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Original Research Article

Role of CD 138 for the diagnosis of chronic endometritis in unexplained infertility and recurrent pregnancy loss

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ABSTRACT

Background: Chronic endometritis (CE) is persistent inflammation of the endometrium in response to bacterial infection, which may be mostly asymptomatic. However, patients may present with pain abdomen, abnormal uterine bleeding, pelvic discomfort, leukorrhea and dyspareunia. In this study, we have compared the role of hysteroscopy and CD 138 IHC for the diagnosis of CE in unexplained infertility and RPL. We have also studied the reproductive outcome following cure of CE with antibiotics.
Methods: A prospective study, recruiting 107 participants, was carried out in the department of reproductive medicine and surgery at Mahatma Gandhi hospital, Jaipur, India. The study duration was between September 2022 and April 2024, including 8 months follow up.
Results: The mean age of the patients in unexplained Infertility group was 34.4±4.9 years (range, 25-41 years) and in RPL group was 33.7±3.9 years (range, 20-40 years). Out of the total 107 patients, 75 patients presented with unexplained infertility and 32 presented with RPL.
Conclusions: It was found that both hysteroscopy and immunohistochemical analysis of CD138 cells are equally effective to diagnose CE. While hysteroscopy can be used to obtain a guided biopsy, from the most suspicious areas, it is an invasive procedure and diagnosis is observer dependent.

Keywords: Chronic endometritis, Unexplained infertility, Recurrent pregnancy loss, CD 138, Hysteroscopy

INTRODUCTION

The field of reproductive medicine has made huge advancement; however, a major challenge, yet to overcome by reproductive medicine specialists is that of a failed implantation of transferred embryos and recurrent miscarriages and unexplained infertility.[1] One of the major contributing factors is impaired endometrial receptivity which leads to recurrent implantation failure, unexplained infertility and repeated pregnancy losses (RPL).[2] CE is persistent inflammation of the endometrium in response to bacterial infection, which may be mostly asymptomatic.[3] However, patients may present with pain abdomen, abnormal uterine bleeding, pelvic discomfort, leukorrhea and dyspareunia.[4] The causative organisms include different species of *Mycoplasma*, *Ureaplasma*, *E. coli* and *Streptococcus*.[5,6] The disease is characterized by plasma cell infiltration in the stroma, stromal edema, increased

stromal cell density and dissociated maturation of the stroma and epithelium.[6-8]

Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies.[9] The prevalence of CE varies between 27% to 67.6% in patients with RPL.[11] On the other hand, CE is highly prevalent among patients with unexplained infertility; a prevalence of 56.8% has been found in a study.[12] Studies have shown a significantly higher pregnancy rate among women who were adequately treated compared to women who were not treated or had persistent disease even after antibiotic therapy.[13,14]

The diagnosis of CE can be made by conventional H and E staining, by identifying plasma cell infiltration in Histopathological examination of endometrial biopsy specimen.[7,8,15] However, owing to difficulty in distinguishing between plasma cells and leukocytes in the stroma, the diagnostic accuracy is not very high.[7,8] Hysteroscopic diagnostic features of CE include strawberry appearance of endometrium, focal hyperemia, endometrial micropolyp (measuring less than 1 mm), hemorrhagic spots and stromal edema.[8,16] Another novel method of diagnosing CE is CD138 immunohistochemistry (IHC) of plasma cells. Antibodies recognize CD 138 antigen on the plasma cells.[16]

In this study, we have compared the role of hysteroscopy and CD 138 IHC for the diagnosis of CE in unexplained infertility and RPL. We have also studied the reproductive outcome following cure of CE with antibiotics.

METHODS

A prospective study, recruiting 107 participants, was carried out in the department of reproductive medicine and surgery at Mahatma Gandhi hospital, Jaipur, India. The study duration was between September 2022 and April 2024, including 8 months follow up. Ethical clearance was obtained by the institutional ethics committee.

