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Prevalence of chronic endometritis in women with recurrent implantation failure and recurrent pregnancy loss: The role of hysteroscopy and immunohistochemistry in diagnosis

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Abstract
Background: Chronic Endometritis (CE) is a clinically significant inflammatory condition of the endometrial lining, which has been implicated in a range of gynecological disorders, most notably Recurrent Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL). The aim of this study was to evaluate the prevalence of CE in women with a history of RIF and RPL, and to assess the diagnostic accuracy of hysteroscopy for detecting CE in these patients.
Methods: This prospective cross-sectional observational study was carried out on 81 women with a history of RIF or RPL. All women underwent office hysteroscopy followed by Immunohistochemistry staining for the diagnosis of CE in both RIF and RPL cases. The diagnostic accuracy for detecting CE was calculated based on the IHC findings.
Results: the prevalence of CE in the RIF group was found to be 19.44% by hysteroscopy and 22.22% by IHC. In the RPL group, the prevalence was 35.56% by hysteroscopy and 31.11% by IHC. The sensitivity, specificity, PPV, NPV, and overall accuracy of hysteroscopy revealed 86.96% sensitivity, 96.55% specificity, 90.91% PPV, 94.92% NPV, and 93.83% accuracy for all patients, 100.00%, 96.55%, 87.50%, 100.00%, and 97.22% respectively for the RIF group, and 81.25%, 96.55%, 92.86%, 90.32%, and 91.11% respectively for the RPL group.
Conclusions: Hysteroscopy plays a crucial role in diagnosing CE, but its limitations underscore the importance of IHC as a confirmatory test. Hysteroscopy should be used in conjunction with IHC for more accurate diagnosis and management of women with RIF and RPL.

Keywords: Chronic endometritis, recurrent implantation failure, recurrent pregnancy loss, immunohistochemistry, hysteroscopy

Introduction

Chronic Endometritis (CE) is a clinically significant inflammatory condition of the endometrial lining, which has been implicated in a range of gynecological disorders, most notably Recurrent Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL). Both RIF and RPL represent complex, multifactorial conditions where the underlying etiology often remains elusive, making effective diagnosis and management a challenge for clinicians. Recent studies have shown that CE plays a critical role in the pathophysiology of these conditions, contributing to poor embryo implantation and pregnancy loss, thus requiring precise diagnostic methods to improve patient outcomes [1, 2].

Hysteroscopy, a minimally invasive procedure, has emerged as a key tool in diagnosing endometrial abnormalities, including CE. By directly visualizing the endometrial cavity, hysteroscopy offers real-time insight into the endometrial environment, potentially revealing signs of inflammation and other pathological changes. However, while hysteroscopy is valuable in detecting gross endometrial abnormalities, its sensitivity for diagnosing CE remains limited, particularly in cases of subtle or early-stage inflammation [3].

Immunohistochemistry (IHC) has become a valuable complementary diagnostic tool, providing a more definitive confirmation of CE. By identifying the presence of specific markers of inflammation, IHC enhances the diagnostic accuracy of hysteroscopy, enabling clinicians to more confidently diagnose CE in women with RIF and RPL [4]. Despite the diagnostic benefits of both hysteroscopy and IHC, their individual limitations underscore the importance of

employing them together for optimal diagnostic precision and patient management.

The aim of this study was to evaluate the prevalence of CE in women with a history of RIF and RPL, and to assess the diagnostic accuracy of hysteroscopy for detecting CE in these patients.

Patients and methods

This prospective cross-sectional observational study was carried out on 81 women who attended the outpatient clinic of …… University Hospital from the period between …….. and ……. with a history of RIF (defined as failure to achieve pregnancy after the transfer of at least three high-quality embryos) or RPL (defined as two or more consecutive early pregnancy losses <14 weeks gestation).

An informed written consent was obtained from the patient. The study was done after approval from the Ethical Committee …… University Hospitals.

