

# Risk Factors for Recurrence of Ovarian Endometriosis in Chinese Patients Aged 45 and Over

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## Abstract

**Background:** When considering the issue of recurrence, perimenopausal women may have more dilemma during management comparing with young women, for example, whether to retain the uterus and ovary during surgery, whether it is necessary to add adjuvant medicine treatment after operation, and there is no evidence for reference about using of gonadotropin-releasing hormone agonist. This study aimed to study the risk factors for the recurrence of ovarian endometriosis (EM) in patients aged 45 and over.

**Methods:** This is a retrospective nested case-control study. We reviewed the medical records of patients aged over 45 years who underwent surgical treatments for ovarian EM from 1994 to 2014, in Peking Union Medical College Hospital of Chinese Academy of Medical Sciences. By following up to January 2016, 45 patients were found to have relapses and regarded as the recurrence group. The patients with no recurrence during the same follow-up period were randomly selected by the ratio of 1:4 as the nonrecurrence group (180 patients in total). Stratified Cox regression was used to analyze the risk factors of the recurrence.

**Results:** Univariate analysis showed that there was a significant difference in the postoperative treatment (the percentage of patients who received postoperative treatment in non-recurrence group and recurrence group, 23.9% vs. 40.0%,  $\chi^2 = 4.729$ ,  $P = 0.030$ ) and ovarian preservation (the percentage of patients who received surgery of ovarian preservation in non-recurrence group and recurrence group, 25.0% vs. 44.4%,  $\chi^2 = 19.462$ ,  $P < 0.001$ ) between the nonrecurrence group and the recurrence group. There was no correlation between recurrence and the following factors including patient's age, menarche age, gravidity, parity, CA125 level, ovarian lesions, menopausal status, combined benign gynecological conditions (such as myoma and adenomyoma) and endometrial abnormalities, and surgical approach or surgical staging (all  $P > 0.05$ ). Multivariate analysis indicated that whether to retain the ovary was the only independent risk factor of recurrence for patients aged 45 years and over with ovarian EM (odds ratio: 5.594, 95% confidence interval: 1.919–16.310,  $P = 0.002$ ).

**Conclusion:** Ovarian preservation might be the only independent risk factor of recurrence for patients aged 45 years and over with ovarian EM.

**Key words:** Ovarian Endometriosis; Recurrence; Risk Factor

## INTRODUCTION

Endometriosis (EM) is one of the most common benign gynecological diseases. It has high incidence and high recurrence rate after treatment. The recurrence rate has been reported to be 2% to 47% in China and abroad, whereas about 33% of the patients would receive a second operation.<sup>[1]</sup> Recurrence is one of the difficulties in the clinical management of EM. The mechanism of recurrence is not fully understood and is generally believed to be the followings:<sup>[2]</sup> (1) the lesion is not removed cleanly, leading to the recurrence from the

residual lesion and (2) eutopic endometrium is the key factor in the onset of EM. Despite the complete surgical removal of

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the EM lesion, the retrograde menstruation will bring debris of eutopic endometrium into the pelvic cavity again and cause the recurrence.<sup>[2]</sup> By far there is no consensus on the high-risk factors for the recurrence of EM, the measures taken to reduce the recurrence rate at the beginning of treatment or the proposed management plan after recurrence. In addition, relatively few studies have reported the recurrence of EM in perimenopausal women. However, compared with young women, perimenopausal women may have more dilemma during management, for example, whether to retain the uterus and ovary during surgery, and whether it is necessary to add adjuvant medicine treatment after operation when considering women elder than 40 years, to whom the use of oral contraceptives is not recommended any more, and there is no evidence for reference about using of gonadotropin-releasing hormone agonist (GnRHa). The study of related factors of postoperative recurrence of perimenopausal women with EM would help to provide some reference for making the strategy of surgery and postoperative adjuvant treatment. In this study, based on the medical records in our clinical center, we retrospectively analyzed the related risk factors of recurrence in patients aged 45 years and over with ovarian EM.

## METHODS

### Ethical approval

This retrospective study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. S-k332).

