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ARTICLE

Reproductive History and Clinical Symptom-Related Risk Factors for Chronic Endometritis in Infertile Women: A Retrospective Case-Control Study

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Abstract

Aims/Background The diagnosis of chronic endometritis (CE) in infertile women without demonstrable intrauterine abnormalities remains a significant clinical challenge. The primary aim of this study was to identify the independent risk factors for CE regarding reproductive history and clinical symptoms in infertile women, providing evidence-based guidance for targeted CE screening in this population.

Methods In this retrospective case-control study, a total of 180 infertile female patients undergoing hysteroscopy between October 2022 and July 2024, who fulfilled the enrollment criteria, were included. The participants were divided into two groups: non-chronic endometritis (NCE) group (n = 78) and CE group (n = 102). CE was diagnosed based on the syndecan-1 (CD138) immunohistochemical staining results. To evaluate the association of CE with reproductive history and clinical symptoms, both univariate and multivariate logistic regression analyses were conducted.

Results The prevalence of CE in this study was 56.67% (102/180). Univariate logistic regression analysis revealed statistically significant differences in gravidity, parity, abortion history, and prolonged menstruation between the two groups ($p < 0.05$), indicating their correlations with CE. Further multivariate analysis identified abortion history (odds ratio [OR] = 2.521, 95% confidence interval [CI]: 1.307–4.864, $p = 0.006$) and prolonged menstruation (OR = 3.624, 95% CI: 1.141–11.513, $p = 0.029$) as independent risk factors for CE, while gravidity and parity showed no significant associations after adjustment.

Conclusion Abortion history and prolonged menstruation are independent risk factors for CE. For infertile women presenting with a history of abortion or prolonged menstruation but without apparent intrauterine abnormalities, hysteroscopy combined with CD138 immunohistochemical staining is recommended to facilitate early diagnosis and prompt therapeutic intervention for CE.

Key words: infertility; endometritis; abortion history; menstruation disturbances; risk factors

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Introduction

Chronic endometritis (CE) is characterized by chronic inflammation of the endometrium, distinguished by the abnormal presence of plasma cells in the endometrial stroma consequent to microbial infections (Klimaszyk et al., 2023; Park et al., 2016). Most women diagnosed with CE typically exhibit no prominent clinical signs or present with only mild symptoms such as abdominal discomfort, abnormal uterine bleeding, abnormal leukorrhea, and menstrual disorders (Kitaya et al.,

2016; Yasuo and Kitaya, 2022). Given their rarity or clinical inconspicuity, these signs and symptoms are frequently overlooked by clinicians and even patients themselves. However, over the past few years, a growing body of evidence has verified the association of CE with reproductive conditions such as infertility, recurrent miscarriage, repeated implantation failure, intrauterine adhesions, endometrial polyps, and premature birth (Chen et al., 2017; Hosseini et al., 2024; Kannar et al., 2012; Kimura et al., 2019; Lin et al., 2024). The prevalence of CE varies widely across different patient populations, reported as 2.8–56.8% in infertile women, 14–67.5% in women with recurrent implantation failure (RIF), and 9.3–67.6% in those experiencing recurrent pregnancy loss (RPL) (Kimura et al., 2019). Compared with women of reproductive age without CE, those with CE face a 60% increased risk of developing infertility later in life (Kitaya et al., 2016). Moreover, compared with patients who have received treatment for CE, untreated patients exhibit lower natural conception, embryo transfer success, and live birth rates (Szafarowska et al., 2025; Yasuo and Kitaya, 2022). The development of CE is pathogenically driven by the imbalance of the immune microenvironment triggered by microbial infections in the uterine cavity, which activates the local inflammatory response, leading to impaired endometrial receptivity and ultimately causing adverse pregnancy outcomes (Kuroda et al., 2020; You et al., 2025). Despite its significant impact on reproductive outcomes, the identification of women who are vulnerable to CE poses a substantial challenge. Therefore, having a high awareness of CE and avoiding its missed diagnosis remains crucial in the clinical treatment of infertility.

