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Chronic endometritis — is it time to clarify diagnostic criteria?

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ABSTRACT

Chronic endometritis is a persistent, low-intensity inflammation of endometrial mucosa, characterized by the infiltration of plasma cells into the endometrial stroma This immunological alteration is thought to be a consequence of a bacterial infection. For a long time, chronic endometritis was poorly investigated and rarely considered in clinical practice because it is either asymptomatic or presents with no specific symptoms. Its association with adverse effects on fertility and retrospectively reported effectiveness of antibiotic treatment were the main reasons for a growing interest in this endometrial pathology. Chronic endometritis is now a hot topic in recurrent pregnancy loss and recurrent implantation failure research.

Nevertheless, there are still no recommendations to include chronic endometritis investigation in a clinical evaluation of infertile patients. The uncertain role of this condition is an effect of significant differences in study results presented by different research groups. One important reason for these inconsistent findings is a lack of standardised chronic endometritis diagnostic methods.

We present a review of the literature, focusing on the currently available chronic endometritis diagnostic techniques. The review is subdivided into three parts concerning the diagnostic accuracy of three main diagnostic modalities. Histopathological examination of endometrial tissue, hysteroscopic evaluation of uterine cavity and identification of the bacterial factor.

In conclusion, it is of great importance to establish a consensus on the diagnostic criteria for chronic endometritis. This is the only way to enhance international cooperation and create well-design multicenter studies to evidence the role of this endometrial pathology in infertility.

Key words: chronic endometritis; diagnostic techniques; immunohistochemistry; hysteroscopy; endometrial microbiome

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INTRODUCTION

The past few years have seen a notable increase in the number of publications focused on chronic endometritis. This increase is associated with a growing interest in understanding the endometrial factors in infertility and their roles in the implantation process.

Chronic endometritis (CE) is a persistent but low-intensity inflammation of the endometrium, mostly asymptomatic or correlated with non-specific symptoms, namely pelvic pain, dysfunctional uterine bleeding, and vaginal discharge [1]. Nevertheless greater interest in this long-known endometrium pathology is associated with the appearance of data showing a correlation between CE and adverse reproduction outcomes [2–4].

Classic methods used in the CE investigation process include microbial culture, hysteroscopy, and histopathology examination of endometrial samples. As the diagnostic gold standard serves histopathological identification of plasma cells in the endometrial biopsy [5, 6].

The first step in the clinical concern regarding CE was proving the higher than previously believed prevalence of this pathology [3]. The immunohistochemistry staining

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used in the histopathological evaluation of endometrial tissue demonstrated that CE is underdiagnosed and in fact more common in patients with recurrent pregnancy losses [3]. This finding gave a basis for further investigation into CE effects on fertility.

The reported effectiveness of antibiotic treatment in CE resolution, confirmed in repeated histological examination of endometrial tissue, was another milestone in building the significance of this diagnosis [2, 7–11]. Some publications showed improvement in reproductive outcomes of patients after effective antibiotic treatment of CE [10, 12]. These reports caused even greater interest in CE investigation, as there is great value in finding potentially treatable causes of fertility alternation. Despite all the promising reports, CE investigation is not recommended in guidelines for the clinical management of patients with infertility [13, 14]. The main reason is the lack of sufficient evidence from prospective observational studies and randomized controlled trials on the predictive value of a positive test for CE. Performing a meta-analysis of the available data is biased by the significant heterogeneity of the CE diagnostic criteria used by different researchers [15, 16].

The CE estimated rate in the general population is hard to define due to the lack of a characteristic clinical manifestation. The reported range in the population of infertile patients varies between 2.8% and 39.0%, while in a selected group of women diagnosed with unexplained recurrent miscarriage or repeated implantation failure it may be as high as 60% or 66%, respectively [2, 6, 9, 17, 18].

This wide range of reported CE prevalence is a consequence of the fact that its diagnosis depends on the method of detection. As shown in a study by Moreno, when the three classic diagnostic techniques are applied to the same patients it may yield contradictory results [19].

In this paper, we aim to review the literature regarding diagnostic techniques used in CE investigation.

MATERIAL AND METHODS

We studied the diagnostic techniques and diagnostic criteria used by researchers investigating chronic endometritis. A search of PubMed and Embase was performed to identify relevant studies, with a restriction to English language articles. The following keywords and their combinations were used: "chronic endometritis", "infertility", and "diagnostic criteria". Additional searches included references from identified publications.

