Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(9): 182
https://doi.org/10.31083/j.ceog5009182

Systematic Review

Factors that Increase the Likelihood of Ovarian Endometriosis Relapsing after Surgical Excision: A Systematic Review and Meta-Analysis

Chang Su[1], Jian Yang[1], Jin Ding[1,*], Huafeng Ding[1,*]

[1]Department of Obstetrics and Gynecology, First Affiliated Hospital of Wannan Medical College, 241000 Wuhu, Anhui, China
*Correspondence: dingjin@wnmc.edu.cn (Jin Ding); dinghuafeng@wnmc.edu.cn (Huafeng Ding)
Academic Editor: Felix Wong
Submitted: 6 May 2023 Revised: 31 May 2023 Accepted: 13 June 2023 Published: 31 August 2023

Abstract

Background: Determine potential triggers for ovarian endometriosis recurrence to provide individualized long-term management and follow-up for improved patient outcomes. **Methods**: Relevant data were acquired through systematic retrieval from PubMed, Embase, Web of Science, and Cochrane Library before October 2022. We determined the odd ratio or the mean difference with their corresponding 95% confidence interval (CI) to explore the relationship between relevant risk factors and postoperative endometriosis relapse. **Results**: This meta-analysis ultimately covered 6388 patients from 18 trials, and the findings demonstrated that postoperative endometriosis recurrence was associated with the age at surgery [mean difference (MD) (95% CI) = –0.69 (–1.33~–0.05), $p = 0.04$], family history [odds ratio (OR) (95% CI) = 2.18 (1.10~4.29), $p = 0.02$], preoperative carbohydrate antigen (CA-125) [MD (95% CI) = 24.08 (–7.55~40.61), $p = 0.004$], laterality of endometriosis (EMs) [OR (95% CI) = 1.19 (1.00~1.40), $p = 0.04$], presence of adenomyosis [OR (95% CI) = 1.53 (1.11~2.11), $p = 0.009$], presence of myoma [OR (95% CI) = 1.44 (1.07~1.94), $p = 0.02$], previous endometriosis-related surgery [OR (95% CI) = 1.90 (1.45~2.51), $p < 0.00001$], and r-American Fertility Society (r-AFS) stage [OR (95% CI) = 0.30 (0.19~0.46), $p < 0.00001$]/[OR (95% CI) = 0.57 (0.48~0.66), $p < 0.00001$]. In addition, postoperative pregnancy [OR (95% CI) = 0.40 (0.19~0.82), $p = 0.01$] and postoperative medication [OR (95% CI) = 1.64 (1.02~2.62), $p = 0.04$] were indicated protective factors for the prevention of postoperative ovarian endometriosis relapse. **Conclusions**: Risk factors for postoperative endometriosis recurrence included the age at surgery, family history, CA-125, laterality of EMs, presence of adenomyosis, presence of myoma, previous endometriosis-related surgery, and r-AFS stage. In addition, protective factors for preventing postoperative recurrence included postoperative pregnancy and postoperative medication. However, the age of menarche, infertility, the extent of surgery, cyst size, body mass index, and dysmenorrhea were unrelated to postoperative recurrence. The sample size could be increased for further investigations.

Keywords: endometriosis; factor; recurrence; risk; meta-analysis

1. Introduction

Endometriosis is a common disease affecting women of childbearing age, where the endometrium tissue (both interstitial and glandular) grows out of the uterine cavity. The periodic bleeding from the ectopic endometrium and fibrosis of the surrounding tissue often form ectopic nodules and other lesions. Pathologically, endometriosis presents benign morphological changes but invasive, metastatic, and recurrent biological behaviors of malignant tumors, earning it the moniker of benign cancer. The major symptoms include dysmenorrhea, chronic pelvic pain, irregular menstruation, and infertility [1]. Endometriosis can occur in all pelvic tissues and organs, particularly the ovaries [2].

Surgery is the standard treatment for ovarian endometriosis, but the postoperative recurrence rate is high. Recurrent endometriosis is the regeneration or reappearance of lesions after standard surgery and drug treatment, with clinical symptoms returning to or even exceeding the level before treatment after symptom relief. According to previous studies, the five-year recurrence rate after conservative surgery is over 40% [3]. The high postoperative recurrence rate severely affects patients' physical and mental health and quality of life [4,5] and increases their social and economic burden, making it a challenging issue clinically. Preventing or delaying postoperative recurrence of ovarian endometriosis is a difficult problem to tackle. However, the pathogenesis of endometriosis has not been fully elucidated, and no single theory can explain its occurrence [6]. Therefore, it is necessary to determine the factors associated with its clinical recurrence rate.

This study collected data on relapse-related factors from long-term follow-ups of childbearing-age patients with ovarian endometriosis. Assessing the association between these factors and ovarian endometriosis recurrence to identify the risk factors may help to provide individualized long-term management and follow-up based on clinical conditions and reduce postoperative recurrence.

2. Methods

2.1 Search Strategy

Systematical searches were performed on PubMed, Embase, Web of Science, and Cochrane Library for studies published online before October 2022 on postoperative recurrence of ovarian endometriosis. The search terms included "endometriosis" (e.g., "endometrioses", "endometrioma", and "endometriomas"), "recurrence" (e.g., "recurrences", "relapse", "relapses", and "recrudescence") and "factors" (e.g., "reasons" and "element"), as shown in **Supplementary Table 1**.

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

(1) Studies of factors related to the postoperative recurrence in patients with ovarian endometriosis;

(2) Cohort studies or case-control studies;

(3) With subjects concerning patients with ovarian endometriosis confirmed by postoperative pathological examination;

(4) With a postoperative follow-up time of at least six months;

(5) The postoperative recurrence was confirmed by ultrasound and reoperation.

2.2.2 Exclusion Criteria

(1) Reviews, abstracts, case reports, meta-analyses, and other non-clinical studies;

(2) Postmenopausal endometriosis;

(3) Endometriosis in adolescents;

(4) Studies with incomplete original data;

(5) Repeated studies.

2.3 Data Extraction and Quality Assessment

With the search terms and inclusion and exclusion criteria, relevant studies were retrieved from the above databases. The relevant literature was initially screened by reading the titles and abstracts, and those that failed to meet the requirements were excluded. Then, the full texts were read, and those that failed to meet the requirements were further excluded. Disagreements on literature inclusion were resolved through discussion or judgment by a third researcher. Studies with similar contents were carefully checked in terms of the title, author, and affiliation to determine whether they were duplications. Only one of the confirmed duplications was included.

After the literature selection, two researchers extracted the data from the included literature using the prepared table. Any discrepancies were settled by a third researcher. The extracted data included the first author, year of publication, age at surgery, age of menarche, dysmenorrhea, postoperative pregnancy, infertility, endometriosis operation history, combined myoma, combined adenomyosis, postoperative medication, family history, preoperative carbohydrate antigen (CA-125), ovarian cyst, body mass index (BMI), laterality of endometriosis (EMs), r-American Fertility Society (r-AFS) stage, and extent of surgery. The included studies were evaluated using the Newcastle-Ottawa Scale (NOS). Studies with a NOS score $\geq$6 were considered high quality. The NOS scores of each study are included in Tables 1,2 (Ref. [7–24]). **Supplementary Table 2** shows the findings on the certainty of evidence.

2.4 Statistical Analysis

Review Manager 5.4 (the International Cochrane Collaboration, Nordic Cochrane Centre, Oxford, United Kingdom) was employed for the analysis. Efficacy analysis statistics were expressed by odds ratio (OR) for dichotomous variables and by mean difference (MD) and 95% confidence interval (CI) for continuous variables to evaluate the impact of related factors on recurrence. The test level was $p < 0.05$, and the I^2 statistic was used to assess heterogeneity. The fixed effects model was adopted since homogeneity was indicated by $p > 0.1$ and $I^2 \leq 50\%$. If $p \leq 0.1$ and $I^2 > 50\%$, the random effects model was used considering the large heterogeneity among studies. Sensitivity analysis was performed to assess the stability and reliability of the pooled results. Publication bias was evaluated using funnel plots.

