



Correlation of hysteroscopic findings of chronic endometritis with CD138 immunohistochemistry and their correlation with pregnancy outcomes

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Received: 5 April 2024 / Accepted: 10 July 2024 / Published online: 4 September 2024

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Abstract

Purpose To investigate the correlation between hysteroscopic findings of chronic endometritis and CD138 immunohistochemistry positive in endometritis and to analyze the pregnancy outcomes and associated risk factors following embryo transfer in women diagnosed with chronic endometritis via hysteroscopy.

Methods A retrospective observational study carried out at the Reproductive Medicine Center of Tangdu Hospital of Air Force Medical University, from January 2021 to December 2021, was performed by obtaining data from 194 medical records of women who underwent hysteroscopies for infertility and were diagnosed with chronic endometritis based on Delphi criteria. Spearman correlation analysis was used to evaluate the correlation between hysteroscopic findings and endometrial CD138 immunohistochemistry. The study also observed the differences in relevant indexes between the CD138-positive and CD138-negative groups after embryo transfer and analyzed factors influencing implantation failure using logistic regression analysis.

Results The correlation analysis between hysteroscopic findings and CD138 immunohistochemistry showed that micropolyps were correlated with CD138 immunohistochemistry positivity. The correlation coefficient was 0.32 ($P < 0.01$). After embryo transfer, the clinical pregnancy rate of the CD138-positive group was lower compared to that of the CD138-negative group [64.79% (46/71) vs. 81.30% (100/123), $P < 0.05$]. The results of the multivariate logistic regression analysis revealed that age ($P = 0.43$) and CD138 immunohistochemistry positivity ($P = 0.008$) were the independent risk factors for predicting whether or not embryo implantation was successful.

Conclusion Hysteroscopic findings do not correlate strongly with endometrial CD138 immunohistochemistry, and chronic endometritis cannot be diagnosed by hysteroscopy alone. CD138 immunohistochemistry positivity is an independent factor contributing to the decrease in clinical pregnancy rate following embryo transfer.

Keywords Chronic endometritis · Hysteroscopy · Histology · Immunohistochemistry (IHC) · CD138 · Reproductive outcomes

Introduction

Chronic endometritis (CE) is a persistent, focal, or diffuse inflammation of the endometrium, characterized by plasma cells penetrating the endometrial stroma [1]. CE is often asymptomatic or mild, such as abnormal uterine bleeding (AUB), pelvic discomfort, dyspareunia, and leucorrhea, making it easy to overlook the diagnosis of the disease in the clinic. In recent years, there has been increasing evidence suggesting that CE is associated with poor reproductive outcomes [2, 3], such as infertility, repeated implantation failure (RIF), and recurrent pregnancy loss (RPL). CE has gained increasing attention in reproductive medicine,

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and the treatment of CE can improve patients' pregnancy outcomes; oral antibiotics are commonly used to treat CE [4, 5]. To date, numerous studies on CE have been published; however, there is no consensus regarding diagnostic criteria for CE, which is mostly diagnosed via hysteroscopy, endometrial biopsy, and microbial detection. Clinically, the diagnosis generally relies on identifying endometrial stromal plasma cells using two methodologies: hematoxylin and eosin (HE) staining and immunohistochemistry (IHC) staining for plasma cell-specific surface antigen CD138. Recent studies have shown that CD138 immunohistochemistry positivity has a high sensitivity for the diagnosis of CE [6]. The sensitivity of the diagnosis of CE via hysteroscopy may be dependent upon the physician's experience [5, 7]. Bacterial culture is limited in clinical practice due to its long-time requirement, high false-positive rate, and susceptibility to contamination by vaginal secretions.

Materials and methods

Study population and study design

This was a retrospective study conducted between January 2021 and December 2021; the study collected the medical records of 194 patients who underwent hysteroscopies for infertility at the Reproductive Medicine Center of Tangdu Hospital, Air Force Medical University. These patients were diagnosed with CE based on Delphi criteria, which include strawberry aspect, focal hyperemia, hemorrhagic spots, micropolyps, and stromal edema (see Figs. 1, 2, 3, and 4). In this study, all patients were diagnosed with CE by hysteroscopy and at least 5 CD138-positive cells in one HPF were visible in the endometrial stroma as the diagnostic criteria for CE. This study was approved by the Ethics Committee of Tangdu Hospital of Air Force Medical University (Assigned No. TDLL-202403–05).