The gold-standard strategy for diagnosing CE is the identification of plasma cells infiltrating into the endometrial stroma. However, identifying plasma cells via hematoxylin-eosin (HE) staining is not feasible (Břečka et al., 2024). Given the specificity of syndecan-1 (CD138) in plasma cells (Dang et al., 2024), CD138 immunohistochemical staining emerges as the most extensively used approach to clinically diagnosing CE (Singh and Sethi, 2022). Regardless of the staining methods used, hysteroscopy is required to obtain samples of endometrial tissue. However, the invasiveness and high cost of this tissue collection technique limit its feasibility as a routine screening method, especially for infertile women without intrauterine abnormalities.

Mounting evidence has identified intrauterine abnormalities—such as endometrial polyps, intrauterine adhesions, and submucosal myomas—as risk factors for CE (Hosseini et al., 2024; Kuroda et al., 2022). In clinical practice, CE is typically detected during surgery in infertile women with these intrauterine abnormalities. However, for infertile women without intrauterine abnormalities, the diagnosis of CE is often delayed because there are no indications for hysteroscopy. Several studies have pinpointed the possible associations of factors related to reproductive history and clinical symptoms, such as gravidity, parity, abortion history, and abnormal uterine bleeding, with CE (Chen et al., 2016; Kitaya et al., 2016; Song et al., 2018; Xie et al., 2024). However, this aspect has rarely been investigated, leaving much of the conclusions controversial.

Considering the current state of the knowledge gap, this study aimed to conduct a retrospective case-control study to identify independent risk factors for CE in infertile women based on their reproductive history and clinical symptoms.

Methods

Study Design

In this retrospective study, infertile patients who underwent hysteroscopy and endometrial biopsy at the Department of Reproductive Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University, between October 2022 and July 2024, were enrolled due to infertility alone or infertility combined with endometrial polyps, intrauterine adhesions, abnormal uterine bleeding, and other related conditions. Inclusion criteria for this study include: (1) diagnosis of infertility, which is defined as pregnancy failure by fertile-aged couples engaging in normal sexual activity without contraception for at least one year; (2) no surgical contraindications (e.g., acute genital tract infection, severe uncontrolled systemic diseases such as thyroid disorders, diabetes, hypertension, liver or kidney function impairment, and immune system diseases); and (3) availability of clinical treatment data. Individuals fulfilling the following criteria were excluded: (1) the use of antibiotics or hormonal medications (e.g., oral contraceptives, gonadotropins) within three months prior to hysteroscopy; (2) a history of intrauterine-related surgery within three months prior to hysteroscopy; and (3) endometrial pathology indicating non-benign lesions. CD138 staining of endometrial specimens was used for facilitating CE diagnosis. Patients were categorized into two groups: the chronic endometritis group (CE group) and the non-chronic endometritis group (NCE group), according to the histopathological results. The baseline data of patients (such as age, body mass index [BMI], duration of infertility, and reasons for hysteroscopy), reproductive history (such as gravidity, parity, abortion history, history of ectopic pregnancy, history of biochemical pregnancy), and clinical symptoms (prolonged menstruation, intermenstrual bleeding, dysmenorrhea, menstrual disorders) were collected. Biochemical pregnancy was defined as a pregnancy confirmed only by positive detection of serum beta-human chorionic gonadotropin (β-hCG) without ultrasound evidence of a gestational sac. Ectopic pregnancy was defined as a pregnancy implanted outside the uterine cavity. Prolonged menstruation was defined as a typical menstrual period lasting more than 7 days.

Hysteroscopy and CD138 Immunohistochemical Staining

Hysteroscopy was conducted in all patients 2 to 7 days post-menstruation. For patients without intrauterine abnormalities, only a small amount of endometrial tissue was obtained by curettage, while for those with intrauterine abnormalities, surgical treatment was performed. The endometrial specimens were immediately fixed in 10% formalin solution postoperatively and then sent to the pathology department for routine pathological examination and CD138 staining. CD138 antibody reagent (catalog number: ZA-0584, ZSGB-BIO, Beijing, China) was used for CD138 staining, and all steps were carried out in strict accordance with the in-

struction manual. The stained sections were observed under an optical microscope (BX-43, OLYMPUS, Japan). Brown-yellow staining of target cells in the tissue section was considered indicative of positive plasma cell staining. CE was defined by $\geq$1 CD138-positive plasma cell per 10 high-power fields (HPFs). All specimens were independently reviewed by two pathologists who were blinded to patient's clinical history or symptoms. When there was a significant discrepancy, a third, more senior pathologist would be consulted to make the final decision.

