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How does chronic endometritis influence pregnancy outcomes in endometriosis associated infertility? A retrospective cohort study

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Abstract

Background Endometriosis (EMS) and chronic endometritis (CE) frequently coexist. This study aimed to examine the impact of CE on reproductive outcomes in patients with EMS.

Methods We enrolled 685 patients with endometriosis-associated infertility from January 2018 to December 2020. The patients were divided into CE (318) and non-CE (367) groups. A subset of 123 clinically pregnant women from the CE group and 369 from the non-CE group was selected for detailed comparison. Pregnancy and delivery data were meticulously collected from hospital records and through telephone interviews.

Results CE was diagnosed in 46.42% of EMS patients. Higher pregnancy rates were observed in patients with Endometriosis Fertility Index (EFI) scores of 7–10. EMS patients with CE had increased risks of placenta previa (13.01%), gestational hypertension (5.69%), and cesarean sections (59.34%).

Conclusions CE, which is prevalent among EMS patients, is linked to increased risks of pregnancy complications, including placenta previa, gestational hypertension, and cesarean delivery. Although combined hysteroscopy and laparoscopy improve pregnancy rates, they demand careful management of these complications.

Keywords Chronic endometritis, Endometriosis, Infertility, Reproductive outcomes, Laparoscopy

Introduction

Endometriosis (EMS) is characterized by the ectopic proliferation of endometrial tissue, comprising BOTH glands and stroma, extending beyond the confines of the uterine cavity's endometrial and myometrial layers [1]. This pathological condition leads to the development of lesions, resulting in local infiltration, recurrent hemorrhage, and the formation of nodules and masses. Moreover, EMS is one of the most prevalent gynecological disorders, significantly impairing the quality of life and fertility of patients worldwide. The peak incidence of EMS occurs between 24 and 29 years of age, with an incidence rate reaching up to 10%–15% of the general population [2, 3]. Additionally,

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EMS often causes patients to endure chronic pain, infertility, and pelvic masses, which can severely impact their personal and professional lives, leading to a continuous increase in medical costs and economic burdens for both the state and individuals [4]. In some cases, EMS has even been associated with bacterial infections [5].

Chronic endometritis (CE) and EMS share similar characteristics. CE is defined by persistent inflammation of the endometrium, characterized by the infiltration of plasma cells into the endometrial stroma [6]. Among infertile women, the incidence of CE can reach up to 56.8% [7], with repeated implantation failure rates ranging from 4.0 to 67.5% [8, 9], and recurrent abortion rates from 9.3 to 67.6% [10]. Patients with CE often exhibit no symptoms or only mild, non-specific signs, such as abnormal uterine bleeding and leucorrhea. Moreover, CE is notably prevalent among individuals with endometriosis-associated infertility (EAI) [11, 12]. The strikingly similar features of EMS and CE suggest a potential link between the two conditions. However, it remains unclear whether CE acts as a risk factor or an etiologic contributor to EAI. Previous studies have demonstrated a higher frequency of CE in patients with EMS compared to those without the condition [13–15], indicating a significant association between EMS and CE.

Currently, these disorders are associated with relatively high infertility rates, yet their precise contributions remain poorly defined. Both EMS and CE are known to contribute to infertility. EMS, in particular, is widely recognized for impairing fertility during a woman's reproductive years. Several factors contribute to this, including altered pelvic anatomy, extensive adhesions, hormonal imbalances, and inflammation. Additionally, CE may lead to infertility through mechanisms such as promoting intrauterine adhesions via endometrial fibrosis and mechanically interfering with sperm transport or embryo implantation. Consequently, these two disorders collectively diminish endometrial receptivity. However, the exact etiology remains unclear [16]. Over the past two decades, the use of minimally invasive surgery, including laparoscopy and hysteroscopy, has steadily increased. These techniques have proven especially beneficial for treating patients with EAI. However, when addressing the mechanisms that disrupt fertility in women with these disorders, it is crucial to consider the potential negative effects on maternal and neonatal health. The relationship between EMS and adverse pregnancy outcomes has garnered significant attention [17–24]. Nevertheless, comprehensive clinical data on pregnancy complications and perinatal outcomes in post-surgical patients with these disorders who subsequently conceive is still lacking.

This study aimed to investigate the correlation between endometriosis and chronic endometritis in infertile individuals and evaluate pregnancy outcomes following combined laparoscopy and hysteroscopy. Specifically, the primary objective was to develop a comprehensive treatment strategy for patients facing the dual challenges of EMS and CE.

Methods

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and relevant guidelines and regulations. Ethical approval was obtained from the Ethics Committee of Fujian Provincial Maternity and Child Health Hospital (grant number 2018-4133). As a retrospective study, it did not adversely affect the health of patients or involve personal identity information. The Ethics Committee waived the requirement for informed consent due to the use of anonymized data.

Patient consent and privacy protection

To ensure privacy, all data were anonymized before analysis, with patient identifiers removed and data coded to protect individual identities. Although informed consent was waived, patients were provided with general information about the study during follow-up visits, ensuring transparency and maintaining trust. Confidentiality was strictly maintained throughout the study, with data securely stored and access restricted to authorized research personnel only.

