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**Original Research Article**

# Chronic endometritis in cases with recurrent embryo implantation failure

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## ABSTRACT

**Background:** Chronic endometritis (CE) is a cause of recurrent implantation failure (RIF) in patients undergoing intracytoplasmic sperm injection (ICSI). CE is diagnosed based on the presence of plasma cell infiltration of the endometrial stroma in endometrial biopsies. Hysteroscopy may be suggestive of CE while the immunohistochemistry with specific cell markers for CD138 cells has been suggested as a more accurate test for the diagnosis of CE.
**Methods:** This study included 110 patients with recurrent ICSI failure (two or more), despite using good-quality embryos. Hysteroscopy and endometrial biopsy were performed as an outpatient procedure. Immunostaining was then performed using a mouse monoclonal CD138 antibody. The prevalence rate of CE was calculated, and the correlation between hysteroscopic findings and immunohistochemical results was assessed.
**Results:** In the included patients in this study there was 32 cases (29%) were diagnosed as CE by hysteroscopy, while 27 cases (24.5%) were positive by CD138 immunohistochemistry (IHC), and 18 cases (16.36%) were positive for CD138 IHC with hysteroscopic features of CE. The presence of more than one abnormal hysteroscopic features was considered positive for CE rather than single abnormal feature, the sensitivity, specificity, positive and negative predictive values of hysteroscopy would be 22.2%, 98.8%, 85.7%, and 79.6%, respectively.
**Conclusions**: The negative diagnostic value of hysteroscopy is high, the combination of the two diagnostic modalities (hysteroscopy and CD138 IHC) will aid in the detection of most cases of CE.

**Keywords:** Chronic endometritis, Hysteroscopy, CD138 antibody

## INTRODUCTION

Embryo implantation is a critical phase in IVF. An effective interaction between high-quality embryos and a receptive endometrium is necessary for successful pregnancy.[1,2] Recurrent implantation failure (RIF) is one of the great challenges of current reproductive medicine. The term RIF refers to the failure of implantation with repeated transfers of embryos of good morphological quality.[3,4] Some experts diagnose RIF after just two prior unsuccessful IVF-ET attempts. Its failure can be caused by variables related to embryo quality and anatomical, immunological, or inflammatory factors.[5-7]

Embryo-endometrial attachment can be hampered by fibroids, polyps, and adhesions that form after surgery or infection.[8] Moreover, mullerian abnormalities and hydrosalpinx should be taken into consideration as they can have a negative impact on implantation rates.[9,10]

Chronic endometritis (CE) is a persistent inflammatory disorder of the endometrial lining, characterized by superficial endometrial edematous change, high stromal

cell density, dissociated maturation between the epithelium and stroma, and infiltration of endometrial stroma by plasma cells.[11] In most cases, women with CE are asymptomatic or display mild disturbances, such as abnormal uterine bleeding (AUB), dyspareunia, vague pelvic pain, and leukorrhea.[12,13] Moreover, CE cannot be identified by ultrasound examination because of a lack of specific ultrasound markers. For these reasons, CE is frequently underestimated or accidentally diagnosed during workups for AUB, infertility, or chronic pelvic pain.[14]

CE may have an impact on female fertility in a variety of ways, beginning with changes to the endometrial microbiota and continuing with inflammation and its adverse effects.[15] Overexpression of cytokines and leukocytes could impair the immunological tolerance of the endometrium to the embryo and alter endometrial vascular permeability, potentially hindering trophoblast invasion and damaging embryo viability.[15,16] Furthermore, altered uterine contractions during the midluteal phase may prevent fertilization and interfere with sperm and embryo transuterine migration before implantation. Finally, in women with CE, aberrant autophagy may influence endometrial cell commitment and compromise endometrial decidualization.[16,17]

CE is diagnosed based on the detection of abnormal plasma cell infiltration in the endometrial stroma. Histopathological examination of endometrial biopsies to detect abnormal plasma cell infiltration in the endometrial stroma can be performed using conventional hematoxylin and eosin (HE) staining. However, it is sometimes difficult to distinguish the plasma cells from the fibroblasts and monocytes of the endometrial stroma; thus, the success rate of accurate diagnosis and treatment of chronic endometritis is not high.[18]

