Original Article

Yonsei Med J 2023 Mar;64(3):204-212
https://doi.org/10.3349/ymj.2022.0278

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Recurrence, Reoperation, Pregnancy Rates, and Risk Factors for Recurrence after Ovarian Endometrioma Surgery: Long-Term Follow-Up of 756 Women

Su Hyeon Choi[1*], Sujin Kim[2*], Si Won Lee[3], Seyeon Won[1], So Hyun Shim[1], Nara Lee[1], Mi Kyoung Kim[1], Yong Wook Jung[1], Seok Ju Seong[1], and Mi-La Kim[1]

[1]Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul;
[2]Department of Obstetrics and Gynecology, Dong-A University Medical Center, Dong-A University College of Medicine, Busan, Korea
[3]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN, USA.

Purpose: The aims of this study were to evaluate the cumulative recurrence, reoperation, and pregnancy rates after ovarian endometrioma surgery at a single institution for more than a 5-year follow-up period.

Materials and Methods: This study was conducted as a retrospective chart review of patients with ovarian endometrioma who underwent surgery between January 2008 and March 2016. Study subjects included premenopausal women with at least 5 years of follow-up. Exclusion criteria were patients with stage I or II ovarian endometrioma, those who underwent hysterectomy or bilateral oophorectomy, and presence of residual ovarian lesions on the first postoperative ultrasonography at 3–6 months. Recurrence was defined as a cystic mass by ultrasonography.

Results: A total of 756 patients were recruited. The median follow-up duration was 85.5 months (interquartile range, 71–107 months). Recurrent endometrioma was detected in 27.9% patients, and reoperation was performed in 8.3% patients. Cumulative rates at 24, 36, 60, and 120 months were 5.8%, 8.7%, 15.5% and 37.6%, respectively, for recurrence and 0.1%, 0.5%, 2.9%, and 15.1%, respectively, for reoperation. After multivariable analysis, age ≤31 years [hazard ratio (HR)=2.108; 95% confidence interval (CI)=1.522–2.921; $p<0.001$], no subsequent pregnancy (HR=1.851; 95% CI=1.309–2.617; $p<0.001$), and postoperative hormonal treatment ≤15 months (HR=2.869; 95% CI=2.088–3.941; $p<0.001$) were significant risk factors for recurrent endometrioma. Among 315 patients who desired pregnancy, 54.0% were able to have a successful pregnancy and delivery.

Conclusion: Considering that longer postoperative hormonal treatment is the sole modifiable factor for recurrent endometrioma, we recommend long-term hormonal treatment until subsequent pregnancy, especially in younger women.

Key Words: Endometriosis, recurrence, reoperation, pregnancy, long-term follow-up

INTRODUCTION

Ovarian endometrioma is among the most common benign gynecologic diseases, affecting approximately 2%–10% of women of reproductive age and up to 50% of women with infertility.[1-3] Laparoscopic ovarian cystectomy is the treatment of choice for ovarian endometrioma-related pain or technical difficulties during oocyte retrieval.[4-6] However, according to Guo's pooled

Received: July 13, 2022 **Revised:** December 27, 2022 **Accepted:** January 11, 2023 **Published online:** February 13, 2023
Corresponding author: Mi-La Kim, MD, PhD, Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, 566 Nonhyeon-ro, Gangnam-gu, Seoul 06135, Korea.
E-mail: mila76@naver.com

*Su Hyeon Choi and Sujin Kim contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

analysis (analyzing 23 studies including 4368 patients), the calculated recurrence rate after conservative surgery was as high as 21.5% and 40%–50% at 2 and 5 years, respectively.[7] Additionally, in one questionnaire survey study, subsequent surgery was reported to be necessary after the initial conservative surgical treatment in 21.6%, 46.7%, and 55.4% of patients at 2, 5, and 7 years, respectively.[8] After second-line conservative laparoscopic surgery, cumulative recurrence rates were still 13.7% and 37.5% at 2 and 5 years, respectively.[9] Repeated surgeries can lead to decreased ovarian function, which may cause premature ovarian insufficiency and increased morbidity.[10] The goals of endometriosis treatment are to reduce endometriosis-associated pain, improve pregnancy rates for women who desire it, and delay recurrence for as long as possible.[11]

The recurrence rate can vary according to recurrence definition, endometriosis type, surgery type (cyst enucleation vs. drainage and ablation), postoperative medical treatment, disease severity, surgeon skills, and follow-up duration.[7] However, most publications focus on comparing different surgery types (e.g., electrofulguration vs. cyst enucleation) or recurrence rates after various medical treatments for a short-term follow-up of 1–3 years.[10,12-21] Studies to date of recurrent ovarian endometrioma after surgical removal with a long-term follow-up (≥5 years) are limited.[20-22]

Therefore, in this study, we aimed to evaluate cumulative recurrence, reoperation, and pregnancy rates, as well as risk factors for recurrence of surgically treated ovarian endometrioma, at a single institution with a follow-up period of ≥5 years.

MATERIALS AND METHODS

This retrospective cohort study was conducted in a single gynecological surgery center between January 2008 and March 2016. During the 8-year study period, a total of 2484 patients with pathologically confirmed ovarian endometrioma were treated surgically. The inclusion criteria were as follows: 1) premenopausal status; 2) no residual ovarian lesions as confirmed by the first postoperative transvaginal or transrectal ultrasonography (TVS or TRS, respectively); and 3) a follow-up period of at least 60 months after surgery. Patients were excluded if they underwent hysterectomy or bilateral oophorectomy (n=26) or had revised American Society for Reproductive Medicine (rASRM) classification I or II (n=4). Of note, 13 patients with a borderline or malignant ovarian tumor, in addition to ovarian endometrioma, which did not meet the exclusion criteria, were included in the study for analysis (Fig. 1).