Data collection

Patients were retrospectively identified by querying the Tangdu Hospital electronic medical record system using the search term "chronic endometritis" (we used the Delphi standard to record patients with chronic endometritis in the electronic medical record system). The inclusion criteria were (1) infertile woman; (2) age 20 to 45 years; (3) in vitro fertilization and embryo transfer (IVF-ET)/intracytoplasmic sperm injection (ICSI) for fertility treatment; (4) complete preservation of hysteroscopic pictures and other clinical data; and (5) patients with hysteroscopy and endometrial biopsy signed informed consent. Exclusion criteria were (1) uterine adhesions; (2) congenital malformations of the uterus (unicornuate uterus, septate uterus, etc.); (3)

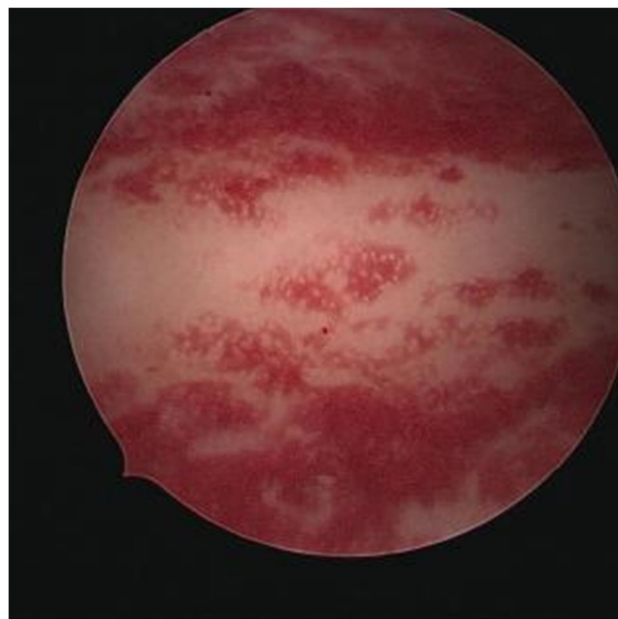


Fig. 1 Strawberry aspect

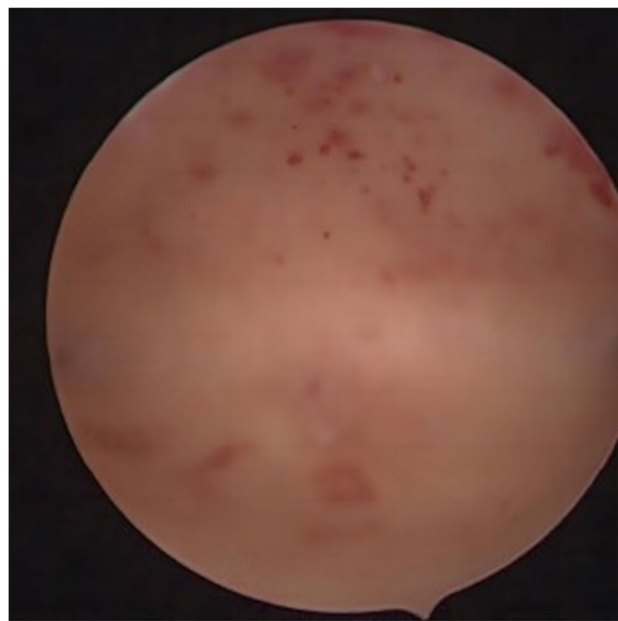


Fig. 2 Hemorrhagic spots

untreated thyroid dysfunction, hyperprolactinemia, diabetes, etc.; (4) pelvic or genital tuberculosis; (5) chromosomal abnormalities in either male or female; (6) in preimplantation genetic testing (PGT) for fertility treatment; and (7) combined with submucosal myoma.

The patient underwent hysteroscopy under non-anesthesia at the Reproductive Medicine Clinic of Tangdu Hospital

