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Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence

A randomized controlled study

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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 devicefor 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.[1] Seventeen to fifty-five percent of women with endometriosis have an endometrioma, and ovarian endometrioma is usually an advanced disease stage of endometriosis.[2]

Postoperative medical therapies have been considered to reduce surgical treatment failures.[3-5] Current postoperative hormonal treatments include gonadotropin-releasing hormone agonists (GnRHas), progestin, and combined oral contraceptives (OC).[6-9] However, endometriosis-associated pain symptoms usually return after the cessation of postoperative hormonal therapy.[10] For example, the long-term recurrence rates reported 5 years after therapy with GnRHas are more than 40 % for patients with endometrioma.[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 μg/day of levonorgestrel into the uterine cavity over its 5-year lifespan.[12] According to three randomized trials, the device significantly reduced recurrent endometriosis- related pelvic pain at postoperative year 1.[4, 6, 13] One retrospective study showed that the device provided symptom control for laparoscopically

confirmed endometriosis throughout the 3-year study period.[14] Few studies have evaluated the long-term effectiveness of the device for preventing endometrioma recurrence.[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 preventin endometrioma recurrence.

Materials and Methods

The study was designed as a prospective, randomized, controlled clinical trial (RCT) to examine the effects 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 [11] and 0.05 for the intervention group,[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.[17] 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.[17] 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.[18] The patients in both groups received GnRHa in 3.75 mg leuprorelin 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.[19] Dysmenorrhea and noncyclic pelvic pain were measured using a linear VAS.[20] 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.[6]

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 > 3cm), 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 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.[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.[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 preventingendometrioma 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.[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.[26] 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.[23] 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.[22, 27]

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.[28] Combined GnRHa and LNG-IU treatment reduced the device expulsion rate.[29] 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.[30] 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.[31] 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.[21] Second, double blinding was not performed in our study. A true double-blind study would be quite difficult to perform.[6] 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.[6] 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.[32] 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 endometrima size in our study is larger than those of previous study (55.9±20.3 mm vs 42±21mm).[15] Compare to the Chao et al retrospective study, we exactly evaluated the endometrioma recurrence by regular sonography follow-up.[15] 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.

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REFERENCE

1. Tu FF, Du H, Goldstein GP, Beaumont JL, Zhou Y, Brown WJ. The influence of prior oral contraceptive use on risk of endometriosis is conditional on parity. Fertil Steril 2014;101:1697-704.
2. Liu X, Yuan L, Shen F, Zhu Z, Jiang H, Guo SW. Patterns of and risk factors for recurrence in women with ovarian endometriomas. Obstet Gynecol 2007;109:1411-20.
3. Kim ML, Kim JM, Seong SJ, Lee SY, Han M, Cho YJ. Recurrence of ovarian endometrioma after second-line, conservative, laparoscopic cyst enucleation. Am J Obstet Gynecol 2014;210:216 e1-6.
4. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 2003;80:305-9.
5. Vercellini P, Crosignani PG, Mangioni C, Imparato E, Ferrari A, De Giorgi O. Treatment with a gonadotrophin releasing hormone agonist before hysterectomy for leiomyomas: results of a multicentre, randomised controlled trial. Br J Obstet Gynaecol 1998;105:1148-54.
6. Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstet Gynecol 2012;119:519-26.
7. Takamura M, Koga K, Osuga Y, et al. Post-operative oral contraceptive use

reduces the risk of ovarian endometrioma recurrence after laparoscopic excision. Hum Reprod 2009;24:3042-8.

8. Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. Obstet Gynecol 1988;72:323-7.

9. Jee BC, Lee JY, Suh CS, Kim SH, Choi YM, Moon SY. Impact of GnRH agonist treatment on recurrence of ovarian endometriomas after conservative laparoscopic surgery. Fertil Steril 2009;91:40-5.

10. Fedele L, Bianchi S, Di Nola G, Candiani M, Busacca M, Vignali M. The recurrence of endometriosis. Ann N Y Acad Sci 1994;734:358-64.