Baseline data, including age at surgery, parity, body mass index, endometrioma size [largest diameter (cm); if ovarian cysts were bilateral, the sum of the largest diameters was recorded], preoperative cancer antigen 125 (CA125) levels, preoperative anti-Müllerian hormone levels, previous surgery for ovarian endometrioma, preoperative symptoms, ovarian cyst(s) location, cyst nature (unilocular or multilocular), presence of leiomyoma or adenomyosis, presence of cul-de-sac obliteration, rASRM stage, surgery type (cyst enucleation or unilateral oophorectomy, laparotomy or minimally invasive surgery), duration of postoperative medication use, subsequent pregnancy, time to recurrence, and time to reoperation, were collected in the medical chart review.

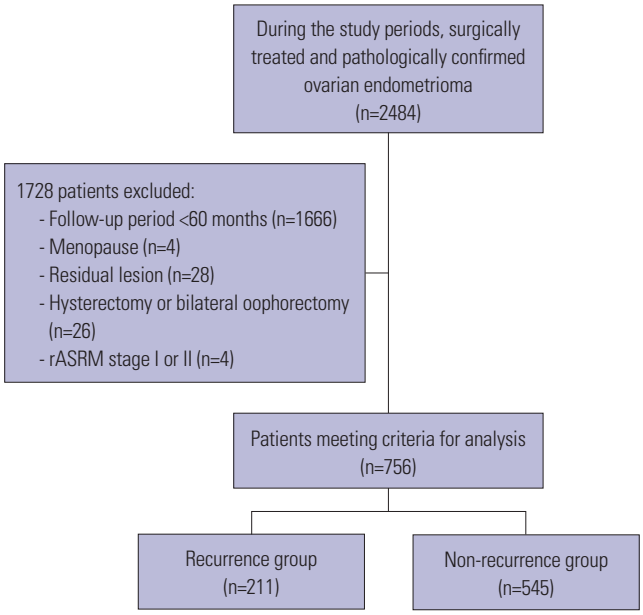


Fig. 1. Flow diagram of the patient selection process. rASRM, revised American Society for Reproductive Medicine.

The duration of postoperative medication was calculated using the sum of individual medication use before confirmed recurrence, for example, gonadotrophin-releasing hormone agonist (GnRH agonist), oral progestin including dienogest, oral contraceptives pills (OCPs), or levonorgestrel-intrauterine system (LNG-IUS).

In our institution, postoperative checks include the following: routine gynecological examination, TVS or TRS at 3–6 months postoperatively, and if unremarkable, follow-up at 6- to 12-month intervals. Additional follow-up was performed if the patient developed any symptoms. During every follow-up visit, patients were asked to fill out pain scales and specify marital, pregnancy, and childbirth status. According to pregnancy plans, we categorized patients as no plan, failure to conceive, successful delivery, miscarriage or ectopic pregnancy, ongoing pregnancy, or lost to follow up (unknown pregnancy outcome after confirmed intrauterine pregnancy). Time to recurrence was defined as the time in months from surgery to detection of a newly developed ovarian endometrioma measuring 2 cm or more. Recurrence of ovarian endometrioma was defined when TVS or TRS showed the following findings: a round cystic mass ≥20 mm with thick walls, irregular margins, homogenous low echogenic fluid content, scattered internal echoes, or negative papillary proliferation.[23] If a patient had two endometriomas, each measuring <20 mm, the sum of the diameters measuring

≥20 mm was used to define recurrence.[12-14] The study protocol was approved by the Institutional Review Boards and ethics committee of CHA Gangnam Medical Center on the Use of Human Subjects in Research (GCI 2021-05-007); informed consent requirements for the study were waived given its retrospective nature.

Statistical analysis was performed using the SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Between the recurrent group (n=211) and non-recurrent group (n=545), categorical variables were compared using chi-square and Fisher's exact tests. Quantitative variables were compared using the Mann–Whitney U test after normality test for data using the Shapiro–Wilk test. The Kaplan–Meier method was used to calculate the cumulative probability of recurrence and reoperation. Comparison between the curves was performed using the log-rank test. Multivariable analyses using Cox's proportional hazards models, including significant variables in univariable analysis, were used to obtain a subset of independent risk factors for recurrent ovarian endometrioma. Among these variables, those with a p value <0.2 were subjected to multivariable regression analyses. p values <0.05 were considered statistically significant.

RESULTS

A total of 756 patients were recruited. The median follow-up duration was 85.5 months [interquartile range (IQR), 71–107 months]. Baseline characteristics of the patients are listed in Table 1. The median age was 31 years (IQR, 27–36 years), and 605 (80.0%) patients were nulliparous. The median duration of postoperative hormonal treatment was 15 months (IQR, 4–47 months). Recurrent ovarian endometrioma was detected in 27.9% (211 of 756 patients), and reoperation was performed in 8.3% (63 of 756 patients). A total of 29.9% (63 of 211) patients with recurrent endometrioma were treated with repeated surgery. Using the Kaplan–Meier method, the cumulative recurrence rates at 24, 36, 60, and 120 months after surgical treatment of ovarian endometrioma were 5.8%, 8.7%, 15.5%, and 37.6%, respectively [mean: 116.6 months, 95% confidence interval (CI)=112.62–120.58 month] (Fig. 2). The cumulative reoperation rates at 24, 36, 60, and 120 months were 0.1%, 0.5%, 2.9%, and 15.1%, respectively (mean: 142.93 months, 95% CI= 139.93–145.94 months) (Fig. 3). To identify possible risk factors for recurrent ovarian endometrioma, recurrent (n=211) and non-recurrent (n=545) groups were compared (Table 1). The recurrent group showed younger age at surgery, larger cyst size, positive surgical history of previous ovarian endometrioma, presence of bilateral cysts, multilocular cysts, rASRM stage IV, surgery with exploratory laparotomy rather than minimally invasive surgery, and a shorter duration of postoperative hormonal treatment (p<0.05). The Kaplan-Meier curve showed statistically significant differences in the duration of hormonal treatment by log-rank test (Fig. 4).

Additionally, we evaluated the recurrence rates of only single type of hormonal treatment after surgery (Table 2). To avoid hormonal effects caused by pregnancy, all the pregnant patients (including missed abortion and ectopic pregnancy cases) were excluded in this sub-analysis. Kaplan-Meier curves showed no statistically significant differences in the type of hormonal treatment by log-rank test (p=0.284) (Fig. 5).