The inclusion criteria included: Unexplained infertility of more than 1 year duration (excluding anovulation, tubal and male factor infertility), females with ≥2 RPL/miscarriages, cervicitis and pelvic inflammatory disease (PID). The exclusion criteria included: Females with intrauterine contraceptive devices (as it is characterized by prolonged plasma cell accumulation even after their removal from the uterine cavity), presence of endometriosis and adenomyosis, post-gestational long-term retention of products of conception, acute suppurative endometritis (recognized as neutrophil invasion and micro abscess formation in the endometrium), uterine and/or cervical tumors, previous recent treatments with chemotherapy, specific disease as tuberculosis, diabetes, liver or renal chronic diseases and uterine abnormalities.

The participants were explained about the study and an informed consent was taken. Hysteroscopy was performed in the follicular phase under general anesthesia. Systematic evaluation of the cervical canal, uterine cavity and endometrium was done. CE was diagnosed on the basis of presence of stromal edema, endometrial hyperemia or micropolyps. Endometrial biopsy was taken, fixed in formalin, and sent for CD 138 IHC examination and H and E staining. The immune-stained slides for CD 138 IHC examination, were scored for the presence of immunostaining of plasma cells using light microscopy, in at least 10 high power field (HPF). Each section was graded as negative, when no plasma cells stained with CD138; positive, when at least 1 or more than 1 plasma cells were seen. We categorised CE as mild, when the number of plasma cells identified on IHC were between one and five; and CE was categorised as severe, when five or more plasma cells were seen.[10] The formalin fixed slides were stained with routine H and E stain, for detection of plasma cells and diagnosing CE.

The hysteroscopic findings, H and E staining results and CD 138 report were recorded and results analysed. The patients, in whom CE was diagnosed by either Hysteroscopy or CD 138 IHC staining or H and E staining or any combination of the three tests, were given antibiotic treatment, doxycycline 100mg twice daily and metronidazole 600 mg twice daily for 14 days for both partners. A repeat endometrial biopsy with Pipelle cannula was taken and sent for CD 138 IHC analysis, to assess for the cure of CE, after 2 weeks of completion of first line antibiotics. The second line antibiotic ofloxacin 400mg once daily or clindamycin 600mg once daily was given when CE did not subside after the first line treatment. All the participants were followed for a period of 8 months for reproductive outcome.

RESULTS

The mean age of the patients in unexplained Infertility group was 34.4±4.9 years (range, 25-41 years) and in RPL group was 33.7±3.9 years (range, 20-40 years). Most of the patients belonged to lower socio-economic status as per the modified Kuppuswamy scale. There was no significant difference between the demographic characteristics in the groups (Table 1).

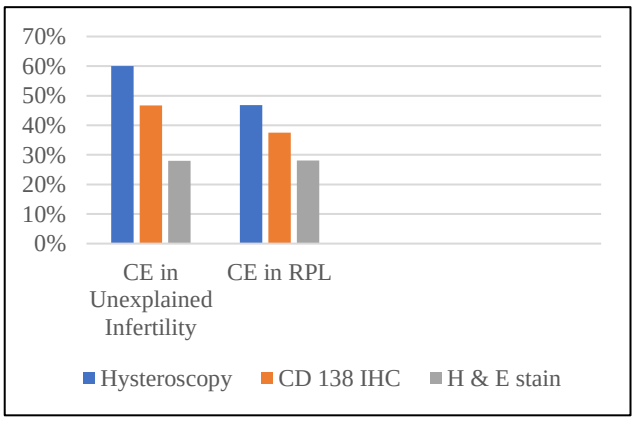

Figure 1: Comparison of different diagnostic modalities for the diagnosis of CE.

Out of the total 107 patients, 75 patients presented with unexplained infertility and 32 presented with RPL. Of the 75 patients with unexplained infertility, CE was positive on hysteroscopy in 45 patients (60%); CE was positive on H and E staining in 21 patients (28%) and CE was positive by CD 138 staining in 35 patients (46.66%) (Figure 1). Out of these 35 patients who were diagnosed by CD 138 IHC, 10 patients had severe CE (number of plasma cells were 5 or more than 5/ 10 HPF) (Table 2).

Of the 32 patients who presented with RPL, CE was positive on hysteroscopy in 15 patients (46.8%); CE was positive on H and E in 9 patients (28.12%) and CE was positive on CD 138 staining in 12 patients (37.5%). Out of these 12 patients who were diagnosed by CD 138 IHC, 6 patients had severe CE (Table 2).

