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CLINICAL ARTICLE

# The efficacy of long-term maintenance therapy with a levonorgestrel-releasing intrauterine system for prevention of ovarian endometrioma recurrence

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ABSTRACT

*Objective:* To evaluate the cumulative recurrence rates of ovarian endometrioma among patients using a levonorgestrel-releasing intrauterine system (LNG-IUS) after conservative laparoscopic surgery. *Methods:* A retrospective review was conducted of premenopausal women who underwent conservative laparoscopic surgery for ovarian endometrioma and subsequent treatment with LNG-IUS at two gynecologic surgery centers in South Korea between January 1, 2007, and September 30, 2014. Eligible patients had no residual ovarian lesions before LNG-IUS insertion, underwent insertion within 12 months of primary surgery, and were followed up for at least 6 months afterwards. Recurrence was defined as a cystic mass (≥2 cm in diameter) detected by transvaginal ultrasonography. *Results:* Overall, 61 patients were included. The mean duration of follow-up was 42.9 ± 22.0 months (range 8–98). Recurrence of ovarian endometrioma was detected among 7 (11%) of the patients. On Kaplan–Meier analysis, the cumulative recurrence rates were 4.0%, 6.3%, and 25.5% at 24, 36, and 60 months after surgery, respectively. In multivariate analysis, nulliparity at surgery was the only risk factor for recurrence (hazard ratio 5.892, 95% confidence interval 1.139–30.484; $P=0.034$). *Conclusion:* Long-term maintenance therapy with LNG-IUS after conservative surgery might be a treatment option to consider to prevent ovarian endometrioma recurrence among premenopausal women.


## 1. Introduction

Endometriosis is a chronic and recurrent condition characterized by the development and expansion of extrauterine endometrial stroma and/or glands. This condition affects 10%–20% of women of reproductive age worldwide [1], and negatively influences the physical, mental, and social well-being of affected individuals.

Despite its invasive nature, surgery is considered the treatment of choice for endometriosis; however, treatment-related morbidity and complications can occur [2]. The recurrence rate following surgical intervention remains high, even among patients who receive postoperative medical therapy. A pooled analysis of 23 studies [3] estimated recurrence rates of 21.5% at 2 years and 40.0%–50.0% at 5 years after the primary surgery. A study by Weir et al. [4] found that 27% of patients were readmitted for additional surgical treatment of endometriosis within 4 years of the initial surgery. Furthermore, Cheong et al. [5] reported that greater than half of all patients with endometriosis underwent reoperation, with approximately 27% requiring three or more surgeries. In a Korean study [6], the cumulative recurrence rates of ovarian endometrioma after second-line treatment with conservative laparoscopic cyst enucleation were 13.7%, 21.3%, and 37.5% at 24, 36, and 60 months, respectively.

Given that a curative treatment for endometriosis has not yet been established, the main goals of intervention are to reduce pain, increase fertility among women who plan to conceive, and delay the onset of recurrence [7]. In 2014, the European Society of Human Reproduction and Embryology published revised guidelines for the management of endometriosis, which addressed the issue of secondary prevention [8]. This document outlined various interventions to prevent recurrence of pain symptoms or disease during the postoperative period (>6 months after surgery). The choice of intervention should be made on the basis of patient preference, cost, availability, and adverse effects. Combined oral contraceptives can be used for secondary prevention of recurrent ovarian endometrioma if the patient does not wish to conceive straight after surgery. A levonorgestrel-releasing intrauterine system (LNG-IUS) or combined oral contraceptives can be used for the secondary prevention of endometriosis-associated dysmenorrhea, but not for nonmenstrual pelvic pain or dyspareunia, for at least 18–24 months after

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surgery [8]. The non-contraceptive benefits of LNG-IUS, including effects on dysmenorrhea and heavy menstrual bleeding, make it an effective option for the treatment of endometriosis [9]. Although the LNG-IUS effectively reduces pain associated with endometriosis [10,11], its efficacy in preventing recurrence of ovarian endometrioma is not proven.

The aim of the present study was to evaluate the efficacy of LNG-IUS as long-term maintenance therapy to prevent recurrence of ovarian endometrioma after conservative laparoscopic surgery.

## 2. Materials and methods

A retrospective review was conducted of patients who underwent conservative laparoscopic enucleation of ovarian endometrioma and subsequent treatment with LNG-IUS at two gynecologic surgery centers in South Korea between January 1, 2007, and September 30, 2014. The inclusion criteria were premenopausal status, pathologically proven ovarian endometrioma, treatment by conservative laparoscopic surgery, no residual ovarian lesions detected by transvaginal ultrasonography before LNG-IUS insertion, less than 12 months elapsed between primary surgery and LNG-IUS insertion, and at least 6 months of follow-up after LNG-IUS insertion. Among patients who received a gonadotropin-releasing hormone (GnRH) agonist after surgery, those who received 3.75 mg leuprorelin every 28 days after surgery for a period of 3–6 months before the LNG-IUS was inserted were included. Exclusion criteria were laparotomy or laparoscopic hysterectomy (with or without oophorectomy) and the use of postoperative treatments other than a GnRH agonist before LNG-IUS insertion (e.g. a progestin or combined oral contraceptive). The protocol was approved by the institutional review boards of the two study centers (CHA Gangnam Medical Center, Seoul, and Dong-A University Medical Center, Busan). Patient records and data were anonymized and de-identified before analysis, so informed consent was not required.

