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Should we stop screening for chronic endometritis?

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ABSTRACT

Chronic endometritis is a poorly understood infectious or inflammatory process, potentially disrupting the correct implantation of a human embryo (*Puente et al., 2020*). The exact prevalence is a subject of discussion and ranges across the available literature from 2% to almost 60%, with a higher suspicion of the condition being present in women with recurrent early pregnancy loss and recurrent implantation failure (*Puente et al., 2020*). The impact of chronic endometritis on reproductive outcomes following IVF remains questionable given the lack of proper data convincingly showing an improvement after diagnosis and treatment. This article aims to provide the reader with a critical appraisal of current diagnostic methods, treatments and patient populations to be tested for chronic endometritis.

CAN WE ACCURATELY DIAGNOSE CHRONIC ENDOMETRITIS?

So far, there is no consensus definition or diagnostic tool for chronic endometritis. Most fertility specialists rely on an endometrial biopsy and an analysis of plasma cells in the endometrial stroma by a pathologist to histologically diagnose chronic endometritis (*Cicinelli et al., 2019*). This analysis is, however, prone to inter- and intraobserver variation, and the accuracy can be compromised by conditions such as mononuclear inflammatory cell infiltration, stromal cell proliferation, a plasmacytoid appearance of the stromal cells, or a pronounced pre-decidual reaction in the late secretory endometrium. (*Liu et al., 2018*). Immunohistochemistry staining for syndecan-1 (CD138) has been shown to have a higher sensitivity to recognize plasma cells compared with conventional haematoxylin/eosin staining, and an expert pathologist is thought to be crucial for accurate diagnosis (*Liu et al., 2018*). