

Surgical Therapy of Ovarian Endometrioma: Recurrence and Pregnancy Rates

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ABSTRACT

Background and Objectives: The study was designed to analyze preoperative clinical and surgical findings at enucleation of ovarian endometrioma with their impact on recurrence and pregnancy rates.

Methods: This is a retrospective study of 550 histologically verified ovarian endometriomas operated on at the Department of Obstetrics and Gynecology, University Hospital Kiel, Germany, between 1995 and 2004. Preoperative data, surgical findings, and postoperative outcomes of 289 cases were analyzed. The average follow-up period was 12.9 years.

Results: Ovarian endometriomas recurred in 23.9% of patients. Risk factors identified for recurrence of endometriomas were preoperative pain ($P = .013$), dysmenorrhea ($P = .013$), larger cyst size (>8 cm), younger age (<25 years), and preoperative cyst rupture. Factors associated with postoperative dysmenorrhea were younger age <25 years ($P < .001$), nulliparity ($P = .020$), and larger cyst size >8 cm ($P = .048$). Recurrence of pain was influenced by previous surgery of endometrioma ($P < .05$). Laparoscopy had a higher percentage of symptom-free patients than laparotomy did (49.0% vs 33.3%). Additional postoperative hormonal treatment resulted in a higher spontaneous pregnancy rate (41.4% vs 12.6%; $P < .001$) but a lower recurrence-free interval rate (70.5% vs 82.6%; $P = .050$) when compared with surgery only.

Conclusions: We identified preoperative and intraoperative findings associated with higher risk of recurrence of endometrioma, pain, and dysmenorrhea. Patients desiring pregnancy benefited from postoperative hormone treat-

ment, but no favorable results from combined therapy were observed with regard to recurrence rate.

Key Words: Hormone therapy, Laparoscopy, Ovarian endometrioma, Recurrence, Risk factor.

INTRODUCTION

In the clinical treatment of endometriosis, 3 issues need to be adequately considered: pain, recurrence, and infertility. As a common chronic disease, endometriosis with its pathological findings influences patients' quality of life. Women with endometriosis are impaired by diverse factors physically, mentally, and socially. Without causal treatment options, endometriosis is a challenge in gynecological diagnosis and treatment.¹ Currently, laparoscopy is considered an effective and proven treatment option due to its good tolerance, low morbidity, and low total cost.² Combined surgical and medical treatment is often the most effective plan for improving the incidence of recurrence and the improvement of pregnancy rate in patients with endometriosis.³ The high recurrence rate of ovarian endometrioma and its concurrent symptoms represents one of the less satisfactory aspects of the surgical treatment of endometriosis.⁴

The definition and identification of risk factors for onset and recurrence of endometriosis cysts are essential to improve preoperative and postoperative therapy. Most studies examined operation type, size of the cyst, and medical treatment.⁵ Prognostic value for predicting recurrent pain associated with endometriosis includes age, previous treatments, and the severity of the revised American Society for Reproductive Medicine score.^{4,6,7}

The purpose of the present study was to identify risk factors for endometriomas, recurrence of endometriomas, and pain with the aim to identify an optimal matching of surgical and medical treatment for an individual therapy concept. Because of the long-term follow-up of our patients, we attempted to obtain further evidence on the effectiveness of ovarian endometrioma surgery and its impact on pregnancy rate.

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Figure 1. Transvaginal ultrasonogram of a 6-cm (diameter), left ovarian endometrioma and its corresponding laparoscopic image.

MATERIALS AND METHODS

In this study, patients with suspected endometriosis cyst or benign ovarian cyst, based on the medical and surgical reports at the Department of Obstetrics and Gynecology, University Hospital Kiel in Germany from 1995 to 2004, were analyzed retrospectively. Of 3057 patients' medical records and surgical reports, we histologically verified 550 patients with ovarian endometriosis cysts undergoing either laparoscopic conservative excision or laparotomy. Their data regarding general patient characteristics, endometrioma symptoms, and diagnostic and surgical findings were collected from clinical records and reviewed (**Figure 1**). Patient characteristics are summarized in **Table 1**. In August 2011, these 550 patients with endometriomas were approached via letter and asked to complete a questionnaire and return it to the clinic. In cases of invalid addresses, the current addresses of the patients were traced by the registration offices up to their second change of residence so that a maximum of 3 attempts were made to contact the patients. With a final return rate of 52.5%, there were 289 patients in the follow-up study. In the questionnaire, patients were asked about a postoperative occurrence of another endometriosis cyst, the temporal occurrence, and dignity. Furthermore, possible reoperation rate, operation type, and recurrent pain symptoms (pain lasting >1 week, dysmenorrhea, and dyspareunia) were inquired. Patients were questioned about their preoperative and postoperative fertility, whether a planned spontaneous pregnancy with or without complications occurred, and, in cases of infertility and pregnancy, desire if artificial insemination