Statistical Analyses

Data analysis was performed using SPSS 27.0 software (IBM Corp., Armonk, NY, USA). In the analysis of baseline data, the normality of continuous data was evaluated using the Kolmogorov–Smirnov test. An independent samples *t*-test was conducted to compare the normally distributed continuous data (including age, BMI), which are presented as mean ± standard deviation (SD). The Mann–Whitney U test was employed for between-group comparisons of non-normally distributed data (such as infertility duration), which are presented as median (interquartile range). Data of categorical variables, such as reasons for hysteroscopy, were analyzed using the chi-square test, and the data are expressed as frequencies and percentages. Univariate logistic regression was used to analyze the possible risk factors for CE. Variables achieving $p < 0.2$ in the univariate analysis were entered into the multivariate logistic regression (forward selection, likelihood ratio test) for variable screening. This relatively lenient inclusion criterion was chosen to minimize the omission of potential confounding variables. Multicollinearity among the candidate independent variables was first assessed using the variance inflation factor (VIF) before multivariate logistic regression analysis. A VIF value of less than 10 was indicative of the absence of severe multicollinearity. Both the odds ratio (OR) and 95% confidence interval (CI) were computed, with a p-value < 0.05 deemed statistically significant.

Results

In this study, a total of 180 infertile patients who met the enrollment criteria were included (Fig. 1). Based on the CD138 staining results, these patients were categorized into two groups: the NCE group ($n = 78$) and the CE group ($n = 102$). The prevalence of CE was 56.67% (102/180). There were no meaningful differences in baseline characteristics such as age, infertility duration, BMI, and reasons for hysteroscopy between NCE and CE groups (all $p > 0.05$) (Table 1).

Univariate regression was utilized to identify potential risk factors of CE related to reproductive history and clinical symptoms. The results showed that gravidity ($p = 0.033$), parity ($p = 0.026$), abortion history ($p = 0.007$), and prolonged menstruation ($p = 0.033$) were associated with CE. However, no statistically significant differences in biochemical pregnancy history, ectopic pregnancy history, dysmenorrhea, intermenstrual bleeding, and menstrual cycle characteristics existed between the two groups (Table 2).

Four variables showing statistical significance in the univariate analysis were included in the multivariate logistic regression for variable screening. To account

