

# Correlative factors associated with the recurrence of ovarian endometriosis: a retrospective study

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DOI: [10.31083/j.ceog4804152](https://doi.org/10.31083/j.ceog4804152)

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Submitted: 14 March 2021 Revised: 25 April 2021 Accepted: 1 June 2021 Published: 15 August 2021

**Background:** The aim of this study was to confirm and analyze the correlative factors that could influence the recurrence of ovarian endometriosis after conservative surgery, including both risk and protective factors. **Methods:** From January 2010 to January 2018, a retrospective study was conducted which included 1080 patients with ovarian endometriosis who received a minimum of 2 years of follow-up after conservative surgery at a university-based tertiary care hospital. Recurrence was defined as the presence of ovarian cysts larger than 2 cm detected by ultrasonography within 2 years after surgery. The effects of twenty correlative variables on recurrence were evaluated. **Results:** The cumulative 2-year recurrence rate of ovarian endometriosis after conservative surgery was 15%. According to the logistic regression analysis, the significant risk factors that were independently associated with high recurrence of endometriosis were previous medical treatment of endometriosis (odds ratio [OR] = 2.06; 95% confidence interval [95% CI] = 1.27–3.34;  $P = 0.004$ ), painful nodules in the pouch of Douglas (OR = 2.44; 95% CI = 1.23–4.85;  $P = 0.011$ ), largest cyst diameter (OR = 1.54; 95% CI = 1.08–2.18;  $P = 0.016$ ) and bilateral ovarian involvement (OR = 1.69; 95% CI = 1.19–2.39;  $P = 0.003$ ). Moreover, the protective factors that were independently associated with low recurrence of endometriosis were postoperative medical treatment (OR = 0.59; 95% CI = 0.42–0.84;  $P = 0.003$ ) and postoperative pregnancy (OR = 0.34; 95% CI = 0.19–0.62;  $P < 0.0001$ ). **Conclusions:** The results of this retrospective analysis of 1080 patients might help predict the prognosis of patients with ovarian endometriosis after conservative surgery and benefit the clinical management of ovarian endometriosis.

## Keywords

Ovarian endometriosis; Conservative surgery; Recurrence; Risk factor; Protective factor

## 1. Introduction

Endometriosis, as one of the most common benign gynaecological diseases, is histologically characterized by the presence of endometrial glands and stroma outside the uterine cavity. The prevalence of endometriosis has been reported to range from 10% to 20% among reproductive-aged women and from 20% to 50% among infertile women [1, 2]. The most common symptoms of this progressive condition are chronic pelvic pain, dysmenorrhea and infertility impacting

the patient's quality of life and ability to work. Endometriosis is usually classified into four types: peritoneal, ovarian, deep infiltrating and others (lung, intestine, bladder, surgical incision scar and other distant locations) [3]. The ovaries are the most common site for endometriosis accounting for 55% of all cases [3].

Conservative surgery is considered the 'gold standard' treatment for ovarian endometriosis as this disorder is most frequently diagnosed in women of reproductive age [4]. However, a challenging and worrisome problem for conservative surgical treatment is disease recurrence, and the rate of recurrence might progressively increase over time. Previous studies have reported that the recurrence rate of ovarian endometriosis after conservative surgery varies from 6.4% to 43.3% [5, 6]. Disease recurrence and repeat surgery increase morbidity and health care costs while significantly damaging ovarian reserve and adversely affecting fertility [7]. Therefore, to prevent the recurrence of ovarian endometriosis after conservative surgical treatment, it is essential to better understand the correlative factors associated with the recurrence of this disease.

Although several studies have explored the potential factors related to the recurrence of ovarian endometriosis, no consensus has been reached in terms of the risk and protective factors related to recurrence [8–13]. Few studies on the recurrence of ovarian endometriosis have involved a large sample size. We conducted this study with 1080 patients with ovarian endometriosis to determine and analyze the correlative factors related to the recurrence of ovarian endometriosis after conservative surgery.

