RESEARCH PAPER

Chronic Endometritis and Infertility: Analyzing Hysteroscopic Manifestations and CD138 Expression

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ABSTRACT

Background:

Chronic endometritis (CE) is a persistent inflammatory condition of the endometrium strongly associated with infertility, implantation failure, and recurrent miscarriage.

Methods:

This prospective cross-sectional observational study was conducted at the Department of Obstetrics & Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, from January 2024 to January 2026. Sixty women with primary unexplained infertility underwent diagnostic hysteroscopy followed by endometrial biopsy and CD138 immunohistochemistry (IHC).

Results:

The mean age was 32.07 ± 3.99 years. CD138 positivity was found in 73.3% of participants. Hysteroscopic findings of endometrial micropolyps (35%), hyperemia (50%), and edema (50%) were each significantly associated with CD138 positivity ($p = 0.001$, $p < 0.001$, and $p = 0.02$, respectively) and with significantly elevated plasma cell counts per 10 high-power fields (HPFs) ($p < 0.001$ for all). Severe CE (≥10 plasma cells/10 HPFs) was the most frequent histological category (35%). Hysteroscopy demonstrated sensitivity of 93.2%, specificity of 75%, positive predictive value (PPV) of 91.1%, negative predictive value (NPV) of 80%, and overall accuracy of 88.3% against CD138 IHC as the reference standard.

Conclusion:

Hysteroscopy is a highly sensitive screening tool for CE; however, CD138 IHC remains the diagnostic gold standard. A severity-based classification of CE is advocated for improved clinical decision-making in infertile women.

Keywords: Chronic endometritis; CD138 immunohistochemistry; Hysteroscopy; Infertility; Plasma cells; Endometrial receptivity

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INTRODUCTION: Infertility is a major global reproductive health concern. In a comprehensive population survey, Boivin et al. reported that primary infertility prevalence ranged from 3.5% to 16.7% in more developed nations and 6.9% to 9.3% in less-developed nations, with an estimated overall median prevalence of 9%.[1] Chronic endometritis (CE) is a persistent inflammatory condition of the endometrium that is frequently overlooked due to its largely asymptomatic or mildly symptomatic presentation, which may include pelvic pain, dysfunctional uterine bleeding, dyspareunia, or persistent leukorrhea.[2] Conventional investigations such as ultrasound and hysterosalpingography often fail to detect CE, and the diagnosis typically relies on hysteroscopy or endometrial histopathology.[3-5]

Chronic endometritis adversely impacts endometrial receptivity, leading to negative reproductive outcomes including decreased pregnancy rates, implantation failure, and recurrent

miscarriage.[6,7] The reported incidence of CE varies widely: 2.8%–56.8% in infertile women,[8–11] 9.3%–67.6% in recurrent pregnancy loss (RPL),[12–14] and 14%–67.5% in recurrent implantation failure (RIF).[3,15–18] This variability reflects the lack of a universally accepted diagnostic threshold and underscores the need for a structured diagnostic approach.

Hysteroscopy allows direct visualization of the endometrial cavity and can identify characteristic CE features such as micropolyps, hyperemia, and edema. CD138 (syndecan-1) immunohistochemistry is currently considered the most sensitive method for detecting plasma cells in the endometrial stroma and serves as the gold standard for CE diagnosis.[19-21] The present study aims to document hysteroscopic manifestations of CE in infertile women, evaluate their correlation with CD138 IHC expression, and assess the diagnostic performance of hysteroscopy against CD138 IHC as the reference standard.

MATERIALS & METHODS

Study Design, Setting, and Duration: This prospective cross-sectional observational study was conducted in the Department of Obstetrics & Gynecology, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pimpri, Pune, from January 2024 to January 2026. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to inclusion.

Sample Size and Sampling: The minimum required sample size was calculated using an online sensitivity–specificity sample size calculator. Assuming an expected sensitivity of 48%, specificity of 75%, an estimated disease prevalence of 30%, precision of 20%, and a confidence level of 90%, the minimum required sample size was 57 participants.[33] After accounting for an anticipated 4% dropout rate, the final sample size was rounded to 60 participants. A convenient sampling technique was employed, with the individual as the sampling unit.

Inclusion and Exclusion Criteria

Inclusion criterion: Women presenting with primary unexplained infertility.

