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Prevalence and confounders of chronic endometritis diagnosed using CD138 in patients with recurrent implantation failure

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Objective: This retrospective study aimed to investigate the prevalence of chronic endometritis, diagnosed using CD138 immunohistochemistry, among infertile women and to assess the association between chronic endometritis and recurrent implantation failure (RIF).
Methods: In total, 266 patients who underwent hysteroscopy due to infertility between 2019 and 2020 were included in the analysis. Of these, 136 patients with RIF and 130 non-RIF patients were included in the study. CD138 immunohistochemistry test results, blood biomarkers (including natural killer cells, white blood cells, and the lymphocyte-to-neutrophil ratio), and data on pregnancy outcomes were obtained. If the CD138 test yielded a positive result, the patients received antibiotic treatment.
Results: The overall proportion of CD138-positive patients was 32.7% (87/266). The CD138 positivity rate was not related to the number of cycles with implantation failure. In the RIF patient group, no significant associations were found between CD138 positivity and peripheral blood markers. The clinical pregnancy rates were similar between infertile women treated with antibiotics for chronic endometritis and those without chronic endometritis.
Conclusion: To improve the pregnancy rate in infertile patients, it may be helpful to combine CD138 testing with other laboratory tests and administer antibiotic treatment if the result is positive.

Keywords: Endometritis; Hysteroscopy; Immunohistochemistry; Infertility; Pregnancy rate

Introduction

Despite improvements in the pregnancy rate through *in vitro* fertilization (IVF) and intracytoplasmic sperm injection for infertile women, recurrent implantation failure (RIF) remains a persistent challenge. RIF is defined as failure to conceive following two or three embryo transfer cycles, or a cumulative transfer of 10 good-quality embryos [1]. While various factors, such as parental age, embryonic genetic ability, autoimmune factors, and hormonal abnormalities, have been identified as contributors to RIF, the underlying cause is often elusive [2,3].

According to Quaas and Dokras [4], chronic endometritis (CE) was found in 30.3% of patients with RIF, and women diagnosed with CE had a significantly lower implantation rate (IR; 11.5%) than those without CE. CE is associated with lower ongoing pregnancy rates (OPRs), live birth rates (LBRs), clinical pregnancy rates (CPRs), and IRs compared to those without CE. Recent studies have also indicated that women with intrauterine pathologies, such as submucosal uter-

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ine fibroids, endometrial hyperplasia, and endometrial polyps, are at a higher risk of developing CE [5].

As CE is often asymptomatic, a histological diagnosis is necessary when the condition is suspected. The conventional method for diagnosing CE involves assessing plasma cells in the endometrial stroma following hysteroscopy [6]. However, the histological method of diagnosis has several limitations. Leukocytes are normally present in the endometrium before menstruation, and variations among pathologists may arise when counting the number of plasma cells.

A recent study showed that using the immunochemistry marker CD138 can enhance the sensitivity and specificity of CE diagnosis. McQueen et al. [7] reported that CD138 immunochemistry in patients with recurrent pregnancy loss (RPL) yielded a higher CE detection rate than the identification of plasma cells using hematoxylin and eosin (H&E) staining (56% vs. 13%, respectively).

Although it remains a matter of debate, abnormal levels of various immune indicators, such as an increase in the fraction and function of natural killer (NK) cells, have been linked to RIF [8]. Nevertheless, the association between CE and immunological factors requires further evaluation.

In this study, we assessed the utility of CD138 for diagnosing CE in patients with RIF and its connection to peripheral blood markers, including peripheral NK cells. Additionally, we explored the relationship between CD138 expression and pregnancy outcomes to better understand how CE contributes to RIF, which can contribute to the development of treatment methods.

Methods

1. Subjects

We analyzed data from 266 patients who visited Seoul Maria Fertility Hospital from October 2019 to June 2020 for infertility treatment and underwent hysteroscopy due to infertility. Peripheral blood markers, such as NK cells, white blood cells (WBCs), and the lymphocyte-to-neutrophil ratio, were obtained retrospectively from 113 patients and recorded in a case record form. Patients underwent CD138 testing (syndecan-1, transmembrane heparin sulfate proteoglycan), and if it was positive (defined as 1 plasma cell/high-power field [HPF]), they received doxycycline treatment. Out of the total 266 patients, 136 patients with RIF and 130 non-RIF patients were included in the study. RIF was defined as the failure to achieve a clinical pregnancy despite undergoing at least three cycles of embryo transfer.