### Study samples

We searched the database in our center for patients who received surgical treatments in the Department of Obstetrics and Gynecology at Peking Union Medical College Hospital between December 1994 and December 2014. Inclusion criteria were (1) postoperative histopathological diagnosis of ovarian EM; (2) aged 45 years and over at the time of surgery; and (3) the clinical and pathological data were complete. Exclusive criteria were the combination of malignant or borderline tumors.

### Study design

The clinic visiting was undertaken for follow-up; the endpoint of this study was until January 2016. Among 1008 patients in total, 45 were found to have a recurrence of EM and defined as the recurrence group. The patients with no recurrence during the same operation and follow-up period were randomly selected by the ratio of 1:4 as the control group, respectively. By classified random sampling and match, a total of 180 patients were defined as the nonrecurrence group, as seen in Table 1.

This is a retrospective nested case-control study. The following clinical data were obtained: (1) demographic characteristics such as patient's age, menarche age, menopausal status, gravidity, and parity; (2) chief complaints such as pelvic mass, dysmenorrhea, chronic pelvic pain, and abnormal menstruation; (3) preoperative serum CA125 level within 1 month before surgery; (4) surgical approach such as laparoscopic or

**Table 1: Random match grouping by follow-up time for ovarian endometriotic disease patients**

Follow-up (months)	Recurrence (N = 45), n	No recurrence (N = 180), n
0–5	8	32
6–11	13	52
12–17	7	28
18–23	4	16
24 and above	13	52

open surgery (without conversions to open operation happened); (5) surgical procedure: fertility preservation (to keep the uterus and at least one side of the ovary), ovarian function preservation (hysterectomy, to retain at least one side of the ovary), uterus preservation (bilateral varicectomy), radical surgery (hysterectomy and bilateral adnexectomy); (6) lesion size (maximum diameter, cm); (7) combined benign gynecological diseases such as myoma and adenomyoma; (8) coexisting endometrial abnormality; (9) postoperative medication; (10) disease stage classified according to the revised American Fertility Society (rAFS) classification system (1996);<sup>[3]</sup> (11) recurrence during postoperative follow-up. A retrospective analysis was carried out to study the potential risk factors of the recurrent EM.

### Definition of recurrence

The distinguishing between uncontrolled EM and recurrence is difficult to define. This study adopted the currently widely accepted diagnostic standard for recurrent EM: 3 months after the surgery or the combination treatment of surgery and medication; recurrence is considered if the patient meets at least two of the following criteria: (1) the symptoms recur, (2) adnexal mass reappears, (3) the serum CA125 level is higher than normal, and (4) ultrasound findings accord to recurrence of EM based on the criteria proposed by Kupfer *et al.*<sup>[4]</sup>

### Statistical methods

Statistical analysis was performed using SPSS22.0 software (SPSS Inc., Chicago, IL, USA). The random digital generator was applied in the stratified random sampling. The measurement data in accordance with a normal distribution (expressed by mean and standard deviation) were analyzed by independent *t*-test. The measurement data not in accordance with a normal distribution (expressed by median and interquartile range [IQR]) were analyzed by nonparametric *U*-test. Numeration data (expressed by rate) were analyzed by Chi-square test or Fisher's test. The stratified Cox regression model was performed in the univariate analysis. The variables of statistically significant difference in the univariate analysis were then introduced into the multivariate analysis. *P* < 0.05 was accepted as the degree of statistical significance.

## RESULTS

### General clinical characteristics

Among all 1008 patients with ovarian EM, 80.6% were followed up for a median duration of 3 months (IQR: 3–12 months; range from 1 month to 17 years) after the operation, and 62.0%

patients were followed up for >3 months. In the 45 cases of recurrence, the median recurrence interval was 12 months (IQR: 6–24 months, range: 3–60 months). The cumulative recurrence rate was 10.0% in 1 year and 27.0% in 5 years after the operation.