was successful. The recurrence of ovarian endometrioma was defined as a positive response to the presence of an endometriosis cyst (as reported by the patient) in the questionnaire. In the analysis of recurrence rate, patients with a previous diagnosis of endometriosis were excluded. The average follow-up period was 12.9 years with a minimal time of 7.0 years and a maximal time of 16.9 years between operation and follow-up.

Data for analysis were recorded using Microsoft (Redmond, Washington) Access software. Statistical analysis was performed using Microsoft Excel and SPSS (IBM Corporation, Armonk, New York) programs. Patient identification numbers were assigned for granting data protection. The percentages are based primarily on the total number; in the absence of information, the corrected probability is given. In the analysis of categorical values, the χ^2 was used. The statistical significance level was set at 5% ($P < .05$). The recurrence-free interval probabilities were estimated according Kaplan-Meier method. The log-rank test (Mantel-Cox) was used to compare the survival time of 2 groups with each other. In postmenopausal cases, the women were not considered in the postoperative analysis of dysmenorrhea.

RESULTS

The clinical characteristics of the patients are reported in Table 1. At the time of surgery, the mean age of all endometrioma patients was 37.2 (\pm 9.0) years and at follow-up, 50.5 (\pm 9.3) years.

Table 1.
Patient Characteristics (n = 550)

Factors	Cases, n (%)
Age, y	37.2 ± 9.0 ^a
BMI, kg/m ²	
<19	43 (7.8)
19–24	344 (62.5)
25–30	123 (22.4)
>30	40 (7.3)
Sterility	
primary	261 (47.5)
secondary	52 (9.5)
Parity ≥1	194 (35.3)
Abortion or miscarriage ≥1	72 (13.1)
Pain	338 (61.5)
Dysmenorrhea	214 (38.9)
Recurrence of previous endometrioma	153 (27.8)
Previous laparoscopic surgery of endometrioma	226 (41.1)
Presence of uterine myoma	105 (19.1)
CA-125, ^b U/mL, increased (>35 U/mL)	147 (47.6)
Cyst size, cm	
2–4	316 (57.5)
5–8	209 (38.0)
>8	25 (4.5)
Cyst rupture	
Preoperative	23 (4.2)
Intraoperative	281 (51.1)
Age, y, mo	50.5 ± 9.3 ^a
Postoperative medical treatment	162 (56.1)
Postoperative pain	96 (33.2)
Postoperative dysmenorrhea ^b	93 (34.8)
Recurrence of first diagnosed ovarian endometrioma ^b	47 (23.9)
Reoperation rate of first diagnosed ovarian endometrioma ^b	32 (68.1)
Postoperative pregnancy desire	111 (38.4)
Postoperative pregnancy ^b	60 (54.1)

BMI, body mass index.

^aMean ± SD.

^bThe sum does not add up to the total because of missing values or because of a new subtotal.

Preoperatively younger age, nulliparity, and previous laparoscopic surgery for ovarian endometrioma predicted positively the presence of pain and dysmenorrhea. Larger cyst size (>8 cm) was also associated with occurrence of pain, while primary or secondary sterility was associated with a higher rate of dysmenorrhea.

Factors associated with recurrence of dysmenorrhea were younger age ($P < .01$), nulliparity ($P < .05$), and larger cyst size ($P < .05$). Previous laparoscopic surgery for ovarian endometrioma ($P < .05$) was the only significant risk factor for recurrence of pain that was found (**Table 2**).