Inclusion criteria

- History of RIF or RPL
- Normal Hysterosalpingography (HSG) or Hysterosonography (HSSG) findings
- Normal chromosomal karyotype
- Normal serum thyroid function and prolactin levels
- Absence of other known causes for RIF or RPL (e.g., male factor infertility, polycystic ovary syndrome)

Exclusion criteria

- Active infections
- Uterine malformations
- Polycystic ovarian syndrome

Hysteroscopy

Patients underwent office hysteroscopy between the third to fifth day of their menstrual cycle to assess the uterine cavity. The procedure involved the use of a rigid 3mm hysteroscope with a 30° oblique lens. Distention of the uterine cavity was achieved using a 0.9% saline solution. The hysteroscopic examination focused on identifying visual signs of CE, including:

- Mucosal edema
- Endometrial hyperemia
- Micropolyp formation (focal or diffuse)
- Strawberry aspect (areas of hyperemia with white central points)

Following hysteroscopy, patients underwent an endometrial biopsy using a Pipelle de Cornier under direct visualization to avoid contamination. Biopsy samples were fixed in neutral formalin and sent for histological examination.

Immunohistochemistry

To diagnose CE, a vaginal speculum was placed and the pipelle was inserted under visual control into the uterine cavity without any contact with the vaginal walls. All specimens were sent to the same laboratory and interpreted by the same pathologist, who specialized in endometrial pathology and was unaware of hysteroscopic findings. Immunohistochemical staining was performed by incubation with a 1:100 dilution of mouse monoclonal antibodies directed against syndecan-1, a specific marker of plasma cells (Biocare Medical) for 1 hour at room temperature. The diagnosis of CE was considered positive if five or more plasma cells were observed on 10 nonoverlapping high-power fields (×400) in the endometrial tissue samples.

Outcomes

The primary outcome was to evaluate the prevalence of CE in patients with RIF and RPL by hysteroscopy and immunohistochemistry. The secondary outcomes were to assess the diagnostic accuracy of hysteroscopy in the diagnosis of CE in patients with RIF and RPL and to estimate the pregnancy rate following the *In vitro* Fertilization (IVF).

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative data were presented as mean and Standard Deviation (SD) and were analyzed by unpaired student t-test. Qualitative data were presented as frequency and percentage (%) and were analyzed by the Chi-square test or Fisher's exact test when appropriate. A two tailed P value ≤ 0.05 was considered statistically significant.

Results

A total of 81 women participated in this study, with 36 women in the RIF group and 45 women in the RPL group. The mean age of the participants was 36.08 ± 5.76 years for the RIF group and 34.8 ± 5.12 years for the RPL group with a P value of 0.294.

Prevalence of CE

The prevalence of CE was evaluated based on hysteroscopic findings and IHC staining. The prevalence of CE in both groups was as follows:

RIF group

- **Hysteroscopy:** The prevalence of CE in the RIF group diagnosed by hysteroscopy was 19.44% (7 out of 36 women).
- **IHC:** The prevalence of CE confirmed by IHC staining in the RIF group was 22.22% (8 out of 36 women).

RPL group

- **Hysteroscopy:** The prevalence of CE in the RPL group diagnosed by hysteroscopy was 35.56% (16 out of 45 women).
- **IHC:** The prevalence of CE confirmed by IHC staining in the RPL group was 31.11% (14 out of 45 women).

Overall, hysteroscopy identified 28.4% (23 women) CE cases of the total study population when considering both RIF and RPL groups combined, while IHC confirmed the diagnosis in 27.16% (22 women) of the patients.

Diagnostic accuracy of hysteroscopy in diagnosing CE

The diagnostic accuracy of hysteroscopy for detecting CE was calculated based on the comparison with IHC, which served as the gold standard for diagnosis. Overall, the sensitivity, specificity, PPV, NPV, and accuracy of hysteroscopy in diagnosing CE were 86.96%, 96.55%, 90.91%, 94.92%, and 93.83% respectively. The diagnostic rates in the RIF group were 100.00%, 96.55%, 87.50%, 100.00%, and 97.22% and while in the RPL group, they were 81.25%, 96.55%, 92.86%, 90.32%, and 91.11% (Table 1).