More recently, immunohistochemistry with specific cell markers for CD138 cells has been suggested as a more accurate test for the diagnosis of chronic endometritis. Immunohistochemical analysis of CD138+ cells are an effective method to detect CE, which can be identified by the presence of ≥5 plasma cells in at least one of 30 high-power fields (HPF).[19]

It is well accepted that the presence of micro-polyps (small endo-uterine ingrowths less than 1 mm size with a vascular axis), mucosal edema, focal or diffuse endometrial hyperemia are recognized hysteroscopic findings of patients diagnosed with CE. Endometrial hyperemia may show a strawberry appearance, revealing prominent white glands surrounded by hyperemia.[18,19,20]

### *Aim*

The aim of our study was to assess the prevalence of chronic endometritis in women with recurrent ICSI failure and to determine the correlation between hysteroscopic findings and CD138 immunohistochemistry (IHC) of endometrial biopsies in the diagnosis of chronic endometritis.

## METHODS

This is a prospective observational cross-sectional study was conducted, after approval of ethical committee, on 110 patients with recurrent ICSI failure from Middle East fertility center in Alexandria from May 2021 to April 2022. The patients included in the study were infertile women with a history of recurrent ICSI failure (two or more), despite using good-quality embryos. The patients were age between 20-40 years old with a BMI of less than 30 kg/m$^2$. Patients with endocrine, hematologic, and autoimmune disorders, hydrosalpinx, or any intracavitary defects such as fibroids, synechiae, or septum, and those who received empirical antibiotics for chronic endometritis were excluded from the study.

All cases were subjected to detailed history-taking, general and local examinations, and routine laboratory investigations. Three-dimensional ultrasound was performed in all studied cases to exclude structural abnormalities of the uterus and to assess the endometrial cavity.

Hysteroscopy and endometrial biopsy were performed as outpatient procedures without anesthesia. Hysteroscopy was performed using a 3-mm 30 rigid hysteroscope with normal saline solution as the distension medium of the uterine cavity. Cervical canal examination was performed to exclude cervicitis or any associated pathology. Hysteroscopic features such as endometrial micropolyps, endometrial hyperemia, and edema were recorded.

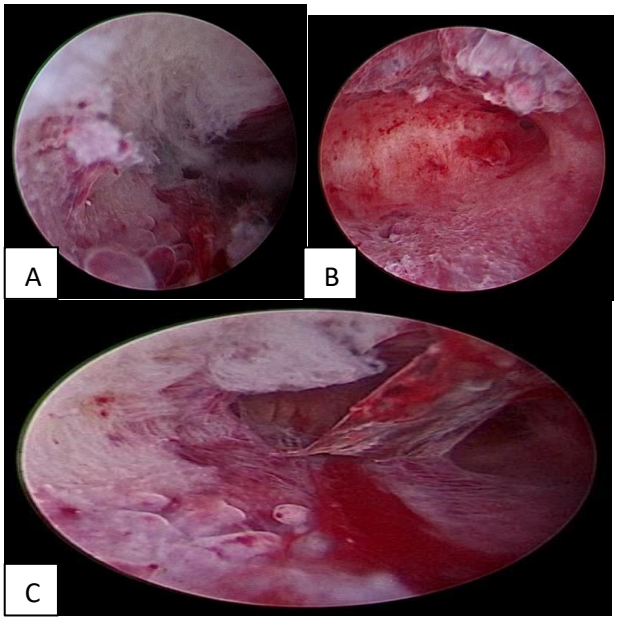


**Figure 1: (A) Micro-polyps with mucosal edema; (B) Diffuse hyperemia with mucosal edema; (C) Endometrial hyperemia with mucosal edema and micro-polyps.**

Endometrial biopsy was performed blindly in each case using a 3-mm Novac metallic curette connected to a 20 ml syringe after hysteroscopic evaluation of the uterine cavity. Thereafter, the endometrial samples were fixed in 10% formalin overnight. The following day, the samples were processed into paraffin blocks. Hematoxylin and eosin (H&E) stained sections were used to assess histopathological findings.