There were statistically significant differences in the postoperative treatment (the percentage of patients who received postoperative treatment in non-recurrence group and recurrence group, 23.9% vs. 40.0%,  $\chi^2 = 4.729$ ,  $P = 0.030$ ) and ovarian preservation (the percentage of patients who received surgery of ovarian preservation in non-recurrence group and recurrence group, 25.0% vs. 44.4%,  $\chi^2 = 19.462$ ,  $P < 0.001$ ) between the recurrence group and the nonrecurrence group. There was no statistically significant difference ( $P > 0.05$ ) between the two groups in patient's age, menarche age, gravidity, parity, CA125 level, ovarian lesions, menopausal status, combined benign gynecological

conditions (such as myoma and adenomyoma) and endometrial abnormalities, and surgical approach or surgical staging, as seen in Table 2. In addition, 1 out of 4 patients who were treated with hormone replacement therapy (HRT) after the radical operation showed recurrence.

### Univariate analysis

The Cox regression model was performed in the univariate analysis of risk factors for the postoperative recurrence of ovarian EM in patients aged 45 years and over. The results showed that recurrence was correlated with the postoperative treatment and the preservation of the ovary ( $P < 0.05$ ). However, the recurrence was unrelated to patient's age, menopausal status, gravidity, parity, CA125 level, ovarian lesion size, combined benign gynecological conditions, endometrial abnormalities, uterus preservation, and surgical staging [ $P > 0.05$ , Table 3].

**Table 2: The comparison of clinical and pathological characters between two groups**

Variables	Nonrecurrence (n = 180)	Recurrence (n = 45)	Statistical values	P
Age (years)				
Mean $\pm$ SD	47.3 $\pm$ 2.6	46.7 $\pm$ 1.5	0.814 <sup>‡</sup>	0.416
Range	45–59	45–50		
Postmenopause, n (%)	10 (5.6)	1 (2.2)	0.860 <sup>§</sup>	0.698
Menarche age (years)				
Mean $\pm$ SD	14.0 $\pm$ 1.5	13.7 $\pm$ 1.6	0.894 <sup>‡</sup>	0.372
Range	11–18	10–18		
Gravidity times				
Mean $\pm$ SD	2.3 $\pm$ 1.3	2.5 $\pm$ 1.4	1.147 <sup>‡</sup>	0.252
Range	0–7	0–6		
Parity, n				
Mean $\pm$ SD	1.0 $\pm$ 0.4	1.0 $\pm$ 0.4	0.538 <sup>‡</sup>	0.591
Range	0–3	0–2		
CA125 (U/ml)				
Median (IQR)	40.4 (25.1–74.1)	51.2 (28.0–92.6)	1.112 <sup>  </sup>	0.266
Range	5.4–2928.0	10.0–250.8		
Tumor diameter (cm)				
Mean $\pm$ SD	5.5 $\pm$ 3.0	6.2 $\pm$ 3.7	1.176 <sup>‡</sup>	0.241
Range	1–20	1–9		
Other benign disease*, n (%)	125 (69.4)	30 (66.7)	0.130 <sup>§</sup>	0.719
Endometrial disorders <sup>†</sup> , n (%)	7 (3.9)	4 (8.9)	2.473 <sup>§</sup>	0.124
Postoperative medication, n (%)	43 (23.9)	18 (40.0)	4.729 <sup>§</sup>	0.030
Surgical approach, n (%)				
Open	100 (55.6)	18 (40.0)	3.493 <sup>§</sup>	0.062
Laparoscopy	80 (44.4)	27 (60.0)		
Extent of surgery, n (%)				
Fertility preservation	54 (30.0)	20 (44.4)	19.462 <sup>§</sup>	<0.001
Ovarian preservation	45 (25.0)	20 (44.4)		
Uterine preservation	2 (1.1)	0		
Radical surgery	79 (43.9)	5 (11.1)		
rAFS stage, n (%)				
I	9 (5.0)	1 (2.2)	1.251 <sup>§</sup>	0.741
II	87 (48.3)	22 (48.9)		
III	26 (14.4)	5 (11.1)		
IV	58 (32.2)	17 (37.8)		

\*The patients with other coexisting gynecological benign diseases, including myoma, and adenomyosis identified by pathology; <sup>†</sup>The patients with coexisting endometrial disorders identified by pathology (118 patients in nonrecurrence group and 27 in recurrence group obtained the pathological evaluation of endometrial during the surgery); <sup>‡</sup>t values; <sup>§</sup> $\chi^2$  values; <sup>||</sup>Z values. rAFS: Revised American Fertility Society classification system; SD: Standard deviation; IQR: Interquartile range.