Table 1: Diagnostic accuracy of hysteroscopy in diagnosing CE

	Overall diagnostic accuracy	Diagnostic accuracy in the RIF group	Diagnostic accuracy in the RPL group
Sensitivity (%)	86.96	100.00	81.25
Specificity (%)	96.55	96.55	96.55
PPV (%)	90.91	87.50	92.86
NPV (%)	94.92	100.00	90.32
Accuracy (%)	93.83	97.22	91.11

CE: chronic endometritis, RIF: recurrent implantation failure, RPL: recurrent pregnancy loss, PPV: positive predictive value, NPV: negative predictive value.

Pregnancy outcomes post-IVF

In this study, 10 patients with positive hysteroscopic findings for CE were randomly selected for IVF therapy. Among them, only 1 (10%) patient became pregnant following the IVF cycle, suggesting that hysteroscopy and the detection of CE may be associated with improved reproductive outcomes in this subset of women.

Discussion

CE is a persistent inflammatory disorder of the endometrial lining, characterized by superficial endometrial edematous change, high stromal cell density, dissociated maturation between epithelium and stroma, and infiltration of Endometrial Stromal Plasmacytes (ESPCs). The pathogenesis of CE seems to be related to a qualitative and quantitative alteration of endometrial microbioma, with the abnormal proliferation of different types of microorganisms, mainly gram-negative and intracellular bacteria (i.e., *Enterococcus faecalis*, *Mycoplasma*, *Ureaplasma*, *Chlamydia*, *Escherichia coli*, and *Streptococcus* spp.) [5].

This study aimed to evaluate the prevalence of CE in women with a history of RIF and RPL, and to assess the diagnostic accuracy of hysteroscopy for detecting CE in these patients.

The results of this study revealed that hysteroscopy and IHC were both effective diagnostic methods for detecting CE in women with RIF and RPL.

In this study, the prevalence of CE in the RIF group was found to be 19.44% by hysteroscopy and 22.22% by IHC. In the RPL group, the prevalence was 35.56% by hysteroscopy and 31.11% by IHC. These findings are consistent with previous research, such as Zargar *et al*. [6], who reported a 36.8% prevalence of CE in women with RPL and 23.4% in the RIF group. Similarly, Bouet *et al*. [2] observed a 22% prevalence of CE in RIF patients and a 27% prevalence in RPL patients. These findings reflect the relatively high prevalence of CE in both RPL and RIF groups, especially in RPL patients, suggesting that CE may play a significant role in reproductive failure in these populations.

The higher prevalence of CE in the RPL group could be attributed to chronic inflammation in the endometrial lining, which disrupts embryo implantation and early pregnancy maintenance. CE impedes endometrial receptivity, a critical factor for successful implantation and pregnancy. The RPL group may also show more severe or chronic forms of CE, leading to higher prevalence rates compared to RIF patients, as suggested by Zolghadri *et al*. [7]. Additionally, the findings are in line with McQueen *et al*. [8], who noted that CE significantly contributes to poor reproductive outcomes, and diagnostic screening for CE should be considered in RPL patients.

The sensitivity, specificity, PPV, NPV, and overall accuracy of hysteroscopy for diagnosing CE were calculated in this study, revealing impressive results: 86.96% sensitivity, 96.55% specificity, 90.91% PPV, 94.92% NPV, and 93.83% accuracy. These findings are consistent with Zargar *et al*. [6], who reported a sensitivity of 86.36% and specificity of 97.2% for hysteroscopy in diagnosing CE, further supporting the role of hysteroscopy as a reliable diagnostic tool in this context.