Exclusion criteria: Symptoms of intrauterine pathology; transvaginal ultrasound abnormality; presence of an intrauterine device; suspected reproductive tract infection; previous hysteroscopy or genital examination.

Data Collection and Hysteroscopy Procedure: All women attending the outpatient department were screened for primary unexplained infertility. Those fulfilling the inclusion criteria underwent hysteroscopy and endometrial biopsy as outpatient procedures without anesthesia, performed exclusively during the proliferative phase of the menstrual cycle. A 3-mm rigid hysteroscope was used with uterine cavity distension achieved using normal saline at 100 mm Hg pressure. Hysteroscopic findings - endometrial micropolyps (single or multiple), hyperemia, and edema - were systematically recorded and video-documented. Following hysteroscopy, endometrial biopsy samples were obtained blindly using a metal curette from the upper uterine cavity.

Histology and Immunohistochemistry: Endometrial biopsy specimens were fixed in formalin and paraffin-embedded for histopathological examination and CD138 IHC. Five-micrometer sections were incubated with mouse anti-human monoclonal CD138 antibody (clone MI15, Cell Marque). At least 50 HPFs were examined per specimen. Biopsies were classified as CD138-negative when fewer than one plasma cell was identified per 10 HPFs, and CD138-positive when one or more plasma cells were identified per 10 HPFs. CE severity was graded as: mild (1–5 plasma cells/10 HPFs), moderate (6–10/10 HPFs), and severe (>10/10 HPFs). All specimens were evaluated by a single consultant histopathologist.

Data Analysis: Data were compiled in Microsoft Excel and analyzed using SPSS version 20. Continuous variables are presented as mean ± standard deviation; categorical variables as frequencies and percentages. Qualitative variables were compared using the Chi-square test or Fisher's exact test. Diagnostic performance of hysteroscopy was evaluated by calculating sensitivity, specificity, PPV, NPV, and overall accuracy using CD138 IHC as the reference standard. A p-value of <0.05 was considered statistically significant.

RESULTS

Age Distribution: The age of participants ranged from 26 to 41 years, with a mean age of 32.07 ± 3.99 years. The majority belonged to the 26–30 years age group (41.7%), followed by the 31–35 years group (36.7%), together comprising 78.4% of the study population (Table 1).

Table 1: Age Distribution of Study Participants

Age Group	Frequency (n)	Percentage (%)

26–30 years	25	41.7
31–35 years	22	36.7
36–40 years	12	20.0
41–45 years	1	1.7
Total	60	100.0

Baseline Reproductive and Menstrual Profile: A family history of infertility was reported by 33.3% of participants. The mean BMI was 25.92 ± 3.36 kg/m² (range 20–33 kg/m²). Most women reported regular menstrual cycles (81.7%), while 18.3% had irregular cycles (Table 2).

Table 2: Baseline Reproductive and Menstrual Profile of Study Participants

Variable	Category	Frequency (n)	Percentage (%)
Family History of Infertility	Absent	40	66.7
	Present	20	33.3
BMI (kg/m²)	Mean ± SD: 25.92 ± 3.36; Range: 20–33		
Menstrual Regularity	Regular	49	81.7
	Irregular	11	18.3

Hysteroscopic Findings: Endometrial micropolyps were present in 21 participants (35%). Endometrial hyperemia and endometrial edema were each present in 30 participants (50%) (Table 3).

Table 3: Distribution of Hysteroscopic Endometrial Findings

Hysteroscopic Finding	Absent n (%)	Present n (%)
Endometrial Micropolyps	39 (65.0)	21 (35.0)
Endometrial Hyperemia	30 (50.0)	30 (50.0)
Endometrial Edema	30 (50.0)	30 (50.0)

Plasma Cell Density and CD138 Expression: Plasma cell density assessment revealed mild CE in 10 participants (16.7%), moderate CE in 13 (21.7%), and severe CE in 21 (35%). Sixteen participants (26.7%) had no detectable plasma cells. CD138 IHC was positive in 44 participants (73.3%) and negative in 16 (26.7%) (Tables 4 & 5).