In patients with unexplained infertility, 46.66% patients were found to have CE on CD 138 IHC evaluation and 60% patients found to have CE on hysteroscopy (p=0.10). In patients with RPL, 37.5% patients were found to have CE on CD 138 IHC evaluation and 46.8% patients found to have CE on hysteroscopy (p=0.45). Thus, our study didn't find significant difference between hysteroscopic diagnosis and CD 138 IHC diagnosis of CE (Table 2).

In patients with unexplained infertility, a statistically significant difference was found on comparing the diagnosis of CE on CD 138 IHC analysis and H and E staining (p=0.04). In patients with RPL, a statistically significant difference was found on comparing the diagnosis of CE on CD 138 IHC analysis and H and E staining (p=0.02) (Table 3).

First line antibiotic treatment with doxycycline 100 mg twice daily and metronidazole 600 mg twice daily for 14 days was given to both partners after female partner was diagnosed with CE, either on hysteroscopy, CD 138 IHC or both. Two weeks after completion of the antibiotic course, a repeat endometrial biopsy was taken using a Pipelle's cannula on Out Patient basis and sent for CD 138 IHC evaluation, to assess the cure of CE.

Among 35 patients with CE diagnosed on CD 138 IHC evaluation in patients with unexplained infertility, 10 patients had severe CE (5 or more plasma cells/10 HPF). Of these 10 patients, 6 (60.9%) patients required second line treatment for CE. Among the remaining 25 patients with mild CE, 3 (12%) patients required second line antibiotics (Table 4).

Among 12 patients with CE diagnosed on CD 138 IHC evaluation in patients with RPL, 6 patients had severe CE (5 or more plasma cells/10 HPF). Of these 6 patients, 4 (66.67%) patients required treatment with second line antibiotics. Of the remaining 6 patients with mild CE, 2 (33.3%) patients needed second line antibiotic therapy (Table 5). Thus, in our study, the need for second line antibiotic was higher among patients with severe CE, diagnosed with CD 138 IHC. The second line antibiotics, ofloxacin 400mg once daily or clindamycin 600mg were given once daily for both partners for 10 days. We did not assess for the cure after completion of second line antibiotic therapy.

A total of 18 (24%) patients conceived in the Unexplained infertility group during the study period, of which 4 patients conceived spontaneously, 11 patients conceived with intra uterine insemination (IUI) and 3 patients conceived with *in vitro* fertilisation (IVF). Fourteen (77.78%) pregnancies were ongoing at the completion of the study period. A total of 19 (59.37%) patients conceived in the RPL group during the study period, of which 14 patients conceived spontaneously, 3 patients conceived with IUI treatment and 2 patients conceived with IVF. Thirteen (68.4%) pregnancies were ongoing at the end of the study period (Table 6). Remaining (4 pregnancies in unexplained group and 6 pregnancies in RPL group) had spontaneous or missed abortions between 6-8 weeks of gestation.

Table 1: Demographic characteristics.

Variables	Unexplained infertility	RPL	P value
Number of patients	75	32	0.08
Age (in years)	34.4±4.9	33.7±3.9	0.12
BMI (kg/m^2)	23.71±1.2	22.9±2.6	0.22
History of PID, cervicitis	53	22	0.19
History of abnormal uterine bleeding	46	18	0.27

Table 2: CD 138 versus hysteroscopic diagnosis of CE.

Variables	CE positive with CD 138 IHC	CE positive on hysteroscopy	P value
Unexplained infertility	35 (46.66%)	45 (60%)	0.10
RPL	12 (37.5%)	15 (46.8%)	0.45

Table 3: CD 138 versus H and E diagnosis of CE.

Variables	CE positive with CD 138 IHC	CE positive on H and E stain	P value
Unexplained infertility	35 (46.66%)	21 (28%)	0.04
RPL	12 (37.5%)	9 (28.12)	0.02

Table 4: Number of patients requiring second line antibiotics in unexplained infertility group.

Variables	N (%)
CE positive with CD 138 IHC	35
Severe CE on CD 138 IHC evaluation	10
Patients with severe CE requiring second line antibiotics	6 (60)
Patients with mild CE (n=25) needing second line antibiotics	3 (12)

Table 5: Number of patients requiring second line antibiotics in RPL group.

Variables	N (%)
CE positive with CD 138 IHC	12
Severe CE on CD 138 IHC evaluation	6
Patients with severe CE requiring second line antibiotics	4 (66.67)
Patients with mild CE (n=6) needing second line antibiotics	2 (33.3)

Table 6: Reproductive outcome after treatment of CE.

Variables	Spontaneous conception	IUI pregnancies	IVF pregnancies	Total clinical pregnancies	Total ongoing pregnancies
Unexplained infertility, (n=75)	4	11	3	18 (24%)	14 (77.78%)
RPL, (n=32)	14	3	2	19 (59.37%)	13 (68.4%)

DISCUSSION

The possible association of CE and infertility has developed a new found area of research among clinicians, especially among reproductive medicine specialists, in the recent years. Previously, CE was often overlooked as it is clinically silent and it was thought that the condition is apparently benign.[4] Some risk factors for CE include, a previous history of prolonged menstrual bleeding episodes, previous history of pregnancy losses, a history of obstruction of fallopian tube, PID, chronic cervicitis or recurrent vaginitis.[17] We found 60% prevalence of CE among patients with unexplained infertility and 46.8% prevalence of CE among patients with RPL. A study by Gu et al has reported a very high prevalence of CE (67.5%) among patients with RPL.[21] Study by Elnashar et al have found that CE was seen in 28% patients with unexplained infertility and in 12% patients with recurrent implantation failure.[18] Another study by Ticconi et al found a 19.46% prevalence of CE among patients with unexplained infertility and a 37.6% prevalence of CE among RPL patients.[30] The diagnosis of CE is a challenge to the clinicians as the disease is pauci-symptomatic.[18] However, it has been shown that there is an association between CE and poor reproductive outcomes.[12,19] The high prevalence of CE in our study could be due to the fact that most of the patients belonged to lower socio economic status. They either do not access healthcare for management of vaginitis and PID, or they do not complete the proper course of antibiotics.

CE is often asymptomatic and there are no standard clinical or diagnostic methods available for diagnosis. Hence, it may be easily missed. The diagnostic modalities used in our study for the diagnosis of CE are hysteroscopy, H and E staining and CD 138 IHC. Hysteroscopy serves as a useful tool for identification of specific visual signs of CE. The diagnostic signs on hysteroscopy include micropolyps, edema and hemorrhagic spots. Our study found that the diagnosis of CE via hysteroscopy and CD 138 IHC is equally good (p value being non-significant). The advantage of hysteroscopy includes visual assessment of the endometrial cavity and signs of CE. However, the diagnosis of CE by hysteroscopy is strongly operator dependent, i.e., different perception by different observer. Another disadvantage includes the invasive nature of the procedure. CD 138 IHC staining, on the other hand, improves diagnostic accuracy and sensitivity. Moreover, an endometrial biopsy sample can be taken in the outpatient department, and sent for CD 138 IHC analysis, (as we have done in our study). This method is less invasive and is preferred by the patients.

Several studies have assessed the diagnosis of CE on hysteroscopy and IHC staining. We found 46.8% positivity on hysteroscopy and 37.5% positivity by CD 138 staining, among women with RPL. A study by Farghali et al found

that among women with RPL, 31.8% women had CE findings on hysteroscopy, and 38.2% were diagnosed by IHC staining, which was close to the findings of our study.[11,21] A study by Zarger et al reported 36.8% and 31.6% positivity on the basis of hysteroscopy and CD 138 IHC staining respectively among women with RPL.[22] These findings are close to the findings from our study.

Among patients with Unexplained Infertility, we found that, CE was found on hysteroscopy in 60% patients and by CD 138 IHC in 46.66% of the patients. A study by Cicinelli et al found that among women with unexplained infertility, hysteroscopy showed signs of CE in 56.8% which is consistent with the finding in our study.[12] Bouet et al in their study, have shown that endometrial biopsy with IHC staining has higher diagnostic accuracy as compared with hysteroscopy alone.[10,20] Our study, however, found that both modalities (CD 138 and hysteroscopy) are equally good for CE diagnosis. A less invasive mode for obtaining endometrial biopsy for CD 138 IHC might be preferred by the patient.