**Table 3: Univariate analysis of recurrence among ovarian endometriotic disease patients using Cox regression model**

Variables	OR	95% CI	P
Age < or ≥47 years	0.749	0.401–1.398	0.364
Gravidity times ≤ or >1	0.912	0.465–1.788	0.789
Parity times ≤ or >1	1.481	0.519–4.229	0.463
Menopause Yes or no	0.327	0.044–2.442	0.276
Tumor diameter < or ≥6 cm	1.109	0.599–2.052	0.742
CA125 (U/L) Normal or not	1.477	0.712–3.060	0.295
Other benign disease Yes or no	0.782	0.405–1.509	0.463
Endometrial disorders Yes or no	1.276	0.927–1.757	0.135
Postoperative medication Yes or no	2.087	1.093–3.985	0.026
Ovarian preservation Yes or no	6.015	2.142–16.889	0.001
Uterine preservation Yes or no	1.839	0.988–3.408	0.055
rAFS stage I–II or III–IV	1.551	0.788–3.052	0.204

rAFS: Revised American Fertility Society classification system; OR: Odds ratio; CI: Confidence interval.

### Multivariate analysis

Multivariate analysis was performed by logistic regression analysis to assess the independent risk factors of ovarian EM recurrence after surgery in patients aged 45 years and over. The results showed that ovarian preservation was the independent risk factor of postoperative recurrence (odds ratio [OR]: 5.594, 95% confidence interval [CI]: 1.919–16.310,  $P = 0.002$ ) but was not postoperative medication (OR: 1.2, 95% CI: 0.601–2.359,  $P = 0.597$ ).

### DISCUSSION

Currently reported recurrence rate of EM includes cumulative recurrence rate and simple recurrence rate (number of recurrence/initial number of patients). In this study, we adopted the cumulative recurrence rate. The boundaries between uncontrolled EM and recurrence are difficult to define. As a result, the recurrence rate reported in the literature varies significantly from 6% to 67% due to different follow-up duration and diagnostic criteria.<sup>[5,6]</sup> The recurrence rate of EM was reported to be 20.5–53.5% in the 3–5 years after the operation, while the recurrence rate of other manifestations such as ovarian mass and increased serum CA125 level was 9–28%. Moreover, 24% of the patients with recurrent EM had no symptoms.<sup>[1]</sup> Due to the various manifestations, the diagnosis of recurrent EM is relatively difficult to make. In addition, the rate of patient's lost-to-follow-up tends to be

relatively high in EM because it is a benign gynecological disease. About 40% of the total 1008 patients in our clinical center were followed up for <3 months, so the actual recurrence rate may be greater than the current report. In a study by Tobiume *et al.*,<sup>[7]</sup> rAFS score was an independent factor associated with recurrence. Chon *et al.*<sup>[8]</sup> reported that dysmenorrhea and ovarian cyst septations significantly affected the postoperative recurrence rate. Selcuk *et al.*<sup>[9]</sup> reported that the depth of penetration of the endometrial tissue into the ovarian cyst wall was the independent risk factor for recurrence. Guzel *et al.*<sup>[10]</sup> reported that CA125 level, ovarian cyst size, and past history of pelvic surgery would affect the recurrence rate. However, it is difficult to compare the results of the above studies due to the differences in the study population, follow-up duration, and definition of recurrence.

Our study is a retrospective nested case-control study to assess the risk factors for the recurrence of ovarian EM in patients aged 45 and over. We divided the potential risk factors into two major categories of discussion, which were patient-related factors and surgery or treatment-related factors (including surgical approach, surgical procedure, and postoperative treatments). Our study showed no significant association between recurrence rate and the patient-related factors such as patient's age, menopausal status, menarche age, gravidity, parity, preoperative serum CA125 level, maximum cyst diameter, combined benign gynecological conditions (such as myoma and adenomyoma), combined endometrial abnormalities, or surgical staging (rAFS score). On the other hand, multivariate analysis showed that ovarian preservation procedure was the independent risk factor, while none of other surgery-related factors were found to be associated with the postoperative recurrence rate.