Table 4: Distribution of Endometrial Plasma Cell Density per 10 HPFs

CE Category	Plasma Cells/10 HPFs	Frequency (n)	Percentage (%)
Mild	1–5	10	16.7
Moderate	6–10	13	21.7
Severe	>10	21	35.0
Negative	0	16	26.7
Total	—	60	100.0

Table 5: CD138 Immunohistochemistry Expression

CD138 IHC	Frequency (n)	Percentage (%)
Positive	44	73.3
Negative	16	26.7
Total	60	100.0

Association between Hysteroscopic Findings and CD138 Expression: All 21 participants (100%) with micropolyps were CD138 positive, compared to 23 of 39 (59%) without micropolyps ($\chi^2 = 11.748$, $p = 0.001$). All 30 participants (100%) with hyperemia were CD138 positive, compared to only 14 of 30 (46.7%) without hyperemia ($\chi^2 = 21.818$, $p < 0.001$). Among those with edema, 26 of 30 (86.7%) were CD138 positive versus 18 of 30 (60%) without edema ($\chi^2 = 5.455$, $p = 0.02$) (Table 6).

Table 6: Association between Hysteroscopic Findings and CD138 Expression

Finding	Status	CD138 Negative	CD138 Positive	Total	χ^2	p-value

		n (%)	n (%)			
Micro polyps	Absent	16 (41.0)	23 (59.0)	39	11.748	0.001
	Present	0 (0.0)	21 (100.0)	21		
Hyperemia	Absent	16 (53.3)	14 (46.7)	30	21.818	<0.001
	Present	0 (0.0)	30 (100.0)	30		
Edema	Absent	12 (40.0)	18 (60.0)	30	5.455	0.02
	Present	4 (13.3)	26 (86.7)	30		

Association of Hysteroscopic Findings with Plasma Cell Count: Participants with micropolyps had significantly higher mean plasma cell counts (13.86 ± 6.72) compared to those without (4.64 ± 5.20). Similarly, those with hyperemia had higher counts (12.13 ± 6.31 vs. 3.60 ± 5.40) and those with edema had higher counts (11.73 ± 7.40 vs. 4.00 ± 4.58). All associations were statistically significant ($p < 0.001$) (Table 7).

Table 7: Association of Hysteroscopic Findings with Plasma Cell Count per 10 HPFs

Variable	Status	Mean ± SD (Plasma Cells/10 HPFs)	p-value
Micropolyps	Present (n=21)	13.86 ± 6.72	<0.001
	Absent (n=39)	4.64 ± 5.20	
Hyperemia	Present (n=30)	12.13 ± 6.31	<0.001
	Absent (n=30)	3.60 ± 5.40	
Edema	Present (n=30)	11.73 ± 7.40	<0.001
	Absent (n=30)	4.00 ± 4.58	

Diagnostic Performance of Hysteroscopy: Against CD138 IHC as the reference standard, hysteroscopy correctly identified 41 true positives and 12 true negatives, with 4 false positives and 3 false negatives (Table 8). The calculated diagnostic parameters are presented in Table 9: sensitivity 93.2%, specificity 75%, PPV 91.1%, NPV 80%, and overall accuracy 88.3%.

Table 8: Contingency Table — Hysteroscopy vs. CD138 IHC

Hysteroscopy	CD138 Negative	CD138 Positive	Total
Negative	12 (TN)	3 (FN)	15
Positive	4 (FP)	41 (TP)	45
Total	16	44	60

Table 9: Diagnostic Performance Parameters of Hysteroscopy

Parameter	Formula	Value (%)
Sensitivity	TP / (TP + FN) × 100	93.2
Specificity	TN / (TN + FP) × 100	75.0
Positive Predictive Value (PPV)	TP / (TP + FP) × 100	91.1
Negative Predictive Value (NPV)	TN / (TN + FN) × 100	80.0
Overall Accuracy	(TP + TN) / Total × 100	88.3

DISCUSSION: This study investigated the relationship between hysteroscopic findings and CD138-based diagnosis of CE in infertile women and found a high prevalence of CE, a strong correlation between hysteroscopic features and CD138 positivity, and high diagnostic accuracy of hysteroscopy using structured evaluation criteria.

Prevalence and Diagnostic Threshold: CE was detected in 73.3% of our cohort using a threshold of ≥1 CD138+ plasma cell per 10 HPFs. This is substantially higher than the 27.1% reported by

Song et al.[22] and the 31.5% by Liu et al.,[11] who used stricter thresholds (≥5 cells/HPF). However, it aligns with the 84% reported by Abdelsamie et al.[23] in a similar small-sample unexplained infertility cohort. As Herlihy et al.[24] demonstrated, low-level plasma cell infiltration (1–4 cells) may not be clinically significant, with reproductive outcomes similar to CE-negative patients. Conversely, Bulut et al.[25] confirmed that a threshold of ≥5 CD138+ cells/HPF identified patients with drastically lower live birth rates (20.0%) and higher pregnancy loss (66.7%). Our severity-based grading - mild (16.7%), moderate (21.7%), and severe (35%) - reflects this clinical relevance and moves beyond a binary positive/negative diagnosis.