3. Results

3.1 Literature Retrieval

The literature retrieval process yielded 6768 potentially eligible studies. In addition, 3 studies were identified from the reference lists of the included studies. A total of 4615 studies were screened out by two reviewers independently after excluding duplicate studies. After reading the titles and abstracts, 4542 studies not associated with recurrent risk factors for ovarian endometriosis were further excluded. The remaining 73 studies were then fully reviewed. Among them, 5 were excluded due to insufficient data; 3 studies were excluded due to inconclusive postoperative pathologic findings; 25 studies were disqualified due to the lack of a control group or a non-recurrent group as the control group; 19 studies were excluded as cyst recurrence was not selected as an outcome; and 14 studies were disregarded due to insufficient postoperative follow-up. Finally, this meta-analysis included 18 studies satisfying the inclusion criteria. The flow chart of the literature selection process is shown in Fig. 1.

3.2 Study Characteristics

The included literature was retrospective studies published between 2006 and 2022, which covered 6388 patients with endometriosis, with 1138 and 5250 in the relapsing and non-relapsing groups. The basic information of the included literature is presented in Table 3 (Ref. [7–24]). The comprehensive analysis of relapsing-related factors is listed

Table 1. Literature quality evaluation of the included cohort studies.

Research	Selection	Comparability	Outcome	Score
Vercellini *et al*. 2006 [7]	* * * *		* *	6
Sengoku *et al*. 2013 [8]	* * * *		* * *	7
Selcuk *et al*. 2016 [9]	* * * *	*	* * *	8
Küçükbaş *et al*. 2018 [10]	* * * *	* *	* *	8
Hidari *et al*. 2019 [11]	* * * *		* * *	7
Li *et al*. 2019 [12]	* * * *	*	* * *	8
Zhang *et al*. 2019 [13]	* * * *	*	* * *	8
Won *et al*. 2020 [14]	* * * *	*	* * *	8
Del Forno *et al*. 2021 [15]	* * * *	* *	* *	8
Wacharachawana *et al*. 2021 [16]	* * * *	*	* * *	8
Yu *et al*. 2022 [17]	* * * *	* *	*	7
Tarumi *et al*. 2022 [18]	* * * *	*	* * *	8
Huang *et al*. 2022 [19]	* * * *	* *	* *	8

Refer to the Newcastle-Ottawa Scale, from lowest to highest * (one point) to **** (four points).

Table 2. Literature quality evaluation of the included case-control studies.

Research	Selection	Exposure	Outcome	Score
Hayasaka *et al*. 2011 [20]	* * * *		* * *	7
Campo *et al*. 2014 [21]	* * * *	*	* *	7
Chon *et al*. 2016 [22]	* * * *	* *	* *	8
Han *et al*. 2017 [23]	* * * *	*	* * *	8
He *et al*. 2018 [24]	* * * *	* *	* *	8

Refer to the Newcastle-Ottawa Scale, from lowest to highest * (one point) to **** (four points).

in Table 4. The analyzed potential risk factors included age of menarche, age (years), infertility, postoperative pregnancy, BMI (kg/m^2), preoperative CA-125 (U/mL), family history, dysmenorrhea, r-AFS stage, presence of adenomyosis, presence of myoma, cyst size, laterality of EMs, cystectomy of the affected site, postoperative medication, and previous endometriosis-related surgery. With 18 studies having NOS scores between 6 and 8, the included studies were of moderate to high quality (Tables 1,2).

3.3 Pooled Results for Potential Risk Factors

Age at surgery: In total, 12 studies [8,10–14,16,20–24] with 4611 patients reported the connection between age at surgery and postoperative endometriosis recurrence. Since the heterogeneity was significant ($I^2 = 52\%$, $p = 0.02$), the random-effects model was applied. The findings revealed that the recurrence rate of endometrioma decreased significantly with age (MD = –0.69, 95% CI = –1.33~–0.05, Z = 2.11, $p = 0.04$; Fig. 2A).

Age of menarche: A total of 3 studies [20,23,24] reported the connection between the age of menarche and postoperative recurrence ($I^2 = 0\%$, $p = 0.72$). With little heterogeneity among the 3 studies, the fixed-effects model was used, and the results revealed no significant difference in the age of menarche between the recurrence group and the non-recurrence group (MD = –0.18, 95% CI = –0.44~0.08, Z = 1.35, $p = 0.18$; Fig. 2B).

Dysmenorrhea: The effect of dysmenorrhea on recurrence was reported in 6 studies [9,11,16,17,21,22]. With significant heterogeneity between the studies ($I^2 = 57\%$, $p = 0.04$), the random-effects model was applied, and the findings revealed that dysmenorrhea had no effect on recurrence (OR = 1.95, 95% CI = 0.95~4.02, Z = 1.82, $p = 0.07$; Fig. 2C).

Postoperative pregnancy: There were 7 studies [8,12,14,17,19–21] investigating the effect of postoperative pregnancy on recurrence. As the heterogeneity among the studies was significant ($I^2 = 83\%$, $p < 0.00001$), the random-effects model was employed. The results revealed that patients impregnated after surgery had a lower risk of recurrence (OR = 0.40, 95% CI = 0.19~0.82, Z = 2.52, $p = 0.01$; Fig. 2D).

Infertility: Exactly 8 studies [8,9,11,12,14,16,19,21] covered the relationship between infertility and postoperative endometriosis recurrence. The fixed-effects model was used due to the absence of significant heterogeneity among the 8 studies ($I^2 = 41\%$, $p = 0.10$), which demonstrated no significant difference in infertility between the recurrence group and the non-recurrence group (OR = 0.95, 95% CI = 0.71~1.26, Z = 0.37, $p = 0.71$; Fig. 2E).

Endometriosis operation history: There were 4 studies [8,10,14,16] investigating the effect of previous relevant surgery history on postoperative endometriosis recurrence. Due to the little heterogeneity among the 4 studies

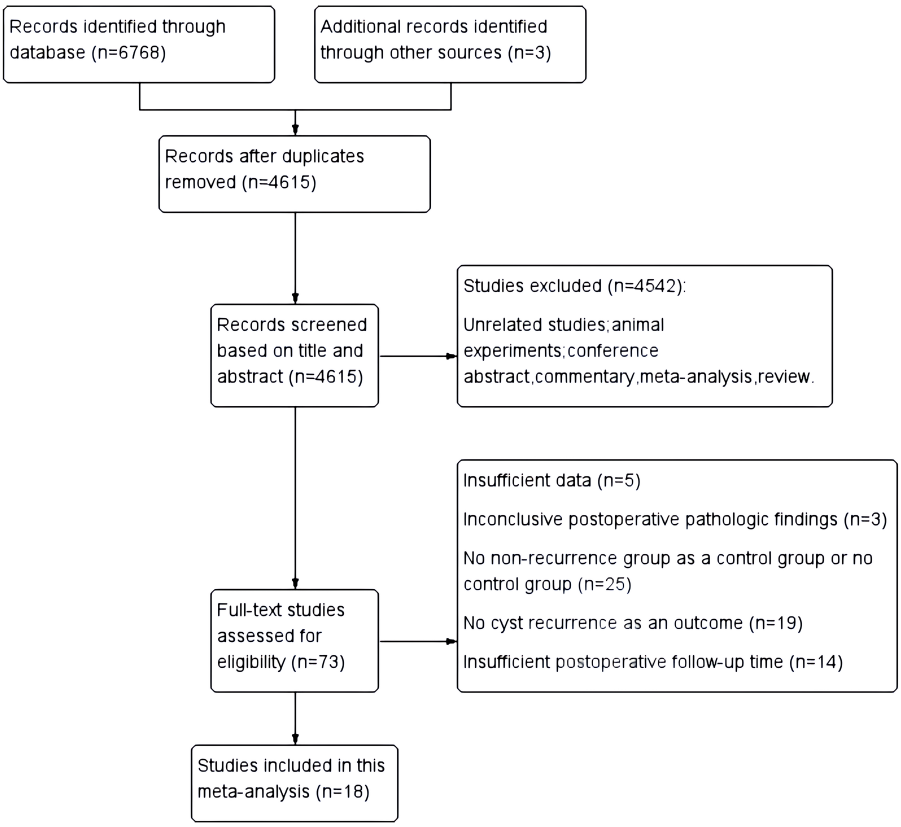

Fig. 1. Flow chart of the literature selection process.