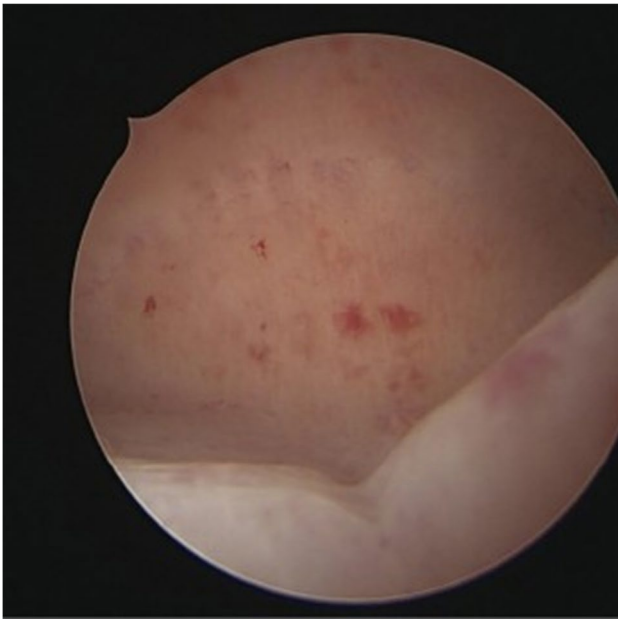


Fig. 3 Stromal edema

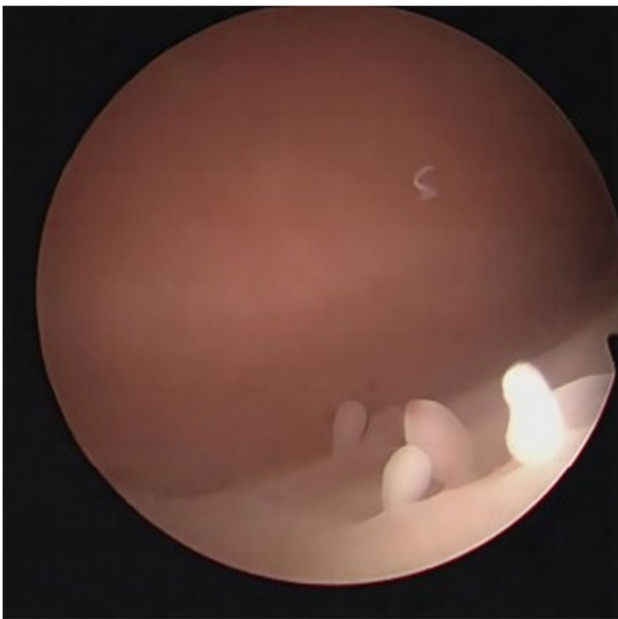


Fig. 4 Micropolyps

between 3 and 7 days after menstruation. The hysteroscopy and diagnosis were conducted by experienced medical professionals. The hysteroscopic outer sheath had a diameter of 4.5 mm, and 0.9% sodium chloride solution was used as the dilatation medium (a pressure between 80 and 110 mmHg and a flow rate between 100 and 200 mmHg). After hysteroscopy, a metal curette was used to obtain endometrial

tissue for pathology. The specimens were fixed with formaldehyde solution and sent for HE staining and CD138 immunohistochemistry.

Referring to the diagnostic criteria in previous literature [8, 9], the diagnostic criteria for CE of hysteroscopy were mainly based on the Delphi standard in 2019: (1) endometrial strawberry aspect; (2) endometrial focal hyperemia; (3) endometrial hemorrhagic spots; (4) endometrial micropolyps; and (5) thick and pale appearance of the endometrium in the follicular phase owing to stromal edema (a normal finding during the secretory phase). Histopathological diagnostic criteria [10]: we used at least five CD138+ cells in the endometrial stroma per 400× magnification as the criteria, and an experienced histopathologist examined the pathological findings. Patients with CD138+ endometrial biopsy were given doxycycline hydrochloride (100 mg, Bid, 14 days). Repeat hysteroscopy and endometrial biopsy between 3 and 7 days after menstruation, if CD138 remained positive, received metronidazole (500 mg, Bid, 14 days) and levofloxacin (200 mg, Bid, 14 days). Repeat hysteroscopy and endometrial biopsy between 3 and 7 days after menstruation, if CD138 remained positive, received azithromycin (500 mg, Bid, 14 days). All patients were treated with IVF-ET/ICSI for fertility treatment; blood HCG levels were checked on the 13th day after embryo transfer. If HCG levels were greater than 5 U/L, the implantation was considered successful. Intrauterine pregnancy confirmed by transvaginal ultrasound 42 days after embryo transfer was considered clinical pregnancy. According to this criterion, patients can be divided into the clinical pregnancy group and the non-pregnancy group.

Statistical analysis

SPSS v.23.0 software was used for statistical analysis. Normally distributed measurements were expressed as mean \pm standard deviation ($\bar{X} \pm S$), and independent samples *t*-test was used for comparison between groups; count data were presented as frequency and constitutive ratios and the chi-square test was used for comparison between groups; the correlation between hysteroscopic findings and CD138 results was expressed using Spearman's correlation coefficient; independent risk factors were screened using univariate and multivariate logistic regression analysis. Statistical significance for all tests was based on a *P* value < 0.05 .