Participants and procedure

This study included women who underwent laparoscopy combined with hysteroscopy due to tubal infertility, infertility associated with EMS, or unexplained infertility. Infertility was defined as the inability to conceive after engaging in regular, unprotected intercourse for more than 1 year. From January 2018 to December 2020, 1574 infertile patients meeting the inclusion criteria were enrolled. The inclusion criteria were: (1) no hormone therapy within 3 months before surgery; (2) normal ovarian reserve function; (3) regular menstruation without abnormal vaginal bleeding; (4) normal semen parameters of the male partner; (5) an active intention to conceive naturally after surgery; and (6) participation in follow-up interviews over a 24-month period. Exclusion criteria included: (1) ovulation disorders, such as polycystic ovarian syndrome (PCOS); (2) uterine abnormalities, including uterine septum, uterine fibroid, and intrauterine adhesion; (3) acute pelvic inflammatory disease (PID), oligospermia, and asthenospermia; (4) other medical comorbidities, including thyroid disorders, diabetes, hypertension, hyperprolactinemia, and connective tissue diseases; and (5) antibiotic use within the past 4 weeks. Notably, none of the patients in this study required

assisted reproductive technologies, such as intrauterine insemination (IUI) or in vitro fertilization (IVF); all pregnancies were achieved through natural conception. This clarification underscores the study's exclusive focus on naturally conceived pregnancies, thus eliminating potential bias related to antenatal complications associated with IVF/ICSI.

All patients in this study underwent combined laparoscopy and hysteroscopy to address menorrhagia during their menstrual cycles. The laparoscopic procedure involved exploring the uterus, adnexa, and pelvic cavity. If pelvic adhesions were present, they were lysed before the removal of ovarian cysts. Additionally, pelvic ectopic foci were excised, and bilateral tubal patency tests were performed as needed. The hysteroscopic procedure included a detailed examination of anatomical structures such as the internal cervical os, cervical canal, uterine walls, uterine fundus, and bilateral fallopian tube ostia. Special attention was given to identifying endometrial congestion, interstitial edema, and the precise location for endometrial biopsy.

The histopathological detection of plasma cells in the endometrium is crucial for diagnosing CE, and identifying typical features under hysteroscopy is invaluable for diagnosis [25]. In this study, the diagnostic criteria included the presence of one or more CD138-positive and/or CD38-positive plasma cells in the endometrial stroma per 400× high-power field.

Chart reviews revealed that all patients diagnosed with CE received a single course of doxycycline (100 mg orally, twice daily for 14 days; Chinese Guangdong Huanan Pharmaceutical). Additionally, in cases of advanced EMS (stages 3 and 4), gonadotropin-releasing hormone agonists (GnRH-a, 3.75 mg triptorelin acetate; French IPSEN Pharmaceutical) were administered for 3 months, followed by active preparation for pregnancy after discontinuation. Outpatient and telephone follow-up assessments were conducted every 3 months for at least 24 months to monitor postoperative recovery and pregnancy outcomes. The follow-up period extended until the end of December 2022.

Statistical analysis

Data analysis was performed using SPSS 26.0 statistical software (IBM, Armonk, NY, USA). Normally distributed continuous variables are presented as mean ± standard deviation, and comparisons between the two groups were made using a t-test. Categorical data were expressed as percentages (%), and group comparisons were conducted using a chi-square test. When the chi-square test conditions were not met, the corrected chi-square test, Fisher's exact test, and rank-sum test were employed. Kaplan–Meier survival analysis was used to compare cumulative pregnancy rates between the CE and Non-CE groups over different time periods. All reported *p*-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 1842 infertility patients were included in the study. Of these, 889 cases without endometriosis were excluded. Among the cohort of 953 women experiencing infertility due to EMS, 237 individuals (24.87%) were excluded from the study due to various factors, including ovulation disorders (n = 33), uterine fibroids (n = 49), uterine abnormalities (n = 65), male factor infertility (n = 54), and other medical comorbidities (n = 36). Additionally, 22 patients (12.66%) were lost to follow-up, and nine individuals (2.53%) had postponed their conception plans during the 24-month observation period. Consequently, the final analysis included 685 cases of EAI (Fig. 1). Among these patients, 318 individuals (24.38%) were diagnosed with CE, while the remaining cases did not exhibit this condition. Adenomyosis was identified in 182 of the 685 patients—85 in the CE group and 97 in the non-CE group. The prevalence of adenomyosis did not differ significantly between the groups (P = 0.999), so it was not analyzed as an independent variable. The baseline characteristics of the CE and non-CE groups showed no significant differences (Table 1).

The prevalence of CE among patients with EAI was found to be 46.42% (318 out of 685). Among women with stage 1 to 4 EMS, the occurrence rates of CE were 47.25% (103 out of 218), 46.59% (82 out of 176), 44.87% (70 out of 156), and 46.67% (63 out of 135), respectively (Fig. 2). Specifically, the CE incidence rate was 46.95% (185 out of 394) in patients with stage 1 and 2 EMS, and 45.70% (133 out of 291) in patients with stage 3 to 4 EMS, with no statistically significant differences observed ($P = 0.513$). Additionally, the CE incidence rate was slightly lower in patients with peritoneal endometriosis (PEM) (42.80%, or 101 out of 236) compared to those with ovarian endometriosis (OEM) (48.58%, or 154 out of 317) and deep infiltrating endometriosis (DIE) (47.72%, or 63 out of 132), although the difference was not statistically significant ($P = 0.142$) (Fig. 3).