The criteria for defining CE used in our study was presence of one or more plasma cells/ 10 HPF. We defined severe CE as 5 or more plasma cells/ 10 HPF. However, there is no definite cut off of the number of plasma cells to diagnose CE with CD 138 IHC. Various studies have used different thresholds. Presence of only one Plasma cell in the slide was used to diagnose CE in the study by Cicinelli et al.[12] Bouet et al and Farghalli et al have found that low number of plasma cells may not be sufficient to diagnose CE.[10,11] Study by Liu et al defined CE on the basis of number of plasma cells per mm square and said that less than 5 plasma cells per mm square is considered normal.[5] Other studies have defined CE on the basis of number of plasma cells per HPF. Johnson et al defined CE when more than one plasma cell was identified per HPF and Chen et al defined CE when more than 5 plasma cells were identified per HPF.[27,28] Elnashar et al defined CE when one or more plasma cells were found in 20 HPF.[18]

We found a statistically significant difference when comparing the diagnosis of CE by CD 138 IHC and by H and E staining (p=0.04 in unexplained infertility group and 0.02 in RPL group). The disadvantage of H and E staining is that it is time consuming and the accuracy is also compromised due to stromal cell proliferation and mononuclear cell infiltration.[4,10,20] On comparing CD 138 IHC and H and E staining, study by Mcqueen et al found that CD 138 has increased sensitivity of diagnosing CE, which is also consistent with our study.[31]

The management includes a course of broad spectrum oral antibiotics, like doxycycline, quinolones, macrolides, for 14 days for both partners.[14] We gave first line course of antibiotics for 14 days for both partners, when CE was positive by any method. Cure of CE was assessed after 2 weeks of antibiotic completion, by performing an endometrial biopsy in out patient. It was found that most of the patients with severe CE diagnosed by CD 138 IHC, required second line antibiotic therapy. Study by Sakkai et al prescribed the first line antibiotics doxycycline and metronidazole for 14 days and re assessed for the cure of CE. They gave second line antibiotics to the patients with persistent disease, as was done in our study. Zargar et al prescribed antibiotics (doxycycline and metronidazole) for 21 days.[23,32]

Various studies have shown the effect of cure of CE on the reproductive outcomes. Our study also found that reproductive outcomes improved after antibiotic therapy of CE. In the unexplained infertility group (75 in total), there were 18 (24%) clinical pregnancies, with 14 ongoing pregnancies (77.78%). In the RPL group (32 in total), there were 19 (59.37%) clinical pregnancies, with 13 ongoing pregnancies (68.4%). A study by Vaduva et al has shown positive effect of antibiotic treatment of CE on the outcome of IVF.[14] Another study by Kaku et al has reported significantly high clinical pregnancy rates (74%) after antibiotic treatment of CE in patients with RPL and unexplained infertility.[24] Yang et al found improved implantation rate (IR) and CPR after antibiotic treatment of CE.[25] Gay et al showed improved live birth rate (LBR) after treatment of CE in women with RPL.[26] One study showed that clinical pregnancy and LBR was higher in patients who were cured, as compared to patients with persistent CE.[21] Thus, effective treatment improves the clinical and reproductive outcomes in patients with CE. We also found, that the patients who had severe CE, had to be treated with second line antibiotics. However, we did not assess the cure of CE after giving second line antibiotics.

The limitations of the study include a small sample size. Secondly, patients were followed for a short duration for Reproductive outcomes. Thirdly, LBR was not assessed.

Studies are limited and more prospective RCT, with large sample size and a longer follow up time, need to be conducted. Studies to determine the threshold of plasma cells for diagnosis of CE are also needed.

CONCLUSION

The prevalence of CE is high among RPL patients and in patients with unexplained infertility. Timely diagnosis and management can lead to a good reproductive outcome.

It was found that both hysteroscopy and immunohistochemical analysis of CD138 cells are equally effective to diagnose CE. While hysteroscopy can be used to obtain a guided biopsy, from the most suspicious areas, it is an invasive procedure and diagnosis is observer dependent.

The diagnosis of CE via CD 138 IHC can even be done on endometrial Pipelle sample, thus avoiding an invasive operative (hysteroscopic) procedure. However, a unified diagnostic criterion has not been defined for the diagnosis of CE.

Resolution of CE after antibiotic therapy may lead to improved reproductive outcomes, as compared to women without CE. Patients with severe CE mostly need treatment with second line antibiotics.

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