Diagnostic techniques

Histopathology

The histological detection of plasma cells in endometrial tissue is a generally accepted gold standard CE diagnostic method [5, 6]. Although plasma cell identification in endometrium specimens stained with hematoxylin and eosin (H&E) is possible, it can be challenging, time-consuming and subjective. Therefore immunohistochemistry (IHC) has been introduced to detect plasma cell marker syndecan-1 (CD 138).

Syndecan-1 (CD138) is a transmembrane heparan sulfate proteoglycan, involved in cell-cell and cell-matrix adhesion. The expression of syndecan-1 is typically observed on the cell membrane of plasma cells and mature epithelial cells [20]. This type of plasma cell identification has been successfully used in diagnosing plasma cell tumors, including multiple myelomas [21].

One advantage of IHC CD138 staining is the ability to identify not only typical round plasma cells with classic features of clock-face chromatin in an eccentrically placed nucleus with a perinuclear halo but also untypical spindle-shaped ones [22]. This is important, because abundant stromal mitoses and stromal cell proliferation in CE may mask the characteristic features of the plasma cells and increase the chance of them being overlooked by a pathologist.

Moreover, IHC CD138 is found to be an objective plasma cell identification method and can decrease the number of false-positive results. It reduces the chance of counting other cells by mistake, such as mononuclear and plasmacytoid stromal cells instead of plasma cells and increases intra-observer inter-observer agreement in the diagnosis [23].

Studies by McQueen show that the use of IHC CD138 staining significantly increased the number of plasma cells detected in endometrium samples of women with recurrent pregnancy loss. This confirms the increased sensitivity of IHC CD 138 plasma cell identification compared to H&E staining [3, 24].

Lately, two research groups introduced the multiple myeloma 1 (MUM1) protein as a plasma cell marker in the chronic endometritis study [25, 26]. MUM1 also known as interferon regulatory factor 4 (IRF4) is a transcription factor protein expressed in plasma cells, activated B and T cells. MUM1 IHC staining pattern is primarily nuclear and overcomes the disadvantage of background reaction present in the CD138 staining.

Due to the greater sensitivity of plasma cell detection, researchers now must answer the question: how many plasma cells per tissue sample area is enough for the diagnosis of CE?

In examining recently published original articles, we find a huge variety in the applied histopathological diagnostic criteria. Many investigators use different methods of quantification, while the threshold number of plasma cells per tissue sample can be set between strict and broad [15].

The results obtained from studies designed with such heterogeneity in the basic diagnostic criteria range vary

significantly, causing bias in metanalysis and comparative analysis [15].

Few research groups have chosen to analyse this problem and compare the prevalence of CE determined by means of different histopathological criteria, to evaluate the most accurate one [16, 27, 28].

Hirata et al. [27] analysed four threshold numbers of plasma cells used in the same group of patients undergoing in vitro fertilisation (IVF) procedures. Based on the comparison of differences in pregnancy rate, live birth rates and miscarriage rate among CE and non-CE groups defined by four different criteria, they concluded that CE should be defined as the presence of ≥ 1 plasma cell per 10 high-power fields (HPF) [27].

Another approach to this problem was demonstrated by Y. Liu et al. in their study [16]. They set the reference range of plasma cells derived from the examination of endometrium tissue samples from a control group of 40 fertile patients. In the study group of females with recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF), they considered plasma cell numbers above the 95th percentile of the reference value as indicative of CE diagnosis. The threshold level for three different methods of quantification were: 1.95 CD138 plasma cells per ten randomly chosen HPFs, 2.95 CD138 plasma cells per section, and 5.15 CD138 plasma cells per 0.1 mm^2 [16].

To tackle the problem of redefining chronic endometritis, McQueen et al. [24] carried out a study to compare the prevalence of CE among women with RPL and the control group, using various histopathological definitions. The novelty of the concept was to include endometrial stromal changes defined as the spindling of cells, oedema, breakdown pigment deposition, areas of hypercellularity and the presence of inflammatory cells other than plasma cells. The authors achieved the highest diagnostic sensitivity and specificity when CE was defined as the presence of one or more plasma cells per 10 HPFs in the setting of endometrial stromal changes.

The lack of worldwide consensus on histopathological criteria of CE is demonstrated in the results of the survey of pathologists, asking about diagnostic criteria they follow in clinical practice [29]. This study shows that we need clarification of histopathological CE criteria, especially as it is a verification method in the search for other CE diagnostic modalities.

Hysteroscopy

Hysteroscopy assessment of uterine anatomy is one of the recommended procedures in the diagnostic process of abnormal uterine bleeding, RPL, infertility, and suspected intrauterine lesions [14]. The possibility to identify changes in endometrium appearance caused by persistent inflammation led to a number of studies investigating this CE diagnostic modality.