The inclusion criteria were as follows: (1) a clinical diagnosis of fallopian tube-factor infertility, male factor infertility, or unexplained infertility and (2) patients who underwent CD138 testing via hysteroscopy and peripheral blood marker assessments such as NK cells. The exclusion criteria encompassed prior diagnoses of CE via hysteroscopy or bacterial culture with prior antibiotic treatment, known clinical autoimmune disease, antiphospholipid syndrome, a thrombophilic condition necessitating anticoagulant therapy, and the presence of antisperm antibodies.

2. Diagnosis and treatment of CE

All patients underwent hysteroscopy without prophylactic antibiotics. Following anesthesia, an endometrial biopsy was performed, including samples from polyps, stromal edema, and focal or diffuse hyperaemic lesions.

The commonly detected bacteria in culture from these patients were *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma species*, and *Ureaplasma urealyticum*, which generally respond well to doxycycline. Consequently, 1 week after hysteroscopy, patients were treated with doxycycline twice a day for 14 days after the pathological diagnosis was confirmed. No follow-up hysteroscopy was performed separately to confirm the treatment outcomes.

At the end of the treatment, some women proceeded with their planned IVF treatment cycle at the same center as their previous attempts. The IVF protocol was chosen and implemented based on patient characteristics. Intravenous immunoglobulin (IVIG) was administered on the day of embryo transfer if the NK count exceeded 12%.

3. Calculation of reproductive parameters

The following outcomes were retrospectively evaluated in 171 patients: the CPR, first-trimester miscarriages, and the ectopic pregnancy rate. Clinical pregnancy was defined as the presence of at least one intrauterine gestational sac documented via ultrasonography.

4. Statistical analyses

Data were analyzed using the Mann-Whitney test, chi-square test, Fisher test, and Pearson correlation analysis. The adjusted odds ratios (aORs) and their corresponding 95% confidence intervals (CIs) for clinical pregnancy were calculated for patients in the CD138-positive and CD138-negative groups after adjusting for confounding factors, including patients' age, body mass index (BMI), the number of previous embryo transfer cycles, the number of embryos transferred, and the administration of IVIG. Statistical analysis was performed using SPSS ver. 25 (IBM Corp.), and a p-value <0.05 was considered to indicate statistical significance.

5. Ethics approval

The Institutional Review Board of the Seoul National University Bundang Hospital approved this study (B-2007-624-107). This retrospective study received approval from the Seoul Maria Fertility Hospital ethical committee, and informed consent was not applicable.

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Results

Among all patients, the CD138 positivity rate was 32.7% (87/266). The clinical characteristics are presented in Table 1. No significant differences were observed in age, BMI, infertility type, causes of infertility, or serum levels of follicle-stimulating hormone and anti-Müllerian hormone between the CD138-positive and CD138-negative patient groups.

1. Relationship between CD138 and the number of IVF cycles with implantation failure

As shown in Table 2, the CD138 positivity rate was not associated with the number of cycles experiencing implantation failure.

2. Relationship of CD138 with peripheral NK cells and other immunologic markers in CD138-positive and CD138-negative RIF patients

Among RIF patients, we examined immunologic marker tests in 113 patients to determine whether RIF was associated with the expression of CD138 and peripheral blood markers such as lupus anticoagulant, NK cells, anticardiolipin antibody (ACA), protein C/S, homocysteine, antinuclear antibody (ANA), methylenetetrahydrofolate reductase (MTHFR) 678, and MTHFR 1298 (Table 3). An NK cell percentage above 12% and the ANA positivity rate were not associated with the CD138 positivity rate. Moreover, there were no associations between CD138 and other laboratory parameters, including WBC values.

3. CD138 positivity rate according to the NK cell levels

In the subgroup analysis of immunologic markers in RIF patients, 71.7% (n=81/113) of patients had more than 12% NK cells. When comparing the groups with more than 12% NK cells and less than 12% NK cells, the positivity rate of CD138 was not correlated with the RIF group. In the group with more than 12% NK cells, the CD138-positive rate was 25.9% (n=21/81), while in the group with less than 12% NK cells, the CD138-positive rate was 40.6% (n=13/32). However, among RIF patients, the NK cell testing rate was 83.7%, which was higher than that in the non-RIF patient group (30.6%). Consequently, there are limitations to the above analysis, and further research is needed to determine whether these results are specific to the RIF group.

4. Comparison of the pregnancy rate between CD138-positive and CD138-negative patients in the group with RIF

As shown in Table 4, no statistically significant differences were found in the pregnancy rate between CD138-positive patients with RIF and CD138-negative patients with RIF (46.4 % vs. 40.3%; aOR, 1.048; 95% CI, 0.403 to 2.726; p=0.924). Additionally, the CPR was similar between infertile women treated for CE and those without CE.