(I^2 = 45%, p = 0.14), the fixed-effects model was applied. The results revealed that previous relevant surgery history significantly affected the recurrence, and the recurrence rate was high in patients with previous related surgeries (OR = 1.90, 95% CI = 1.45~2.51, Z = 4.58, $p < 0.00001$; Fig. 2F).

Combined myoma: The effect of combined myoma on recurrence was reported in 8 studies [8,11,12,16,18–20,23], with no significant heterogeneity (I^2 = 39%, p = 0.12). The findings revealed that the recurrence rate increased with combined myoma (OR = 1.44, 95% CI = 1.07~1.94, Z = 2.42, p = 0.02; Fig. 2G).

Combined adenomyosis: In total, 7 studies [8,11,12,16,18,19,23] with 1287 patients reported the connection between combined adenomyosis and the postoperative recurrence rate of ovarian endometriosis, with minimal heterogeneity (I^2 = 4%, p = 0.40). The findings based on the fixed-effects model revealed that combined adenomyosis enhanced the recurrence rate (OR = 1.53, 95% CI = 1.11~2.11, Z = 2.60, p = 0.009; Fig. 2H).

Postoperative medication: There were 8 studies [8,12,14,17,20–22,24] reporting the effect of postoperative medication on postoperative recurrence, with significant heterogeneity (I^2 = 71%, p = 0.001). Analysis of the results based on the random-effects model revealed that patients treated with medication had a lower risk of recurrence (OR = 1.64, 95% CI = 1.02~2.62, Z = 2.06, p = 0.04; Fig. 2I).

Family history: The effect of family history on recurrence was reported in 2 studies [10,21], which had no significant heterogeneity between them (I^2 = 47%, p = 0.17). The findings based on the fixed-effects model revealed that family history affected the recurrence (OR = 2.18, 95% CI = 1.10~4.29, Z = 2.24, p = 0.02; Fig. 2J).

Preoperative CA-125: In total, 5 studies [10,12,14,22,23] with 3548 patients reported the connection between preoperative CA-125 and postoperative recurrence rate of ovarian endometriosis. Since the heterogeneity was significant (I^2 = 78%, p = 0.001), the random-effects model was applied. The findings showed a statistically significant correlation between CA-125 and the endometriosis recurrence rate (MD = 24.08, 95% CI = –7.55~40.61, Z = 2.85, p = 0.004; Fig. 2K).

Size of ovarian cyst: There were 10 studies [8,10,11,14,16,20–24] concerning the relationship between cyst size and postoperative recurrence. With significant heterogeneity among the 10 studies (I^2 = 85%, $p < 0.00001$), the random-effects model was used, which showed no significant difference in cyst size between the recurrence group and the non-recurrence group (MD = 0.48, 95% CI = –0.21~1.17, Z = 1.37, p = 0.17; Fig. 2L).

Table 3. Baseline characteristics of all included studies.

Study cohort	Year	Affiliation	Study design	Inclusion criteria	Exclusion criteria	Recurrence/Non-recurrence	Indicators of observation
Vercellini *et al.* [7]	2006	The First Department of Obstetrics and Gynaecology of the University of Milan	Retrospective Study	(1) Consecutive women with any type of endometriotic lesion.	(1) Previous clinical or endoscopic diagnosis of endometriosis; (2) Participated in controlled clinical trials; (3) Previous abdominal surgery except appendectomy; (4) Diagnosis of gastrointestinal, urological, or orthopedic diseases with potential pain irradiation to the pelvic area; (5) Known psychiatric disturbances.	69/660	⑨
Hayasaka *et al.* [20]	2011	Tohoku University Hospital or Sendai Social Insurance Hospital	Retrospective Study	(1) At least one year of postoperative follow-up after undergoing laparoscopic excision of an ovarian endometrioma; (2) Patients were followed up every six months for the first year after the operation, followed by any follow-up as needed.	(1) Any prior surgery for ovarian endometriomas.	78/95	①②④⑤⑩⑫⑮
Sengoku *et al.* [8]	2013	Asahikawa Medical University Hospital	Retrospective Study	(1) At least two years of postoperative follow-up; (2) Underwent laparoscopic excision of ovarian endometriomas of >3 cm in diameter.	(1) No follow-up within two years; (2) Irregular menstruation cycles; (3) Malignancy.	73/175	②③④⑤⑨⑩⑪⑫⑬⑮⑯
Campo *et al.* [21]	2014	The Department of Obstetrics and Gynecology of the Catholic University of the Sacred Heart	Retrospective Study	(1) At least 1 ovarian endometrioma >2 cm in diameter.	(1) Minimal or mild endometriosis; (2) Rectovaginal endometriosis, neoadjuvant treatment with estroprogestins; (3) Gonadotropin-releasing hormone (GnRH) analogs; (4) Follow-up period under 12 months.	27/121	②③⑤⑦⑧⑬⑮
Selcuk *et al.* [9]	2016	Zeynep Kamil Training and Researching Hospital	Retrospective Study	(1) Underwent laparoscopic ovarian endometriotic cystectomy; (2) Regular postoperative follow-up period.	(1) Underwent bilateral oophorectomy at the time of endometrioma surgery; (2) Ovarian endometrioma treated with drainage, ablation, fenestration techniques, or incompletely stripped; (3) Postmenopausal status; (4) No postoperative follow-up; (5) Postoperative medical therapy for endometriosis.	27/36	②③⑥⑧⑨⑫⑬
Chon *et al.* [22]	2016	Department of Obstetrics and Gynecology, Gil Hospital, Gachon University College of Medicine	Retrospective Study	(1) Suspected of endometrioma using ultrasonography and pathologically diagnosed with endometrioma.	(1) Not diagnosed with pathologically; (2) Without endometrioma; (3) Previously underwent surgery due to endometrioma in other hospitals.	37/199	②⑤⑥⑧⑨⑫⑬⑮
Han *et al.* [23]	2017	Kyungpook National University Hospital	Retrospective Study	(1) Underwent surgical operation including at least ovarian cystectomy for ovarian endometrioma; (2) Reproductive ages (20–40 years old).	(1) Incomplete medical records; (2) Loss of follow-up before 24 months after primary surgery; (3) Concurrently hysterectomized; (4) Menopaused; (5) History of previous endometriosis-related surgery.	27/77	①②③⑤⑥⑧⑨⑩⑪⑫⑬⑭
Küçükbaş *et al.* [10]	2018	The Zeynep Kamil Research and training hospital in Turkey	Retrospective Study	(1) Underwent laparoscopic unilateral/bilateral endometrioma cystectomy; (2) Followed for more than 6 months.	(1) Underwent oophorectomy or hysterectomy; (2) Diagnosis of malignancy; (3) Intraoperatively diagnosed adnexal pathology requiring subsequent unilateral or bilateral oophorectomy.	56/113	②⑤⑥⑦⑨⑫⑬⑯
He *et al.* [24]	2018	Department of Obstetrics and Gynecology at Peking Union Medical College Hospital	Retrospective Study	(1) Postoperative histopathological diagnosis of ovarian endometriosis; (2) Aged 45 years and over at the time of surgery; (3) The clinical and pathological data were complete.	(1) The combination of malignant or borderline tumors.	45/180	①②⑥⑫⑮

Table 3. Continued.