## 2. Materials and methods

### 2.1 Subjects

A retrospective study was performed on patients with ovarian endometriosis who underwent conservative surgery by either laparotomy or laparoscopy at the Fourth Hospital of Hebei Medical University between January 2010 and January 2018. The inclusion criteria included a pathologic diagnosis of ovarian endometriosis, treatment by conservative surgery and at least 2 years of follow-up after surgery.

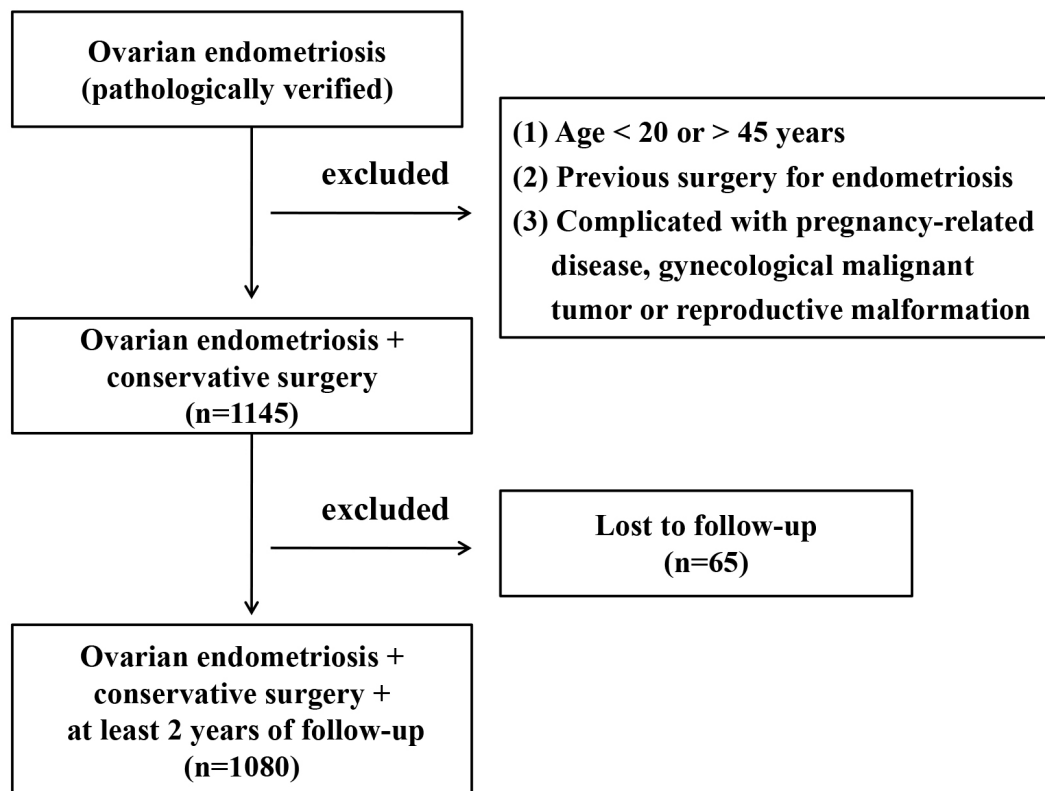


Fig. 1. Screening process of patients.

The exclusion criteria were as follows: (1) age <20 or >45 years, (2) previous surgery for endometriosis, (3) complications with pregnancy-related disease, malignant gynaecological tumours or reproductive malformation. After screening, 1080 patients who met the inclusion criteria were enrolled in the study (Fig. 1). The study was approved by the Institutional Review Board of the Hebei Obstetrics and Gynecology Institute. Written informed consent was obtained from all the participants.

## 2.2 Management of patients

Prior to surgery, patient management was not uniform. One hundred and six patients in the study underwent endometriosis-related medical therapy prior to surgery to relieve symptoms, such as chronic pelvic pain.

All the conservative surgical procedures ( $n = 1080$ ) were performed by senior experienced gynaecological surgeons. Conservative surgery was defined as complete excision of all the visible ovarian and peritoneal lesions, separation of the pelvic adhesions, restoration of the anatomical structure if necessary, retention of the uterus and ovaries and preservation of fertility. Adhesions were sufficiently separated and the capsule of the cyst was stripped away from the normal ovarian tissue completely. Other endometriotic peritoneal implants were excised with scissors or coagulated with bipolar electrocoagulation completely. Endometriosis was staged according to the classifications in the revised American Society for Reproductive Medicine (ASRM) scoring system.