Visual signs suggesting CE, described in the literature are micro polyps, focal hyperaemia, stromal oedema, and endometrial strawberry aspect, defined as large areas of hyperaemic endometrium flushed with white central points [30–32]. Nevertheless, the exact diagnostic criteria and reliability of this method remain a subject of debate [5, 30–35].

The most common method used to evaluate the diagnostic accuracy of hysteroscopic findings is to perform a hysteroscopic examination with subsequent endometrial biopsy and histopathological verification of the CE diagnoses.

In most studies, a hysteroscopic examination was performed in the proliferative phase of the endometrium cycle. Reported sensitivity, specificity, and the positive and negative predictive values differed depending on which set of visual features the diagnosis was based on. For example, in the study by Cicinelli et al., when detection of oedema and hyperaemia was set as a criterium of CE, 92% sensitivity, 93% specificity, 64% positive and 99% negative predictive values were reported [31, 32]. However, when the presence of micro polyps was also included, the specificity increased to 99.0% while the sensitivity decreased to 55.4% [31]. The authors concluded that the absence of endometrial hyperaemia and oedema was sufficient to rule out chronic endometritis, while the presence of micro polyps was a very reliable visual feature, although not very common in CE patients. It is worth noting that these studies can be biased because no ICH staining was used in the histopathological verification process [32].

The next research group aiming to evaluate the role of hysteroscopy also included the same three hysteroscopic features suggestive of CE in a large cohort of 1189 patients [5]. An advantage of this study was the fact that the verification method was a histopathological examination with the use of IHC for CD138 plasma cell identification. The reported sensitivity of a hysteroscopic diagnosis based on the presence of at least one of three features was only 59.3% and a specificity of 69.7%. The specificity increased to 99% when at least two features were found simultaneously in the same patient, while the sensitivity dropped to 5% [5]. The conclusion from that study was that the presence of the hysteroscopic features of CE should lead to a diagnosis, increasing the likelihood of histological confirmation, but the lack of alarming features cannot rule out the diagnosis. The authors highlighted that hysteroscopy should not replace histopathological examination as a CE diagnostic method of choice. Another interesting aspect analysed in Dongmei Song's study was the correlation between the number of plasma cell counts and the hysteroscopic findings. The study showed that the higher the rate of plasma

cells per 10 HPF, the more likely occurrence of the hysteroscopic features of CE was [5].

The need to develop a diagnostic consensus emerged from the variety of hysteroscopy diagnostic accuracy reported by different research groups. In 2019, the 'Working Group for Standardization of Chronic Endometritis Diagnosis' reached a consensus with the use of the Delphic method. Experts established diagnostic criteria which included the presence of at least one of the following hysteroscopic findings: strawberry aspect, focal hyperaemia, haemorrhagic spots, micro polyps, and stromal oedema in the follicular phase [36]. The major disadvantage of hysteroscopic examination is the fact that visual assessment of the uterine cavity is subjective and may depend upon the physician`s experience. That is why the reproducibility of newly established diagnostic criteria was evaluated. According to an international randomized-controlled observer study, knowledge of unified criteria increases physicians' ability to detect and diagnose cases of CE without increasing false-positive diagnoses [36].

In a systemic review aimed at answering whether hysteroscopy was suitable for setting the CE diagnosis, the authors did not manage to support the hypothesis. They included 15 studies with a total of 5526 participants, but due to the heterogeneity of the diagnostic criteria used in those studies, the data was not sufficient to confirm that hysteroscopy alone was not adequate for setting the diagnosis [37].

It is worth emphasising that the lack of standardized histopathological CE criteria results in a lack of a concise verification method of hysteroscopic findings in various studies.

Identification of the bacterial factor

Microbial infection is believed to be the primary cause of persistent inflammation of the endometrial lining present in chronic endometritis [33, 38]. The main finding supporting the theory of the infectious genesis of CE is the effectiveness of antibiotic treatment on the histopathologically confirmed resolution of this endometrial pathology shown in a prospective randomized control trial [7].

The classic technique of bacterial identification used in CE investigations is a microbial culture of the endometrial tissue. It is worth noting that the study by Cicinelli et al. [39] showed a low concordance of vaginal and endocervical bacterial findings with those from endometrium sampling. These findings implicate that samples obtained from the lower genital tract cannot be used in the CE diagnostic process.

The main advantage of microbial culture is the objective identification of the endometrial pathogens and the possibility of administering a targeted antibiogram-guided treatment.

Findings from the Cicineli and Kitaya research groups show us that the pathogens detected by microbial culture in patients with a CE diagnosis were mostly the common bacteria *Streptococcus species*, *Escherichia coli*, *Enterococcus faecalis* and *Staphylococcus species*, *Mycoplasma*/*Ureaplasma species*, *Proteus species*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Gardnerella vaginalis*, *Corynebacterium species* and yeast [33, 39, 40].