Medical charts were reviewed to collect data on age at surgery, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical history, symptoms of dysmenorrhea, parity, size of the ovarian endometrioma, location of the ovarian cysts; revised American Society for Reproductive Medicine stage [12], postoperative medications, and time to recurrence. The size of the ovarian endometrioma was defined as the diameter of the largest cyst in centimeters. The sum of the diameters of the largest cysts was recorded if the ovarian cysts were bilateral.

Recurrence was recorded when transvaginal ultrasonography revealed a round cystic mass (diameter ≥2 cm), thick walls, irregular margins, homogenous low echogenic fluid content, and scattered internal echoes, without papillary proliferation, as previously described [13]. The use of LNG-IUS does not fully inhibit ovulation [14]; therefore, all newly developed hypoechoic masses with features characteristic of functional cysts were re-evaluated by transvaginal ultrasonography after 2–3 months. If a patient had two ovarian endometriomas (each <2 cm in diameter), recurrence was recorded when the sum of the diameters was at least 2 cm, as previously reported [15–17]. The time to recurrence was defined as the time in months from surgery to detection of a newly developed ovarian endometrioma greater than 2 cm in diameter.

All patients underwent postoperative insertion of the LNG-IUS either for contraception or to control dysmenorrhea and/or heavy menstrual bleeding. The patients were fully informed of the advantages, disadvantages, and complications of LNG-IUS. If patients opted to use LNG-IUS immediately after surgery without GnRH agonist use because of the associated hypoestrogenic symptoms, insertion was performed either on the day of operation or at an outpatient clinic on days 5–7 of the next menstrual cycle.

Clinical postoperative follow-up was conducted at regular intervals (every 3–6 months initially, then every 6–12 months) or whenever medical evaluation was required. Transvaginal ultrasonography was performed at every follow-up visit; symptoms, medical treatment, and clinical data were also recorded.

The data were analyzed using SPSS version 22 (IBM, Armonk, NY, USA). Descriptive data were compared using the Mann–Whitney *U* test. Categorical data were analyzed using the $\chi^2$ and Fisher exact tests, as appropriate. Univariate analysis and multivariate Cox proportional hazards models were fitted for recurrence-free experience, and adjusted for the effects of clinical characteristics among patients with or without recurrent disease. The Kaplan–Meier method was used to calculate the cumulative probability of recurrence. $P<0.05$ was considered statistically significant.

## 3. Results

A total of 61 patients were included in the present study. The mean age was 36.2 ± 5.9 years (range 23–48). The mean duration of LNG-IUS use was 34.6 ± 20.2 months (range 4–77), with a mean duration of follow-up of 42.9 ± 22.0 months (range 8–98).

Overall, 41 (67%) patients received postoperative treatment with a GnRH agonist before LNG-IUS placement; the remaining 20 (33%) patients opted for LNG-IUS insertion without GnRH agonist use. The baseline clinical and surgical characteristics by use of a GnRH agonist are shown in Table 1. No statistically significant differences were observed between patients who did and did not receive a GnRH agonist.

Recurrence of ovarian endometrioma was detected among 7 (11%) patients on follow-up transvaginal ultrasonography. The cumulative recurrence rates at 24, 36, and 60 months after surgery were 4.0%, 6.3%, and 25.5%, respectively (Fig. 1).

Univariate analysis suggested that younger age and nulliparity were possible risk factors for recurrence of ovarian endometrioma ($P<0.001$ and $P=0.004$, respectively) (Table 2). Multivariate analysis identified nulliparity as the only statistically significant risk factor for recurrence of ovarian endometrioma during long-term postoperative maintenance therapy with LNG-IUS (Table 2). The hazard ratio was 5.892 (95% confidence interval 1.139–30.484; $P=0.034$).

At the last follow-up during the study period, 44 (72%) patients were still using LNG-IUS; use of the LNG-IUS was discontinued by 17 (28%) patients. Six (10%) patients had the LNG-IUS removed to aid conception (1 conceived naturally 10 months after removal), 2 (3%) had the LNG-IUS removed after menopause, and 1 (2%) had the LNG-IUS removed after a diagnosis of progesterone-receptor-positive breast cancer. Three (5%) patients experienced dislocation or expulsion of

**Table 1**
Baseline clinical and surgical characteristics (n=61).[a]

| Characteristic | GnRH agonist and LNG-IUS (n=41) | LNG-IUS only (n=20) | *P* value |
|---|---|---|---|
| Age at surgery, y | 35.7 ± 6.3 | 37.4 ± 5.0 | 0.423 |
| Age at LNG-IUS insertion, y | 36.2 ± 6.2 | 37.7 ± 5.0 | 0.543 |
| Parity | | | 0.544 |
| 0 | 12 (29) | 4 (20) | |
| ≥1 | 29 (71) | 16 (80) | |
| Body mass index [b] | 20.8 ± 1.9 | 20.4 ± 2.5 | 0.544 |
| Size of ovarian cyst, cm | 7.2 ± 3.3 | 6.4 ± 2.4 | 0.489 |
| Revised American Society for Reproductive Medicine stage | | | 0.166 |
| III | 24 (59) | 8 (40) | |
| IV | 17 (41) | 12 (60) | |
| Laterality | | | 0.246 |
| Unilateral | 26 (63) | 16 (80) | |
| Bilateral | 15 (37) | 4 (20) | |
| Duration of LNG-IUS use, mo | 34.1 ± 18.5 | 35.6 ± 23.9 | 0.969 |
| Duration of follow-up, mo | 43.3 ± 21.2 | 42.2 ± 24.2 | 0.836 |

Abbreviations: GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system.

[a] Values given as mean ± standard deviation or number (percentage), unless indicated otherwise.

[b] Calculated as weight in kilograms divided by the square of height in meters.

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