Cox regression analysis was performed for univariable and multivariable analyses of independent risk factors for recurrent endometrioma (Table 3). We divided quantitative variables into two groups according to median baseline characteristic values (Table 1). In the univariable analysis, age ≤31 years [hazard ratio (HR)=1.421; 95% CI=1.078–1.872; p=0.013], size of ovarian cysts >6.2 cm (HR=1.354; 95% CI=1.031–1.778; p=0.029), preoperative CA125 >47.3 IU/mL (HR=1.486; 95% CI=1.110–1.991; p=0.008), previous surgical history for ovarian endometrioma (HR=1.674; 95% CI=1.110–2.525; p=0.014), bilateral ovarian endometrioma (HR=1.524; 95% CI=1.146–2.026; p=0.004), multilocular cysts (HR=1.465; 95% CI=1.118–1.920; p=0.006), cul-de-sac obliteration (HR=1.437; 95% CI=1.063–1.943; p=0.018), rASRM stage IV (HR=1.623; 95% CI=1.234–2.136; p=0.001), laparotomy (HR=1.660; 95% CI=1.090–2.526; p=0.018), and duration of postoperative hormonal treatment ≤15 months (HR=2.294; 95% CI=1.722–3.056; p<0.001) were significant risk factors. Among variables with p values <0.2 in univariable regression analysis, age ≤31years (HR=2.108; 95% CI=1.522–2.921; p<0.001), no subsequent pregnancy (HR=1.851; 95% CI=1.309–2.617; p<0.001), and postoperative hormonal treatment ≤15 months (HR=2.869; 95% CI=2.088–3.941; p<0.001) were significant risk factors for recurrent ovarian endometrioma in multivariable analysis.

We defined "recurrence" as an adnexal mass with features of endometrioma measuring 2 cm or more. During the follow-up period, 27.9% of our study population met this definition for recurrence, and most of them remained stable with medical treatment only. However, some patients trying to conceive or who had to stop the medication due to adverse effects reported worsening symptoms or growth of ovarian endometrioma. Some patients who required surgical treatment for symptomatic myoma, growth of other types of ovarian cysts (e.g., dermoid, cystadenoma), or symptomatic adenomyosis were cooperated with recurrent small endometrioma. A total of 8.3% of these patients ended up undergoing re-operation; the characteristics of these patients are listed in Table 4.

Among the study patients, 315 (41.7%) women were planning to conceive. 224 (71.1%) were confirmed intrauterine or extrauterine pregnancy, and of them, 170 (54.0%) confirmed delivery. Eighteen (5.7%) women experienced spontaneous abortion or ectopic pregnancy, and 36 (11.4%) were pregnant at the time of the data collection or were lost to follow-up after confirmation of intrauterine pregnancy. Among the 315 patients who desired pregnancy, 91 (28.9%) failed to conceive. Of the 170 patients with successful pregnancy, 67.1% conceived

https://doi.org/10.3349/ymj.2022.0278

Table 1. Baseline Characteristics of the Patients

Clinical characteristics	All (n=756)	Recurrence group (n=211)	Non-recurrence group (n=545)	*p* value
Age (yr)	31 (27–36)	30 (26–34)	32 (27–37)	0.001*
Nulliparity	605 (80.0)	176 (83.4)	429 (78.7)	0.157
BMI (kg/m^2)	20.1 (18.8–21.7)	19.9 (18.7–21.6)	20.1 (18.9–21.8)	0.297
Cyst size (cm)	6.2 (4.7–8.5)	7.0 (5.1–9.7)	6.0 (4.6–8.2)	0.001*
Follow-up duration (months)	85.5 (71–107)	94 (74–115)	83 (70–103)	<0.001*
Preoperative CA125 (IU/mL) (n=667)	47.3 (4.4–5203)	56.6 (32.5–106.3) (n=186)	44.2 (30.4–73.9) (n=481)	0.002*
Preoperative AMH (ng/mL) (n=168)	3.39 (1.915–5.615)	3.64 (2.1–6.48) (n=50)	3.36 (1.81–5.40) (n=118)	0.249
History of ovarian endometrioma surgery	64 (8.5)	26 (12.3)	38 (7.0)	0.028*
Symptoms				0.087
Pain	441 (58.3)	133 (63.0)	308 (56.5)	
Bleeding	39 (5.2)	6 (2.8)	33 (6.0)	
Infertility	15 (2.0)	1 (0.5)	14 (2.6)	
Enlarging cyst	56 (7.4)	13 (6.2)	43 (7.9)	
Incidental finding	205 (27.1)	58 (27.5)	147 (27.0)	
Laterality				0.006*
Unilateral	553 (73.1)	139 (65.9)	414 (76.0)	
Bilateral	203 (26.9)	72 (34.1)	131 (24.0)	
Cyst nature				0.013*
Unilocular	457 (60.4)	112 (53.1)	345 (63.3)	
Multilocular	299 (39.6)	99 (46.9)	200 (36.7)	
Associated disease (n=378)				
Myoma	233 (30.8)	62 (29.4)	171 (31.4)	0.661
Adenomyosis	145 (19.2)	46 (21.8)	99 (18.2)	0.259
Cul-de-sac obliteration				0.075
None	251 (33.2)	59 (28.0)	192 (35.2)	
Partial	210 (27.8)	57 (27.0)	153 (28.1)	
Complete	295 (39.0)	95 (45.0)	200 (36.7)	
rASRM stage				<0.001*
Stage III	392 (51.9)	87 (41.2)	305 (56.0)	
Stage IV	364 (48.1)	124 (58.8)	240 (44.0)	
Surgical approach				0.001*
Laparotomy	51 (6.7)	25 (11.8)	26 (4.8)	
MIS	705 (93.3)	186 (88.2)	519 (95.2)	
Types of surgery				0.415
Cystectomy	706 (93.4)	200 (94.8)	506 (92.8)	
Oophorectomy	50 (6.6)	11 (5.2)	39 (7.2)	
Hormonal treatment duration before recurrence (months)	15 (4–47)	6 (3–21)	21 (5–59)	<0.001*
Hormonal treatment before recurrence				<0.001*
0– <6 months	221 (29.2)	83 (39.3)	138 (25.3)	
6– <24 months	221 (29.2)	82 (38.9)	139 (25.5)	
24– <60 months	174 (23.0)	39 (18.5)	135 (24.8)	
≥60 months	140 (18.6)	7 (3.3)	133 (24.4)	
Pregnancy plans				0.389
No plan for pregnancy	441 (58.3)	123 (58.3)	318 (58.3)	
Failure to conceive	91 (12.0)	32 (15.2)	59 (10.8)	
Successful delivery	170 (22.5)	45 (21.3)	125 (23.0)	
Miscarriage or ectopic pregnancy	18 (2.4)	4 (1.9)	14 (2.6)	
Ongoing pregnancy or lost to follow-up	36 (4.8)	7 (3.3)	29 (5.3)	