In the CE group, women with stage 1 to 4 EMS experienced cumulative pregnancy rates of 52 (50.49%), 40 (48.78%), 25 (35.71%), and 18 (28.57%), respectively. The cumulative pregnancy rate for patients with stage 1 and 2 EMS was significantly higher compared to patients with stage 3 and 4 EMS (49.73% [92/185] versus 32.33% [43/133]). Furthermore, the cumulative pregnancy rate and live birth rate at different time periods for the CE group were consistently lower than those for the non-CE

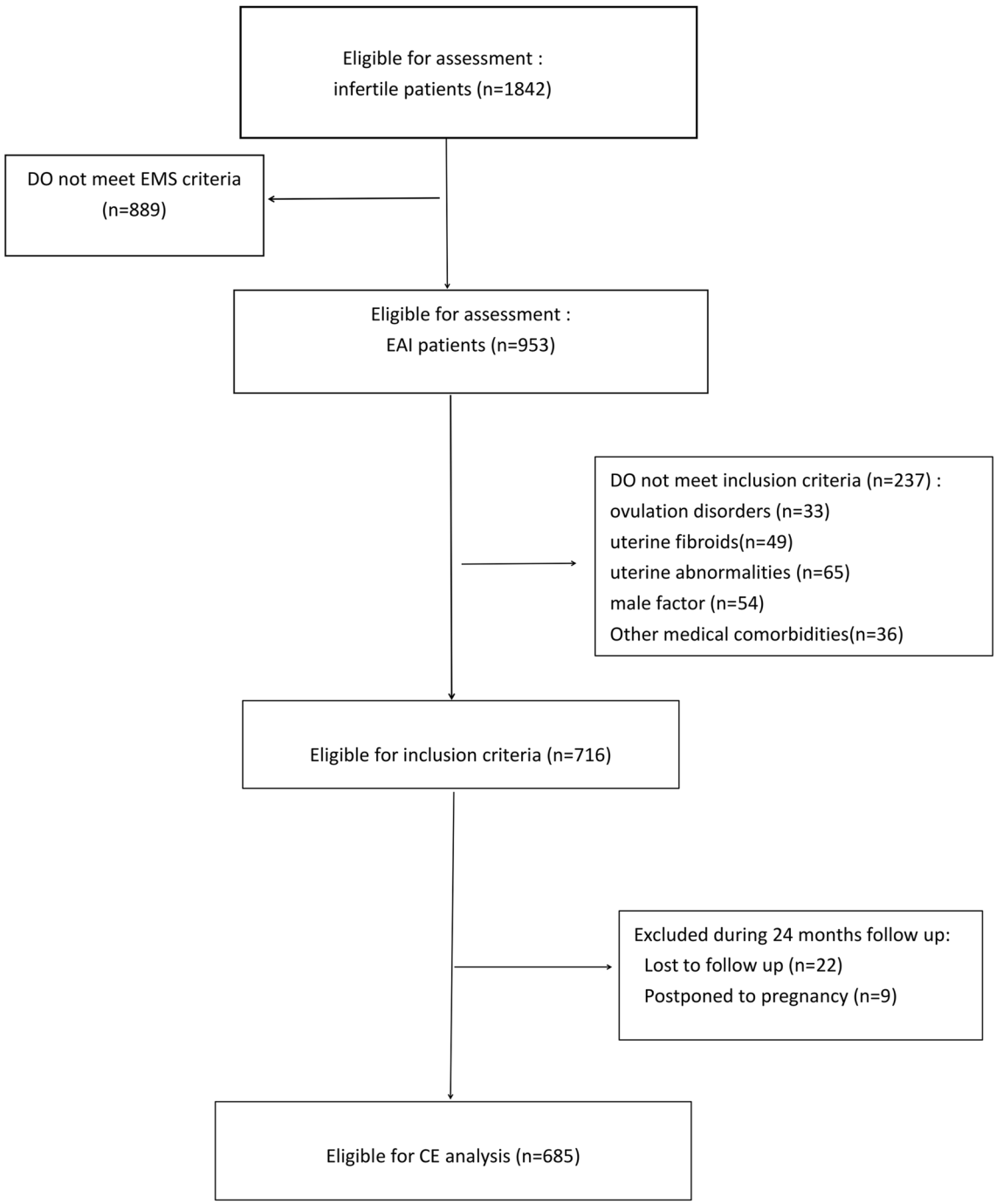

Fig. 1 Patients inclusion flow chart

group, although the differences were not statistically significant (Table 2).