Discussion

Various efforts have been made to improve the pregnancy rate in patients with RIF, and one of the etiologies of RIF is CE [9]. CE is persistent inflammation of the endometrial lining and is found in 15% of infertile women, although its prevalence has been reported to be substantially higher (42%) in RIF patients [10,11]. Patients with CE

Table 1. Clinical characteristics of patients

Characteristic	CD138-positive (n=87)	CD138-negative (n=179)	*p*-value
Age (yr)	37.15±4.197	37.59±4.165	0.326
Age-H (yr)	39.48±5.108	39.42±4.733	0.663
BMI (kg/m^2)	21.92±3.35	22.17±3.47	0.605
Type of infertility			0.598
Primary	80 (92.0)	161 (90.0)	
Secondary	7 (8.0)	18 (10.1)	
Causes of infertility			0.605
Male factor	13 (14.9)	30 (16.9)	
Endometriosis	1 (1.1)	5 (2.8)	
Tubal factor	7 (8.0)	7 (3.9)	
POR	11 (12.6)	22 (66.7)	
PCOS	5 (5.7)	5 (2.8)	
Uterine	5 (5.7)	11 (6.2)	
Unexplained	10 (11.5)	36 (20.2)	
Combined	35 (40.2)	62 (34.8)	
FSH (mIU/mL)	15.76±65.10	8.73±6.47	0.637
AMH (ng/mL)	3.05±3.77	3.78±12.05	0.208

Values are presented as mean±standard deviation or number (%).
H, husband; BMI, body mass index; POR, poor ovarian reserve; PCOS, polycystic ovarian syndrome; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone.

Table 2. Relationship between CD138 and RIF

	IF						RIF			
	No IF (n=49)	IF=1 time (n=21)	IF=2 times (n=60)	IF ≥3 times (n=136)	Total (n=266)	*p*-value	Non-RIF (n=130)	RIF (n=136)	Total (n=266)	*p*-value
CD138-positive	12 (24.5)	8 (38.1)	26 (43.3)	41 (30.1)	87 (32.7)	0.153	46 (35.4)	41 (30.1)	87 (32.7)	0.433

Values are presented as number (%).
RIF, recurrent implantation failure; IF, implantation failure.

Table 3. Relationship between CD138 and immunologic markers in RIF patients

Variable	CD138-positive (n=34)	CD138-negative (n=79)	*p*-value
NK cells ≥ 12%	61.8 (21/34)	75.9 (60/79)	0.171
Lupus anticoagulant+	0 (0/31)	1.5 (1/68)	1.000
ACA IgM+	19.4 (6/31)	24.6 (16/65)	0.615
ACA IgG elevated	9.7 (3/31)	1.5 (1/65)	0.097
A-B2GP1 IgM elevated	13.3 (4/30)	10.8 (7/65)	0.738
A-B2GP1 IgG elevated	0 (0/30)	1.5 (1/65)	1.000
Antinuclear Ab			0.627
Weakly positive	13.8 (4/29)	10.0 (7/70)	
Positive	6.9 (2/29)	12.9 (9/70)	
MTHFR 678 C/T	46.9 (15/32)	51.4 (38/74)	0.903
MTHFR 678 T/T	21.9 (7/32)	18.9 (14/74)	
MTHFR 1298 A/A	50 (1/2)	83.3 (5/6)	0.464
A/C	50 (1/2)	16.7 (1/6)	
Variable	[a]	[b]	
IgA	R=0.115, *p*=0.256	R=0.119, *p*=0.240	
ATIII	R=–0.046, *p*=0.649	R=–0.061, *p*=0.546	
Protein C	R=–0.032, *p*=0.746	R=–0.048, *p*=0.622	
Protein S	R=–0.025, *p*=0.801	R=–0.023, *p*=0.810	
Precision protein S Ag	R=–0.115, *p*=0.529	R=0.025, *p*=0.892	
Precision protein S (free)	R=0.318, *p*=0.076	R=0.250, *p*=0.168	
Homocysteine	R=–0.089, *p*=0.374	R=–0.122, *p*=0.221	
WBC (10^3/μL)	R=–0.128, *p*=0.140	R=–0.116, *p*=0.179	

Values are presented as percentage (number/total number).
RIF, recurrent implantation failure; NK, natural killer; ACA, anticardiolipin antibody; Ig, immunoglobulin; Ab, antibody; MTHFR, methylenetetrahydrofolate reductase; AT, antithrombin; WBC, white blood cell.
[a]Pearson correlation; [b]Spearman correlation