Study cohort	Year	Affiliation	Study design	Inclusion criteria	Exclusion criteria	Recurrence/Non-recurrence	Indicators of observation
Hidari *et al*. [11]	2019	The University of Tokyo Hospital	Retrospective Study	(1) Age between 35 and 45 years; (2) Preoperative magnetic resonance imaging (MRI)-confirmed unilateral ovarian endometrioma.	(1) The presence of bilateral endometriomas; (2) Previous unilateral or bilateral oophorectomy; (3) Pathological diagnosis of malignancy.	8/42	②③④⑧⑩⑪⑫⑬
Li *et al*. [12]	2019	Peking Union Medical College Hospital	Retrospective Study	(1) Diagnosis confirmed by pathologists; (2) Conducted ultrasonography to determine endometrioma recurrence at least 6 months after surgery; (3) Patients were observed without postoperative medications or were treated with postoperative GnRHa injections for 3–6 cycles; (4) The duration of follow-up was at least 5 years.	(1) Age $<$20 or $>$45 years; (2) Having undergone bilateral oophorectomy or hysterectomy; (3) Intra-operative conversion to laparotomy.	68/290	②③④⑤⑥⑧⑨⑩⑪⑬⑭⑮
Zhang *et al*. [13]	2019	The Gynaecology and Obstetrics Department of Tianjin Centre Hospital	Retrospective Study	(1) Patients who previously underwent surgery; (2) Ovarian endometriosis malignancy or non-malignant ovarian endometriosis confirmed by postoperative pathology; (3) Patients with complete clinical data.	(1) Patients with primary ovarian carcinoma or ovarian metastases; (2) Patients who refused surgical therapy or accepted conservative treatment; (3) Patients who had incomplete clinical data.	39/74	②⑥⑨⑫
Won *et al*. [14]	2020	CHA Gangnam Medical Center	Retrospective Study	(1) Patients were surgically treated and displayed pathologically confirmed ovarian endometriosis.	(1) Gynecologic malignancy; (2) Underwent bilateral oophorectomy; (3) Menopause; (4) Revised American Society of Reproductive Medicine (rASRM) stage of I or II (n = 18) at initial surgery; (5) Follow-up duration of $<$6 months.	362/2319	②③④⑤⑥⑨⑫⑬⑭⑮⑯
Del Forno *et al*. [15]	2021	Gynecology and Human Reproduction Physiopathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna	Retrospective Study	(1) The presence of a histological diagnosis of ovarian endometrioma; (2) A minimum follow-up period of 12 months.	(1) Bilateral oophorectomy; (2) Hormonal therapies other than EPs and Ps pregnancy; (3) Menopausal state diagnosed postoperatively or during follow-up.	45/161	⑨
Wacharachawana *et al*. [16]	2021	Bhumibol Adulyadej Hospital	Retrospective Study	(1) Underwent laparoscopic surgery with a provisional diagnosis of ovarian endometriosis; (2) Follow-up visits of at least one full year postoperation.	(1) Non-ovarian endometriosis from pathologic reports; (2) Incomplete follow-up (follow-up of less than one full year); (3) Incomplete medical data.	24/82	②③⑤⑧⑨⑩⑪⑫⑯
Yu *et al*. [17]	2022	Department of Gynaecology, Zhoushan Women and Children Hospital	Retrospective Study	(1) Not pregnant for more than 1 year without contraception; (2) Ultrasonography showed that there was growth and infiltration outside the endometrium, and repeated bleeding formed nodules and masses, which caused pain; (3) Patients who did not take hormone drugs within 6 months before the study; (4) The clinical data are complete.	(1) Cognitive dysfunction or mental illness; (2) Accompanied by dysfunction of the heart, liver, kidney, and other organs; (3) With contraindications for operation; (4) There are drug contraindications; (5) Failed to meet the follow-up conditions.	30/128	②④⑤⑧⑨⑬⑮

Table 3. Continued.

Study cohort	Year	Affiliation	Study design	Inclusion criteria	Exclusion criteria	Recurrence/Non-recurrence	Indicators of observation
Tarumi *et al*. [18]	2022	Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine	Retrospective Study	(1) Reproductive age; (2) Underwent total laparoscopic cystectomy for ovarian endometriosis with or without excision of deep endometriosis (DE).	(1) Less than 2-year postoperative follow-up period; (2) Pregnancy within 12 months after surgery.	36/96	②⑤⑥⑨⑩⑪⑫⑬
Huang *et al*. [19]	2022	The Department of Gynecology and Tumors, Changzhou Maternal and Child Health Care Hospital, Affiliated with Nanjing Medical University	Retrospective Study	(1) Aged 18 to 45 years at the time they underwent surgery; (2) Surgery was laparoscopic ovarian cyst debulking, which is a fertility-preserving surgery that is done without removing fallopian tubes and ovaries; (3) Complete clinical history data and follow-up information were available; (4) Postoperative follow-up time was more than 12 months.	(1) Patients treated with radical surgery or having gynecologic malignancies or other malignancies; (2) Patients with incomplete medical records or lost visits or who were unwilling to cooperate with a follow-up visit; (3) Patients who had laparoscopic intermediate open surgery; (4) Patients with pelvic tuberculosis, ovulation disorders, genital malformations, and other causes of infertility.	49/240	②③④⑨⑩⑪⑫⑬

Indicators of observation: ① Age of menarche; ② Age (years); ③ Infertility; ④ Postoperative pregnancy; ⑤ Body mass index (kg/m^2); ⑥ Preoperative CA-125 (U/mL); ⑦ Family history; ⑧ Dysmenorrhea; ⑨ r-AFS stage; ⑩ Presence of adenomyosis; ⑪ Presence of myoma; ⑫ Cyst size; ⑬ Laterality of EMs; ⑭ Cystectomy of affected site; ⑮ Postoperative medication; ⑯ Previous endometriosis related surgery. GnRHa, gonadotropin-releasing hormone agonist; CA-125, carbohydrate antigen; r-AFS, r-American Fertility Society; EMs, endometriosis; EPs, exaggerated placental site; Ps, placental site.

Table 4. Pooled analysis of each relapse-related factor.

Correlation factors	Number of studies	Recurrence /Non-recurrence	Aggregate effect			Heterogeneity		Effect model
			OR/MD	95% CI	*p* value	*p* value	I^2 %	
Age at surgery	12	844/3767	–0.69	–1.33~–0.05	0.04	0.02	52%	Random-effects model
Age of menarche	3	150/352	–0.18	–0.44~0.08	0.18	0.72	0%	Fixed-effects model
Dysmenorrhea	6	153/608	1.95	0.95~4.02	0.07	0.04	57%	Random-effects model
Postoperative pregnancy	7	687/3368	0.40	0.19~0.82	0.01	<0.00001	83%	Random-effects model
Infertility	8	638/3305	0.95	0.71~1.26	0.71	0.10	41%	Fixed-effects model
Endometriosis operation history	4	515/2689	1.90	1.45~2.51	<0.00001	0.14	45%	Fixed-effects model
Combined myoma	8	363/1097	1.44	1.07~1.94	0.02	0.12	39%	Fixed-effects model
Combined adenomyosis	7	285/1002	1.53	1.11~2.11	0.009	0.40	4%	Fixed-effects model
Postoperative medication	8	720/3507	1.64	1.02~2.62	0.04	0.001	71%	Random-effects model
Family history	2	83/234	2.18	1.10~4.29	0.02	0.17	47%	Fixed-effects model
Preoperative CA-125	5	550/2998	24.08	–7.55~40.61	0.004	0.001	78%	Random-effects model
Size of ovarian cyst	10	737/3403	0.48	–0.21~1.17	0.17	<0.00001	85%	Random-effects model
BMI	9	752/3471	–0.21	–0.46~0.03	0.08	0.58	0%	Fixed-effects model
Laterality of EMs	11	792/3794	1.19	1.00~1.40	0.04	0.04	48%	Fixed-effects model
r-AFS stage	13	1005/4652	0.57	0.48~0.66	<0.00001	0.46	0%	Fixed-effects model
Cystectomy of the affected site	3	457/2686	3.94	0.07~216.5	0.50	<0.00001	98%	Random-effects model

OR, odds ratio; MD, mean difference; BMI, body mass index; CI, confidence interval; EMs, endometriosis; r-AFS, r-American Fertility Society.