A definitive histolog diagnosis of ovarian endometriosis was made after surgery and patients who did not express a desire to become pregnant in the near future were presented with the option of receiving injections of gonadotropin-releasing hormone agonist (GnRHa, 3.75 mg every 28 days) for 3–6 cycles. Overall, 578 patients received GnRHa injections after surgery, 379 patients declined secondary to the desire to become pregnant and 123 patients refused GnRHa due to economic or other personal reasons.

For each patient, information was collected through an analysis of their medical records. All the patients were reviewed every 3 months during the first year, every 6 months during the next two years and then yearly thereafter. All 1080 patients received a minimum of 2 years of follow-up after conservative surgery which included special clinic reexamination, telephone calls and letters. At each follow-up visit, an ultrasound and pelvic examination was performed along with an assessment of improvements in the patient's main symptoms and a discussion was held regarding postoperative medications and desire for pregnancy.

## 2.3 Definition of recurrence

Recurrence was defined as the presence of ovarian cysts greater than 2 cm in diameter detected by ultrasonography with typical characteristics (round cystic mass, irregular margins, homogeneous low echogenic fluid content, scattered internal echoes and no solid components or papillary proliferation) within 2 years after surgery. Other ovarian cysts were

**Table 1. Comparison of characteristics between enrolled patients and those who were lost to follow-up.**

Factors	Follow-up (n = 1080)	Lost to follow-up (n = 65)	P
Age of onset (years)	34.16 ± 7.58 <sup>a</sup>	35.37 ± 6.55 <sup>a</sup>	0.210
Infertility	76 (7.0%)	7 (10.8%)	0.318
Preoperative pregnancy	1.62 ± 1.47 <sup>a</sup>	1.46 ± 1.32 <sup>a</sup>	0.389
Preoperative delivery	0.80 ± 0.70 <sup>a</sup>	0.88 ± 0.90 <sup>a</sup>	0.378
Previous intrauterine operation	527 (48.8%)	30 (46.2%)	0.679
Previous cesarean section	200 (18.5%)	9 (13.8%)	0.344
Previous medical treatment	106 (9.8%)	6 (9.2%)	0.878
Serum CA125 levels (U/mL)	50.25 (59.77) <sup>b</sup>	55.42 (60.56) <sup>b</sup>	0.255
Pain	417 (38.6%)	19 (29.2%)	0.130
Painful nodules in the pouch of Douglas	44 (4.1%)	3 (4.6%)	0.746
Presence of uterine myoma	165 (15.3%)	9 (13.8%)	0.755
Presence of adenomyosis	121 (11.2%)	6 (9.2%)	0.623
Coexistence of deep endometriosis	82 (7.6%)	2 (3.1%)	0.224
Laparoscopy	950 (88.0%)	60 (92.3%)	0.291
III–IV (Revised ASRM stage)	901 (83.4%)	58 (89.2%)	0.218
Multiple cysts	162 (15.0%)	7 (10.8%)	0.350
Largest cyst diameter (cm)	6.25 ± 2.32 <sup>a</sup>	5.92 ± 1.91 <sup>a</sup>	0.269
Bilateral ovarian involvement	379 (35.1%)	19 (29.2%)	0.335
Postoperative medical treatment	578 (53.5%)	—	—
Postoperative pregnancy	218 (20.2%)	—	—

ASRM, American Society for Reproductive Medicine.

<sup>a</sup> Mean ± SD, <sup>b</sup> Median (QR).

excluded when calculating recurrence rates [14, 15]. If the ovarian cyst could not be distinguished from a transient corpus luteum or an intraovarian haematoma, the diagnosis of recurrence was made only when the cyst had persisted or the diameter had not decreased significantly after several consecutive menstrual cycles.