11. Lee DY, Bae DS, Yoon BK, Choi D. Post-operative cyclic oral contraceptive use after gonadotrophin-releasing hormone agonist treatment effectively prevents endometrioma recurrence. Hum Reprod 2010;25:3050-4.

12. Luukkainen T, Lahteenmaki P, Toivonen J. Levonorgestrel-releasing intrauterine device. Ann Med 1990;22:85-90.

13. Bayoglu Tekin Y, Dilbaz B, Altinbas SK, Dilbaz S. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril 2011;95:492-6.

14. Lockhat FB, Emembolu JO, Konje JC. The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up. Hum Reprod 2005;20:789-93.

15. Cho S, Jung JA, Lee Y, et al. Postoperative levonorgestrel-releasing intrauterine system versus oral contraceptives after gonadotropin-releasing hormone agonist treatment for preventing endometrioma recurrence. Acta Obstet Gynecol Scand 2014;93:38-44.

16. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2010;50:273-9.

17. Muzii L, Bellati F, Palaia I, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part I: clinical results. Hum Reprod 2005;20:1981-6.

18. Gong L, Zhang S, Han Y, Long Q, Zou S, Cao Y. Initiation of GnRH agonist treatment on 3-5 days postoperatively in endometriosis patients: a randomized controlled trial. J Clin Pharmacol 2015;55:848-53.

19. O'shaughnessy A, Check JH, Nowroozi K, Lurie D. CA 125 levels measured in different phases of the menstrual cycle in screening for endometriosis.

Obstet Gynecol 1993;81:99-103.

20. Chen YJ, Wang PH, Ocampo EJ, Twu NF, Yen MS, Chao KC. Single-port compared with conventional laparoscopic-assisted vaginal hysterectomy: a randomized controlled trial. Obstet Gynecol 2011;117:906-12.

21. Exacoustos C, Zupi E, Carusotti C, et al. Staging of pelvic endometriosis: role of sonographic appearance in determining extension of disease and modulating surgical approach. J Am Assoc Gynecol Laparosc 2003;10:378-82.

22. Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol 2008;198:504 e1-5.

23. Koga K, Takamura M, Fujii T, Osuga Y. Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis. Fertil Steril 2015;104:793-801.

24. Lockhat FB, Emembolu JE, Konje JC. Serum and peritoneal fluid levels of levonorgestrel in women with endometriosis who were treated with an intrauterine contraceptive device containing levonorgestrel. Fertil Steril 2005;83:398-404.

25. Kriplani A, Awasthi D, Kulshrestha V, Agarwal N. Efficacy of the levonorgestrel-releasing intrauterine system in uterine leiomyoma. Int J Gynaecol Obstet 2012;116:35-8.

26. Vercellini P, Vigano P, Somigliana E. The role of the levonorgestrel-releasing intrauterine device in the management of symptomatic endometriosis. Curr Opin Obstet Gynecol 2005;17:359-65.

27. Seracchioli R, Mabrouk M, Frasca C, et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil Steril 2010;93:52-6.

28. Maybin JA, Critchley HO. Medical management of heavy menstrual bleeding. Women's health (London, England) 2016;12:27-34.

29. Zhang P, Song K, Li L, Yukuwa K, Kong B. Efficacy of combined levonorgestrel-releasing intrauterine system with gonadotropin-releasing hormone analog for the treatment of adenomyosis. Med Princ Pract 2013;22:480-3.

30. Kovacs G. Progestogen-only pills and bleeding disturbances. Hum Reprod 1996;11 Suppl 2:20-3.

31. Pakarinen P, Luukkainen T, Laine H, Lahteenmaki P. The effect of local intrauterine levonorgestrel administration on endometrial thickness and uterine blood circulation. Hum Reprod 1995;10:2390-4.

32. Mol BW, Bayram N, Lijmer JG, et al. The performance of CA-125

measurement in the detection of endometriosis: a meta-analysis. Fertil Steril 1998;70:1101-8.

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

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

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

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

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.