BMI: The effect of BMI on recurrence was reported in 9 studies [8,10,12,14,16,20–23], which had no significant heterogeneity (I^2 = 0%, p = 0.58). Using the fixed-effects model, the results revealed that the difference between the recurrence group and the non-recurrence group was not statistically significant (OR = –0.21, 95% CI = –0.46~0.03, Z = 1.73, p = 0.08; Fig. 2M).

Laterality of EMs: In total, 11 studies [8–10,12,14,17–19,21–23] with 4586 patients reported the effect of laterality of EMs on the recurrence rate. Since the heterogeneity was significant (I^2 = 48%, p = 0.04), the fixed-effects model was applied. The findings revealed that the recurrence rate of patients with bilaterality of cyst was significantly higher than that of patients with unilaterality (OR = 1.19, 95% CI = 1.00~1.40, Z = 2.02, p = 0.04; Fig. 2N).

r-AFS stage: There were 6 studies [7,10,12,13,19,22] that reported on the difference between stages I and II versus stages III and IV on endometriosis relapse, which had little heterogeneity (I^2 = 43%, p = 0.12). The fixed-effect model was used to reveal the effect of the r-AFS stage on postoperative recurrence. The recurrence rate of stage I and II patients was 0.30 compared to stage III and IV patients (OR = 0.30, 95% CI = 0.19~0.46, Z = 5.46, $p < 0.00001$; Fig. 2O).

There were also 13 studies [7–10,12–19,22] reporting the difference between stage III and stage IV on endometriosis relapse, with little heterogeneity (I^2 = 0%, p = 0.46). The fixed-effect model was used to reveal the effect of the r-AFS stage on postoperative endometriosis recurrence. The recurrence rate of stage III patients was 0.57 compared to stage IV patients (OR = 0.57, 95% CI = 0.48~0.66, Z = 7.13, $p < 0.00001$; Fig. 2P).

Cystectomy of the affected site: The effect of cystectomy of the affected site on postoperative recurrence was reported in 3 studies [12,14,23], which had significant heterogeneity (I^2 = 98%, $p < 0.00001$). Using the random-effect model, the results revealed no effect on recurrence by removing only the affected part (OR = 3.94, 95% CI = 0.07~216.50, Z = 0.67, p = 0.50; Fig. 2Q).

3.4 Sensitivity Analysis

Sensitivity analysis was performed on postoperative pregnancy, infertility, combined myoma, combined adenomyosis, endometriosis operation history, ovarian cyst size, BMI, and r-AFS stage. After removing the data one by one, no significant change was found in the analysis results, indicating the reliability of the summary results. Sensitivity analysis was also performed on dysmenorrhea. Following the exclusion of the study by Wacharachawana *et al.* [16], the heterogeneity was statistically changed (I^2 = 44%, p = 0.13).

The results revealed that dysmenorrhea had an effect on endometriosis recurrence, and the recurrence rate of patients with dysmenorrhea was high (OR = 2.44, 95% CI = 1.26–4.73, Z = 2.65, p = 0.008).

3.5 Publication Bias

r-AFS stage was used for the funnel plot analysis to assess the publication bias. As shown in Fig. 3, all the included studies are in inverted funnel plots with good symmetry. Therefore, the publication bias of the included studies has relatively little impact on the results.

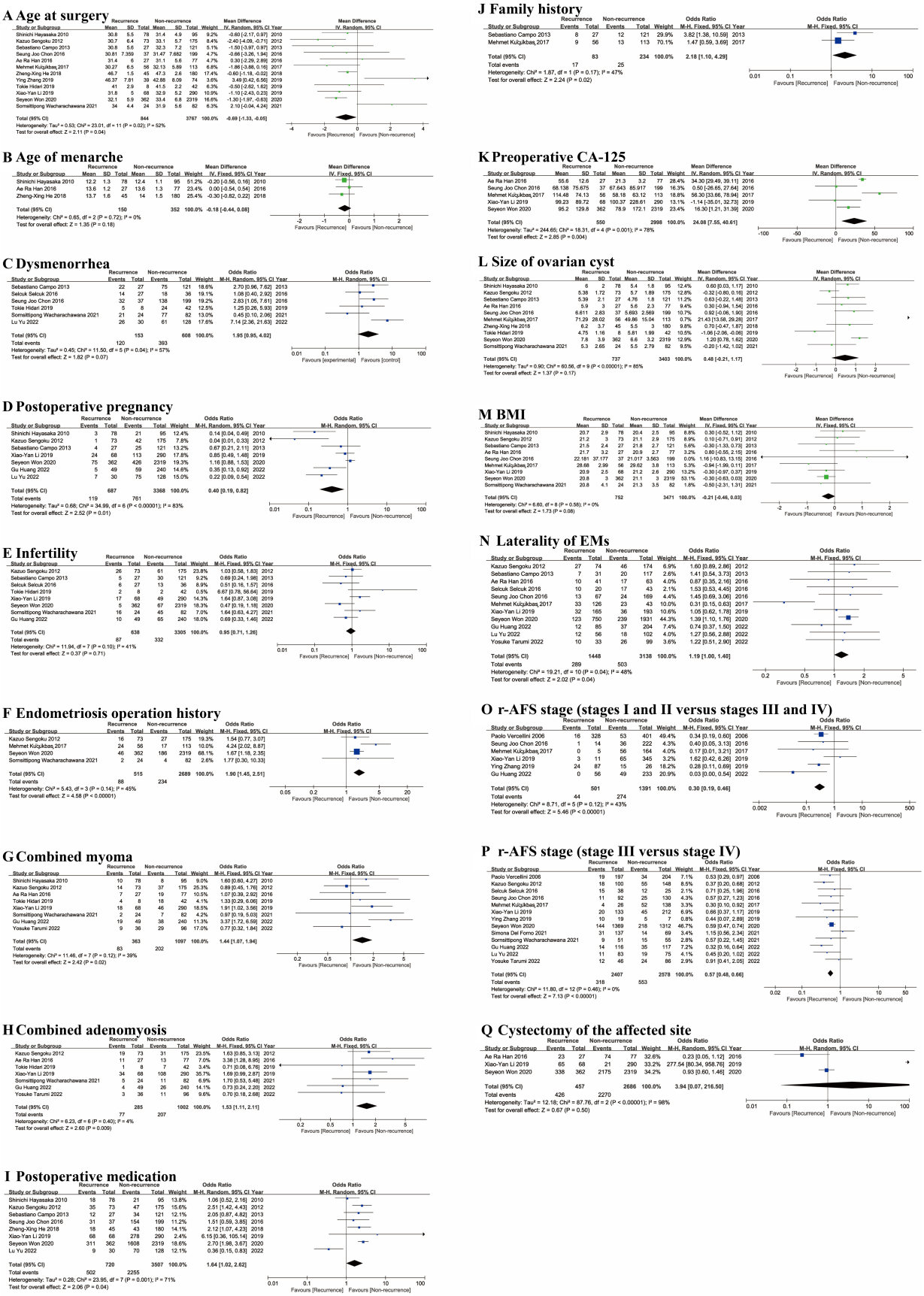

Fig. 2. Pooled results for potential risk factors.

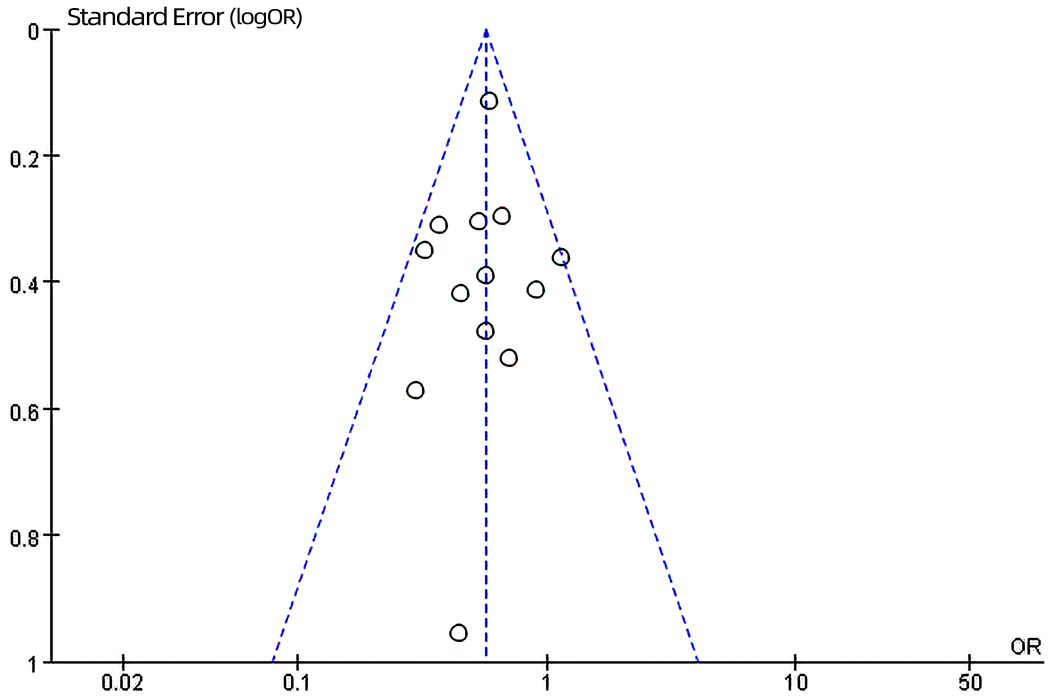

Fig. 3. The funnel plot of studies included in the r-AFS stage analysis.

4. Discussion

As a benign disease, the exact pathogenesis of endometriosis has not been fully elucidated. The numerous theories include endometrial implantation theory [25], lymphatic and venous dissemination theory [26], coelomic metaplasia theory [27], and immunity and inheritance theory [28]. However, it is difficult to explain the exact mechanisms of endometriosis with one theory, and many hypotheses are linked to the pathogenesis and progression of endometriosis. Currently, the most widely accepted theory of endometriosis is endometriotic implantation caused by retrograde menstruation, in which endometrial glandular epithelial and mesenchymal cells are ectopically implanted in the ovary by retrograde menstruation, where they continue to grow and spread to form ectopic lesions [6]. Endometriosis does not, however, occur in all women with retrograde menstruation. The hypothesis of abnormal eutopic endometrium partly explains why most women of childbearing age have retrograde menstruation and only a few develop endometriosis, which constitutes an important supplement and extension to the theory of ectopic implantation [29,30]. This hypothesis may provide a satisfactory explanation for the same mutations carried by the true and ectopic endometrial tissues in patients. However, in the study by Koppolu *et al.* [31], no variants were found common to both tissues from the same patient, thus not supporting this hypothesis.

Recurrence is one of the many difficulties in the clinical management of endometriosis. Identifying the factors related to postoperative endometriosis recurrence can provide insights into the individualized treatment of endometriosis to help clinicians determine the risk of recurrence and formulate treatment plans from the perspective of personalized medicine.

4.1 Risk Factors for Endometriosis Recurrence

Age at surgery: Studies have revealed that the endometriosis recurrence rate decreases with age, while the age at the time of surgery is a risk factor for recurrence. Higher estrogen levels in young women induce persistent growth of residual lesions. The study by Yang *et al.* [32] also demonstrated that younger age at surgery was a significant risk for postoperative recurrence of ovarian endometriosis. Therefore, more attention should be attached to young female patients, and the number of follow-up visits should be increased.

Family history: This study suggests that family history has some impacts on postoperative endometriosis recurrence and confirms the existence of genetic trait changes in the pathogenesis of endometriosis. The genetic differences lead to molecular biological differences between the eutopic endometrium of patients and normal subjects.

Preoperative CA-125: Carbohydrate antigen CA-125 is a glycoprotein derived from coelomic epithelial cells and expressed in normal tissues, which could offer some insights into the diagnosis of endometriosis [33]. The above studies concluded that postoperative CA-125 was a risk factor for postoperative endometriosis recurrence. However, CA-125 is a sensitive but poorly specific indicator, and many other diseases also cause marked increases in CA-

125. Therefore, CA-125 can be used as a follow-up index but not a diagnostic index of postoperative recurrence. In addition, CA-125 levels can vary with the menstrual cycle. An increased sample size is needed to improve the accuracy of this study.

Laterality of EMs: This study revealed that the recurrence rate of patients with bilaterality of cysts was significantly higher than that of patients with unilaterality. It is speculated that bilateral cysts may increase the possibility of residual lesions. This conclusion is consistent with the current clinical consensus but contrary to the conclusion of Han *et al*. [34] and Koga *et al*. [35], suggesting no significant association between bilateral cysts and postoperative recurrence. Therefore, it is necessary to expand the sample for further study.

Presence of adenomyosis: The results revealed that adenomyosis was also a risk factor for postoperative endometriosis recurrence as the pathogenesis of endometriosis and adenomyosis overlap [36,37]. Therefore, the correct identification of endometriosis combined with adenomyosis and the formulation of personalized long-term postoperative management plans play a crucial part in recurrence prevention.

Presence of myoma: Fibroids in the uterus were regarded as estrogen-dependent tumors. An animal model of fibroid xenotransplantation revealed that steroids, including estradiol and progesterone, were necessary for tumor growth [37]. Therefore, the high estrogen in patients with uterine fibroids affects the endometriosis recurrence rate. Clinically, long-term management plans and regular follow-ups should be made for postoperative patients with uterine fibroids to prevent recurrence.

Previous endometriosis-related surgery: The results suggested that patients with previous endometriosis surgeries had a higher postoperative recurrence rate, possibly because of the more aggressive endometriosis type in patients with previous related surgeries. The mainstream view is that whether the lesion is completely removed during the operation determines the postoperative recurrence. Therefore, surgeons should remove the lesion as much as possible during the operation rather than relying on postoperative adjuvant drugs. Radical surgery is recommended for patients at high risk of recurrence and without fertility requirements.

r-AFS stage: r-AFS stage is determined based on endometriosis lesion size, location, degree of adhesion, etc. [1,38]. This study concluded that the postoperative recurrence rate was higher with higher surgical scores and more severe stages. In short, extensive lesion adhesions during surgery tend to cause residual lesions and increase the risk of recurrence. Therefore, through clinical analysis, the r-AFS stage is of certain reference significance to evaluate the prognosis and disease severity. When selecting treatment plans, the patient's r-AFS stage should be considered.

4.2 Protective Factors for Endometriosis Recurrence

Postoperative pregnancy: The combined data analysis confirmed the benefit of postoperative pregnancy in preventing endometriosis recurrence, possibly because pregnancy and postpartum lactation can lead to ovarian non-ovulation and endometrium decidual-like changes, causing the necrosis of endometriosis lesions and reducing the postoperative recurrence rate [39]. Therefore, Vercellini *et al*. [40] also found that after endometriosis surgery, patients with fertility requirements were preferably impregnated sooner.