Notably, postsurgical pregnancy outcomes of patients with PEM were slightly better compared to those with OEM or DIE, but the differences were not statistically significant ($P=0.823$). Groups with EFI scores of 7 to 8 and 9 to 10 exhibited significantly higher cumulative clinical pregnancy rates compared to groups with EFI scores below 7. However, no significant differences were found between the 7–8 and 9–10 subgroups ($P=0.729$). Additionally, no significant differences ($P=0.138$) were observed among the three subgroups (i.e., 5–6, 3–4,

Table 1 Baseline characteristics of women with and without endometriosis

Variables	Endometriosis (N = 685)		*P* value
	CE (N = 318)	Non-CE (N = 367)	
Mean age (years)	28.1 ± 4.7	27.6 ± 4.9	0.398
BMI (kg/m^2)	20.5 ± 3.4	21.2 ± 2.6	0.175
Gravidity	1.92 ± 1.61	2.01 ± 1.23	0.235
Parity	1.73 ± 1.05	1.62 ± 1.32	0.374
Menarche age (years)	12.1 ± 2.3	12.7 ± 1.9	0.856
Menstrual cycle length (days)	27.6 ± 2.7	28.3 ± 2.5	0.673
Menstrual duration (days)	6.4 ± 1.5	6.1 ± 1.7	0.147
Infertility duration (years)	2.9 ± 1.3	3.1 ± 1.5	0.536
Primary infertility (n, %)	113 (55.39%)	142 (57.49%)	0.176
Secondary infertility (n, %)	91 (44.61%)	105 (42.51%)	0.287
Preoperative serum CA125 level (U/mL)	45.1 ± 6.5	51.2 ± 8.1	0.864
r-AFS total score	55.8 ± 16.3	61.1 ± 13.6	0.951
EFI score	7.98 ± 1.15	8.18 ± 0.93	0.188

The probability of all values was above 0.05

BMI body mass index, *r-AFS* Revised American Fertility Society, *EFI* Endometriosis Fertility Index

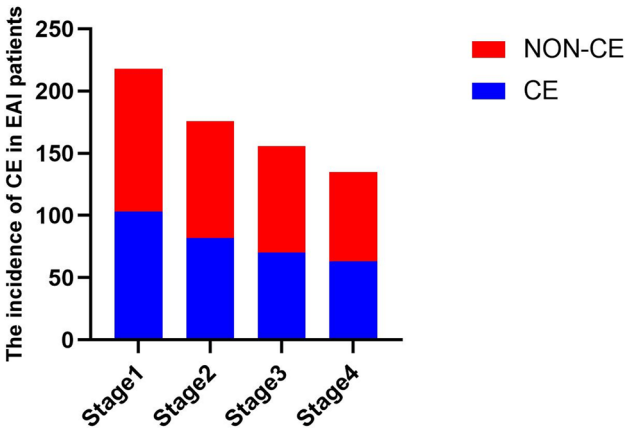

Fig. 2 The incidence rate of CE in patients with different stages of EAI. *CE* chronic endometritis, *EAI* endometriosis associated infertility

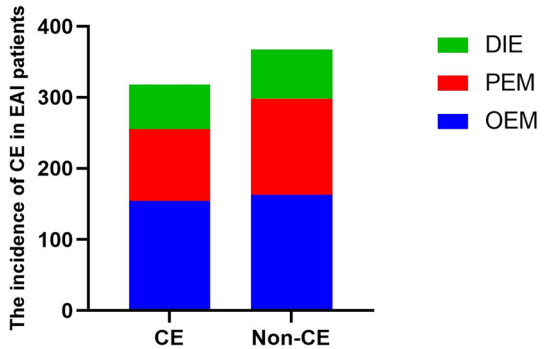

Fig. 3 The incidence rate of CE in patients with different types of EAI. *PEM* peritoneal endometriosis, *OEM* ovarian endometriosis, *DIE* deep infiltrating endometriosis

and 0–2) in relation to adverse pregnancy outcomes (Table 3).

Table 4 presents the main findings regarding the association between EMS and adverse pregnancy outcomes. In comparison to women experiencing a typical pregnancy, the study group exhibited an elevated likelihood of developing placenta previa, preeclampsia, and requiring cesarean delivery. Additionally, no significant association were found between postpartum hemorrhaging, premature rupture of fetal membranes, infants with low birth weights, stillbirths, perinatal mortality, or fetal distress (Table 4).

In addition to the original comparison, we conducted an additional analysis comparing pregnancy outcomes between women with both endometriosis and chronic endometritis to those with endometriosis alone. This comparison was aimed at isolating the specific impact of chronic endometritis on pregnancy outcomes. There was no significant difference in maternal-infant outcomes between patients with endometriosis alone and those with endometriosis combined with CE, as shown in Table 5.