Immune staining was then performed using a mouse monoclonal CD138 antibody (#760-4248, clone B-A38, Roche Diagnostics, USA). The Ventana benchmark GX autostainer was used. The specimens were graded as ''positive'' for CE if there were ≥ 5 plasma cells per out of 30 high-power fields (HPF).

The prevalence rate of CE was calculated, and the correlation between hysteroscopic findings and immunohistochemical results was assessed.

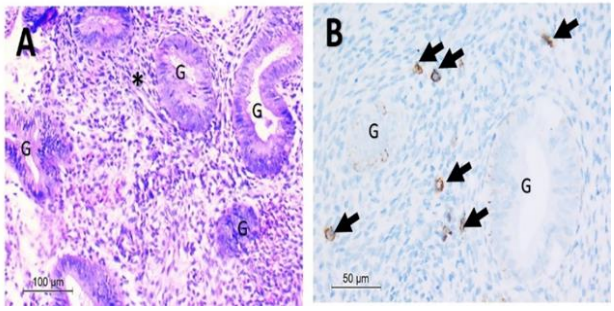


**Figure 2: (A) H and E stained section of an endometrial biopsy showing disorganized glands (G) of variable sizes in edematous cellular stroma. Stromal spindling and swilling around glands (*) is seen (H&E, x200); (B) CD138 immune staining of same case showing multiple positive plasma cells in stroma (> 5/HPFs) indicating the diagnosis of chronic endometritis (IHC, x400).**

***Statistical analysis of the data***

The sample size was calculated based on a previous study using the MedCalc statistical software. Assuming area under ROC to be 0.80, an alpha of 0.05, and power of study 90.0%, the beta error was 0.1. A typical suggestion is to reject the null hypothesis H0 if the corresponding p-value is smaller than 0.05. A minimum sample size of 100 patients was required for this study, with 70 patients in each group. This was a tailed study.

Data were fed to the computer and analyzed using the IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)**. Qualitative data are described as numbers and percentages. Quantitative data were described using the range (minimum and maximum), mean, standard deviation, median, and inter quartile range (IQR). significance of the obtained results was determined at the 5% level.

Chi-square test-For categorical variables, to compare between different groups, Fisher's exact-Correction for chi-square when more than 20% of the cells had expected count less than 5.

## RESULTS

Our study included 110 women: 23 women had normal body weight and 87 women were overweight. 85 women had primary infertility and 25 women had secondary infertility. 84 women underwent two failed ICSI, and 26 women underwent three or more failed ICSI. Most of the cases were asymptomatic, except for 13 cases, as shown in Table 1.

**Table 1: Distribution of the studied cases according to patients history (n=110).**

| Patients' history | N | Percentages (%) |
|---|---|---|
| **Age (years)** | | |
| <30 | 51 | 46.4 |
| ≥30 | 59 | 53.6 |
| Min.-Max. | 24.0-39.0 | |
| Mean ± SD. | 30.40±4.09 | |
| Median (IQR) | 30.0 (27.0-34.0) | |
| **BMI (kg/m$^2$)** | | |
| Normal (18.5-24.9) | 23 | 20.9 |
| Overweight (25-30) | 87 | 79.1 |
| Min.-Max. | 22.0-30.0 | |
| Mean ± SD. | 26.75±2.50 | |
| Median (IQR) | 27.0 (25.0-29.0) | |
| **Infertility** | | |
| 1 try | 85 | 77.3 |
| 2 try | 25 | 22.7 |
| **Number of failed ICSI** | | |
| 2 | 84 | 76.4 |
| >3 | 26 | 23.6 |
| **Symptoms** | | |
| Free | 97 | 88.2 |
| AUB | 6 | 5.45 |
| Chronic pelvic pain | 7 | 6.4 |

IQR: Inter quartile range, SD: Standard deviation.