Postoperative medication: The integrated data revealed that patients treated with medication had a lower risk of endometriosis recurrence. Gonadotropin-releasing hormone agonist (GnRHa) can effectively inhibit the secretion of endogenous gonadotrophins and lead to a hypoestrogenic state *in vivo*, causing deciduosis of endometrium and necrosis of endometriosis lesions [41]. The study by Adachi *et al*. [42] showed that the endometriosis recurrence rate was significantly reduced after 24 months of dienogest (DNG) administration. In recent years, as an important means of long-term maintenance management after surgery, drug therapy has become a common clinical treatment. In the meantime, Chiu *et al*. [43] also showed that postoperative adjuvant plus maintenance therapy might be the most effective intervention to prevent endometriosis recurrence. However, the variety of drugs and the complex action mechanisms require more accurate and extensive studies to clarify the efficacy and safety of drugs [44].

4.3 Unrelated Factors for Endometriosis Recurrence

Age of menarche: Ponomarenko *et al*. [45] concluded that some single nucleotide polymorphisms (SNPs) for the age of menarche were associated with endometriosis. Meanwhile, Vercellini *et al*. [40] found in their study on endometriosis that the early age of menarche in modern women was closely related to the high incidence of endometriosis. However, this meta-analysis suggested that the age of menarche had no significant effect on postoperative endometriosis recurrence. The increased incidence of contemporary endometriosis may be attributed to the improved detection rate. The understanding of the disease is gradually deepened, and the disease becomes treatable, thus increasing the detection rate of endometriosis.

Infertility: The mechanisms by which endometriosis induces infertility are multifactorial, involving mechanical, molecular, genetic, and environmental causes. New research has found that changes in gene expression and gene defects are also responsible [46]. However, infertility could be caused by a variety of factors, the most common one being female pelvic inflammatory diseases, which cause the fallopian tubes to adhere to prevent the ovum and sperm from bonding and have no significant association with en-

dometriosis incidence. Therefore, the fallopian factor accounting for a large proportion of infertility may affect the accuracy of the study results.

Cystectomy of the affected site: It is generally accepted in clinical practice that lesion resection alone leads to an increased likelihood of endometriosis recurrence. However, the combined evidence here suggested that postoperative recurrence rates were not significantly increased in patients with lesion resection alone.

Cyst size: Jiang *et al*. [47] revealed that greater cyst diameters led to higher possibilities of endometriosis recurrence. On the one hand, the intraoperative residual lesions of large cysts are more likely to conceal the potential factors for recurrence. On the other hand, large cysts often represent greater ectopic cell vitality, thus increasing the recurrence rate. Nevertheless, the findings revealed no association between cyst size and recurrence. We concluded from the overall review that the possible cause was the lack of an objective standard for the intraoperative cyst size evaluation, which was mainly based on the subjective judgment of the surgeon, thus bringing errors to cyst size calculation. Therefore, improving the objective evaluation criteria for cyst size is suggested to increase the accuracy of results.

BMI: As the endometrial tissue grows outside the uterine cavity, the progesterone and estrogen signals are interfered with, leading to progesterone resistance and estrogen dominance in patients with endometriosis [27,48]. Hormone disorders may lead to obesity in the patients and thus increased BMI. It can be inferred that BMI may be related to the recurrence of endometriosis. The study of the relationship between ovarian endometriosis and obesity here revealed no significant association between BMI and endometriosis recurrence.

Dysmenorrhea: Previous studies have shown that the direct and indirect effects of local bleeding in endometriosis tissue, the actions of celiac inflammatory cytokines, and stimulation or direct infiltration of pelvic floor nerve may be the causes of dysmenorrhea [49]. Meanwhile, patients with dysmenorrhea generally have more extensive lesions, which are difficult to completely remove by surgery, thus explaining the increased recurrence rates in patients with dysmenorrhea. However, this analysis suggested that dysmenorrhea was not a risk factor for recurrent endometriosis, contrary to previous findings by Chon *et al*. [22]. After removing the study by Wacharachawana *et al*. [16] with heterogeneous source, we found that patients with dysmenorrhea had a higher recurrence rate after surgery (OR = 2.44, 95% CI = 1.26~4.73, Z = 2.65, $p = 0.008$), which was consistent with the research findings of Chon *et al*. [22]. After carefully studying the research by Wacharachawana *et al*. [16], no cause for heterogeneity was found. Therefore, an increased sample is crucial for further exploration to enhance the reliability of the results.

5. Conclusions

In summary, the pooled evidence suggested that the following risk factors were significantly associated with endometriosis recurrence, namely, age of surgery, family history, preoperative CA-125, laterality of EMs, presence of adenomyosis, presence of myoma, previous endometriosis-related surgery, r-AFS stage, postoperative pregnancy, postoperative medication. The age of menarche, infertility, the extent of surgery, cyst size, BMI, and dysmenorrhea were not associated with endometriosis recurrence. The risk factors for relapse could be identified, and individualized long-term management and follow-up could be tailored to patient conditions. The sample size can be increased for large-scale studies to confirm the inevitable limitations of this meta-analysis.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

JD and HD: conception and design of the research. CS: wrote and revised the manuscript. CS and JY: analysis and interpretation of the data and statistical analysis. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank all those who have contributed to the preparation of this manuscript.

Funding

This work was supported by the grants from National Natural Science Foundation of China (No. 82201820).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5009182.

References

[1] Zondervan KT, Becker CM, Missmer SA. Endometriosis. The New England Journal of Medicine. 2020; 382: 1244–1256.

[2] Yılmaz Hanege B, Güler Çekıç S, Ata B. Endometrioma and ovarian reserve: effects of endometriomata per se and its surgi-