Table 1. Baseline Characteristics of the Patients (Continued)

Clinical characteristics	All (n=756)	Recurrence group (n=211)	Non-recurrence group (n=545)	*p* value
Postoperative pregnancy				0.287
Yes	224 (29.6)	56 (26.5)	168 (30.8)	
No	532 (70.4)	155 (73.5)	377 (69.2)	
Mode of pregnancy in successful delivery (n=170)				0.854
Natural pregnancy	114 (67.1)	31 (68.9)	83 (66.4)	
ART (IUI or IVF)	56 (32.9)	14 (31.1)	42 (33.6)	

BMI, body mass index; CA125, cancer antigen 125; AMH, anti-Mullerian hormone; rASRM, revised American Society of Reproductive Medicine; MIS, minimally invasive surgery (laparoscopy or robot); ART, assisted reproductive technology; IUI, intrauterine insemination; IVF, in vitro fertilization.
Data are presented as medians (interquartile range) for quantitative variables and numbers (%) for categorical variables.
*p<0.05.

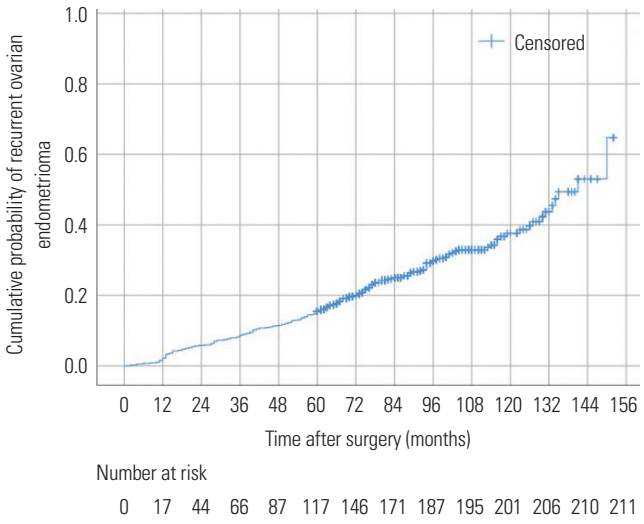


Fig. 2. Kaplan-Meier curve of cumulative recurrence rates for ovarian endometrioma. The cumulative recurrence rates at 24, 36, 60, and 120 months after surgical removal of endometrioma were 5.8%, 8.7%, 15.5%, and 37.6%, respectively.

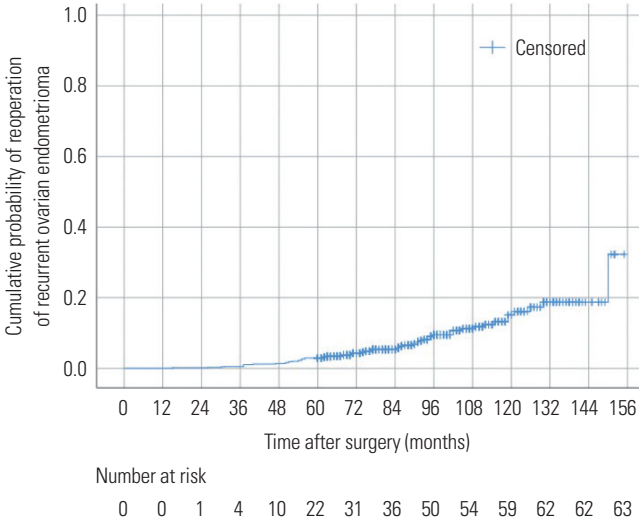


Fig. 3. Kaplan-Meier curve of cumulative reoperation rates for ovarian endometrioma. The cumulative reoperation rates at 24, 36, 60, and 120 months were 0.1%, 0.5%, 2.9%, and 15.1%, respectively.

naturally and 32.9% through intrauterine insemination or in vitro fertilization. A total of 28.9% of the patients who desired pregnancy failed to conceive (Table 1).

Three of the patients who underwent repeated surgery due to recurrent ovarian lesions during the surveillance period had borderline malignancy. However, none of them progressed to clear cell carcinoma or endometrioid adenocarcinoma. Four patients who underwent fertility-sparing surgery for associated borderline or malignant ovarian tumor conceived naturally and successfully delivered.