Result

The patients had an average age of 30.81 ± 3.72 years, an average BMI of 22.07 ± 2.91 kg/m², and a mean duration of infertility of 3.55 ± 2.48 years (Table 1). Of the 194 patients enrolled, 71 (36.6%) were CD138 positive. Out

Table 1 Patient's demographics characteristic [$(\bar{X} \pm S)$, n (%)]

Characteristic	Results
Age (years)	30.81 ± 3.73
Infertility years (years)	3.55 ± 2.48
BMI (kg/m ²)	22.07 ± 2.91
AMH (ng/ml)	4.18 ± 3.22
FSH (mIU/ml)	6.57 ± 2.08
LH (mIU/ml)	6.40 ± 4.36
Antral follicle number	
Left	8.74 ± 3.72
Right	9.11 ± 3.83
Infertility factor	
Primary infertility	106 (54.6%)
Secondary infertility	88 (45.4%)

BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle-making hormone; LH, luteinizing hormone

of 194 patients, 129 had one hysteroscopic finding, 57 had two, and 8 had three. Micropolyps were found in 74 cases, strawberry aspect in 5 cases, focal hyperemia in 140 cases, hemorrhagic spots in 10 cases, and stromal edema in 37 cases. The correlation coefficient between micropolyps and CD138 immunohistochemical positivity was 0.320, which was statistically significant ($P < 0.01$). There was no significant correlation between the strawberry aspect, focal hyperemia, hemorrhagic spots, stromal edema, and CD138 immunohistochemical positivity (Table 2). It can be seen that endometrial micropolyps are most linked with CD138 immunohistochemical positivity.

Based on CD138 immunohistochemistry, the patients were divided into CD138-positive and CD138-negative groups. There were no statistically significant differences in age, infertility years, and body mass index (BMI) between the two groups ($P > 0.05$), indicating comparability (Table 3). After embryo transfer, the clinical pregnancy rate in the CD138-positive group was found to be lower than that in the CD138-negative group ($P < 0.05$). However, there were no statistically significant differences

Table 3 The baseline characteristics of the two groups

Characteristic	CD138(+) ($n = 71$)	CD138(-) ($n = 123$)	P value
Age (years)	30.54 ± 3.36	30.97 ± 3.94	> 0.05
Infertility years (years)	3.46 ± 2.36	3.60 ± 2.56	> 0.05
BMI (kg/m ²)	21.77 ± 2.42	22.24 ± 3.15	> 0.05
AMH (ng/ml)	3.90 ± 2.36	4.33 ± 3.62	> 0.05
FSH (mIU/ml)	6.63 ± 2.34	6.53 ± 1.92	> 0.05
LH (mIU/ml)	6.27 ± 4.60	6.47 ± 4.23	> 0.05
Antral follicle number			
Left	8.92 ± 3.60	8.63 ± 3.79	> 0.05
Right	9.49 ± 3.59	8.89 ± 3.96	> 0.05
Infertility factor			
Primary infertility	38 (53.52%)	68 (55.28%)	> 0.05
Secondary infertility	33 (46.48%)	55 (44.72%)	> 0.05

BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle-making hormone; LH, luteinizing hormone

observed between the two groups in terms of live birth rate, premature birth rate, and abortion rate ($P > 0.05$) (Table 4). Univariate analysis showed significant differences in age, luteinizing hormone (LH), and CD138 immunohistochemical positivity between the CD138-positive group and the CD138-negative group ($P < 0.05$). However, there were no significant differences in infertility type, infertility years, body mass index (BMI), anti-Müllerian hormone (AMH), follicle-making hormone (FSH), and hysteroscopic findings of CE (micropolyps, strawberry aspect, focal hyperemia, hemorrhagic spots, and stromal edema) between the two groups ($P < 0.05$). Age, LH, and CD138 immunohistochemical positivity with statistically significant differences in univariate analysis were included in multivariate logistic regression analysis, and the results showed that age [OR = 0.909, 95%CI (0.829, 0.997), $P < 0.05$] and CD138 immunohistochemical positivity [OR = 0.392, 95%CI (0.196, 0.784), $P < 0.05$] were independent risk factors for predicting whether embryo implantation was successful (Table 5).