Discussion

Both EMS and CE are prevalent gynecological conditions. CE, characterized by chronic inflammation of the endometrium due to pathogenic microorganisms, is a common cause of female infertility [14]. Evidence supports this claim; for instance, the prevalence of CE among the general female population is approximately 10% to 11%. However, this prevalence can vary significantly, reaching up to 72% in patients with chronic PID. Among

Table 2 Comparison of the pregnancy status between CE and non-CE groups in women suffering from endometriosis

Period (months)	Cumulative pregnancy rate (n, %)			Live birth rate (%)			Miscarriage rate (n, %)		
	CE	Non-CE	*P* value	CE	Non-CE	*P* value	CE	Non-CE	*P* value
3	1.26% (4/318)	1.09% (4/367)	0.838	1.26% (4/318)	1.09% (4/367)	0.838	0% (0/318)	0% (0/367)	–
6	9.75% (31/318)	10.08% (37/367)	0.614	9.12% (29/318)	9.81% (36/367)	0.807	0.63% (2/318)	0.27% (1/367)	0.481
9	21.07% (67/318)	18.80% (69/367)	0.723	21.07% (62/318)	19.98% (66/367)	0.538	1.57% (5/318)	0.82% (3/367)	0.359
12	29.25% (93/318)	31.33% (115/367)	0.553	29.25% (87/318)	31.33% (109/367)	0.499	1.89% (6/318)	1.63% (6/367)	0.802
15	36.48% (116/318)	38.96% (143/367)	0.503	36.48% (108/318)	38.96% (133/367)	0.534	2.52% (8/318)	2.72% (10/367)	0.865
18	38.05% (121/318)	42.51% (156/367)	0.236	38.05% (111/318)	42.51% (144/367)	0.242	3.14% (10/318)	3.27% (12/367)	0.926
21	41.82% (133/318)	46.59% (171/367)	0.210	41.82% (121/318)	46.59% (156/367)	0.236	3.77% (12/318)	4.09% (15/367)	0.833
24	42.45% (135/318)	48.50% (178/367)	0.113	42.45% (123/318)	48.50% (163/367)	0.129	3.77% (12/318)	4.09% (15/367)	0.833

The probability of all values was above 0.05

CE chronic endometritis

Table 3 Gestational comparison among patients with endometriosis and chronic endometritis (CE) by stages, types, and endometriosis fertility index (EFI) scores

Items	No. of cases	Cumulative pregnancy (n, %)	Miscarriage rate (n, %)
Endometriosis types	318	135 (42.45%)	12 (3.37%)
OEM	124 (38.99%)	52 (41.93%)	5 (4.03%)
PEM	131 (41.19%)	58 (44.27%)	5 (3.81%)
DIE	63 (19.81%)	25 (39.68%)	2 (3.17%)
P value		0.823	0.958
Endometriosis stages			
Stage 1	103 (32.39%)	52 (50.49%)	2 (1.94%)
Stage 2	82 (25.79%)	40 (48.78%)	3 (3.66%)
Stage 3	70 (22.01%)	25 (35.71%)	4 (5.71%)
Stage 4	63 (19.81%)	18 (28.57%)	3 (4.76%)
P value		0.016	0.604
EFI			
9–10	37	28 (75.68%)[a]	2 (5.41%)
7–8	144	73 (50.69%)[a]	5 (3.47%)
5–6	95	28 (29.47%)	3 (3.16%)
3–4	33	5 (15.15%)	2 (6.06%)
0–2	9	1 (11.11%)	0 (0.00%)
P value		< 0.001	0.872

Data are shown as *n* (%) unless stated otherwise

EFI endometriosis fertility index, *PEM* peritoneal endometriosis, *OEM* ovarian endometriosis, *DIE* deep infiltrating endometriosis

The probability of most values was above 0.05. [a]The probability was below 0.05

infertile women, the incidence rate of CE ranges from 2.8 to 60%, potentially due to the absence of standardized diagnostic criteria [13]. Pathogenic infections in the endometrium disrupt the equilibrium of local immune cells, resulting in the imbalanced expression of inflammatory factors, immune regulatory factors, chemokines, and other relevant components. Consequently, this imbalance diminishes endometrial receptivity and impedes embryo implantation, ultimately leading to infertility [26, 27].

Research has found that the prevalence of CE in patients receiving EMS treatment is 3.7 times higher compared to the control group. Additionally, the occurrence of EMS in CE patients is significantly higher compared to non-CE patients [15], indicating that EMS serves as an independent risk factor for CE development. This study's findings demonstrate that the prevalence of CE in patients with EAI is 46.42% (318 out of 685), aligning with the results reported by Takebayashi et al. [28]. However, our study uniquely highlights the compounded risks of pregnancy complications in EMS patients with CE. While previous research primarily focused on implantation and early pregnancy outcomes, our study extends these findings to later stages of pregnancy, emphasizing the need for comprehensive prenatal care in this patient population. Although adenomyosis was identified in both groups (85 cases in the CE group and 97 cases in the non-CE group), the prevalence did not differ significantly ($P = 0.999$). Therefore, it was not included as an independent variable in the analysis, and it did not affect the study's primary outcomes.