Positive hysteroscopic findings were found in 27.1 % of women with primary infertility (23 cases of 85), and 36% of women with secondary infertility (9 cases=25). Whereas, positive CD138 IHC was found in 24.7% of women with primary infertility (21 cases of 85) and 24% of women with secondary infertility (6 cases of 25) as shown in Table 2.

Positive hysteroscopic findings were found in 26.2 % of women with two failed ICSI (22 cases of 84) and 38.5% of women with three or more failed ICSI (10 cases of 26). Whereas, Positive CD138 IHC was found in 21.4% of women with two failed ICSI (18 cases of 84) and 34.6% of cases with secondary infertility (9 cases of 26), as shown in Table 3.

The prevalence of hysteroscopic features in our study was as follows: focal endometrial hyperemia, 10 of 110 (9.1%); diffuse hyperemia, 10 of 110 (9.1%); micro-polyps, 2 of 110 (1.8%); endometrial interstitial edema, 3 of 110 (2.7%); and cases with combined features, 7 of 110 (6.4%) as shown in Table 4.

In our study, 110 women with RIF were included; 32 cases (29%) were diagnosed with CE by hysteroscopy, while 27 cases (24.5%) were positive by CD138 immunohistochemistry (IHC), and 18 cases (16.36%) were positive for CD138 IHC with hysteroscopic features of CE (Figure 3).

Our study revealed that the sensitivity, specificity, positive and negative predictive values of hysteroscopy were 66.7%, 83.1%, 56.3%, and 88.5%, respectively. The diagnostic accuracy of hysteroscopy in diagnosing CE was 79.1% as shown in Table 5.

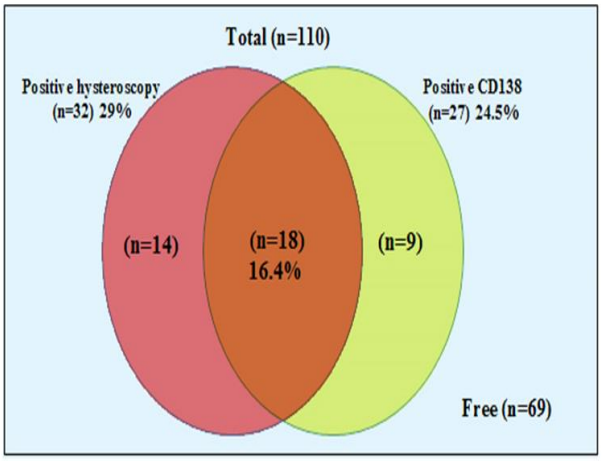


**Figure 3: Distribution of the studied cases according to hysteroscopic finding and CD 138 results**

**Table 2: Relation between type of infertility (primary and secondary) with hysteroscopy findings and CD 138 results, (n=110).**

| Variables | Infertility | | | | P value |
|---|---|---|---|---|---|
| | 1ry, (n=85) | | 2ry, (n=25) | | |
| | N | % | N | % | |
| **Hysteroscopy findings** | | | | | |
| Focal hyperemia | 7 | 8.2 | 3 | 12 | FE p=0.303 |
| Diffuse hyperemia | 8 | 9.4 | 2 | 8.0 | FE p=0.291 |
| Micro-polypi | 1 | 1.2 | 1 | 4.0 | FE p=0.617 |
| Mucosal edema | 2 | 2.4 | 1 | 4.0 | FE p=1.000 |
| Combined | 5 | 5.9 | 2 | 8.0 | FE p=0.656 |
| **Hysteroscopy findings** | | | | | |
| Negative | 62 | 72.9 | 16 | 64.0 | 0.891 |
| Positive | 23 | 27.1 | 9 | 36.0 | |
| **CD 138 results** | | | | | |
| Negative | 64 | 75.3 | 19 | 76.0 | 0.943 |
| Positive | 21 | 24.7 | 6 | 24.0 | |

$\chi^2$: Chi-square test, FE: Fisher's exact p: p value for association between different categories.

