the Mann-Whitney U test for continuous data and the chi-square test or Fisher’s exact test for categorical data.
**TABLE 2. Endometrioma recurrence patterns**

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>P</th>
<th>Difference* (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioma recurrence rate</td>
<td>15/40 (37.5%)</td>
<td>10/40 (25.0%)</td>
<td>0.228</td>
<td>12.5% (-7.6–32.6)</td>
</tr>
<tr>
<td>Largest diameter of</td>
<td>40.4 ±15.6</td>
<td>35.2 ±7.1</td>
<td>0.336</td>
<td>5.2 (-5.7–16.1)</td>
</tr>
<tr>
<td>recurrent endometrioma (mm)</td>
<td>(n=15)</td>
<td>(n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral cysts</td>
<td>2/15 (13.3%)</td>
<td>0/10 (0%)</td>
<td>0.500</td>
<td>NA</td>
</tr>
<tr>
<td>Unilateral cyst</td>
<td>13/15 (86.7%)</td>
<td>10/10 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same side</td>
<td>10/13 (76.9%)</td>
<td>7/10 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral side</td>
<td>3/13 (23%)</td>
<td>3/10 (30%)</td>
<td>1.000</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable.

The data are presented as the mean ± standard deviations or the n (%) unless otherwise specified.

* Mean difference or risk difference.

The data were compared using Student’s t test for continuous data and the chi-square test or Fisher’s exact test for categorical data.
### TABLE 3. Pelvic pain scores and CA125 levels before and 30 months after surgery.

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>P</th>
<th>Mean difference* (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysmenorrhea VAS (mm)</strong></td>
<td>n=40</td>
<td>n=40</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline values†</td>
<td>75.5(67.5–92.3)</td>
<td>82.5(73.5–95.8)</td>
<td>0.146</td>
<td>NA</td>
</tr>
<tr>
<td>30-month values†</td>
<td>34.0(22.3–63.8)</td>
<td>20.0(0.0–32.8)</td>
<td>0.002</td>
<td>NA</td>
</tr>
<tr>
<td>Mean reduction</td>
<td>38.7 ±25.9</td>
<td>60.8 ±25.5</td>
<td>&lt;0.001</td>
<td>22.1 (10.7–33.5)</td>
</tr>
<tr>
<td><strong>Noncyclic pelvic pain VAS (mm)</strong></td>
<td>n=26</td>
<td>n=27</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline values</td>
<td>43.8 ±11.7</td>
<td>42.2 ±12.4</td>
<td>0.634</td>
<td>1.6 (-5.1–8.2)</td>
</tr>
<tr>
<td>30-month values†</td>
<td>11.0(4.3–24.5)</td>
<td>2.0(0.0–5.0)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Mean reduction</td>
<td>30.1 ±14.7</td>
<td>39.1 ±10.9</td>
<td>0.014</td>
<td>9.0 (1.9–16.1)</td>
</tr>
<tr>
<td><strong>CA125 (U/ml)</strong></td>
<td>n=40</td>
<td>n=40</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline values†</td>
<td>47.7(23.9–86.7)</td>
<td>45.9(26.7–66.8)</td>
<td>0.878</td>
<td>NA</td>
</tr>
<tr>
<td>30-month values†</td>
<td>31.5(17.9–50.0)</td>
<td>14.40(8.5–23.8)</td>
<td>0.007</td>
<td>NA</td>
</tr>
<tr>
<td>CA125 reduction†</td>
<td>-15.6(-33.0–5.0)</td>
<td>-32.1(-59.1–14.9)</td>
<td>0.001</td>
<td>NA</td>
</tr>
</tbody>
</table>

**VAS,** visual analog score; **NA,** not applicable.

* Mean difference.

† Median (interquartile range)

The data are presented as the means ± standard deviations or median (interquartile range).

The data were compared using Student’s t tests or the Mann-Whitney U test for independent continuous data and paired t tests or the Wilcoxon signed-rank test for paired continuous data.
TABLE 4. The general side effects of medical treatment

<table>
<thead>
<tr>
<th>Complication</th>
<th>Control Group (n=40)</th>
<th>Intervention Group (n=40)</th>
<th>Risk Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall††</td>
<td>18 (45.0)</td>
<td>29 (72.5)</td>
<td>-27.5% (-48.2--6.8%)</td>
</tr>
<tr>
<td>Bloating</td>
<td>9 (22.5)</td>
<td>10 (25.0)</td>
<td>-2.5% (-21.1--16.1)</td>
</tr>
<tr>
<td>Acne</td>
<td>4 (10.0)</td>
<td>5 (12.5)</td>
<td>-2.5% (-16.3--11.3)</td>
</tr>
<tr>
<td>Vaginal spotting††</td>
<td>2 (5.0)</td>
<td>11 (27.5)</td>
<td>-22.5% (-37.9--7.1)</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>5 (12.5)</td>
<td>7 (17.5)</td>
<td>-5.0% (-20.6--10.6)</td>
</tr>
<tr>
<td>Oily skin</td>
<td>3 (7.5)</td>
<td>6 (15.0)</td>
<td>-7.5% (-21.3--6.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (15.0)</td>
<td>5 (12.5)</td>
<td>2.5% (-12.6--17.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (27.5)</td>
<td>13 (32.5)</td>
<td>-5.0% (-25.1--15.1)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>7 (17.5)</td>
<td>8 (20.0)</td>
<td>-2.5% (-19.6--14.6)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>12 (30.0)</td>
<td>15 (37.5)</td>
<td>-7.5% (-28.2--13.2)</td>
</tr>
<tr>
<td>Amenorrhea†</td>
<td>0 (0.0)</td>
<td>6 (15.0)</td>
<td>-15.0% (-26.1--3.9)</td>
</tr>
</tbody>
</table>

The data are presented as n (%).
† † P value <0.01; † <0.05.

The data were compared using the chi-square test or Fisher’s exact test.
Figure 1

Assessed for eligibility (n=88)

Enrollment

Excluded (n=8)
- Not meet inclusion criteria (n=5)
- Declined to participate (n=3)

Randomization (n=80)

Allocated to expectant management (control) (n=40)

Lost to follow-up (n=0)
Discontinued intervention (n=0)

Analysed (n=40)
- Excluded from analysis (n=0)

Allocated to levonorgestrel-releasing intrauterine system (intervention) (n=40)

Lost to follow-up (n=0)
Discontinued intervention (n=1)
- One patient wanted to remove levonorgestrel-releasing intrauterine system at 15 months

Analysed (n=40)
- Excluded from analysis (n=0)
Figure 2A

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Total</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15</td>
<td>40</td>
<td>0.60</td>
<td>0.209</td>
</tr>
<tr>
<td>Intervention</td>
<td>10</td>
<td>40</td>
<td>(0.27-1.33)</td>
<td></td>
</tr>
</tbody>
</table>

Recurrence rate of endometrioma

Control
No. at risk
40 40 40 40 37 32 32 31 31 28 28

LNG-IUC
No. at risk
40 40 40 40 40 39 38 36 34 33 32