#### 2.4 Variables

We assessed the effects of twenty variables on the recurrence of ovarian endometriosis after conservative surgery. The factors considered were age of onset, infertility, preoperative pregnancy, preoperative delivery, previous intrauterine operation, previous caesarean section, previous medical treatment of endometriosis, serum CA125 levels, pain, painful nodules in the pouch of Douglas, presence of uterine myoma, presence of adenomyosis, coexistence of deep endometriosis, laparoscopy or laparotomy, revised ASRM stage, multiple cysts, largest cyst diameter, anatomical location of the ovarian endometrioma, postoperative medical treatment and postoperative pregnancy [8, 10, 13, 15].

#### 2.5 Statistical analysis

Statistical analysis was performed using the Statistics Package for Social Sciences Version 22.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis of the descriptive data was performed using a *t*-test or Mann-Whitney U test; the categorical variables were compared using a  $\chi^2$  test or Fisher's exact test. The odds ratio (OR) and 95% confidence interval (CI) for multivariate analysis were determined using a logistic regression model. A *P* value of less than 0.05 was considered to be statistically significant.

### 3. Results

Among the 1145 patients with ovarian endometriosis who underwent successful conservative surgery, 65 patients were lost to follow-up in the 2 years after surgery and were therefore excluded from the study. The remaining 1080 patients received 2 years of follow-up, which corresponded to a 2-year follow-up rate of 94.3%. The various characteristics of the enrolled patients and those who were excluded from the study are listed in Table 1. As shown in Table 1, there was no significant differences in the characteristics between the two groups, suggesting that the patients who were lost to follow-up were similar to the enrolled patients and that the latter could represent all cohorts.

Among the 1080 patients who received 2 years of follow-up after conservative surgery, endometriosis recurred in 162 patients resulting in a cumulative 2-year recurrence rate of 15%. The various characteristics of the recurrence group and the non-recurrence group are shown in Table 2.

The results of the univariate analysis indicated that the risk factors associated with high recurrence of ovarian endometriosis after conservative surgery were previous medical treatment of endometriosis, pain, painful nodules in the pouch of Douglas, ASRM III–IV, largest cyst diameter and bilateral ovarian involvement (*P* < 0.05, Table 2). The protective factors associated with low recurrence were postoperative medical treatment and postoperative pregnancy (*P* < 0.05, Table 2).

According to a backward stepwise variable selection, six variables (previous medical treatment of endometriosis, painful nodules in the pouch of Douglas, largest cyst diam-

**Table 2. Univariate analysis of factors related to the recurrence of ovarian endometriosis between recurred and non-recurred group.**

Factors	Recurrent (n = 162)	Non-recurrent (n = 918)	P
Age of onset (years)	33.12 ± 6.64 <sup>a</sup>	34.35 ± 7.72 <sup>a</sup>	0.057
Infertility	11 (6.8%)	65 (7.1%)	0.894
Preoperative pregnancy	1.56 ± 1.41 <sup>a</sup>	1.63 ± 1.48 <sup>a</sup>	0.519
Preoperative delivery	0.77 ± 0.70 <sup>a</sup>	0.80 ± 0.71 <sup>a</sup>	0.623
Previous intrauterine operation	70 (43.2%)	457 (49.8%)	0.123
Previous cesarean section	34 (21.0%)	166 (18.1%)	0.380
Previous medical treatment	28 (17.3%)	78 (8.5%)	0.001*
Serum CA125 levels (U/mL)	50.43 (54.11) <sup>b</sup>	50.14 (60.57) <sup>b</sup>	0.826
Pain	77 (47.5%)	340 (37.0%)	0.011*
Painful nodules in the pouch of Douglas	14 (8.6%)	30 (3.3%)	0.001*
Presence of uterine myoma	21 (13.0%)	144 (15.7%)	0.374
Presence of adenomyosis	20 (12.3%)	101 (11.0%)	0.617
Coexistence of deep endometriosis	15 (9.3%)	67 (7.3%)	0.385
Laparoscopy	137 (84.6%)	813 (88.6%)	0.150
III–IV (Revised ASRM stage)	146 (90.1%)	755 (82.2%)	0.013*
Multiple cysts	31 (19.1%)	131 (14.3%)	0.110
Largest cyst diameter (cm)	6.65 ± 2.27 <sup>a</sup>	6.18 ± 2.32 <sup>a</sup>	0.014*
Bilateral ovarian involvement	75 (46.3%)	304 (33.1%)	0.001*
Postoperative medical treatment	67 (41.4%)	511 (55.7%)	0.001*
Postoperative pregnancy	14 (8.6%)	204 (22.2%)	<0.0001*

ASRM, American Society for Reproductive Medicine.