One hundred ninety-seven patients were initially diagnosed with endometriomas at the time of surgery, and, of those, 47 patients showed recurrent ovarian endometrioma (23.9%) in the follow-up period. Of those 47 patients, 68.1% (32 of 47) underwent a reoperation in the follow-up period (**Table 1**). Of those 32 patients, 17 patients (53.1%) needed 1 reoperation; 9 patients (28.1%), 2 reoperations; and 6 patients (18.8%) required ≥3 reoperations due to new endometriosis cysts.

The probability of a recurrent-free interval was 76.1% for all primarily diagnosed endometriomas in our study period. Patients with preoperative pain showed a significantly higher recurrence rate (log-rank test $P = .013$). The Kaplan-Meier graph demonstrates that patients without preoperative pain had a significantly higher recurrence-free interval of 84.7% when compared with patients with a history of preoperative pain who were recurrence-free only 69.4% by the end of the follow-up period (**Figure 2**). Another statistically significant risk factor for endometrioma recurrence was preoperative dysmenorrhea (log-rank test $P = .013$). The Kaplan-Meier curve (**Figure 3**) illustrates that women without preoperative dysmenorrhea have a recurrence-free interval of 81.4% compared with a recurrence-free interval of only 66.2% in women with preoperative dysmenorrhea.

Other risk factors that were not significant but showed an association with higher recurrence were larger cyst size (>8 cm; rate of recurrence was 33.3% [5 of 15] vs 16.3% [15 of 92] in cyst size 5–8 cm and 16.8% [24 of 143] in cyst size <5 cm), younger age at surgery (<25 years: 6.4% [3 of 47] in the recurrence cohort vs 2.8% [8 of 289] in the follow-up cohort), and preoperative cyst rupture (rate of recurrence was 28.6% [2 of 7] vs 20.5% [26 of 101] in the intraoperative cyst rupture group and 15.4% [18 of 99] in the no cyst rupture group).

Analyzing the effectiveness of endometrioma surgery, laparoscopy showed the best results in terms of being symptom-free postoperatively. After laparoscopic surgery, 49.0% of the patients were symptom-free, while after lap-

Table 2.
Analysis of Factors Related to the Occurrence and Recurrence of Pain and Dysmenorrhea

	Preoperative	Postoperative	Preoperative	Postoperative
	Pain		Dysmenorrhea	
	<i>P</i> Value (n = 550)	<i>P</i> Value (n = 289)	<i>P</i> Value (n = 550)	<i>P</i> Value (n = 267)
Younger age, y	<.01	NS	<.01	<.01
BMI, kg/m ²	NS	NS	NS	NS
Sterility	NS	NS	<.01	NS
Nulliparity	<.05	NS	<.05	<.05
Abortion/miscarriage	NS	NS	NS	NS
Previous laparoscopy of endometrioma	<.01	<.05	<.05	NS
Larger cyst size, >8 cm	<.05	NS	NS	<.05
Cyst rupture	NS	NS	NS	NS

BMI, body mass index; NS, not significant.

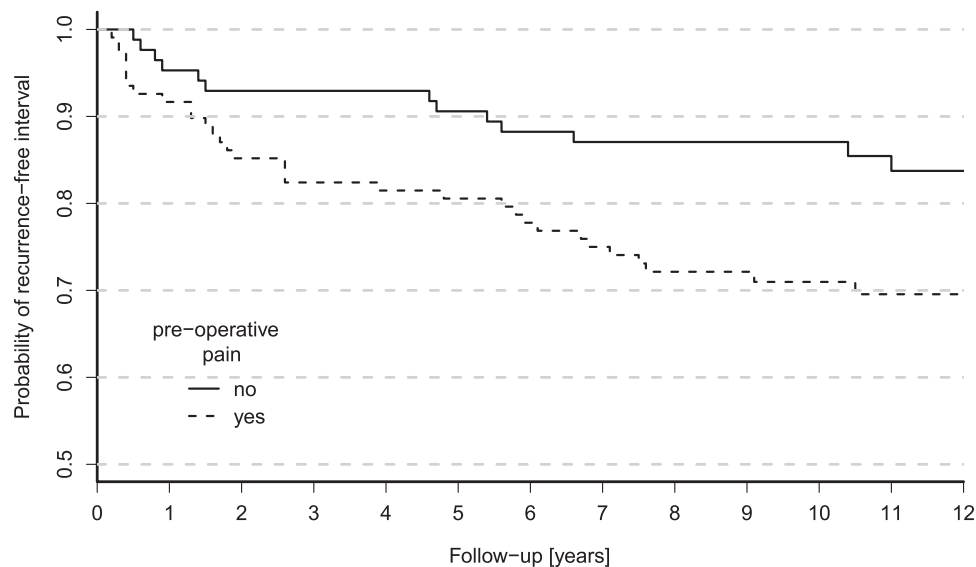


Figure 2. Probability of recurrence-free interval within the follow-up period in patients with and without preoperative pain.

arotomy, only 33.3% were. By transition from laparoscopy to laparotomy, only 43.7% were asymptomatic.