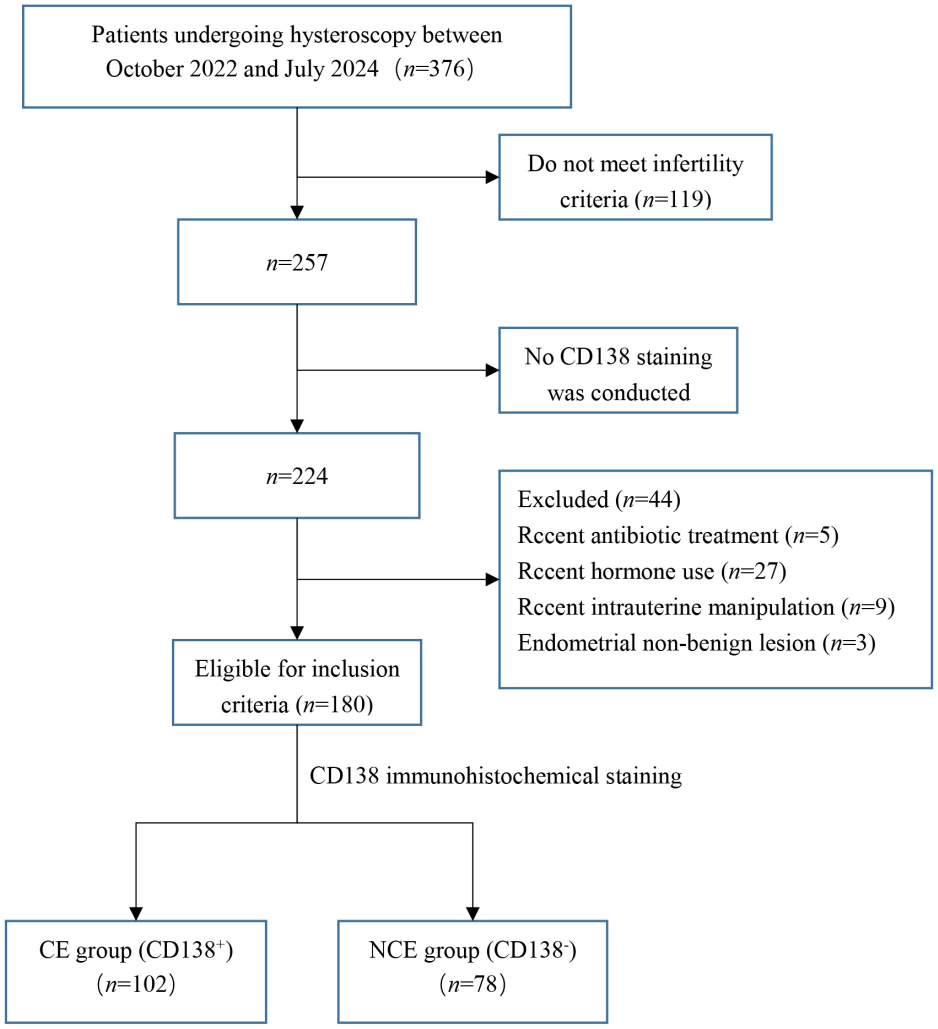

Fig. 1. Flowchart of patient selection in this study. Abbreviations: CE, chronic endometritis; NCE, non-chronic endometritis; CD138, syndecan-1.

Table 1. Baseline characteristics of NCE and CE patients.

	NCE group (n = 78)	CE group (n = 102)	$t/Z/\chi^2$ value	p-value
Age (years), mean ± SD	30.64 ± 4.27	31.21 ± 3.84	−0.931	0.353
Infertility duration (years), M (Q1, Q3)	2 (1, 3)	2 (1, 3)	−1.016	0.310
BMI (kg/m^2), mean ± SD	22.97 ± 4.03	23.56 ± 3.83	−1.000	0.318
Reason for hysteroscopy (n, %)			0.477	0.924
Infertility	52 (66.67)	71 (69.61)		
Endometrial polyps	12 (15.38)	15 (14.71)		
AUB	4 (5.13)	6 (5.88)		
Others	10 (12.82)	10 (9.80)		

Notes: "Others" category encompasses intrauterine adhesion, endometrial hyperplasia, uterine incision diverticulum, and hydrometra.

Abbreviations: AUB, abnormal uterine bleeding; BMI, body mass index; SD, standard deviation; M, median; Q1, 1st Quartile; Q3, 3rd Quartile.

Table 2. Univariate logistic regressive analysis of related risk factors for chronic endometritis.