<sup>a</sup>Mean ± SD, <sup>b</sup>Median (QR), \**P* < 0.05.

eter, bilateral ovarian involvement, postoperative medical treatment and postoperative pregnancy) were included in the regression equation. The significant risk factors that were independently associated with high recurrence of ovarian endometriosis after conservative surgery were previous medical treatment of endometriosis (recurrence rates of the 'previous medical treatment' and 'untreatment' groups were 26.4% and 13.8%, respectively; odds ratio [OR] = 2.06; 95% confidence interval [95% CI] = 1.27–3.34; *P* = 0.004), painful nodules in the pouch of Douglas (recurrence rates of the 'with painful nodules' and 'without painful nodules' groups were 31.8% and 14.3%, respectively; OR = 2.44; 95% CI = 1.23–4.85; *P* = 0.011), largest cyst diameter (recurrence rates of the 'largest cyst diameter >6 cm' and 'largest cyst diameter ≤6 cm' groups were 18.6% and 13.0%, respectively; OR = 1.54; 95% CI = 1.08–2.18; *P* = 0.016) and bilateral ovarian involvement (recurrence rates in the 'bilateral' and 'unilateral' groups were 19.8% and 12.4%, respectively; OR = 1.69; 95% CI = 1.19–2.39; *P* = 0.003). The protective factors that were independently associated with low recurrence were postoperative medical treatment (recurrence rates of the 'postoperative treatment' and 'untreatment' groups were 11.6% and 18.9%, respectively; OR = 0.59; 95% CI = 0.42–0.84; *P* = 0.003) and postoperative pregnancy (recurrence rates in the 'pregnancy' and 'no pregnancy' groups were 6.4% and 17.2%, respectively; OR = 0.34; 95% CI = 0.19–0.62; *P* < 0.0001) (Table 3).

## 4. Discussion

In this relatively large sample study with 1080 patients with ovarian endometriosis, the results of a comprehensive analysis of twenty variables revealed that previous medical treatment of endometriosis, painful nodules in the pouch of Douglas, largest cyst diameter and bilateral ovarian involvement were significant risk factors associated with high recurrence of ovarian endometriosis after conservative surgery, whereas postoperative medical treatment and postoperative pregnancy were favorable protective factors. Previous studies have failed to reach a consensus regarding the potential factors related to the recurrence of ovarian endometriosis after conservative surgery. A previous research demonstrated that the severity of dysmenorrhea and postoperative pregnancy were independent correlative factors for the recurrence of ovarian endometriomas after surgery [10]. And another study showed that age at surgery was the only significant risk factor for recurrence of ovarian endometrioma after laparoscopic excision [9].

The recurrence rate of endometriosis reported in previous studies varies significantly from 6.4% to 43.3%, and this rate might progressively increase over time [5, 6, 10–13]. In our study, the cumulative 2-year recurrence rate of ovarian endometriosis after conservative surgery was 15%. There are many factors that can lead to significant variations in the recurrence rate of endometriosis. Because of the various manifestations, a definitive diagnosis of recurrent ovarian endometriosis is relatively difficult to achieve. Hence, we used

**Table 3. Logistic regression analysis of factors related to the recurrence of ovarian endometriosis.**

Factors	$\beta$	P	OR (95% CI)
Previous medical treatment			
No			1.00
Yes	0.721	0.004	2.06 (1.27–3.34)
Painful nodules in the pouch of Douglas			
No			1.00
Yes	0.893	0.011	2.44 (1.23–4.85)
Largest cyst diameter			
≤6 cm			1.00
>6 cm	0.430	0.016	1.54 (1.08–2.18)
Bilateral ovarian involvement			
No			1.00
Yes	0.524	0.003	1.69 (1.19–2.39)
Postoperative medical treatment			
No			1.00
Yes	–0.526	0.003	0.59 (0.42–0.84)
Postoperative pregnancy			
No			1.00
Yes	–1.069	<0.0001	0.34 (0.19–0.62)

OR, Odds ratio; CI, confidence interval.

the cumulative recurrence rate for the 2-year follow-up of ovarian endometriosis after conservative surgery in this specific study.