Table 2 Correlation analysis between CD138 immunohistochemistry and hysteroscopic findings

	Micropolyps	Strawberry aspect	Focal hyperemia	Hemorrhagic spots	Stromal edema	CD138 positive
Micropolyps	1					
Strawberry aspect	-0.129	1				
Focal hyperemia	-0.593**	+0.101	1			
Hemorrhagic spots	-0.089	-0.038	-0.323	1		
Stromal edema	-0.035	+0.087	+0.038	-0.054	1	
CD138 positive	+0.320**	-0.056	-0.077	-0.129	0.121	1

** $P < 0.01$

Table 4 Comparison of pregnancy outcomes between the two groups

Group	Number	Clinical pregnancy rate	Live birth rate	Preterm birth rate	Abortion rate
CD138 negative	123	81.30% (100/123)	64.23% (79/123)	10.00% (10/100)	14.00% (14/100)
CD138 positive	71	64.79% (46/71)	53.52% (38/71)	19.57% (9/46)	17.39% (8/46)
χ^2		6.591	2.156	1.053	0.001
<i>P</i> value		0.010*	0.142	0.305	0.981

P* < 0.05Table 5** Logistic regression analysis of factors affecting the pregnancy outcomes after embryo transfer

Variables	Univariate analysis		Multivariate analysis	
	<i>P</i> value	OR (95%CI)	<i>P</i> value	OR (95%CI)
Age (years)	0.030*	0.908 (0.832, 0.991)	0.043*	0.909 (0.829, 0.997)
Type of infertility	0.940	0.975 (0.507, 1.876)	–	–
Infertility years	0.602	0.967 (0.852, 1.097)	–	–
BMI/(kg/m ²)	0.082	1.132 (0.993, 1.307)	–	–
AMH	0.073	1.131 (0.989, 1.293)	–	–
FSH	0.148	0.893 (0.766, 1.041)	–	–
LH	0.034*	1.142 (1.010, 1.291)	0.073	1.116 (0.990, 1.257)
Micropolyps	0.226	1.535 (0.767, 3.071)	–	–
Strawberry aspect	0.804	1.324 (0.144, 12.141)	–	–
Focal hyperemia	0.215	0.610 (0.279, 1.332)	–	–
Hemorrhagic spots	0.722	1.333 (0.273, 6.506)	–	–
Stromal edema	0.625	1.239 (0.524, 2.932)	–	–
CD138 positive	0.011*	0.423 (0.218, 0.823)	0.008*	0.392 (0.196, 0.784)

**P* < 0.05

Discussion

CE can adversely affect the immune microenvironment of endometrial, reduce the endometrial receptive, interfere with fertilized egg implantation and embryo implantation, is not conducive to the maintenance of pregnancy after implantation, and affect the reproductive health of women in their reproductive age. At present, most people believe that CE is mainly induced by intrauterine microbial infection [11]. Studies had conducted bacterial culture or microbial detection on the endometrium of patients with CE, showing that compared with broad-spectrum antibiotic treatment for CE patients with negative microbial culture, the cure rate was significantly improved and pregnancy outcome was improved when specific bacteria were found, and targeted therapy with antibiotics is performed [12, 13]. However, microbiological culture is not widely used in clinical practice due to its long-time requirement, high false-positive rate, and susceptibility to contamination by vaginal secretions.

Currently, there is no consensus on the diagnostic criteria for patients with CE; several domestic and international studies suggest that hysteroscopy combined with

CD138 immunohistochemistry is more accurate and comprehensive for diagnosing CE [14]. Nevertheless, due to a lack of consensus on the hysteroscopic finding of CE and the differences in experience among inter-examiners, the accuracy of hysteroscopic diagnosis of CE is different in different studies. Therefore, the establishment of unified diagnostic criteria and the learning of diagnostic criteria can narrow the differences among observers and improve the accuracy of the diagnosis. In 2019, scholars from various countries jointly formulated the diagnostic criteria for CE hysteroscopy, which improved the consistency of clinical CE diagnosis [9]. To study the value of hysteroscopy in diagnosing CE, this paper retrospectively analyzed the correlation between the hysteroscopic findings of CE and the CD138 immunohistochemistry, and further observed the pregnancy outcomes after embryo transfer in both the CD138-positive group and CD138-negative group, analyzed the factors affecting the pregnancy outcomes, and expected to provide evidence-based medical evidence for the diagnosis, treatment, and prognosis of CE. One study showed that [15] hysteroscopic findings did not agree well with histopathological diagnosis. In our study, endometrial conditions were observed under direct vision by hysteroscopy, and HE staining routine histopathological