**Table 3: Relation between number of failed ICSI with hysteroscopy findings and CD 138 results, (n=110).**

| Variables | Number of failed ICSI | | | | P value |
|---|---|---|---|---|---|
| | 2, (n=84) | | 3 or more (n=26) | | |
| | N | % | N | % | |
| **Hysteroscopy findings** | | | | | |
| Focal hyperemia | 8 | 9.5 | 2 | 7.7 | FE p=0.313 |
| Diffuse hyperemia | 6 | 7.1 | 4 | 15.4 | FE p=0.728 |
| Micro-polypi | 2 | 2.3 | 0 | 0 | FE p=0.143 |
| Mucosal edema | 2 | 2.3 | 1 | 3.8 | FE p=0.678 |
| Combined | 4 | 4.8 | 3 | 11.5 | FE p=0.353 |
| **Hysteroscopy findings** | | | | | |
| Negative | 62 | 73.8 | 16 | 61.5 | 0.829 |
| Positive | 22 | 26.2 | 10 | 38.5 | |
| **CD 138 results** | | | | | |
| Negative | 66 | 78.6 | 17 | 65.4 | 0.172 |
| Positive | 18 | 21.4 | 9 | 34.6 | |

$\chi^2$: Chi-square test, FE: Fisher's exact, p: p value for association between different categories.

**Table 4: Distribution of the studied cases according to hysteroscopy findings, (n=110).**

| Hysteroscopy findings | N | Percentages (%) |
|---|---|---|
| **Free** | 78 | 70.9 |
| **Focal hyperemia** | 10 | 9.1 |
| **Diffuse hyperemia** | 10 | 9.1 |
| **Micro-polypi** | 2 | 1.8 |
| **Mucosal edema** | 3 | 2.7 |
| **Combined** | 7 | 6.4 |
| Focal hyperemia + Micro-polypi | 2 | 1.8 |
| Focal hyperemia + edema | 1 | 0.9 |
| Diffuse hyperemia + edema | 2 | 1.8 |
| Focal hyperemia + edema | 1 | 0.9 |
| Focal hyperemia + edema + Micro-polypi | 1 | 0.9 |

**Table 5: Agreement (sensitivity, specificity and accuracy), (n=110).**

| Variables | CD 138 results | | | | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|
| | Negative, (n=83) | | Positive, (n=27) | | | | | | |
| | N | % | N | % | | | | | |
| **Hysteroscopy findings** | | | | | | | | | |
| Negative | 69 | 83.1 | 9 | 33.3 | 66.7% | 83.1% | 56.3% | 88.5% | 79.1% |
| Positive | 14 | 16.9 | 18 | 66.7 | | | | | |
| $\chi^2$ (p) | 24.493* (<0.001*) | | | | | | | | |

$\chi^2$: Chi square test, p: p value for association between different categories, * Statistically significant at P ≤ 0.05. PPV: Positive predictive value, NPV: Negative predictive value

**Table 6: Agreement (sensitivity, specificity and accuracy) of cases with combined hysteroscopic findings (n=110).**

| Variables | CD 138 results | | | | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|
| | Negative, (n=83) | | Positive, (n=27) | | | | | | |
| | N | % | N | % | | | | | |
| **Combined hysteroscopy findings** | | | | | | | | | |
| Negative | 82 | 98.8 | 21 | 77.8 | 22.2 | 98.8 | 85.7 | 79.6 | 80.0 |
| Positive | 1 | 1.2 | 6 | 22.2 | | | | | |
| $\chi^2$ ($^{FE}$p) | 15.103* (0.001*) | | | | | | | | |

$\chi^2$: Chi-square test; FE: Fisher exact test, p: p value for association between different categories. * Statistically significant at p≤0.05. PPV: Positive predictive value NPV: Negative predictive value.

When the presence of more than one of these abnormal hysteroscopic features (combination of two or more hysteroscopic findings) was considered positive for CE rather than single abnormal feature, the sensitivity, specificity, positive and negative predictive values of hysteroscopy would be 22.2%, 98.8%, 85.7%, and 79.6%, respectively, as shown in Table 6.