This extension is critical as it provides a more complete understanding of the impact of CE on pregnancy outcomes. Pelvic peritoneal inflammation can occur following the development of EMS lesions, subsequently spreading to the endometrium via the fallopian tubes. This process leads to aseptic inflammation in the endometrium and triggers the infiltration of plasma cells in the interstitial region [28]. Furthermore, research has demonstrated a notable increase in the microbial community within the endometrium of EMS patients compared to non-EMS patients [29]. Consequently, microbial infection may also contribute to the occurrence of CE

Table 4 Association between endometriosis with CE and maternal-infant outcomes

Variables	EMS and CE (n = 123)	Control (n = 369)	RR (95% CI)	*P* value
Maternal outcomes				
Placenta abruption	9 (7.32%)	29 (7.85%)	0.92 (0.71, 1.28)	0.845
Placental previa	16 (13.01%)	15 (4.07%)	3.53 (1.69, 7.37)	< 0.001[a]
HDP	7 (5.69%)	8 (2.17%)	2.72 (0.97, 7.67	0.049[a]
Small for gestational age	7 (5.69%)	15 (4.07%)	1.42 (0.57, 3.58)	0.450
PPRM	19 (15.45%)	61 (16.53%)	0.92 (0.53, 1.62)	0.778
Cesarean delivery	73 (59.34%)	132 (35.77%)	2.62 (1.73, 3.98)	< 0.001[a]
PPH	12 (9.76%)	20 (5.42%)	1.89 (0.89, 3.98)	0.091
Infant outcomes				
Preterm birth	13 (10.57%)	38 (10.30%)	1.03 (0.53, 2.00)	0.932
Perinatal asphyxia	3 (2.44%)	11 (2.98%)	0.81 (0.22, 2.97)	0.754
Perinatal death	0 (0%)	0 (0%)	–	–
Low birth weight	9 (7.32%)	22 (5.96%)	1.25 (0.56, 2.78)	0.592
NICU admission	3 (2.44%)	8 (2.17%)	1.13 (0.30, 4.32)	0.860

Data are shown as n (%) unless stated otherwise

CI confidence interval, *HDP* hypertensive disorders in pregnancy, *PPRM* preterm premature rupture of membranes, *PPH* postpartum hemorrhage, *NICU* neonatal intensive care unit, *RR* relative risk

The probability of most values was above 0.05. [a]The probability was below 0.05

Table 5 Maternal and infant outcomes: endometriosis with vs. without chronic endometritis

Variables	EMS and CE (n = 123)	EMS alone (n = 147)	RR (95% CI)	*P* value
Maternal outcomes				
Placenta abruption	9 (7.32%)	8 (5.44%)	1.35 (0.54, 3.38)	0.704
Placental previa	16 (13.01%)	17 (11.56%)	1.13 (0.59, 2.13)	0.862
HDP	7 (5.69%)	7 (4.76%)	1.20 (0.43, 3.31)	0.946
Small for gestational age	7 (5.69%)	6 (4.08%)	1.39 (0.57, 3.58)	0.741
PPRM	19 (15.45%)	17 (14.28%)	0.92 (0.53, 1.62)	0.450
Cesarean delivery	73 (59.34%)	74 (50.34%)	1.18 (0.95, 1.46)	0.175
PPH	12 (9.76%)	11 (7.48%)	1.30 (0.60, 2.85)	0.655
Infant outcomes				
Preterm birth	13 (10.57%)	11 (7.48%)	1.41 (0.66, 3.04)	0.501
Perinatal asphyxia	3 (2.44%)	2 (1.36%)	1.79 (0.30, 10.56)	0.840
Perinatal death	0 (0%)	0 (0%)	–	–
Low birth weight	9 (7.32%)	7 (4.76%)	1.54 (0.59, 4.01)	0.531
NICU admission	3 (2.44%)	8 (2.72%)	0.45 (0.12, 1.65)	0.350

Data are shown as n (%) unless stated otherwise

CI confidence interval, HDP hypertensive disorders in pregnancy, *PPRM* preterm premature rupture of membranes, *PPH* postpartum hemorrhaging, *NICU* neonatal intensive care unit, *RR* relative risk

in EMS patients [30]. However, the precise etiology and associated mechanisms of these conditions remain largely unknown, necessitating further investigation.

Research indicates that the pathogenesis of various EMS types may differ [31]. However, there is limited data available in the literature on the impact of r-AFS staging of EMS on the occurrence of CE. Takebayashi et al. [28] observed that the incidence of CE in EMS patients at stages 1 to 4 was 40.0%, 50.0%, 70.0%, and 46.7%, respectively. However, these differences did not reach statistical significance. Furthermore, no significant variation in CE incidence rates was observed across different clinicopathological types. In this study, the prevalence of CE in patients with EAI was 46.42% (318 out of 685). Among women with stage 1 to 4 EMS, the CE occurrence rates were 47.25% (103 out of 218), 46.59% (82 out of

176), 44.87% (70 out of 156), and 46.67% (63 out of 135), respectively.

Specifically, the CE incidence rate was 46.95% (185 out of 394) in patients with stage 1 to 4 EMS and 45.70% (133 out of 291) in those with stage 3 and 4 EMS, with no statistically significant differences ($P=0.513$). Additionally, the CE incidence rate was slightly lower in patients with PEM (42.80%, or 101 out of 236) compared to those with ovarian EMS (48.58%, or 154 out of 317) and DIE (47.72%, or 63 out of 132), although these differences were not statistically significant ($P=0.142$). These findings suggest that the presence of CE in EMS patients may not be associated with a specific clinicopathological type.