In the follow-up period, postoperative medical treatment was given in 56.1% of the cases (162 of 289). Additional postoperative hormone therapy (gonadotropin-releasing hormone agonist, oral contraceptive, medroxyprogesterone acetate, or danazol) led to a higher recurrence of endometrioma, with a recurrence-free interval rate of only 70.5% versus 82.6% in those patients who did not receive hormonal therapy (log-rank test $P = .050$) (**Figure 4**). The

recurrence rates in both groups increased constantly with time from diagnostic surgery. Comparing combined surgical and hormonal treatment with exclusive surgical therapy, the following differences were shown: postoperative pain in 36.4% versus 29.1%, dysmenorrhea in 37.8% versus 26.0%, and dyspareunia in 19.1% versus 18.1%.

Desire for postoperative pregnancy was mentioned by 111 of 289 patients (38.4%). Combined surgical and hormonal treatment was given to 61 of 111 patients (55.0%), whereas surgery alone was performed in 50 of 111 pa-

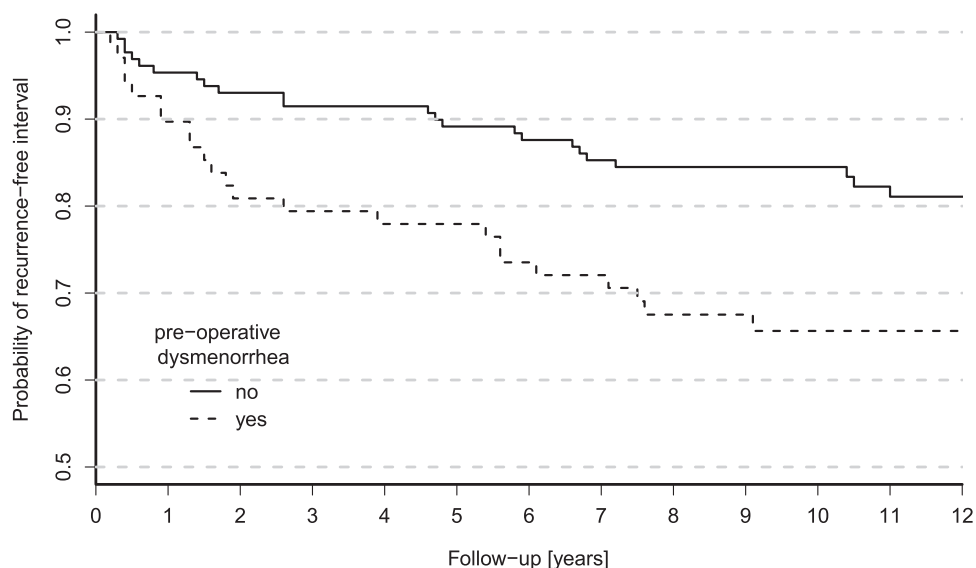


Figure 3. Probability of recurrence-free interval within the follow-up period in patients with and without preoperative dysmenorrhea.