Table 4. Comparison of pregnancy rate in the RIF and non-RIF patients

Variable	CD138-positive	CD 138-negative	aOR (95% CI)	*p*-value
Pregnancy rate	44.4 (24/54)	41.9 (49/117)	1.058 (0.523–2.142)	0.875
Pregnancy rate in RIF	46.4 (13/28)	40.3 (31/77)	1.048 (0.403–2.726)	0.924
Pregnancy rate in non-RIF	42.3 (11/26)	45.0 (18/40)	1.301 (0.429–3.946)	0.642

Values are presented as percentage (number/total number). The *p*-values were adjusted for patients' age, body mass index, number of previous embryo transfer cycles, number of embryos transferred, and the administration of intravenous immunoglobulin. A *p*-value of ≤0.05 was considered statistically significant.
RIF, recurrent implantation failure; aOR, adjusted odds ratio; CI, confidence interval.

have lower IRs (11.5%) than those without CE (32.7%) [12].

A meta-analysis by Vitagliano et al. [13] suggests that treating CE can improve IVF outcomes in infertile patients. Cicinelli et al. [14] reported that in women with CE, the LBR after antibiotic treatment was comparable to that in women without CE. In 61 women diagnosed with CE by hysteroscopy and histology, a higher CPR and LBR were identified in the cured group (n=46) than in the persistent disease group (n=15) after antibiotic treatment (65.2% vs. 33.0%, *p*=0.039; 60.8 vs. 13.3%, *p*=0.02, respectively). A systematic review [13] that included a total of 796 patients with RIF showed that patients with cured CE had a higher OPR/LBR (odds ratio [OR], 6.81; *p*=0.001), CPR (OR, 4.98; *p*=0.003), and IR (OR, 3.24; *p*=0.01) than those who did not undergo CE treatment. There were no differences in the CPR, OPR/LBR, or IR between patients with cured CE and those without CE.

CE is often asymptomatic or accompanied by mild symptoms. The gold standard for diagnosing CE is to count the number of plasma cells in the endometrium histologically [15]. However, H&E staining has limitations such as inadequate staining, variations between pathologists, and misidentification of plasma cells that are morphologically similar to other stromal cells and leukocytes [16].

Moreover, if hyperemia, mucosal edema, and micro-polyps are present on hysteroscopy, CE can be suspected. In 202 RIF cases, the sensitivity and specificity of hysteroscopy were found to be 35.2% and 67.5%, respectively [17]. The accuracy of hysteroscopy in CE diagnosis was only 67% [18]. Hysteroscopy is also dependent on the clinician's experience.

As a result, recent studies have recommended using CD138 immunohistochemistry (IHC) staining for plasma cells as a diagnostic method for CE. IHC can reduce inter- or intra-observer variability [19] and enhance the sensitivity of microscopic plasma cell identification through rapid counting [7,20]. The use of CD138 IHC significantly increased the prevalence of CE from 13% to 56% compared to H&E staining and morphological assessment alone [7]. Furthermore, several studies have reported CE prevalence rates of 7.7% to 44% by using CD138 IHC in patients [12,21,22].

Nevertheless, variations in the criteria used to determine the threshold for CD138-positive plasma cell counts in research studies exist. Some studies [7,12] defined CE as the presence of more than one CD138 (+) plasma cell per HPF, while others [23,24] established the criterion as being ≥1/10 HPFs. Recently, McQueen et al. [25] suggested that CE could be defined as the presence of one or more plas-

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ma cells per 10 HPFs, detectable through either H&E staining or CD138 staining, in the context of endometrial stromal changes after comparing endometrial specimens of RPL patients and non-infertility patients. An alternative argument proposes that CE should be considered when the number of CD138-positive cells per HPF is equal to or greater than 5, considering pregnancy outcomes [26]. However, recent studies [25,27,28] have leaned towards defining CE as the presence of one or more CD138-positive plasma cells, and we have adopted this definition in our study.

The sensitivity and specificity of CE detection through CD138 IHC have been reported to be approximately 40%–86.36% and 53%–87.30%, respectively [11,23,29,30]. Patients with CD138-positive cells showed a significantly lower CPR (52.7%) and IR (46.8%) than patients without CD138-positive cells (80.4% and 64.9%, respectively). The authors concluded that high CD138-positive cell counts could predict poor pregnancy rates, while low levels did not imply better pregnancy rates [29]. Additionally, there was an improvement in pregnancy outcomes when patients with high CD138-positive cells were treated with antibiotics [7,31].