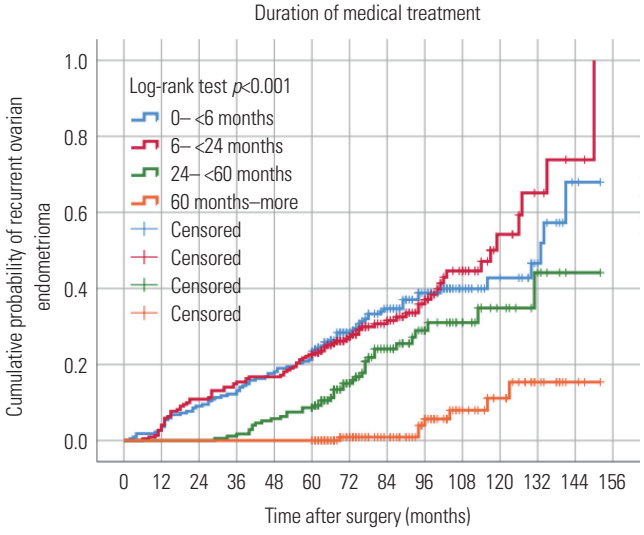
DISCUSSION

In this study, we recorded overall recurrence and reoperation rates of 27.9% and 8.3%, respectively, for ovarian endometrioma during a follow-up period of >5 years. The cumulative 5-year recurrence and reoperation rates were 15.5% and 2.9%, respectively. Among 315 women who desired pregnancy after surgery, 54.0% confirmed delivery, and viable intrauterine pregnancy was confirmed at the last follow-up in 11.4%. Additionally, when we analyzed the risk factors for recurrence, younger age, no subsequent pregnancy, and shorter postoperative hormonal treatment duration were statistically significant factors for recurrence. Among these three risk factors, the sole modifiable risk factor was postoperative medical treatment. To the best of our knowledge, this is the largest cohort study with a long-term follow-up period to assess the recurrence and reoperation rates of ovarian endometrioma.

Three studies covering 5-year follow-up periods have analyzed recurrence after surgery. Levorro, et al.[20] conducted a 5-year prospective study of infertile patients with stage III or IV endometriosis who underwent conservative laparoscopic surgery, comparing outcomes after 3 months of triptorelin treatment (n=29) versus expectant management (n=25). There was no significant difference in pain recurrence [relative risk (RR)= 0.94; 95% CI=0.57–1.55; p=1.000], endometrioma relapse (4 in 19 vs. 2 in 16: overall recurrence rate of 17.1%) (RR=1.29; 95% CI=0.66–2.50; p=0.670) or pregnancy rate in infertile women (RR=0.81; 95% CI=0.37–1.80; p=0.800) between the two groups.[20]

https://doi.org/10.3349/ymj.2022.0278

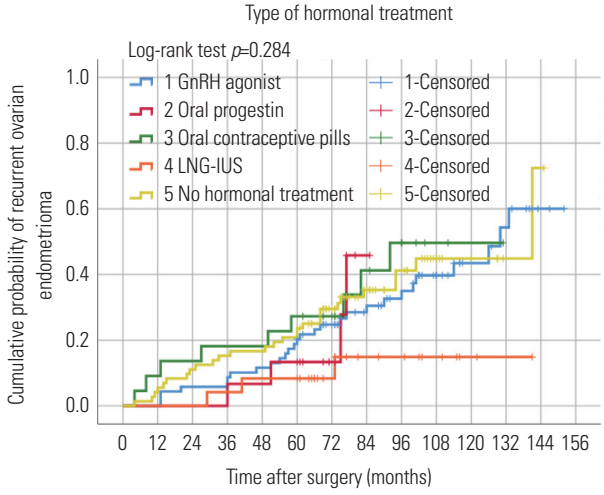
Zhu, et al.[21] reported a comparison study of GnRH agonist only (n=242) versus GnRH agonist+LNG-IUS (n=78). All the patients were followed for at least 5 years since last GnRH agonist injection. With a median of 84.6 months of follow-up, the GnRH agonist+LNG-IUS group showed an 11.5% recurrence rate, compared with 23.6% in the GnRH agonist alone group (p=0.023). In their study, multivariate analysis demonstrated that combined GnRH agonist and LNG-IUS treatment elicited a decrease in recurrence rate (RR=0.369; 95% CI=0.182–0.749; p=0.006).[21] Another long-term follow-up study by Li, et al.[22] analyzed risk factors for recurrence based on recurrence rates and endometriosis-related pain after a minimum of 5 years of follow-up in reproductive age women. The cumulative recurrence rate at 5 years was 15.4%. In their multivariate analysis, extent of dysmenorrhea (RR=1.711; 95% CI=1.175–2.493; p=0.005) and postoperative pregnancy rate (RR=0.649; 95% CI=0.460–0.914; p=0.013) were statistically significant for recurrent endometrioma and/or recurrent endometriosis-related pain.[22] Postoperative medication was not a risk factor for recurrence in their study. The medications they used were limited to GnRH agonist, OCPs, or LNG-IUS. However, 67.6% of these patients used GnRH agonist alone, and because GnRH agonist was administered for about 3–6 months, short-term use of other medications might have affected this outcome. There was no mention of specific medications used for postoperative management.[22] However, in our study, we included various postoperative medications for analysis, either used alone or in combination. In sub-analysis of only a single type of hormonal treatment, no statistically significant differences were noted in the type of hormonal treatment by log-rank test (p=0.284). However, conclusions are difficult to reach because patient age and duration of hormonal treatment according to the type of hormonal treatment differed between groups and because only small numbers of patients were included in this sub-analysis. When 15 months of hormonal treatment was used as a cut-off, the patients who received hormones for ≥15 months demonstrated less recur-



Number at risk

0– <6 months	8	20	29	40	52	62	72	77	78	79	80	83	
6– <24 months	9	24	34	37	50	59	65	70	75	78	80	81	
24– <60 months			3	10	15	24	33	36	37	38	39		
60 months–more						1		4	5	6	7		

Fig. 4. Probability of recurrence according to Kaplan-Meier curves (log-rank test) depending on duration of hormonal treatment.



Number at risk

GnRH agonist	4	6	8	14	17	20	22	24	25	27	28
Oral progestin		1		2		4					
Oral contraceptive pills	3		5	6		8	9				
LNG-IUS		1		2		3					
No hormonal treatment	8	11	12	17	21	24	26	27			28

Fig. 5. Probability of recurrence according to Kaplan-Meier curves (log-rank test) depending on individual types of hormonal treatment. GnRH gonadotrophin-releasing hormone; LNG-IUS, levonorgestrel-intrauterine system.