However, Bouet *et al*. [2] observed a lower sensitivity (40%) for hysteroscopy in detecting CE, which contrasts with the findings of this study. This discrepancy may be attributed to the use of IHC as a gold standard in this study, which helped confirm the hysteroscopic findings and improve diagnostic accuracy. It is well known that hysteroscopy is more effective at detecting severe cases of CE but may miss milder forms of the disease. As observed by Cicinelli *et al*. [9], subtle forms of CE, particularly those with focal lesions, may not be detected by hysteroscopy alone.

In this study, the RIF group demonstrated 100% sensitivity with hysteroscopy, which is notably higher than the 81.25% sensitivity found in the RPL group. This is consistent with Yang *et al*. [10], who found that hysteroscopy in RIF patients was able to accurately detect CE with higher sensitivity compared to RPL patients. The lower sensitivity in the RPL group may be due to the mild presentation of CE in some cases, where hysteroscopy may not detect all instances, especially if inflammatory changes are subtle or focal. These findings are in line with McQueen *et al*. [8], who also reported variability in the sensitivity of hysteroscopy in RPL patients, particularly when CE was mild or localized.

Despite the lower sensitivity in the RPL group, the high specificity (96.55%) and NPV (94.92%) observed in this study suggest that hysteroscopy is an excellent tool for ruling out CE in women with RIF and RPL. When hysteroscopy shows negative findings for CE, clinicians can be confident in excluding the condition, which aligns with the conclusions of Zolghadri *et al*. [7] and Yang *et al*. [10], who reported that hysteroscopy is a reliable method for excluding CE.

A key aspect of this study was the investigation of pregnancy outcomes in patients with positive hysteroscopic findings for CE. Ten women with positive hysteroscopic findings for CE were selected for IVF therapy, and only 1 (10%) of them became pregnant after the IVF cycle. This low pregnancy rate could be attributed to the detrimental effects of CE on endometrial receptivity. The inflammation caused by CE can disrupt the ability of the endometrium to support embryo implantation, leading to poor pregnancy outcomes, as demonstrated by McQueen *et al*. [8] and Johnston-MacAnanny *et al*. [11], who found similarly low implantation rates in women with untreated CE.

This study's findings align with Yang *et al*. [10], who observed that women with RIF and CE had lower implantation rates and ongoing pregnancy rates in subsequent IVF cycles. However, it is important to note that the treatment of CE with antibiotics has been shown to improve pregnancy outcomes, particularly in RPL patients. For instance, McQueen *et al*. [8] found that antibiotic treatment for CE led to significantly higher pregnancy rates in women with untreated CE compared to those without CE.

The findings of this study are consistent with those of Zolghadri *et al*. [7], who reported that hysteroscopy is an effective method for diagnosing CE, with high sensitivity and specificity. Their study also demonstrated that CE was significantly more prevalent in women with unexplained Recurrent Spontaneous Abortion (RSA) compared to controls, similar to the findings in our RPL group. They found that 67.6% of RSA patients had positive hysteroscopic findings for CE, a prevalence rate that is comparable to the 35.56% observed in our RPL group.

In contrast, Johnston-MacAnanny *et al*. [11] reported that hysteroscopy had low sensitivity (35.2%) for detecting CE in RIF patients, similar to the 35.2% sensitivity found in the study by Yang *et al*. [10]. However, both studies indicated that IHC significantly improved the diagnostic sensitivity for CE, which is consistent with our findings that IHC staining for plasma cells provided a more accurate diagnosis of CE than hysteroscopy alone.

Future research should focus on evaluating the role of antibiotic therapy in improving pregnancy outcomes for women with CE. Additionally, further studies with larger sample sizes are needed to assess the long-term effects of CE treatment on fertility outcomes in RIF and RPL patients.

Conclusions

Hysteroscopy plays a crucial role in diagnosing CE, but its limitations underscore the importance of IHC as a confirmatory test. Hysteroscopy should be used in conjunction with IHC for more accurate diagnosis and management of women with RIF and RPL.

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