cal treatment on the ovarian reserve. Facts, Views & Vision in ObGyn. 2019; 11: 151–157.
[3] Falcone T, Flyckt R. Clinical Management of Endometriosis. Obstetrics and Gynecology. 2018; 131: 557–571.
[4] Flores I, Rivera E, Ruiz LA, Santiago OI, Vernon MW, Appleyard CB. Molecular profiling of experimental endometriosis identified gene expression patterns in common with human disease. Fertility and Sterility. 2007; 87: 1180–1199.
[5] Van Gorp T, Amant F, Neven P, Vergote I, Moerman P. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2004; 18: 349–371.
[6] Liu Y, Zhang Z, Yang F, Wang H, Liang S, Wang H, *et al*. The role of endometrial stem cells in the pathogenesis of endometriosis and their application to its early diagnosis†. Biology of Reproduction. 2020; 102: 1153–1159.
[7] Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D, Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. Human Reproduction. 2006; 21: 2679–2685.
[8] Sengoku K, Miyamoto T, Horikawa M, Katayama H, Nishiwaki K, Kato Y, *et al*. Clinicopathologic risk factors for recurrence of ovarian endometrioma following laparoscopic cystectomy. Acta Obstetricia et Gynecologica Scandinavica. 2013; 92: 278–284.
[9] Selcuk S, Cam C, Koc N, Kucukbas M, Ozkaya E, Eser A, *et al*. Evaluation of risk factors for the recurrence of ovarian endometriomas. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016; 203: 56–60.
[10] Küçükbaş M, Kurek Eken M, İlhan G, Şenol T, Herkiloğlu D, Kapudere B. Which factors are associated with the recurrence of endometrioma after cystectomy? Journal of Obstetrics and Gynaecology: the Journal of the Institute of Obstetrics and Gynaecology. 2018; 38: 372–376.
[11] Hidari T, Hirata T, Arakawa T, Koga K, Neriishi K, Fukuda S, *et al*. Contralateral ovarian endometrioma recurrence after unilateral salpingo-oophorectomy. BMC Women's Health. 2019; 19: 59.
[12] 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. Journal of Ovarian Research. 2019; 12: 79.
[13] Zhang Y, Qu P. Factors associated with ovarian endometriosis malignancy and its recurrence in Chinese women. Journal of Obstetrics and Gynaecology: the Journal of the Institute of Obstetrics and Gynaecology. 2019; 39: 1148–1153. (In Chinese)
[14] Won S, Cho YJ, Lee N, Kim M, Kim MK, Jung YW, *et al*. Atypical endometriosis is related to a higher recurrence rate. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2020; 254: 44–51.
[15] 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? Gynecologic and Obstetric Investigation. 2021; 86: 170–176.
[16] Wacharachawana S, Phaliwong P, Prommas S, Smanchat B, Bhamarapravatana K, Suwannarurk K. Recurrence Rate and Risk Factors for the Recurrence of Ovarian Endometriosis after Laparoscopic Ovarian Cystectomy. BioMed Research International. 2021; 2021: 6679641.
[17] Yu L, Sun Y, Fang Q. Efficacy of Laparoscopic Surgery Combined With Leuprorelin in the Treatment of Endometriosis Associated With Infertility and Analysis of Influencing Factors for Recurrence. Frontiers in Surgery. 2022; 9: 873698.
[18] Tarumi Y, Mori T, Shimura K, Izumi Y, Okimura H, Kataoka H, *et al*. Progesterone Receptor Status of Epithelial Cells as a Predictive Marker for Postoperative Recurrence of Endometriosis. The Journal of Clinical Endocrinology and Metabolism. 2022; 107: 1552–1559.
[19] Huang G, Fan X, Zhu P. Analysis of recurrence factors associated with conservative surgery for ovarian-type endometriosis. Annals of Translational Medicine. 2022; 10: 255.
[20] Hayasaka S, Ugajin T, Fujii O, Nabeshima H, Utsunomiya H, Yokomizo R, *et al*. Risk factors for recurrence and re-recurrence of ovarian endometriomas after laparoscopic excision. The Journal of Obstetrics and Gynaecology Research. 2011; 37: 581–585.
[21] Campo S, Campo V, Gambadauro P. Is a positive family history of endometriosis a risk factor for endometrioma recurrence after laparoscopic surgery? Reproductive Sciences. 2014; 21: 526–531.
[22] Chon SJ, Lee SH, Choi JH, Lee JS. Preoperative risk factors in recurrent endometrioma after primary conservative surgery. Obstetrics & Gynecology Science. 2016; 59: 286–294.
[23] Han AR, Lee TH, Kim S, Lee HY. Risk factors and biomarkers for the recurrence of ovarian endometrioma: about the immunoreactivity of progesterone receptor isoform B and nuclear factor kappa B. Gynecological Endocrinology: the Official Journal of the International Society of Gynecological Endocrinology. 2017; 33: 70–74.
[24] He ZX, Sun TT, Wang S, Shi HH, Fan QB, Zhu L, *et al*. Risk Factors for Recurrence of Ovarian Endometriosis in Chinese Patients Aged 45 and Over. Chinese Medical Journal. 2018; 131: 1308–1313. (In Chinese)
[25] Sampson JA. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. The American Journal of Pathology. 1927; 3: 93–110.43.
[26] Brown J, Farquhar C. An overview of treatments for endometriosis. Journal of the American Medical Association. 2015; 313: 296–297.
[27] Vinatier D, Dufour P, Leroy JL. The mechanisms of endometriosis. La Revue Du Praticien. 1999; 49: 254–257.
[28] Borghese B, Zondervan KT, Abrao MS, Chapron C, Vaiman D. Recent insights on the genetics and epigenetics of endometriosis. Clinical Genetics. 2017; 91: 254–264.
[29] Li X, Gong X, Zhu L, Leng J, Fan Q, Sun D, *et al*. Stretch magnitude- and frequency-dependent cyclooxygenase 2 and prostaglandin E2 up-regulation in human endometrial stromal cells: possible implications in endometriosis. Experimental Biology and Medicine. 2012; 237: 1350–1358.
[30] Sha G, Zhang Y, Zhang C, Wan Y, Zhao Z, Li C, *et al*. Elevated levels of gremlin-1 in eutopic endometrium and peripheral serum in patients with endometriosis. Fertility and Sterility. 2009; 91: 350–358.
[31] Koppolu A, Maksym RB, Paskal W, Machnicki M, Rak B, Pępek M, *et al*. Epithelial Cells of Deep Infiltrating Endometriosis Harbor Mutations in Cancer Driver Genes. Cells. 2021; 10: 749.
[32] Yang F, Liu B, Xu L, Liu H. Age at surgery and recurrence of ovarian endometrioma after conservative surgery: a meta-analysis including 3125 patients. Archives of Gynecology and Obstetrics. 2020; 302: 23–30.
[33] Colacurci N, Fortunato N, De Franciscis P, Fratta M, Cioffi M, Zarcone R, *et al*. Serum and peritoneal CA-125 levels as diagnostic test for endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1996; 66: 41–43.
[34] Han S, Lee H, Kim S, Joo J, Suh D, Kim K, *et al*. Risk factors related to the recurrence of endometrioma in patients with long-term postoperative medical therapy. Ginekologia Polska. 2018; 89: 611–617.
[35] Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T,

et al. Recurrence of ovarian endometrioma after laparoscopic excision. Human Reproduction. 2006; 21: 2171–2174.

[36] Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. Human Reproduction Update. 2005; 11: 595–606.

[37] Yang Q, Ciebiera M, Bariani MV, Ali M, Elkafas H, Boyer TG, *et al*. Comprehensive Review of Uterine Fibroids: Developmental Origin, Pathogenesis, and Treatment. Endocrine Reviews. 2022; 43: 678–719.

[38] Weitzman GA, Buttram VC, Jr. Classification of endometriosis. Obstetrics and Gynecology Clinics of North America. 1989; 16: 61–77.

[39] Guo H, Shen A, Xu S, Yang J. Analysis of relevant factors for recurrence of ovarian endometriosis after conservative laparoscopic surgery. Journal of Central South University Medical sciences. 2016; 41: 405–410. (In Chinese)

[40] Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbara G, Fedele L. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reproductive Biomedicine Online. 2010; 21: 259–265.

[41] Lee DY, Lee JY, Seo JW, Yoon BK, Choi D. Gonadotropin-releasing hormone agonist with add-back treatment is as effective and tolerable as dienogest in preventing pain recurrence after laparoscopic surgery for endometriosis. Archives of Gynecology and Obstetrics. 2016; 294: 1257–1263.

[42] Adachi K, Takahashi K, Nakamura K, Otake A, Sasamoto N, Miyoshi Y, *et al*. Postoperative administration of dienogest for suppressing recurrence of disease and relieving pain in subjects with ovarian endometriomas. Gynecological Endocrinology. 2016; 32: 646–649.

[43] Chiu CC, Hsu TF, Jiang LY, Chan IS, Shih YC, Chang YH, *et al*. Maintenance Therapy for Preventing Endometrioma Recurrence after Endometriosis Resection Surgery - A Systematic Review and Network Meta-analysis. Journal of Minimally Invasive Gynecology. 2022; 29: 602–612.

[44] Barra F, Ferrero S. mTor Inhibitors for the Treatment of Endometriosis. Geburtshilfe Und Frauenheilkunde. 2018; 78: 283–284.

[45] Ponomarenko I, Reshetnikov E, Polonikov A, Verzilina I, Sorokina I, Elgaeva EE, *et al*. Candidate genes for age at menarche are associated with endometriosis. Reproductive Biomedicine Online. 2020; 41: 943–956.

[46] Adamson GD. Treatment of endometriosis-associated infertility. Seminars in Reproductive Endocrinology. 1997; 15: 263–271.

[47] Jiang D, Zhang X, Shi J, Tao D, Nie X. Risk factors for ovarian endometrioma recurrence following surgical excision: a systematic review and meta analysis. Archives of Gynecology and Obstetrics. 2021; 304: 589–598.

[48] Marquardt RM, Kim TH, Shin JH, Jeong JW. Progesterone and Estrogen Signaling in the Endometrium: What Goes Wrong in Endometriosis? International Journal of Molecular Sciences. 2019; 20: 3822.

[49] Lee DY, Kim HJ, Yoon BK, Choi D. Factors associated with the laterality of recurrent endometriomas after conservative surgery. Gynecological Endocrinology: the Official Journal of the International Society of Gynecological Endocrinology. 2013; 29: 978–981.