Variables (*n*, %)	NCE group (*n* = 78)	CE group (*n* = 102)	*β*	SE	OR	95% CI	*p*-value
Gravidity			0.658	0.308	1.931	1.056–3.534	**0.033**
0	50 (64.10)	49 (48.04)					
≥1	28 (35.90)	53 (51.96)					
Parity			0.827	0.371	2.286	1.104–4.732	**0.026**
0	65 (83.33)	70 (68.63)					
≥1	13 (16.67)	32 (31.37)					
Abortion history			0.897	0.331	2.452	1.282–4.687	**0.007**
Yes	19 (24.36)	45 (44.12)					
No	59 (75.64)	57 (55.88)					
History of biochemical pregnancy			−0.019	0.528	0.982	0.349–2.763	0.972
Yes	7 (8.97)	9 (8.82)					
No	71 (91.03)	93 (91.18)					
History of ectopic pregnancy			−1.231	0.851	0.292	0.055–1.547	0.148
Yes	5 (6.41)	2 (1.96)					
No	73 (93.59)	100 (98.04)					
Dysmenorrhea			−0.295	0.304	0.745	0.411–1.351	0.332
Yes	37 (47.44)	41 (40.20)					
No	41 (52.56)	61 (59.80)					
Prolonged menstruation			1.236	0.581	3.442	1.102–10.750	**0.033**
Yes	4 (5.13)	15 (14.71)					
No	74 (94.87)	87 (85.29)					
Intermenstrual bleeding			0.803	0.505	2.233	0.830–6.003	0.112
Yes	6 (7.69)	16 (15.69)					
No	72 (92.31)	86 (84.31)					
Menstrual cycle			−0.023	0.340	0.977	0.502–1.902	0.946
Regular	57 (73.08)	75 (73.53)					
Irregular	21 (26.92)	27 (26.47)					

Abbreviations: *β*, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval. *p*-values less than 0.05 are bolded.

for potential confounding factors, the history of ectopic pregnancy ($p = 0.148$) and intermenstrual bleeding ($p = 0.112$) were also included in the multivariate logistic regression analysis to ensure that important risk factors were not overlooked. The variance inflation factor (VIF) values of all factors were all less than 10, indicating that there was no multicollinearity among them. Therefore, these factors were included in the multivariate logistic regression analysis. The multivariate analysis results showed that abortion history (OR = 2.521, 95% CI: 1.307–4.864, $p = 0.006$) and prolonged menstruation (OR = 3.624, 95% CI: 1.141–11.513, $p = 0.029$) were independently associated with CE, whereas gravidity, parity, history of ectopic pregnancy, and intermenstrual bleeding (OR = 0.532, 1.862, 0.223, 1.521,

Table 3. Multivariate logistic regressive analysis of independent risk factors for chronic endometritis.

Variables	β	SE	OR	95% CI	*p*-value
Gravidity	−0.631	0.799	0.532	0.111–2.549	0.430
Parity	0.621	0.411	1.862	0.833–4.163	0.130
History of abortion	0.925	0.335	2.521	1.307–4.864	**0.006**
History of ectopic pregnancy	−1.499	0.890	0.223	0.039–1.278	0.092
Prolonged menstruation	1.288	0.590	3.624	1.141–11.513	**0.029**
Intermenstrual bleeding	0.419	0.545	1.521	0.522–4.428	0.442

p-values less than 0.05 are bolded.

respectively; $p > 0.05$) showed no independent associations after adjustment (Table 3).

Discussion

As demonstrated in recent studies, CE is associated with infertility, recurrent miscarriage, repeated implantation failure, and a range of maternal-fetal complications (Cicinelli et al., 2015; Ticconi et al., 2024). It has been reported that oral antibiotic therapy can notably enhance fertility and pregnancy outcomes in patients with CE (Ilic et al., 2025). This finding suggests a causal link between CE and impaired endometrial receptivity, which has garnered growing attention from clinicians (Kimura et al., 2019). Obtaining a clinical diagnosis of CE is challenging due to the absence of clinical symptoms or the subtle presentation of mild symptoms. Hysteroscopy can aid in the detection of CE; however, there are currently no definite recommendations regarding its inclusion in the CE screening protocol for infertile women without intrauterine abnormalities (Ticconi et al., 2024). In this study, we aimed to identify potential risk factors for CE based on the reproductive history and clinical symptoms of infertile women.