History of a previous prolonged menstrual bleeding episode, submucosal myoma, endometrial hyperplasia, abortion history, fallopian tube obstruction, and the presence of pelvic fluid on the sampling day have been reported as risk factors for a CD138-positive cell count. With this history, a CD138 test can be suggested even if the patient does not have RIF [29,32]. In our study, we observed no significant difference in the CD138-positive rate between patients with RIF and those without RIF. Among the patients in the non-RIF group, which comprised 130 patients, 30 (23.1%) underwent CD138 testing while hysteroscopic endometrial polypectomy was performed concurrently. Additionally, within this non-RIF cohort, 36 patients (27.7%) had a history of abortion, 14 patients (10.8%) had a tubal factor as their primary condition, two patients (1.5%) had endometrial hyperplasia, and one patient (0.8%) had a submucosal myoma. These factors align with previously reported risk factors for CE [5]. Consequently, our findings may differ from studies that have shown a higher CD138 detection rate in patients with RIF [7,11,14]. Therefore, even within the non-RIF population, CD138 testing may be considered when performing hysteroscopic procedures for reasons such as submucosal myoma, endometrial hyperplasia, or endometrial polyps, or if patients have a history of previous miscarriage.

However, debate continues over whether CD138 can be used as a marker for CE. First, some studies used a different method to quantify CD138-positive cells. Second, CD138-positive cells can also be found among epithelial cells, fibroblastic cells, and B-cells [33,34].

Therefore, in this study, we aimed to determine whether the RIF group had a high CD138 positivity rate and whether the pregnancy rate could be increased by performing CD138 testing and giving antibiotic treatment. The CD138 positivity rate was not found to be related to the number of cycles with implantation failure. In RIF patients, the CD138 positivity rate was 30.1%, which was quite high compared to the 7.7%–44% rate suggested in a previous study.

In addition, the pregnancy rate was similar between the CD138-positive and CD138-negative groups. However, since the CD138-positive patients tried to conceive after undergoing antibiotic treatment, it is not known whether CE independently affected the pregnancy rate or whether no difference was detected in the CD138-negative group because CE had already been cured by the antibiotic treatment.

However, previous studies have consistently shown that when doxycycline is administered to patients with CE, the cure rate ranges from 75% to 100% [12,14,31,35,36]. Furthermore, the CPR significantly improved after successful treatment compared to untreated CE patients and was comparable to that of patients without a CE diagnosis. Our study revealed that the CPR was similar between CD138-positive patients with antibiotic treatment and CD138-negative patients without treatment in both the RIF and non-RIF groups. Therefore, it can be inferred that conducting CD138 testing for individuals with risk factors for CE who are planning embryo transfer, and promptly initiating antibiotic treatment upon a positive result, may be beneficial.

The immunological response involves a physiological inflammatory process. Therefore, several studies have examined the association between various immunological markers and CE.

Tang et al. [37] investigated whether there was a relationship between a high percentage of peripheral NK cells and subsequent miscarriage in women with idiopathic recurrent miscarriage and transplant failure, but there was no association. There were no significant differences in peripheral blood T-cells, NK cells, or B-cells between women with and without CE. The levels of NK cell cytotoxicity and Th1 cytokines (interferon-gamma and tumor necrosis factor) were similar in both groups [38]. A previous study also showed that in RIF patients with a high NK cell ratio, the LBR increased from 17.9% to 80.0% after IVIG treatment [39].

Few studies have examined the relationship between immune factors and CE, and there have been no studies on the association with CD138. Therefore, we examined the association between CD138 and other immune-related factors.

CD138 and blood peripheral markers, such as lupus anticoagulant, NK cells, ACA, protein C/S, homocysteine, and ANA, were similar between women with and without CD138-positive cells. Furthermore, an NK cell percentage above 12% and a positivity rate for ANA were not associated with the CD138 positivity rate.

Our study has the limitation that the number of patients assigned to each group was different because the rate of NK cell testing was high in patients with RIF. In our study, we set the normal limit of pe-

ripheral NK cells at 12% based on a study by Beer et al. [40], but there is no normal range that is generally used. In addition, peripheral NK cells can increase in situations such as stress or exercise [41].

This was a retrospective study with limited data. Further research is needed to replace H&E staining with CD138 IHC as a method for diagnosing CE. Moreover, routinely performing CD138 testing in patients with RIF is not recommended. However, to increase the pregnancy rate in RIF patients or patients who are planning to undergo a hysteroscopic operation for endometrial pathology, it may be helpful to combine CD138 IHC with other laboratory tests and administer treatment based on the results.

Conflict of interest

Byung Chul Jee is the Editor-in-Chief , Jung Ryeol Lee is an Editorial Board Member and Seul Ki Kim is an Associate Editor of *Journal of Clinical and Experimental Reproductive Medicine*; however, they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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