Due to its minimally invasive nature, laparoscopy is the preferred method for diagnosing and treating EAI. This procedure allows for the removal of lesions, restoration of pelvic anatomy, and assessment of r-AFS staging and EFI scoring, which can guide post-surgical pregnancy outcomes and improve the likelihood of conception. Additionally, hysteroscopy can be used to identify endometrial hyperemia, endometrial micropolyps (< 1 mm), and interstitial edema, providing valuable diagnostic information for CE [32, 33]. However, the sensitivity and specificity of hysteroscopy in accurately diagnosing CE remain uncertain, making it insufficient as a standalone diagnostic tool. Combining hysteroscopy with pathological examination is recommended, as this approach serves as the preferred method for diagnosing CE and enhancing diagnostic accuracy.

This study's findings revealed a cumulative postoperative pregnancy count of 135 in patients with EAI and CE, resulting in a cumulative pregnancy rate of 42.45%. These results are consistent with findings in the literature [8, 21]. Women with stage 1 to 4 EMS in the CE group had cumulative pregnancy rates of 52 (50.49%), 40 (48.78%), 25 (35.71%), and 18 (28.57%), respectively. Notably, the pregnancy rates in our study were higher than those reported in previous studies, particularly for stage 4 endometriosis, where rates typically hover around 20%. This discrepancy may be attributed to several factors: first, our study population was carefully selected, excluding patients with significant comorbidities and focusing on those intending to conceive naturally post-surgery. Second, the comprehensive post-surgical management and follow-up protocols implemented in our study likely contributed to the enhanced fertility outcomes observed. The cumulative pregnancy rate of patients with stage 1 and 2 EMS was significantly higher than that of patients with stage 3 and 4 EMS (49.73% [92/185] versus 32.33% [43/133]), indicating that the pregnancy rates of patients with mild to moderate EAI and CE are superior to those of patients with moderate to severe EAI and CE. The cumulative pregnancy rate and live birth rate in the CE group were consistently lower compared to the non-CE group at various time periods, with these differences being statistically significant ($P<0.05$). Conversely, no statistically significant differences were observed in the postoperative pregnancy status among patients with combined EAI and CE across different clinicopathological types. This suggests a significant increase in the postoperative pregnancy rate of patients with combined EAI and CE irrespective of the clinicopathological type, warranting further prospective studies.

Microbial pathogen infection is the primary cause of CE, with *Streptococcus*, *Escherichia coli* (*E. coli*), *Proteus*, *Mycoplasma genitalium* (*M. genitalium*), and *Chlamydia* being the most common pathogens [8]. Antibiotics are the cornerstone of CE treatment, effectively eliminating plasma cells that infiltrate the interstitium. After treatment, hysteroscopic-based endometrial biopsy has shown a plasma cell clearance rate ranging from 70 to 96% [9]. The most commonly used therapeutic regimen is doxycycline (200 mg/day) administered for 14 days. In cases of doxycycline resistance, a combination of ciprofloxacin (800 mg/day) and metronidazole (1000 mg/day) for 14 days may also be considered. Most antibiotic treatments are effective after one to two courses; however, patients should undergo a hysteroscopic review and repeat endometrial biopsy to confirm efficacy. In a prospective, double-blind cohort study by Song et al., 120 patients with CE were randomly assigned to either an antibiotic treatment group (60 cases) or a control group (60 cases). The treatment group received oral antibiotics for 14 days, followed by a repeat endometrial biopsy after 4 to 8 weeks. The endometrial conversion rate was 89.8% in the treatment group, compared to only 12.3% in the control group. Based on these findings, a 14-day course of broad-spectrum oral antibiotics is recommended to significantly improve chronic endometrial inflammation [34]. The study also found that the cumulative endometrial conversion rate among patients with CE who received antibiotic treatment was 81.3%, significantly higher than the 6% observed in the untreated group [35]. Our study's results further demonstrate the effectiveness of antibiotic therapy, as evidenced by the similar cumulative pregnancy rates observed in patients with CE after antibiotic treatment compared to those without the condition. Thus, appropriate post-surgery antibiotic treatment can enhance the reproductive prognosis of patients with EAI and CE. Moreover, this investigation revealed that women with elevated EFI scores exhibited superior fertility outcomes, particularly those with EFI scores ranging from 5 to 10, resulting in significantly higher pregnancy rates. This suggests that a higher EFI score correlates with a greater cumulative pregnancy rate, supporting the efficacy of the EFI scoring system in

accurately predicting spontaneous pregnancy in patients with EAI following surgical intervention. These findings align with previous studies [36–43]. The prognostic value of the EFI score in predicting pregnancy outcomes underscores its utility in clinical practice. Clinicians should consider incorporating EFI scores in the management of EMS patients to better predict and improve pregnancy outcomes. However, further research is needed to confirm these observations.

Combined laparoscopy and hysteroscopy were conducted to address EMS lesions impacting pregnancy and fertility, restore pelvic anatomy, and enhance the pelvic microenvironment. Following successful treatment, uterine inflammation can be effectively repaired. Consequently, women who conceive after this intervention should experience comparable pregnancy outcomes to those without a surgical history, thereby eliminating the need to consider delivery modes as a determinant. Nevertheless, there is a scarcity of studies on postoperative pregnancy complications and outcomes in patients with both EAI and CE.