Our study determined that the recurrence rate of ovarian endometriosis in the patients who received previous medical treatment before conservative surgery was 26.4%, whereas the recurrence rate in the patients who did not receive previous medical treatment was significantly lower at 13.8%. Previous medical treatment of endometriosis was a risk factor for recurrence, which was consistent with the results reported in a prior study [16]. The less favorable prognosis for patients with a history of treatment can be explained by the following. First, hormone suppression therapy may lead to morphologic changes in endometriosis lesions, including atrophy or size reduction, which can mask endometriosis lesions and allow them to avoid removal during surgery. These undetected latent endometriosis lesions may remain and recur postoperatively. Second, some scholars have noted that patients who have undergone prior treatment of endometriosis are susceptible to relapse, suggesting that these ectopic endometrial-type glands and stromal implants seem to be of a more aggressive type; hence, these patients are ‘repeaters’ of endometriosis [15]. Third, it is also possible that preoperative hormone ablation therapy may alter some genomic characteristics of the lesions, making the implants more active, progressive and prone to recurrence [17]. For patients who received previous medical treatment for endometriosis, which is an independent risk factor for recurrence, gynaecologists should carefully choose the treatment and ensure that all endometriosis lesions are found and removed during surgery. In addition, these patients must be closely followed after conservative surgery to look for signs of disease recurrence.

Conservative surgery can not only remarkably control pain symptoms and improve reproductive prognosis but may also be superior to medical therapy by the removal of visible endometriosis lesions. However, some lesions, such as subperitoneal implants, microscopic foci or nonpigmented forms of endometriosis, may be difficult to visualize and detect during surgery [18]. These lesions may avoid surgical resection and remain in the pelvic cavity, thereby becoming the source of recurrence. Because painful nodules in the pouch of Douglas are located deep in the pelvic cavity and covered by dense adhesions, it may be difficult surgically to completely resect these nodules [10]. The present study demonstrated that painful nodules in the pouch of Douglas were a significant risk factor for endometriosis recurrence, with an estimated odds ratio of 2.44. One study has reported that incompleteness of the first operation was the only predictor of reoperation for deep endometriosis [19]. Similarly, another study described the long-term outcome of conservative surgery for bladder endometriosis and concluded that the extent of surgical excision was the only factor influencing the recurrence rate [20]. Thus, the extent of surgery might significantly affect the recurrence rate after surgery. The present study confirmed that a larger endometrioma size and bilateral ovarian involvement were both predominant risk factors, with estimated odds ratios of 1.54 and 1.69, respectively. It seems very intuitive that these two variables should be classified as predominant risk factors for endometriosis recurrence. In our study, all remaining visible endometriosis lesions were excised with anatomical restoration being achieved. However, when performing surgery on patients with larger endometrioma size or bilateral ovarian involvement, considering that no conservative treatment has been proven to completely eradicate endometrial implants, a small number of mi-



crossopic lesions may be left in the abdomen resulting in recurrence [11, 13]. Therefore, we speculate that the high rate of recurrence, which was associated with painful nodules in the pouch of Douglas, larger endometrioma size and bilateral ovarian involvement might be due to incomplete resection of endometriosis lesions during surgery.