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

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

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

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

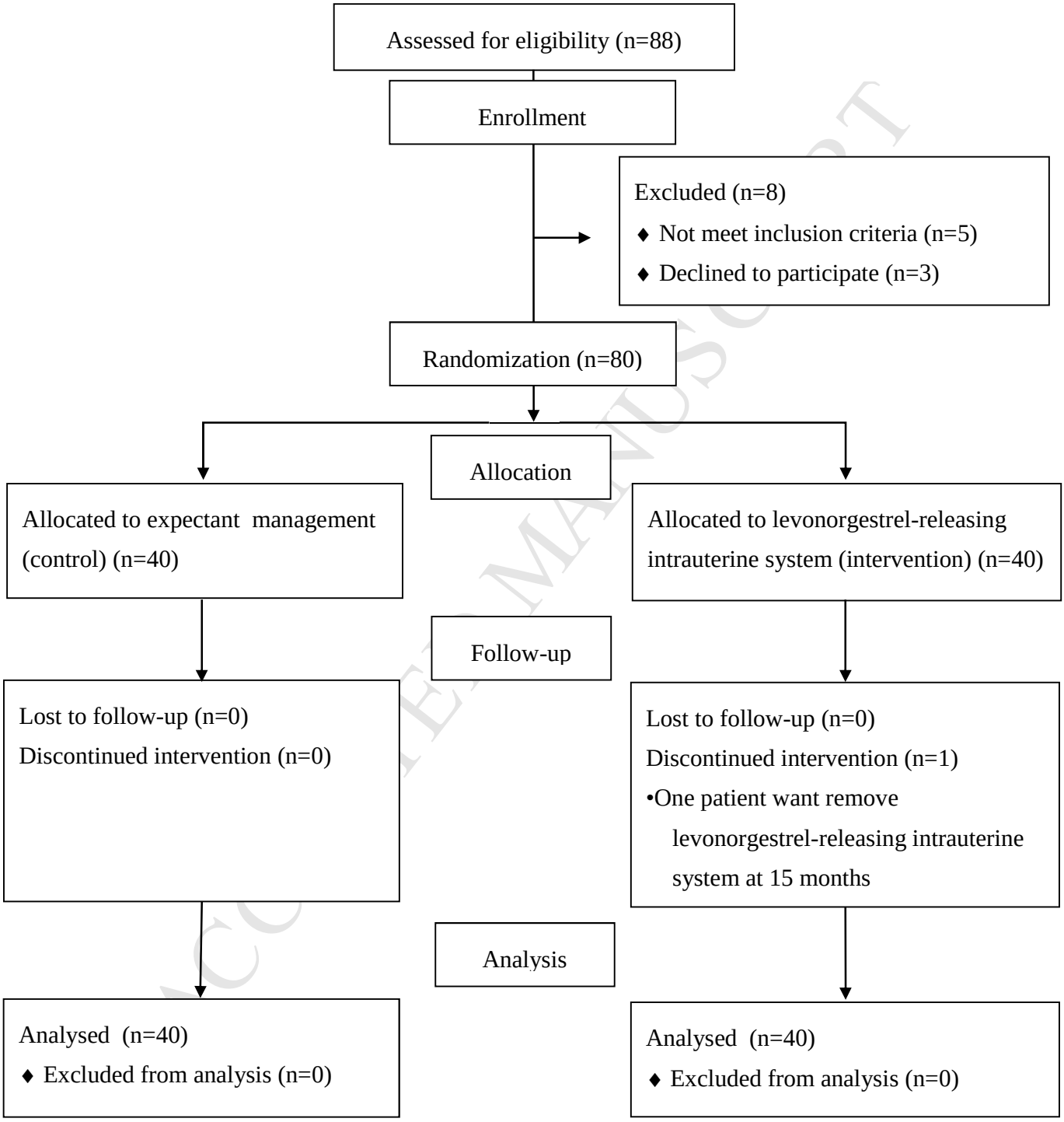


Figure 2A

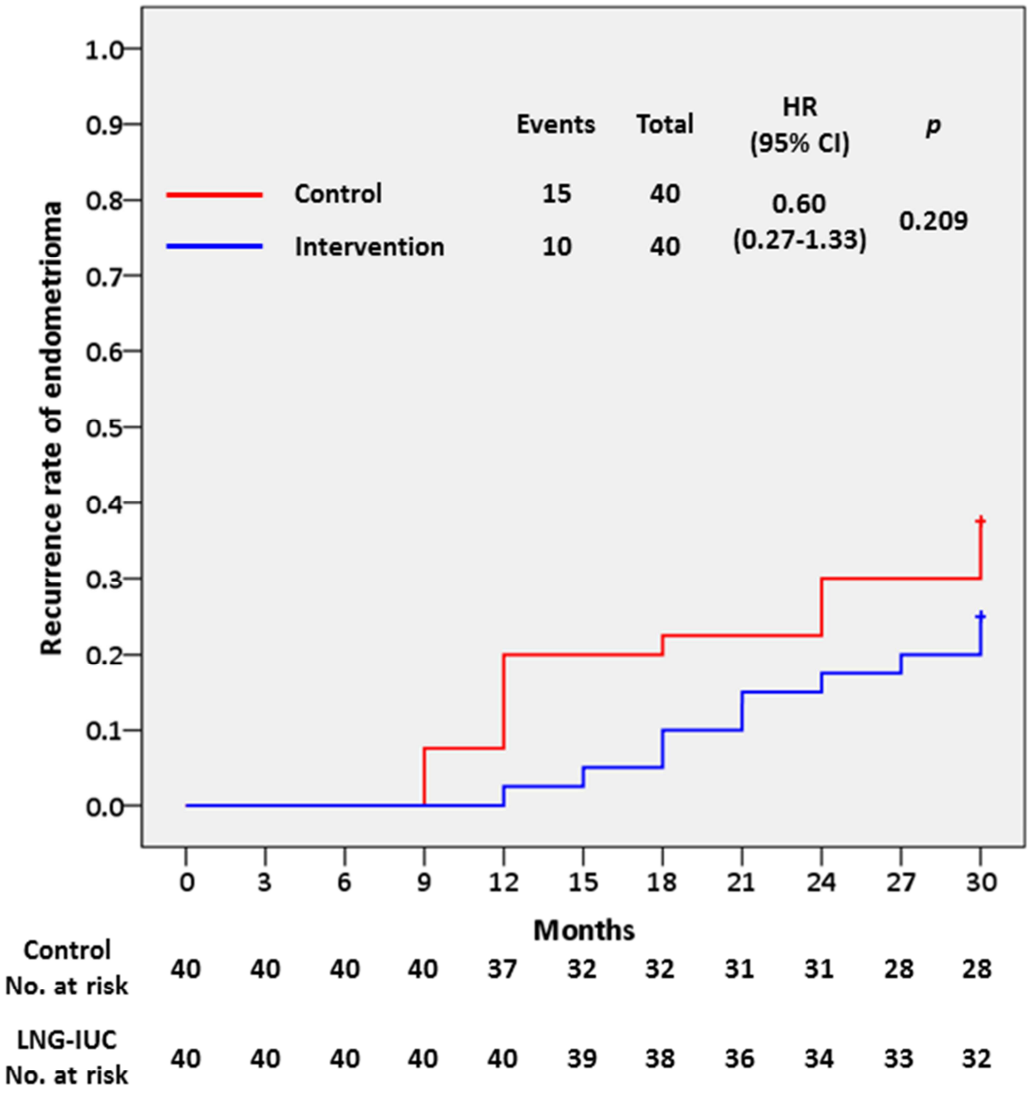