This study's findings indicated that pregnant women who underwent combined laparoscopy and hysteroscopy had higher occurrences of placenta previa, hypertensive disorders of pregnancy (HDPs), and cesarean delivery compared to the control group, which aligns to some extent with results from previous studies [44–46]. The synergistic effect of EMS and CE on the uterine environment may exacerbate inflammatory responses, leading to increased rates of pregnancy complications. This interaction warrants further investigation to elucidate the underlying mechanisms. The presence of CE likely intensifies the inflammatory milieu in the endometrium, which is already compromised in EMS patients. Chronic inflammation can disrupt endometrial receptivity, impair placental development, and elevate the risk of hypertensive disorders. Additionally, immune dysregulation associated with both EMS and CE can contribute to adverse pregnancy outcomes, necessitating targeted therapeutic interventions to modulate inflammatory pathways. For instance, persistent inflammation in CE may lead to increased expression of inflammatory cytokines and immune cells, further impairing endometrial receptivity and placental development. Understanding these mechanisms could help in developing targeted therapies to improve pregnancy outcomes in EMS patients with CE.

Furthermore, the incidence of full-term infants with low birth weights, perinatal asphyxia, stillbirth, and perinatal death in the combined surgery group was slightly lower than in the non-surgical group, while the incidence of premature birth was slightly higher, though these differences were not statistically significant. However, the cesarean section rate in the treatment group was significantly higher compared to the control group. This increase in cesarean section rates can be attributed to factors such as a prolonged history of infertility and the perceived higher value of the fetus. Additionally, concerns among obstetricians regarding potential labor-related accidents have led to a relaxation of cesarean section indications during trial labor, ultimately resulting in higher cesarean section rates influenced by societal factors. Therefore, it is important to consider enhancing pregnancy management for women who have undergone combined laparoscopy and hysteroscopy, with close monitoring of the post-delivery labor process. To prioritize the safety of both mother and child, it is inadvisable to consider cesarean section as a standard delivery method in the absence of specific circumstances. Given the compounded risks, clinicians must adopt a holistic management approach that addresses both EMS and CE, potentially involving specialists from obstetrics, gynecology, and immunology.

This study offers several notable strengths. First, the case data were obtained from a reputable medical center, and all surgical procedures were consistently performed by the same group of doctors, enhancing the reliability of the data and the clarity of diagnoses, effectively mitigating potential selection bias. Second, all women with EMS and CE underwent both surgical and pathological examinations to confirm their conditions, significantly reducing the risk of misclassification. Third, comprehensive clinical data on the stage, type, and EFI of EMS were readily accessible for thorough analysis. Fourth, the follow-up duration was sufficient, with a lost-to-follow-up rate of less than 5%. Finally, we implemented various strategies to mitigate potential confounding variables, including verification of data accuracy and reliability by two qualified experts. However, it is important to acknowledge that this study was observational in nature, and despite efforts to control for confounding factors, residual confounding variables may still exist. Furthermore, the sample size in this study was relatively limited. Considering these limitations, future research will involve comprehensive multi-center investigations with larger sample sizes and prospective cohort studies.

In summary, our findings substantiate the hypothesis that individuals with EMS exhibit a heightened prevalence of CE. However, further investigation into the underlying mechanisms is imperative. Additionally, our study demonstrates that the combined utilization of hysteroscopy and laparoscopy as a surgical procedure is highly efficacious for augmenting pregnancy rates. While both endometriosis alone and endometriosis combined with CE are associated with an increased risk of placenta previa, the presence of CE may further elevate the risks, particularly for gestational hypertension and cesarean

delivery. Furthermore, to minimize the risk of cesarean delivery and prevent delivery-related complications, it is imperative to implement a more stringent monitoring system for these patients.

Abbreviations

EMS	Endometriosis
CE	Chronic endometritis
EAI	Endometriosis associated infertility
GnRH-a	Gonadotropin releasing agonists
BMI	Body mass index
r-AFS	Revised American Fertility Society
EFI	Endometriosis fertility index
HDP	Hypertensive disorders in pregnancy
PPRM	Preterm premature rupture of membranes
PPH	Postpartum hemorrhage
NICU	Neonatal intensive care unit
RR	Relative risk

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Author contributions
Shunhe Lin and Yuyan Guo contributed to designing the study and jointly revised the manuscript. Shunhe Lin, Chaobin Liu, Yishan Chen and Zhenna Wang collected the data and wrote the manuscript. Yuyan Guo, Jinna Zhang, Guan Lin, Yi Wang and Xi Xie contributed to data collection and data analyzing. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. The study was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital (grant number 2018-4133), College of Clinical Medical for Obstetrics & Gynecology and Pediatrics, Fujian Medical University. As this study is a retrospective study, it will not adversely affect the health of patients, nor will it involve the privacy and personal identity information of patients. The Ethics Committee of Fujian Maternity and Child Health Hospital has waived the requirement of informed consent of patients.

Consent for publication
All data were anonymized, therefore individual consent for publication was not required.

Competing interests
The authors declare no competing interests.

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