Previous reports have shown that age and menopausal status are related to recurrent EM, but the conclusions are different from each other due to the differences in the age distribution, age group, and fertility status of the study populations. It is widely believed that EM is a hormone-dependent disease. If the patients are young, far from menopausal status, and have high estrogen level, they are more likely to undergo the conservative surgical procedures, leading to greater likelihood of residual lesions and higher risk of recurrence. Seo *et al.*<sup>[11]</sup> reported that, in a follow-up of 29 months on average with no postoperative medical treatment, the cumulative recurrence rate was 43.3% in patients aged 20–29 years, 22.5% in patients aged 30–39 years, and 10.2% in the 40–45 years' age group. In our study, the cumulative recurrence rate of patients aged over 45 was 5.0%, 10.0%, and 23.0%, respectively, after the follow-up of 6 months, 1 year, and 4 years, which were consistent with the previous literature. In this study, there was no statistical difference in patient's age between the recurrence group and the nonrecurrence group. Moreover, patient's menopausal status did not have a significant effect on the recurrence rate, which may be related to the decline in the hormone level in perimenopausal patients in this study.

Previous studies reported that the cumulative recurrence rates of conservative surgery, semi-radical surgery, and radical

surgery were 28.9%, 17.3%, and 0%, respectively.<sup>[12]</sup> The proportions of patients in our study who showed recurrence and underwent fertility preservation surgery, ovarian preservation surgery, uterus preservation surgery, and radical surgery were 44.4%, 44.4%, 0%, and 11.1%, respectively. Rizk *et al.*<sup>[13]</sup> reported that patients who underwent hysterectomy due to EM had a recurrence rate of up to 60% if the ovaries were retained; in addition, the recurrence of pain would increase by 6 times, and the chance of a second operation would increase by 8 times in those patients as well. In recent years, an increasing number of patients expect to retain the ovaries and uterus. At the same time, doctors pay more attention to the preservation of the reproductive organs in perimenopausal patients. Univariate and multivariate analysis showed that the ovarian preservation surgery was an independent risk factor for recurrence in patients with ovarian EM ( $\geq 45$  years old). Our results also showed the recurrence rates of bilateral ovariectomy, unilateral ovarian preservation, and bilateral ovarian preservation surgeries were 5.8%, 39.7%, and 19.7%, respectively. There were significant differences between the three groups. By further analyzing the clinical characteristics of the patients with different patterns of ovarian preservation surgeries, we found that, compared with the patients of bilateral ovarian preservation, the patients with unilateral preservation tended to have larger lesions and higher stage (rAFS III–IV), which may be the reason for the higher recurrence rate in this group. Moreover, we also found that women who received uterus preservation surgery were less likely to have postoperative recurrence but with no statistical significance. This result is consistent with Bulletti *et al.*'s<sup>[14]</sup> report that laparoscopic resection combined with endometrial ablation could effectively reduce the chance of recurrence. In this way, it is worthy to explore whether eutopic endometrium had some effects on regeneration of EM lesion specifically for women at perimenopausal status. However, Namnoum *et al.*<sup>[15]</sup> reported a recurrence of 10% of all patients after total hysterectomy and bilateral salpingectomy.

EM occurs more frequently in women of child-bearing age. Due to fertility requirements, most EM patients prefer not to undergo radical surgery. However, the recurrence after the conservative surgery is the main problem in treating refractory EM. As a result, most of these patients are treated with the combination of pre- or post-operative medications. At present, the medications used in the treatment of EM include GnRHa, selective progesterone receptor modulators, selective estrogen receptor modulators, aromatase inhibitors, immunomodulatory, and antiangiogenic agents. There is a Cochrane systematic review<sup>[2]</sup> for the use of postoperative medication, reporting no evidence in improving the pain relief, though evidence level is not enough in the reported literature. Seo *et al.*<sup>[11]</sup> reported no difference in the overall postoperative recurrence rate among the patients who received postoperative medication. For patients of 20–29 years and 30–39 years of age, postoperative treatment was associated with a lower recurrence rate (8.1% vs. 43.3% and 5.4% vs. 22.5%), whereas there was no significant difference in the group of 40–45 years of age (4.5% vs. 10.2%). Although other studies have shown