Table 2. Recurrence Rates of Individual Types of Hormonal Treatment Use

Types of medical treatment	Patient number	Age (yr)	Duration of medical treatment	Follow-up months	Treatment free interval (months)	Recurrence/ 5 yr recurrence rate
GnRH agonist	69	35.0 (29.5–39.0)	6.0 (3.0–6.0)	102.0 (74.5–121.0)	77.0 (55.5–106.0)	28 (40.6)/20.3
Oral progestin	15	38.0 (35.0–44.0)	15.0 (9.0–15.0)	73.0 (66.0–82.0)	56.0 (45.0–61.0)	4 (26.7)/13.3
Oral contraceptive pills	22	32.5 (22.8–38.3)	18.0 (2.8–39.5)	90.5 (73.0–106.8)	25.0 (0–54.8)	9 (40.9)/27.3
LNG-IUS	24	37.0 (34.0–40.8)	64.0 (38.8–87.5)	84.5 (66.3–109.8)	0.0 (0.0–0.0)	3 (12.5)/8.3
No medical treatment	72	34.5 (31.0–39.0)	0.0 (0.0–0.0)	86.0 (72.3–107.8)	75.0 (60.3–97.8)	28 (38.9)/20.8

GnRH, gonadotrophin releasing hormone; LNG-IUS, levonorgestrel-intrauterine system.
Data are presented as medians (interquartile range) for quantitative variables and numbers (%) for categorical variables.

Table 3. Univariable and Multivariable Analyses for Independent Risk Factors of Recurrent Ovarian Endometrioma Using Cox Regression

Risk factors for recurrence	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age ≤31 years (vs. >31 years)	1.421 (1.078–1.872)	0.013*	2.108 (1.522–2.921)	<0.001*
Multiparity (vs. nulliparity)	0.796 (0.554–1.145)	0.219		
BMI >20.1 kg/m^2 (vs. ≤20.1 kg/m^2)	0.864 (0.659–1.133)	0.292		
Cyst size >6.2 cm (vs. ≤6.2 cm)	1.354 (1.031–1.778)	0.029*	1.052 (0.742–1.491)	0.776
CA125 >47.3 IU/mL (vs. ≤47.3 IU/mL) (preoperative)	1.486 (1.110–1.991)	0.008*	1.215 (0.894–1.652)	0.214
AMH >3.39 ng/mL (vs. ≤3.39 ng/mL) (preoperative)	1.425 (0.814–2.494)	0.215		
Associated preoperative pain (vs. no)	1.279 (0.966–1.693)	0.085	1.295 (0.950–1.765)	0.102
History of ovarian endometrioma surgery (vs. no)	1.674 (1.110–2.525)	0.014*	1.201 (0.731–1.973)	0.470
Bilateral cysts (vs. unilateral cyst)	1.524 (1.146–2.026)	0.004*	1.226 (0.814–1.848)	0.329
Multilocular cyst (vs. unilocular)	1.465 (1.118–1.920)	0.006*	1.301 (0.958–1.765)	0.092
Myoma (vs. no)	1.006 (0.748–1.354)	0.967		
Adenomyosis (vs. no)	1.273 (0.918–1.766)	0.149	1.289 (0.890–1.868)	0.179
CDS obliteration (vs.no)	1.437 (1.063–1.943)	0.018*	1.125 (0.743–1.702)	0.578
rASRM stage IV (vs. III)	1.623 (1.234–2.136)	0.001*	1.380 (0.892–2.135)	0.148
Oophorectomy (vs. cystectomy)	0.749 (0.408–1.376)	0.352		
Laparotomy (vs. MIS)	1.660 (1.090–2.526)	0.018*	1.612 (0.932–2.788)	0.087
Hormonal treatment ≤15 months (vs. >15 months)	2.294 (1.722–3.056)	<0.001*	2.869 (2.088–3.941)	<0.001*
No subsequent pregnancy (vs. pregnancy)	1.277 (0.940–1.735)	0.118	1.851 (1.309–2.617)	<0.001*

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CA125, cancer antigen 125; AMH, anti-Mullerian hormone; CDS, cul-de-sac; rASRM, revised American Society of Reproductive Medicine; MIS, minimally invasive surgery (laparoscopy or robotic).
*p<0.05.

rence (HR=2.869; 95% CI=2.088–3.941; p<0.001). In these three long-term follow-up studies, reoperation rates were not reported. A population-based cohort study with long-term follow-up analyzed the universal coverage health database of Ontario, Canada.[24] In a major surgery without bilateral salpingo-oophorectomy group (n=21834), any repeated surgery was performed in 3543 (16.2%), and 4528 (20.7%) patients were delivered until the 5th postoperative year. In their study, there was no information about patient age and postoperative medical treatment.[24]

As mentioned above, the cumulative recurrence rates at 60 and 120 months after surgical treatment of ovarian endometrioma were 15.5% and 37.6%, respectively. In addition, the cumulative reoperation rates at the above-mentioned times were 2.9% and 15.1%, respectively, which is considerably lower than the 5-year recurrence and reoperation rates of 40%–50% and 46.7%, respectively, reported by Guo[7] and Shakiba, et al.[8] The low recurrence and reoperation rates in this study are probably due to 47.8% (361/756) of our patients receiving at least 18 months of hormonal therapy as recommended by the European Society of Human Reproduction and Embryology (ESHRE) guidelines, while 54.0% (170/315) of women desiring pregnancy confirmed subsequent delivery.[25] In our study, the duration of hormonal treatment was found to be related to decreases in recurrent ovarian endometrioma (Fig. 4). Vercellini, et al.[14] also reported similar data. They compared duration of postoperative OCP in never, ever, and always users after surgical treatment of ovarian endometrioma. During the 28 months of median follow-up, the 3-year cumulative proportions of recurrence free

Table 4. Clinical Characteristics of Reoperated Patients (n=63)