## DISCUSSION

Hysteroscopy is a minimally invasive outpatient procedure that allows for direct examination of the uterine cavity and identification of any abnormalities or symptoms of inflammation. It can reveal uterine diseases that are not obvious on ultrasonography in patients. CE is one of the uterine disorders for which ultrasound or HSG cannot be diagnosed. Therefore, the two most commonly utilized techniques for diagnosing CE are hysteroscopy and endometrial biopsy for plasma cell identification. Many authors view the detection of plasma cells in the endometrial stroma as the most reliable way to diagnose CE. Focal or diffuse endometrial hyperemia, stromal edema, and micro-polyps (<1 mm) are the most agreeable hysteroscopic findings used by many authors to diagnose CE.

In our study, 72% of cases had primary infertility and 28% had secondary infertility, with no statistically difference between the two groups according to the prevalence of CE. This agrees with Saha et al who found no significant difference in the rate of uterine pathology between women with primary and secondary infertility.[22]

In Our study, 110 women with recurrent ICSI failure were included; 32 cases (29%) were diagnosed with CE by hysteroscopy, while 27 cases (24.45%) were positive by CD138 immunohistochemistry (IHC), and 18 cases (16.36%) were positive for CD138 IHC with hysteroscopic features of CE. These results were consistent with those of El-Sheikh et al who showed 28% of cases were positive by

IHC, and 12% of cases showed both abnormal hysteroscopy and positive histological biopsy of chronic endometritis.[23]

In contrast to patients with two ICSI failures, patients with three or more ICSI failures had a greater prevalence of CE according to our study. Only 9% of the CE cases in our study reported nonspecific symptoms, including nebulous persistent pelvic discomfort, abnormal uterine bleeding, or dyspareunia, and the majority of CE cases were asymptomatic. There were no discernible differences in these symptoms between patients with and without CE.

Our study revealed that the sensitivity, specificity, PPV, and NPV of hysteroscopy were 66.7%, 83.1%, 56.3%, and 88.5%, respectively. The diagnostic accuracy of hysteroscopy in diagnosis CE was 79.1%. The prevalence of hysteroscopic features in our study was as follows: focal endometrial hyperemia, 10 of 110 (9.1%); diffuse hyperemia, 10 of 110 (9.1%); micro-polyps, 2 of 110 (1.8%); endometrial interstitial edema, 3 of 110 (2.7%); and cases with combined features, 7 of 110 (6.4%).

Our findings were contrasted with the majority of earlier research that had been published, which showed a significant range in terms of sensitivity (16.7% to 98.4%) and specificity (56.2% to 99.9%). The sensitivity and PPVs vary greatly, although the specificity and NPV of the majority of studies are still sufficiently high.

Our research supports the findings of Song et al, whose IHC analysis of endometrial specimens revealed the presence of CD138 positive cells in 322 of 1,189 cases (27.1%). The prevalence of abnormal hysteroscopic findings of CE was as follows: endometrial hyperemia, 169 of 322 (52.5%); stromal edema, 27 of 322 (8.4%); and micro-polyps, 11 of 322 (3.4%). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the hysteroscopy for diagnosing CE were 59.3%, 69.7%, 42.1%, 82.8%, and 66.9%, respectively.[24]

Tsonis et al conducted a study on a sizable number of patients (n=2675) who underwent hysteroscopy and CD 138 IHC for endometrial materials, and their findings concur with ours. Hysteroscopic detection of CE has sensitivity, specificity, PPV, and NPV of 49.3%, 91.7%, 60.3%, and 87.7%, respectively.[25]

El-Sheikh et al. conducted a prospective study in 2020 on 100 patients who had two or more unsuccessful IVF cycles. In addition to hysteroscopy, the patient underwent CD138 IHC. Histological CE can be detected hysteroscopically with 63.1% specificity and 50% sensitivity.[23]

Yang et al conducted a study of 202 RIF-afflicted women. For CD 138 IHC, these patients underwent hysteroscopy and endometrial biopsy. histological CE rate was 43.7%, whereas hysteroscopic CE rate was 66%. The sensitivity and specificity of hysteroscopic imaging are 35.2% and 67.5%, respectively.[26]