that progesterone and GnRHa can reduce the recurrence rate after surgery, Vercellini *et al.*<sup>[16]</sup> reported that postoperative use of GnRHa could only prolong the recurrence interval but could not improve the overall recurrence rate. There is no consensus regarding whether the postoperative danazol could reduce the recurrence rate.<sup>[5,17]</sup> Muzii *et al.*<sup>[18]</sup> reported that the periodic or continuous use of oral contraceptive pills (OCPs) could significantly reduce the recurrence rate of EM 24 months after surgery. Theoretically, the effect of continuous use of OCP is better than that of periodic administration. There is no consensus regarding whether the levonorgestrel-releasing intrauterine device could reduce the recurrence rate either.<sup>[19,20]</sup> Our study showed that postoperative medication was not an independent risk factor for ovarian EM in patients aged 45 years and over, nor did it affect the recurrence in patients who underwent ovarian preservation surgery.

Most studies in China and abroad believe that the recurrent EM is related to its staging, and the recurrence risk of severe cases is significantly higher than that of mild cases. Parazzini *et al.*<sup>[21]</sup> reported a 2-year postoperative recurrence rate of 5.7% in patients with rAFS score I–II, compared with 14.3% in patients with score II–IV. However, in this study, no statistical difference was found between patient's rAFS staging in terms of the recurrence. Surgical staging was not shown to be a risk factor in our study, despite the fact that it would influence the choice of surgical procedures. For example, compared with patients with mild symptoms of ovarian EM, perimenopausal patients with severe symptoms were more likely to undergo bilateral ovariectomy in our study (64.0% vs. 43.4%,  $P = 0.009$ ), which was related to the special clinical decision for patients aged 45 years and over.

In conclusion, the prevention of recurrence is an unresolved problem in the treatment of EM. At present, there is no consensus on the high-risk factors of EM recurrence. Although there are many ways aiming to reduce the recurrence rate, the effect is not satisfactory. This study showed that, for patients aged 45 years and over with ovarian EM, whether to retain the ovary was the only independent risk factor of recurrence, while postoperative medication did not affect the recurrence after the ovarian preservation surgery. However, further prospective case-control studies of larger sample scale are required to validate this conclusion. In addition, the problem of postoperative HRT is also worth further discussion for patients who have undergone surgical resection of bilateral ovaries.

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### Conflicts of interest

There are no conflicts of interest.

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# 中国45岁及以上卵巢子宫内膜异位症患者复发危险因素分析

## 摘要

**背景:** 在考虑复发问题时, 围绝经期妇女在治疗过程中可能比年轻妇女面临更多的困境, 如手术中是否保留子宫和卵巢, 术后是否需要加用辅助药物治疗, 以及是否使用促性腺激素释放激素激动剂(GnRHa)等。本研究旨在探讨45岁及以上患者卵巢子宫内膜异位症复发的危险因素。

**方法:** 采用回顾性巢式病例对照研究。回顾性分析1994–2014年在中国医学科学院北京协和医院接受卵巢子宫内膜异位症手术的45岁以上患者的病历资料。随访至2016年1月, 发现45例患者复发, 并将其视为复发组。随访期间无复发者按1:4的比例随机选择为无复发组(共180例)。采用分层Cox回归分析复发的危险因素。

**结果:** 单因素分析显示非复发组与复发组在术后治疗(接受治疗百分比, 23.9% vs. 40.0%,  $\chi^2=4.729$ ,  $P=0.030$ )及卵巢保护(接受保留卵巢手术百分比, 25.0% vs. 44.4%,  $\chi^2=19.462$ ,  $P<0.001$ )方面有显著性差异。复发与患者年龄、初潮年龄、妊娠、产次、CA125水平、卵巢病变、绝经情况、合并良性妇科疾病(如肌瘤、腺肌瘤)及子宫内膜异常、手术入路或手术分期等因素无相关性( $P>0.05$ )。多因素分析表明, 是否保留卵巢是45岁以上卵巢子宫内膜异位症患者复发的唯一独立危险因素(比值比: 5.594, 95% 置信区间: 1.919–16.310,  $P=0.002$ )。

**结论:** 卵巢保留是45岁及以上患者卵巢子宫内膜异位症复发的唯一独立危险因素。