As stated by ESHRE guidelines, the lack of clear-cut evidence leads to many research questions, including the best way of secondary prevention of endometriosis. Clinicians are recommended to prescribe hormonal treatment (hormonal contraceptives, progestagens, anti-progestagens, or GnRHa) as one of the options, as it reduces endometriosis-associated pain [21]. It is recommended that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain. Although oral contraceptives are the designated drugs to be prescribed for secondary prevention of ovarian endometriomas, some forms of post-operative hormonal therapy could be prescribed for other indications, as contraception or secondary prevention [21]. Since endometriosis is an oestrogen-dependent disease, hormone suppression therapy has been advocated as an initial treatment option after surgery [22]. Post-operative treatment and long-term management should be performed after conservative surgery. First-line or second-line drugs can be chosen for post-operative therapy according to patient's condition. The impact of GnRHa on recurrence has been reported in previous studies, but the results of these studies are not uniform [23–25]. Theoretically, recurrent lesions can originate from residual lesions, and ovarian steroids seem to be the main, although not the only, factors that favor the regrowth of endometrial implants. Therefore, it may be necessary and effective to prescribe hormone suppression treatment for a period of time following conservative surgery to prevent the recurrence of endometriosis [26]. Compared with the patients who did not receive postoperative medical treatment, patients who received postoperative GnRHa treatment had a much lower recurrence rate in this study, which indicated that subsequent GnRHa treatment might have a protective effect on the recurrence of endometriosis. Generally, the prevalence of endometriosis recurrence can vary according to whether there is a successful pregnancy after surgical treatment of endometriosis [15]. The results in this study showed that postoperative pregnancy could significantly reduce the recurrence of endometriosis, which is compatible with the results reported in previous studies [6, 10]. Another study has determined that postoperative pregnancy could significantly decrease the rate of endometriosis recurrence (i.e., postoperative pregnancy has a protective effect on endometriosis recurrence) [16]. Pregnancy after surgery will result in anovulation and amenorrhea, which induce decidual changes and eventual necrosis within the lesions, which are thought to be protective factors for the development of ovarian endometriosis. In addition, pregnancy could suppress the growth, implantation and infiltration of ectopic en-

dometrial tissue because of elevated progesterone levels [27]. Hence, gynaecologists should optimize the timing of conservative surgery based on the patient's child bearing requirements. In addition, patients who desire to become pregnant should be encouraged to conceive as soon as possible after surgery. Thus, we speculate that the two favorable protective factors, postoperative medical treatment and postoperative pregnancy, result in hormone suppression preventing the recurrence of endometriosis after conservative surgery.

The merits of our study were the relatively large sample size, detailed clinical data being available for each patient and the procedure were performed by senior gynaecological surgeons at the university-based tertiary care hospital. There were several limitations in our study. First, the recurrence of ovarian endometriosis was defined by ultrasonography, which is extremely reliant on the skill and experience of the physician performing the ultrasound. Second, the results reported in this study were based on data from a single institution, which might cause selection and measurement bias. Third, because of the design of the retrospective nature of the study, this might result in biases with regard to patient characteristics. For the purpose of controlling the inherent biases of retrospective studies, we plan to conduct a prospective study to strengthen the value of this study.

In conclusion, the prevention of endometriosis recurrence after conservative surgery is one of the most important unresolved problems in the management of endometriosis. To date, there is no consensus on the risk factors for endometriosis recurrence. The most important result of this relatively large sample study was the determination of six correlative factors (four risk factors and two protective factors) associated with the recurrence of ovarian endometriosis after conservative surgery. The four risk factors included previous medical treatment of endometriosis, painful nodules in the pouch of Douglas, largest cyst diameter and bilateral ovarian involvement. The two protective factors included postoperative medical treatment and postoperative pregnancy. The results of this study may assist in the prediction for the prognosis of patients and benefit the clinical management of endometriosis.

## Author contributions

XWZ, MMZ and SK designed the study and applied for Research Ethics Board approval. MMZ and XWZ recruited the patients and collected the data. JZ and WZ followed up the patients. MMZ and XWZ analyzed the data and prepared draft figures and tables. MMZ and XWZ drafted and completed the manuscript. All authors approved the final manuscript.

## Ethics approval and consent to participate

The study was approved by the Institutional Review Board (2016MEC04) of the Hebei Obstetrics and Gynecology Institute. Written informed consent was obtained from all the participants.

## Acknowledgment

We greatly acknowledge several doctors in the Department of Obstetrics and Gynecology, the Fourth Hospital of Hebei Medical University, China, for their assistance in recruiting study subjects.

## Funding

This research received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

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