The present study involved a comprehensive analysis of all possible risk factors pertaining to reproductive history and clinical symptoms, which may be associated with the development of CE. Through univariate and multivariate logistic regression analyses, we identified abortion history and prolonged menstruation as independent risk factors for CE in infertile women. While consistent with relevant reports, our results present some notable differences. By analyzing data of 93 infertile patients who underwent hysteroscopic and laparoscopic surgery due to tubal abnormalities or unexplained infertility, Chen et al. (2016) found that prolonged menstruation (including intermenstrual bleeding), prior abortion surgery, and tubal obstruction serve as independent risk factors for CE, while the parity and spontaneous abortion were not related to CE. Different from their investigation, our study incorporated the history of spontaneous abortion as part of abortion history. Future research involving an expanded sample size is necessary to validate the risk-contributing roles of the history of spontaneous abortion and the abortion history. Gao et al. (2024) studied 502 patients who underwent hysteroscopy due to intrauterine disorders and found that prolonged menstruation and intermenstrual bleeding

were independent risk factors for CE. Although the gravidity and abortion history were related to CE, such correlation became insignificant upon the exclusion of confounding factors. In our study, however, intermenstrual bleeding was not identified as a risk factor for CE. Further studies involving larger samples are needed in the future to clarify these discrepancies. By studying the clinical data of 44 patients who underwent hysteroscopy due to cesarean scar diverticulum, Zhang et al. (2024) found a positive correlation between the severity of CE and the duration of prolonged menstruation.

However, most of the previous studies either investigated only a few possible risk factors related to the reproductive history and clinical symptoms or conducted research in populations not including infertile women. To the best of our knowledge, this study is the first to conduct a comprehensive screening of possible CE risk factors associated with reproductive history and clinical symptoms in infertile patients. The results suggest that abortion history and prolonged menstruation in infertile patients are significantly associated with the pathogenesis of CE. During abortion, cervical dilation creates a pathway between the uterine cavity and the external environment, allowing pathogenic bacteria to ascend through the reproductive tract, reach the uterine cavity, and ultimately cause CE (Xie et al., 2024). Prolonged menstruation may cause disorders in the microbial flora of the female reproductive tract, such as a decrease in the proportion of dominant Lactobacillus, and an imbalance in the ratio of pro-inflammatory and anti-inflammatory factors in the endometrium, thus leading to the persistence of chronic inflammation (Yang et al., 2021). Therefore, for infertile patients without intrauterine abnormalities but with an abortion history or symptoms of prolonged menstruation, the possibility of CE should be carefully considered. Thus, hysteroscopy coupled with endometrial CD138 staining is recommended for such patients to timely rule out CE (Kimura et al., 2019). The clinical significance of the current study lies in providing an evidence-based insight into the clinical necessity to perform hysteroscopy for CE screening in infertile patients without intrauterine abnormalities.

The univariate analysis of this study showed that gravidity and parity were associated with CE, but the multivariate logistic regression analysis demonstrated no statistical significance in their correlation. Similarly, a study by Gao et al. (2024) found an association between gravidity and CE in the univariate logistic regression analysis, but such correlation became insignificant following the adjustment of confounding factors; parity was also not determined as a risk factor of CE. These results are probably attributed to the direct confounding effects of other risk factors on gravidity and parity. In another study, no significant correlation between gravidity and CE in infertile patients with adenomyosis was found (Li et al., 2024); however, this finding remains controversial. An analysis of several clinical parameters in 1088 patients who underwent hysteroscopy due to repeated implantation failure revealed that parity $\geq$2, a history of ectopic pregnancy, and moderate-to-severe dysmenorrhea were significantly correlated with an elevated risk of CE (Xie et al., 2024). Kitaya et al. (2016) also found that among patients who underwent hysteroscopy for various gynecological diseases, the parity of patients with CE increased sig-

nificantly compared with patients without CE. Therefore, additional large-sample studies are needed in the future.

A major challenge in the study of CE is its accurate diagnosis. Currently, the primary methods for diagnosing CE include histopathological examination, hysteroscopy, and examination of pathogenic microorganism. Hysteroscopy demonstrates a moderate degree of sensitivity, but its diagnostic accuracy is greatly affected by the subjective judgment of the operator (Ilic et al., 2025). For pathogenic microorganism examination, there is currently no clear standard for the types and abundances of microbial pathogens in the diagnosis of CE. At present, the detection of plasma cells in the endometrial stroma via histopathological examination remains the gold-standard diagnostic method for CE, but the threshold of plasma cell number per specimen or microscope field is still undefined (Huang et al., 2020; Song et al., 2018). In this study, the presence of $\geq$1 CD138-positive plasma cell in 10 non-overlapping HPFs was used as the diagnostic standard for CE, which is consistent with the diagnostic standards used in the previous studies (Xie et al., 2024). However, some studies found that mild CE (1–4 plasma cells / HPF) has no effect on the *in vitro* fertilization (IVF) success rate in infertile patients, while severe CE ($\geq$5 plasma cells / HPF) has an adverse impact on the IVF outcome compared with mild CE (Xiong et al., 2021). Antibiotic treatment can significantly improve implantation and live-birth rates in infertile patients with severe CE, highlighting the need for further studies to refine the diagnostic criteria of CE (Liu et al., 2023; Vitagliano et al., 2022).