Hysteroscopy and endometrial biopsy were used in a controlled clinical investigation by Cicinelli et al infertile women. Hysteroscopy's sensitivity, specificity, PPV, NPV, and diagnostic accuracy were, respectively, 55.4%, 99%, 98.4%, 94.5%, and 93.4%.[27]

Zargar et al conducted a prospective study of 85 women with RIF who underwent diagnostic hysteroscopy and CD138 IHC of endometrial samples. The sensitivity, specificity, PPV, and NPV of hysteroscopy for diagnosing CE were 86.4%, 87.3%, 94.8%, and 70.4%, respectively. [28]

A prospective study by Polisseni et al conducted diagnostic hysteroscopy, endometrial biopsy using H and E staining, and cervical and endometrial Chlamydia infection tests in 50 infertile patients. H&E staining demonstrated that CE occurred in 12% of these patients; hysteroscopy had a sensitivity of 16.7%, a specificity of 93.2%, and was assumed to have a strong predictive value of negative results. [29]

The use of $CO_2$ as the distension medium is largely responsible for the exceedingly low diagnostic value of hysteroscopy reported by Polisseni et al. It is simpler to find tiny lesions such as micropolyps using fluid hysteroscopy. Saline as a distension medium also helps endometrial micropolyps float and has no effect on endometrial vascularity, making fluid hysteroscopy more sensitive than CO2 hysteroscopy in detecting CE. Therefore, using $CO_2$ as a distension medium may account for the low sensitivity and extremely low diagnostic value of hysteroscopy reported by Polisseni et al.[29]

Zolghadri et al demonstrated very high sensitivity (98.4%) and low specificity of hysteroscopy (56.23%), which can be explained by using H&E staining in histopathological analysis of endometrial samples instead of IHC by CD138, and considered only one plasma cell/HPF as a positive result of CE. As mentioned above, it is sometimes challenging to distinguish the plasma cells from the endometrial stromal fibroblasts and monocytes using H&E staining, which can give high false-positive results.[21] In addition, some pathologists found it normal to find few plasma cells in normal endometrial biopsy, so the commonly used histopathological criteria in the diagnosis of CE are the presence of ≥5 plasma cells/HPF.[30]

Our results revealed high specificity and NPV. In other words, CE is unlikely to be diagnosed when abnormal hysteroscopic findings are absent. It has been observed that specificity and NPV in most studies are adequate for high levels, such as Tsonis et al, Cicinelli et al, Zargar et al and Polisseni et al.[25,27-29]

However, we noticed that the presence of more than one of these hysteroscopic features (combination of two or

more abnormal hysteroscopic findings) did significantly increase the likelihood of histologically positive CE (specificity 98.8% and PPV 85%).

### *Limitation*

The main limitation of our study was that there were no bacteriological cultures of the endometrial cavity obtained using traditional culture techniques and transcervical sampling. Only microorganisms that can grow under conventional microbiology laboratory conditions can be recovered, and the procedure may therefore yield biased microbial findings.

Thus, it cannot be excluded that other microorganisms (anaerobic bacteria, viruses, etc.) may also coexist and play a role.

## CONCLUSION

Hysteroscopy has modest accuracy in diagnosing CE due to its slightly low sensitivity; however, hysteroscopy is found to have high specificity and NPV, which means that when hysteroscopic features are absent, the diagnosis of CE is unlikely. It has been observed that the likelihood of histologically confirmed CE is greatly increased by the presence of two or more abnormal hysteroscopic features compared to a single abnormal feature. The negative diagnostic value of hysteroscopy is high, and its ability to exclude the presence of CE should be adequate without the use of histological confirmation. However, in patients with RIF at a high risk of CE, histopathological examination of the endometrium using IHC with CD138 is important. Thus, a combination of the two diagnostic modalities (hysteroscopy and CD138 IHC) will aid in the detection of most cases of CE.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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