Clinical characteristics	Value
Age at initial surgery (years)	34.0 (29–37)
Age at reoperation (years)	39.0 (35–44)
Interval to recurrence (months)	53.0 (23–76)
Interval to reoperation (months)	71.0 (51–95)
Cyst size at operation (cm)	6.7 (4.5–8.2)
Laterality at reoperation	
Initial unilateral (n=47)	
Same side	14 (29.8)
Contralateral side	25 (53.2)
Bilateral	8 (17.0)
Initial bilateral (n=16)	
Unilateral	6 (37.5)
Bilateral	10 (62.5)
Indication for reoperation	
Pain	19 (30.2)
Growing ovarian cysts during follow-up	20 (31.7)
Cooperated with surgical indication for associated disease	24 (38.1)
Myoma	9 (37.5)
Adenomyosis	7 (29.2)
Hydrosalpinx	2 (8.3)
Other ovarian cysts	4 (16.7)
Cesarean section/ectopic pregnancy	2 (8.3)

Data are presented as medians (interquartile range) for quantitative variables and numbers (%) for categorical variables.

https://doi.org/10.3349/ymj.2022.0278

patients were 94% in always users and 51% in never users (Log-rank test, $p<0.001$). In subgroup analysis of ever users, the 3-year cumulative proportion of recurrence free patients was 51% for OCP <12 months, compared to 78% for ≥12 months (log-rank test, $p<0.001$).[14] Del Forno, et al.[26] also reported that long-term medical treatment reduced recurrence and reoperation rates. In their retrospective study, during the median follow-up duration of 3.7 years, 36% of the women were diagnosed with recurrent endometrioma (definition of recurrent endometrioma was typical sonographic features ≥1 cm), and the reoperation rate was 16.2%.[26]

Possible theories for the development of recurrent ovarian endometrioma are 1) in situ regrowth of microscopic residual lesions not completely removed during surgery, 2) growth of microscopic endometriotic lesions undetected at surgery, 3) de novo lesions, or 4) a combination thereof.[7] Postoperative hormonal treatment maintains the minimal disease state by preventing reactivation.[15] According to ESHRE guidelines, postoperative hormonal treatment is recommended for at least 18–24 months to prevent recurrent disease and pain symptoms for those not immediately seeking conception.[24] However, a GnRH agonist can be only a short-term treatment option due to its side effects on bone mineral density.

In a recent meta-analysis, various combinations of hormonal treatment were compared with expectant management.[27] The study reported that pooled relative treatment effects were in the order of GnRH agonist+LNG-IUS, continuous OCP, and GnRH agonist in a randomized controlled trial network meta-analysis. In the cohort network meta-analysis, the most effective method was LNG-IUS, followed by dienogest and GnRH agonist+LNG-IUS. However, short-term use of hormonal therapy for 3–6 months did not elicit a decreased recurrence rate versus expectant management. Accordingly, they reported that all hormonal regimens after surgical treatment of ovarian endometrioma showed better outcomes than no treatment. Nonetheless, only long-term use of hormonal treatment effectively prevented recurrent ovarian endometrioma.[27] Zakhari, et al.[28] also reported a meta-analysis with 2137 patients using various postoperative medications. Their study also showed postoperative hormonal suppression significantly decreased the recurrence risk of endometriosis, compared to expectant management or placebo (RR=0.41; 95% CI=0.26–0.65). Medical treatment either prevents or decreases the recurrent ovarian endometrioma in patients.[29-35] Only 29.9% of our patients with recurrence ended up having reoperation, and the rest of the study population remains under surveillance using medical treatment after the confirmation of recurrent disease.

The limitations of this study are as follows. First, it was a retrospective study, and we were unable to confirm pain recurrence. Approximately 30% and 20% of the study population had associated leiomyoma and adenomyosis, respectively. Therefore, it was difficult to assess whether pain originated from associated pathology or disease recurrence. Second, we were unable to analyze recurrence rates based on the different combinations of hormonal therapy depending on the patient's condition. We only analyzed recurrence rates based on the duration of hormonal treatment and single individual types of hormonal treatment. Added to that limitation could be the fact that patients who used hormonal therapy intermittently and those who started treatment despite not meeting the criteria for recurrence (e.g., cyst <2 cm) were included in the analysis based on duration of use. Third, for those with successful pregnancy outcomes, a delay in the resumption of their period could have affected the recurrence rate. Nevertheless, the biggest strength of this study is the long-term follow-up data for a large cohort of patients and a longer duration of follow-up than previous studies. Also, we included a pregnancy-related analysis of recurrence and reoperation rates.

In conclusion, 27.9% of patients had recurrence and 8.3% required reoperation. Desired pregnancy was achieved in 54% of patients. Since longer postoperative hormonal treatment is the sole modifiable factor for recurrent ovarian endometrioma, we recommend such treatment until a subsequent pregnancy is achieved. Prospective large randomized controlled studies of patient compliance, medical costs, and possible side effects of hormonal treatment should be considered in the future.

ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.co.kr) for English language editing and Statisticspanda for helping with the statistical analysis (https://blog.naver.com/dltpwns85).

AUTHOR CONTRIBUTIONS

Conceptualization: Mi-La Kim. Data curation: Sujin Kim and So Hyun Shim. Formal analysis: Su Hyeon Choi and Nara Lee. Investigation: Sujin Kim and Mi Kyoung Kim. Methodology: Si Won Lee and So Hyun Shim. Project administration: Mi-La Kim and Seok Ju Seong. Resources: Seyeon Won and Mi Kyoung Kim. Software: Nara Lee. Supervision: Mi-La Kim, Yong Wook Jung, and Seok Ju Seong. Validation: Su Hyeon Choi. Visualization: Seyeon Won and Yong Wook Jung. Writing—original draft: Mi-La Kim and Si Won Lee. Writing—review & editing: Su Hyeon Choi and Sujin Kim. Approval of final manuscript: all authors.