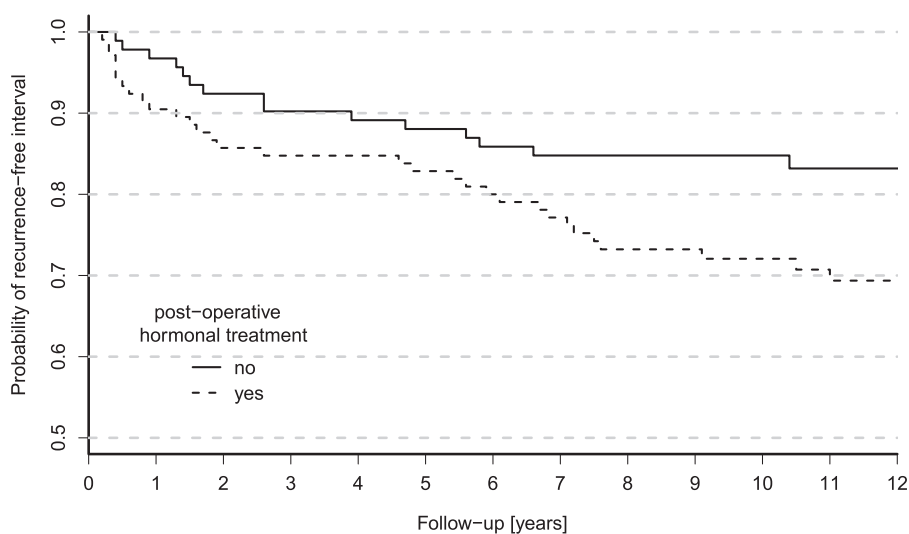


Figure 4. Probability of recurrence-free interval within the follow-up period in patients with and without postoperative hormonal treatment.

tients (45.0%). Among these patients, the postoperative spontaneous pregnancy rate was 54.1% (60 of 111). Of these 60 patients, 46 of 111 (41.4%) had surgical treatment combined with medical treatment and 14 of 111 (12.6%) had surgery alone. A statistically significant difference ($P < .001$) between combined surgical and hormonal therapy and exclusive surgery was observed.

DISCUSSION

In this retrospective cohort study, we analyzed risk factors, the effectiveness of endometrioma surgery compar-

ing laparoscopy versus laparotomy, and the effect of additional medical treatment on recurrence and pregnancy rates.

The preoperative risk factors observed as having significant predictive value for presence of pain and dysmenorrhea were younger age, previous laparoscopic surgery of ovarian endometrioma, and nulliparity. Occurrence of pain seemed to be significantly associated with larger cyst size (>8 cm), while primary or secondary sterility was associated with a higher rate of dysmenorrhea. Concerning the recurrent symptoms, younger age, nulliparity, and

larger cyst diameter significantly influenced the recurrence of dysmenorrhea, while only previous laparoscopic surgery of ovarian endometrioma was determined as significant risk factor for recurrence of pain. This was also reported by Bussacca et al⁴ and Porpora et al.² In agreement with Vercellini et al,⁸ a lower incidence of dysmenorrhea in older age is justifiable due to the postmenopausal changes. The medical condition of a patient can be adversely affected by a previous operation, such as laparoscopy or a longer-existing disease with possible adhesion formation as a natural consequence of the surgical trauma.^{2,4} Other studies also suggest that adhesions are important for the cause of endometriosis-associated pain, whereas the cyst diameter in contradiction to our study has no significant correlation between cyst size and pain symptoms.^{9,10}

In line with earlier studies that indicate pregnancy as a protective factor for endometriosis-associated pain,^{2,5} nulliparity is attributed a predictive value for pain symptoms in the present study. However, only a few prospective studies have tried to determine factors with predictive value for recurrent pain.²

Many studies have analyzed the recurrence rate of endometriomas after laparoscopic surgery, and found that the recurrence rate is between 11.0% and 30.4% after ≥ 2 years of observation.^{5,8} The results of Busacca et al¹¹ showed a recurrence of ovarian endometriomas in 24.6% at 4 years after surgery. These results strongly resemble ours, which showed a recurrence rate of 23.9%. The discrepancy of numbers in the literature could be due to different observation periods and criteria for the definition of recurrence. As recurrent endometriosis is among the significant challenges in this disease, reoperation is currently often regarded as the best treatment option, though the extent and duration of the effect of second-line operation remains unclear.¹² In the present follow-up, a reoperation rate of 68.1% was observed in 32 of 47 patients with recurrent endometrioma who had ovarian endometriomas initially diagnosed at surgery. These observations agree with those of Cheong et al,¹³ but not with the lower requirement of reoperation in other observations.^{12,14}

A history of preoperative pain or preoperative dysmenorrhea was shown to be a significant factor associated with higher recurrence rates, which agrees with a study by Renner et al.¹⁵ In our study, we observed significantly lower recurrence-free intervals for such preoperative complaints. In the present study, larger cyst size, as also reported by Kikuchi et al¹⁶ and Koga et al,⁵ younger age at surgery, and preoperative cyst rupture seemed to increase

the risk of ovarian endometrioma recurrence. An attempt to explain our results regarding preoperative cyst rupture can be derived from the assumptions of Kikuchi et al⁶ that recurrent cysts occur in the lesions, in which a cystectomy was performed, whereby endometrial cells contacted the peritoneal surface.