The major limitation of this diagnostic technique is the fact that not all bacteria are culturable under standard laboratory conditions. The reported rate of positive microbial culture in histopathologically confirmed CE cases varies between 52% and 73% [19, 33].

It is well proven that the uterine cavity is not sterile under normal physiological conditions [41–44]. This is why negative bacterial culture results are most probably a result of method limitations, rather than the actual lack of bacteria in the uterine cavity. The use of molecular techniques enables the detection of low biomass uterine microbiota. These techniques include the quantitive polymerase chain reaction and next-generation sequencing of the 16S RNA bacteria. Therefore, the modern concept behind the CE pathophysiological model focuses more on microbial and immune cross-talk rather than the presence of bacteria in the uterine cavity itself [45].

The role of uterine microbiota and its influence on the decidualization and receptivity of the endometrium in infertile patients is now wildly investigated.

According to the results of a prospective pilot study by Moreno et al [43] bacterial DNA was detected in all of the endometrial fluid samples examined using PCR and 16S RNA sequencing. In a larger group of patients detectable amount of DNA was found in 61% of endometrial fluid samples and 64% of endometrial biopsy samples [44].

Based on the uterine microbiota composition, *Lactobacillus*-dominated microbiota (> 90% *Lactobacillus spp.*) or a non-*Lactobacillus*-dominated microbiota (< 90% *Lactobacillus spp.* with > 10% of other bacteria) was defined [43]. Reported reproductive outcomes of patients with non-*Lactobacillus*-dominated endometrial microbiota undergoing IVF procedures were significantly worse compared to a group with *Lactobacillus*-dominated endometrial microbiota. For example, the implantation rate was 60.7% vs 23.1% while the live birth rate was 58.8% vs 6.7% respectively [43]. Unfortunately, this study did not include a histopathological assessment of CE and its correlation with microbial findings.

The study conducted by Moreno in collaboration with Cicinelli was designed to evaluate the diagnostic accuracy of the molecular diagnostic tools used in a CE investigation. The histology, hysteroscopy and microbial culture results were compared with the RT-PCR identification of nine pathogens in 65 patients. These nine pathogens were

selected based on the findings of the most common bacteria in patients with histopathological confirmed CE. Based on the cases of the concordant finding of all three classic diagnostic techniques compared with RT-PCR findings, 75% sensitivity, 100% specificity and 77% accuracy of this molecular diagnostic tool were reported. This demonstrated an opportunity to overcome the bias of classic diagnostic methods and give new diagnostic tools in this infection pathology of endometrium [19]. It is worth indicating that in this study only 20% of 65 patients got unanimous results of all three classic techniques. Therefore, the vast majority encountered ambiguous results, showing that CE diagnosis determined by means of different diagnostic methods may yield contradictory results.

CONCLUSIONS

Despite accumulating reports on CE association with poor reproductive outcomes and the evidenced effectiveness of antibiotic treatment on CE resolution, this inflammatory condition is not routinely investigated in patients with infertility.

Clinical guidelines do not recommend CE investigation since more prospective observational studies and randomized controlled trials are needed.

The first step towards that is creating precise diagnostic criteria concerning CE for researchers all around the world to follow. Unified diagnostic criteria will lead to an opportunity to perform high-quality meta-analyses to gather results from the rising number of studies investigating this condition.

As was already highlighted in this review, the histopathological examination of endometrial samples is, for now, a diagnostic gold standard in CE. It is also the verification method used for assessing the diagnostic accuracy of other CE diagnostic techniques. Therefore, it is vital to reach an international consensus on universally accepted standardized histopathological criteria for CE. A precise threshold number of plasma cells identified including the use of ICH staining is needed.

With a unified histopathological verification method, further studies on the value of hysteroscopy and microbial identification of bacterial factors will give more precise results.

The use of molecular microbiology technology seems to be the future of understanding the role of the human microbiome in the aetiology of many medical conditions. Reproductive health is not an exception as new possibilities shed light on the relationship between endometrium bacterial community profiling and pregnancy outcomes. However, before implementing this diagnostic technique into clinical practice we need a verification method to access the relevance of these findings.

In conclusion, it is of great importance for the sociates of gynaecologists and pathologists to unify CE diagnostic criteria and create a clinical investigation scheme. This might be the way to reduce the inconsistency of CE study results and help to prove the significance of CE screening in infertile patients.

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Conflict of interest

The authors declare that there are no competing interests in this study.

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