examination combined with CD138 immunohistochemistry was performed by localization biopsy. The results showed that there was only a weak correlation (correlation coefficient of 0.320) between endometrial micropolyps and CD138 immunohistochemistry positivity, while strawberry aspect, focal hyperemia, hemorrhagic spots, and stromal edema were not correlated with CD138 immunohistochemistry positivity. It can be seen that there is a wide variability in the two methodologies. Cicinelli et al. [16, 17] found that endometrial micropolyps under hysteroscopy may be a reliable feature for the diagnosis of CE, and the histological changes were correlated with the results of hysteroscopy [18]. When one or more hysteroscopic findings are present on hysteroscopy, the diagnosis of CE should be vigilant; a concomitant endometrial biopsy should be performed to confirm or negate the diagnosis.

The histological diagnosis of CE is still subjective and may vary among different centers [9]. Although CD138 immunohistochemistry is considered a reliable method for diagnosing CE, recent literature suggests that the technique has some limitations.

Firstly, some studies used different methodologies to quantify CD138-positive cells. Secondly, it should be noted that CD138-positive cells can also be detected in epithelial cells, fibroblasts, and B cells, so CD138-positive cells in endometrial specimens may not always be accurately identified [19]. Additionally, plasma cells can also be found in the endometrium of healthy women without any association with inflammation [20]. Therefore, the results may be different or inconsistent in the same patient. At present, there is a lack of standardized pathological diagnostic criteria. At least 7 histological diagnostic criteria for CE have been reported in the literature. However, there is no agreement on the minimum number of plasma cells required to diagnose CE [21]. The establishment of diagnostic criteria should take into account whether they contribute to improving pregnancy outcomes, and thus the pathological diagnostic criteria for CE should have a strong correlation with pregnancy outcomes to be valuable. The presence of CD138 cells has been found to be associated with the outcomes of embryo transfer in certain studies [22]; however, contrasting findings have been reported by another study [23]. Some studies have indicated that 5 CD138+ cells per 10 HPF are sufficient. This study used at least 5 CD138+ cells in one HPF as a diagnostic criterion. We found that CD138 immunohistochemical positivity was an independent influence on the reduction of the clinical pregnancy rate after embryo transfer, but more studies are needed to further confirm this finding.

The use of stricter diagnostic criteria in this study may reduce the sensitivity, leading to the possibility of missing many cases of CE. As a result, there may be some patients diagnosed by hysteroscopy as CE but with a negative CD138 result, indicating the possibility of false negative cases (only

36.6% of CD138 positive cases were identified in this study). Based on the low concordance rate between hysteroscopic findings and histopathological findings, as well as the limitations of the CD138 technique, it can be speculated that micropolyps and CD138-positive may indicate more severe cases. On the other hand, other findings at hysteroscopy but CD138-negative may be mild or moderate cases. One study showed that embryo transfer after antibiotic treatment in patients with hysteroscopic findings of CE and CD138-negative achieved better clinical pregnancy and full-term live birth rates [24]. Yang et al. came to a similar conclusion [25]. Therefore, we should pay attention to patients with hysteroscopic findings of CE but CD138 negative, which can be appropriately considered for interventional therapy to improve clinical pregnancy rates.

In summary, hysteroscopy, as a diagnostic method for CE, exhibits a certain degree of correlation between hysteroscopic findings and pathological results; however, the correlation is weak. Attention should be paid to the diagnosis of CE when there are characteristic findings in hysteroscopy. This study is a single-center retrospective study, and prospective randomized controlled studies or multi-center clinical trials are needed to further confirm and provide more convincing evidence for the diagnosis and treatment of patients with CE.

Conclusions

Studies on chronic endometritis (CE) and its relation to adverse pregnancy outcomes have been increasing and deepening over time, which has gained significant attention from gynecologists and reproductive doctors. However, the diagnosis rate of CE varies greatly due to variations in diagnostic methods and standards. The current gold standard for diagnosing CE is the detection of plasma cells in the endometrial tissue. Hysteroscopy can improve the detection rate of CE, but it cannot substitute pathology as the gold standard for the diagnosis of CE.

Author contribution Conception and design: Xifeng Xiao, Mao Li. Analysis and/or interpretation of the data: all authors. Drafting of the article: all authors. Critical revision of the article for important intellectual content: all authors. All authors read and approved the final version of the manuscript.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was approved by the Ethics Committee of Tangdu Hospital of Air Force Medical University (TDLL-202403–05).

Consent for publication All authors consent to publication.

Competing interests The authors declare no competing interests.

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