Our study innovatively shifted the focus to infertile women without intrauterine abnormalities and was the first to systematically screen the risk factors related to reproductive history and clinical symptoms that may contribute to the pathogenesis of CE, providing novel insights into symptom-oriented screening. In the future, independent risk factors validated through multicenter studies can be used to develop a hierarchical screening model for the effective identification of high-risk groups for CE.

The present study has several limitations. First, we aimed to screen for the risk factors for CE in infertile women, especially those without intrauterine abnormalities. While most of the enrolled patients (68.33%, 123/180) underwent hysteroscopy due to infertility alone, it should be noted that roughly one-third of the sample (31.67%, 57/180) underwent surgery due to infertility combined with endometrial polyps, intrauterine adhesions, abnormal uterine bleeding, etc. Although the distribution of these surgical indications did not differ between the two groups, they may still represent potential confounding factors. Thus, studies employing a larger sample of infertile patients without intrauterine abnormalities are needed in the future to further verify the result. Second, the short follow-up period limited our ability to observe pregnancy outcomes in all patients, preventing a temporal assessment of CE's impact on pregnancy. Third, the endometrial immunohistochemical staining results may be subject to heterogeneity as the procedure was performed by different pathologists. Fourth, the integration of certain variables with a limited sample size (e.g., prolonged menstruation) may result in unstable estimates and overfitting of the multivariate logistic regression model, as reflected in the wide

confidence intervals. Therefore, larger, prospective cohorts are required to validate these associations.

Conclusion

A history of abortion and prolonged menstruation are critical risk factors for CE in infertile women. For infertile women without intrauterine abnormalities but with an abortion history or prolonged menstruation, it is recommended to perform hysteroscopy combined with CD138 staining to facilitate early diagnosis and treatment of CE. Prospective studies are warranted to examine the effect of antibiotic treatment on pregnancy outcomes in infertile women with CE and to explore the mechanisms underlying the pathogenesis of CE associated with abortion history and prolonged menstruation.

Key Points

- While being highly prevalent among infertile women, chronic endometritis (CE) is often overlooked as a significant contributor to female infertility and warrants greater clinical attention.
- Readily available information on patient history and their symptoms is key to the identification of independent risk factors, which can aid in early detection of CE prior to the implementation of invasive diagnostic procedures.
- Abortion history and prolonged menstruation are identified as critical independent risk factors for CE in infertile women.
- The identified risk factors are of clinical significance for infertile women without intrauterine abnormalities and may ultimately contribute to improved reproductive outcomes.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization, MYL and WYW; methodology, MYL; software, MYL; validation, WYW; formal analysis, MYL; investigation, MYL; resources, MYL; data curation, MYL, TL, XAX, and YLD; writing—original draft preparation, MYL; writing—review and editing, WYW; visualization, MYL; supervision, WYW; project administration, WYW. All authors contributed to revising the manuscript critically for important intellectual content. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This retrospective study was performed in compliance with the Declaration of Helsinki and has been approval by the Ethics Committee of The Affiliated Wuxi People's Hospital of Nanjing Medical University (KY25076). The research involved no additional interventions, procedures, or interactions with the patients. The data were analyzed anonymously, and all patient identifiers were removed prior to analysis. Therefore, the study presented no more than minimal risk to the participants. Based on these factors, the requirement for informed consent was waived by the Ethics Committee.

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Conflict of Interest

The authors declare no conflict of interest.

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