ORCID iDs

Su Hyeon Choi https://orcid.org/0000-0003-1433-2690
Sujin Kim https://orcid.org/0000-0003-0857-2225
Si Won Lee https://orcid.org/0000-0002-1129-6201
Seyeon Won https://orcid.org/0000-0002-2254-2703
So Hyun Shim https://orcid.org/0000-0001-7864-2853
Nara Lee https://orcid.org/0000-0002-9019-5301
Mi Kyoung Kim https://orcid.org/0000-0002-9520-2339
Yong Wook Jung https://orcid.org/0000-0003-2098-8143
Seok Ju Seong https://orcid.org/0000-0003-3820-3412
Mi-La Kim https://orcid.org/0000-0003-1011-5664

REFERENCES

1. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am 1997;24:235-58.
2. Bulun SE. Endometriosis. N Engl J Med 2009;360:268-79.
3. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril 2009;92:68-74.
4. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev 2008;2:CD004992.
5. Somigliana E, Benaglia L, Paffoni A, Busnelli A, Vigano P, Vercellini P. Risks of conservative management in women with ovarian endometriomas undergoing IVF. Hum Reprod Update 2015;21:486-99.
6. Jadoul P, Kitajima M, Donnez O, Squifflet J, Donnez J. Surgical treatment of ovarian endometriomas: state of the art? Fertil Steril 2012;98:556-63.
7. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update 2009;15:441-61.
8. Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008;111:1285-92.
9. 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.
10. Busacca M, Vignali M. Endometrioma excision and ovarian reserve: a dangerous relation. J Minim Invasive Gynecol 2009;16:142-8.
11. Donnez J, Pirard C, Smets M, Jadoul P, Squifflet J. Surgical management of endometriosis. Best Pract Res Clin Obstet Gynaecol 2004;18:329-48.
12. Kikuchi I, Takeuchi H, Kitade M, Shimanuki H, Kumakiri J, Kinoshita K. Recurrence rate of endometriomas following a laparoscopic cystectomy. Acta Obstet Gynecol Scand 2006;85:1120-4.
13. Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, et al. Recurrence of ovarian endometrioma after laparoscopic excision. Hum Reprod 2006;21:2171-4.
14. 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.
15. Seong SJ, Kim D, Lee KH, Kim TJ, Chung HH, Chang SJ, et al. Role of hormone therapy after primary surgery for endometrioma: a multicenter retrospective cohort study. Reprod Sci 2016;23:1011-8.
16. 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.
17. Vercellini P, DE Matteis S, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2013;92:8-16.
18. Seo JW, Lee DY, Kim SE, Yoon BK, Choi D. Comparison of long-term use of combined oral contraceptive after gonadotropin-releasing hormone agonist plus add-back therapy versus dienogest to prevent recurrence of ovarian endometrioma after surgery. Eur J Obstet Gynecol Reprod Biol 2019;236:53-7.
19. Cho S, Jung JA, Lee Y, Kim HY, Seo SK, Choi YS, 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.
20. Loverro G, Carriero C, Rossi AC, Putignano G, Nicolardi V, Selvaggi L. A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;136:194-8.
21. Zhu SY, Wu YS, Gu ZY, Zhang J, Jia SZ, Shi JH, et al. Preventive therapeutic options for postoperative recurrence of ovarian endometrioma: gonadotropin-releasing hormone agonist with or without levonorgestrel intrauterine system insertion. Arch Gynecol Obstet 2021;303:533-9.
22. Li XY, Chao XP, Leng JH, Zhang W, Zhang JJ, Dai Y, et al. Risk factors for postoperative recurrence of ovarian endometriosis: long-term follow-up of 358 women. J Ovarian Res 2019;12:79.
23. Mais V, Guerriero S, Ajossa S, Angiolucci M, Paoletti AM, Melis GB. The efficiency of transvaginal ultrasonography in the diagnosis of endometrioma. Fertil Steril 1993;60:776-80.
24. Bougie O, McClintock C, Pudwell J, Brogly SB, Velez MP. Long-term follow-up of endometriosis surgery in Ontario: a population-based cohort study. Am J Obstet Gynecol 2021;225:270.e1-19.
25. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400-12.
26. Del Forno S, Cofano M, Degli Esposti E, Manzara F, Lenzi J, Raimondo D, et al. Long-term medical therapy after laparoscopic excision of ovarian endometriomas: can we reduce and predict the risk of recurrence? Gynecol Obstet Invest 2021;86:170-6.
27. Wattanayingcharoenchai R, Rattanasiri S, Charakorn C, Attia J, Thakkinstian A. Postoperative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: a systematic review and network meta-analysis. BJOG 2021;128:25-35.
28. Zakhari A, Delpero E, McKeown S, Tomlinson G, Bougie O, Murji A. Endometriosis recurrence following post-operative hormonal suppression: a systematic review and meta-analysis. Hum Reprod Update 2021;27:96-107.
29. Vignali M, Belloni GM, Pietropaolo G, Barbasetti Di Prun A, Barbera V, Angioni S, et al. Effect of dienogest therapy on the size of the endometrioma. Gynecol Endocrinol 2020;36:723-7.
30. Uludag SZ, Demirtas E, Sahin Y, Aygen EM. Dienogest reduces endometrioma volume and endometriosis-related pain symptoms. J Obstet Gynaecol 2021;41:1246-51.
31. Angioni S, Pontis A, Malune ME, Cela V, Luisi S, Litta P, et al. Is dienogest the best medical treatment for ovarian endometriomas? Results of a multicentric case control study. Gynecol Endocrinol 2020;36:84-6.
32. Piacenti I, Viscardi MF, Masciullo L, Sangiuliano C, Scaramuzzino S, Piccioni MG, et al. Dienogest versus continuous oral levonorgestrel/EE in patients with endometriosis: what's the best choice? Gynecol Endocrinol 2021;37:471-5.
33. Mariani LL, Novara L, Mancarella M, Fuso L, Casula E, Biglia N. Estradiol/nomegestrol acetate as a first-line and rescue therapy for the treatment of ovarian and deep infiltrating endometriosis. Gynecol Endocrinol 2021;37:646-9.
34. Capezzuoli T, Vannuccini S, Mautone D, Sorbi F, Chen H, Reis FM, et al. Long-term hormonal treatment reduces repetitive surgery for endometriosis recurrence. Reprod Biomed Online 2021;42:451-6.
35. Lee JH, Song JY, Yi KW, Lee SR, Lee DY, Shin JH, et al. Effectiveness of dienogest for treatment of recurrent endometriosis: multicenter data. Reprod Sci 2018;25:1515-22.

https://doi.org/10.3349/ymj.2022.0278