Regarding the effectiveness of endometrioma surgery, laparoscopy showed the best results in terms of a symptom-free postoperative course and pain reduction. Although other investigators mentioned equivalent therapeutic success under laparoscopy and laparotomy, the laparoscopic approach is preferred.¹⁶ This could be because of its good tolerance, low morbidity, and low total cost of treatment² or because laparoscopy with sampling for histological investigation is the gold standard for diagnosis of endometriosis in the evaluation of persistent complaints and therefore often used.¹⁷

The impact of postoperative hormone therapy on ovarian endometriosis remains currently unclear. To determine the effect of additional postoperative medical treatment, in the present follow-up, patients with hormone therapy (56.1%) were compared with those without (43.9%). Our study was in line with previous observations^{2,12,18–20} that patients do not significantly benefit from additional postoperative hormone therapy (gonadotropin-releasing hormone agonist, oral contraceptive, medroxyprogesterone acetate, or danazol) in terms of reducing the risk of disease and pain recurrence. We observed even lower probabilities for a recurrence-free interval referring to an average of 12.9 years of follow-up in patients receiving hormone therapy versus patients with exclusive surgical therapy. A retrospective study⁵ indicated previous medical treatment of endometriosis as a significant risk factor ($P = .009$) for higher recurrence. Yap et al²¹ indicated that there was a significant improvement in the recurrence rate after postoperative hormone intake, but compared with exclusive surgery, there were no beneficial effects on pain and pregnancy rate recorded.

Among the 111 patients with a desire to become pregnant, the postoperative spontaneous pregnancy rate was 54.1%, correlating with fertility rates in observations by Vercellini et al⁸ and Jones and Sutton.²² As the present study analyzes only the surgical outcome of total endometrioma excision, we were unable to make comparisons with other surgical techniques such as fenestration or ablation. Favorable outcomes under laparoscopic cystectomy were reported by Alborzi et al²³ and Hart et al.²⁴ Littman et al²⁵ declared a positive impact of laparoscopy for the treatment of endometriosis even after multiple in vitro fertil-

ization failures. In contrast, other investigators^{26,27} suggested that laparoscopic endometrioma excision has an adverse effect by reducing the ovarian reserve. The present study indicates that there is a positive impact of additional medical treatment on postoperative spontaneous pregnancy rate in line with previous observations.^{3,28} In contrast, other studies^{29,30} observed a missing hormonal impact on the fertility rate after surgery.^{29,30} Further studies are necessary to determine the most effective treatment of ovarian endometrioma.

A limitation of this study is its study model, a retrospective cohort study, which has lower evidence and validity compared, for example, with a randomized controlled study. The definition of recurrence varies in the literature. Some studies define recurrence as a typical morphological change represented in a vaginal ultrasonogram, whereas others define it as a recurrence or worsening view of subjectively perceived pain. Although the general definition of a recurrent endometriosis remains to be determined, our definition represents a limitation because it is based on a questionnaire. We considered a positive response to the presence of a cyst or tumor in the questionnaire as a recurrence of endometriosis. Biases in this study include the alternating surgeon's experience, the low return rate of questionnaires, and the development in hormonal treatment within the period of data collection and observation (eg danazol is now nearly obsolete due to irreversible side effects). Among the strengths of the study are the long follow-up period, large sample size, and the fact that all patients were operated on in the same hospital.

CONCLUSIONS

This study identifies risk factors for recurrent ovarian endometrioma in our patient population as preoperative pain, preoperative dysmenorrhea, and larger cyst size. Neither pain symptoms nor the risk of recurrence is included in the current endometriosis classifications. The establishment of a modified classification based on risk factors with high prognostic clinical outcome should be sought, allowing an optimal individual therapy concept.

The present study also indicates that patients with ovarian endometriomas and a desire for pregnancy seem to profit from additional postoperative medical treatment. For patients with completed family planning, the indication of additional postoperative medical treatment needs to be well evaluated according to patients' preferences.

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