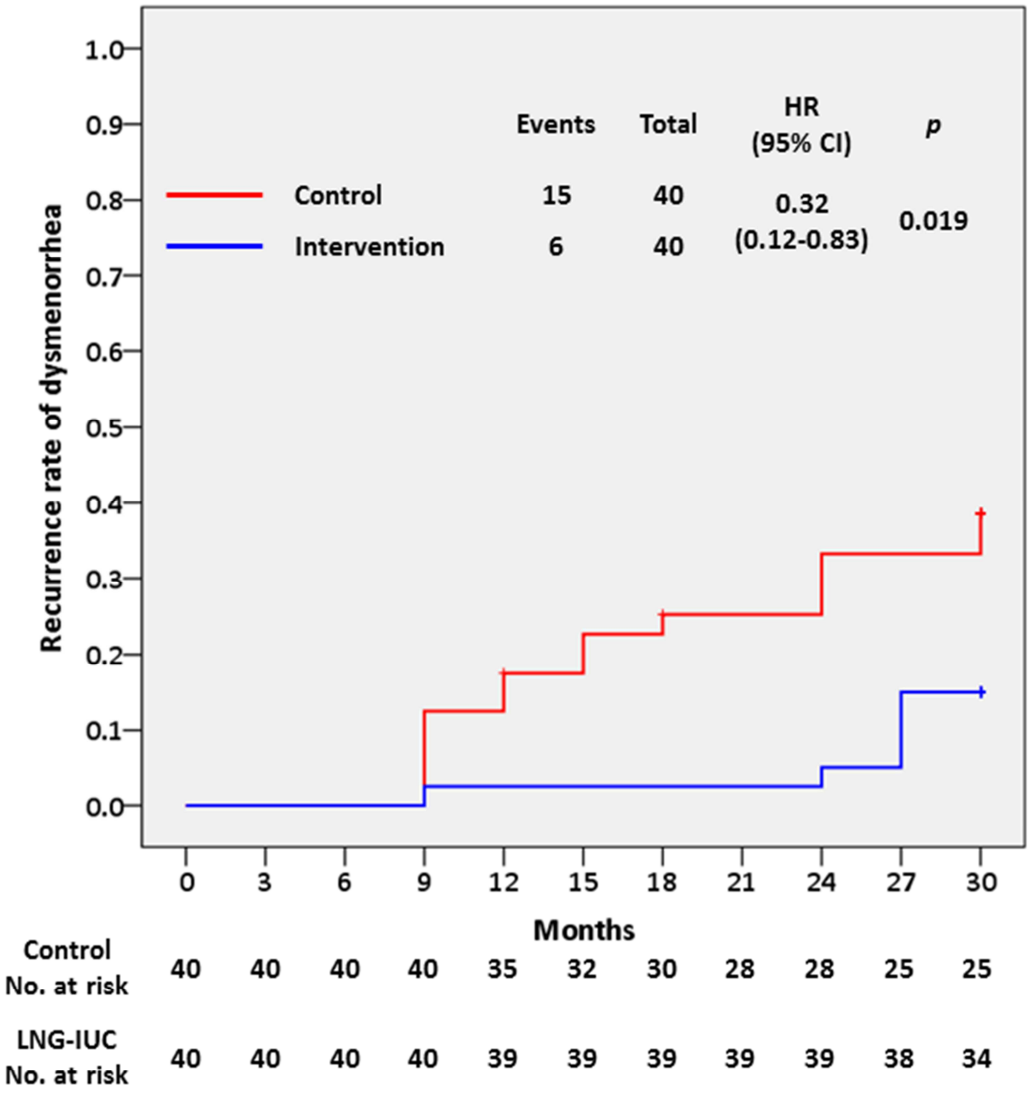

Recurrence rate of endometrioma
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events
Total
HR (95% CI)
p
Control
15
40
0.60 (0.27-1.33)
0.209
Intervention
10
40
0 3 6 9 12 15 18 21 24 27 30
Months
Control No. at risk 40 40 40 40 37 32 32 31 31 28 28
LNG-IUC No. at risk 40 40 40 40 40 39 38 36 34 33 32

Figure 2B


Events
Total
HR (95% CI)
p
Control
15
40
0.32 (0.12-0.83)
0.019
Intervention
6
40
Recurrence rate of dysmenorrhea
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 3 6 9 12 15 18 21 24 27 30
Months
Control No. at risk 40 40 40 40 35 32 30 28 28 25 25
LNG-IUC No. at risk 40 40 40 40 39 39 39 39 39 38 34