Hysteroscopic Manifestations and CD138 Correlation: All participants with micropolyps or hyperemia were CD138 positive (100%), while 86.7% with edema were CD138 positive. All three associations were statistically significant ($p < 0.05$) and linked to significantly elevated plasma cell counts ($p < 0.001$). These findings are broadly consistent with Wang et al.,[26] who reported CD138 positivity in 63.16% of patients with micropolyps and 74% with edema. However, Wang et al.[26] also found that isolated hyperemia was associated with only 10.06% CD138 positivity and 0% response to antibiotics, suggesting a hormonal or metabolic (rather than infectious) etiology - particularly in patients with PCOS and elevated BMI. The discrepancy with our 100% CD138 positivity in hyperemia likely reflects the predominantly inflammatory phenotype of our cohort. This distinction has direct therapeutic implications: infectious CE responds to antibiotics, whereas hormonally driven endometrial changes do not. Concurrent endocrine profiling in future studies would help differentiate these subtypes.

Diagnostic Performance of Hysteroscopy: Our hysteroscopy achieved sensitivity of 93.2%, specificity of 75%, PPV of 91.1%, and accuracy of 88.3% - considerably superior to Song et al.[22] (sensitivity 59.3%, accuracy 66.9%) and Abdelsamie et al.[23] (sensitivity 48%, accuracy 52%). The high PPV (91.1%) indicates that when micropolyps or hyperemia are identified, CE is highly likely and biopsy is warranted. However, the moderate specificity (75%) and NPV (80%) confirm that a normal hysteroscopy does not reliably exclude CE. Song et al.[22] noted that 61.8% of histologically confirmed CE cases had no identifiable hysteroscopic features. This reinforces that CD138 IHC remains indispensable as the confirmatory gold standard.

Clinical Impact and Treatment: The clinical relevance of CE diagnosis is underscored by its impact on reproductive outcomes. Fan et al.[27] demonstrated a dose-response relationship between increasing CD138 cell counts and declining pregnancy rates, with clinical pregnancy rates dropping from 80.4% in CD138-negative women to 27.3% in those with >5 cells. Vitagliano et al.[28] in a meta-analysis of 10 studies confirmed that women with untreated CE had significantly lower ongoing pregnancy and live birth rates (OR 1.97, $p = 0.02$), while successful antibiotic treatment restored outcomes to levels comparable to unaffected women (OR 5.33, $p < 0.0001$). Liu et al.[29] reported a doxycycline cure rate of 79.07%, with significant improvement in pregnancy and live birth rates post-treatment. Wang et al.[26] highlighted that antibiotic response varies by hysteroscopic phenotype, with cure rates of 73.61% for micropolyps, 83.24% for edema, but 0% for isolated hyperemia — further emphasizing the need for phenotype-based management.

Strengths and Limitations: The primary strength of this study is its comprehensive integration of hysteroscopic phenotyping with severity-based histological analysis using CD138 IHC. Limitations include the absence of direct data on pregnancy outcomes and antibiotic treatment response, the relatively small sample size, and the lack of concurrent hormonal or metabolic profiling to differentiate infectious from endocrine-driven CE. A standardized CE diagnostic threshold and multi-centre prospective trials are needed to validate findings and guide evidence-based management guidelines.

CONCLUSION: Chronic endometritis is highly prevalent among infertile women, with 73.3% of participants in this study showing CD138 IHC positivity — predominantly in the severe category. Hysteroscopic findings of micropolyps, hyperemia, and edema showed strong, statistically significant associations with both CD138 positivity and elevated plasma cell infiltration. Hysteroscopy demonstrated high sensitivity (93.2%) and overall accuracy (88.3%), supporting its role as a frontline screening tool. However, CD138 immunohistochemistry remains the diagnostic gold standard, and a severity-based classification system is essential for meaningful clinical decision-making. The combined use of hysteroscopy and CD138 IHC,

together with quantitative plasma cell grading, is recommended for accurate CE diagnosis and appropriate therapeutic selection in infertile women.

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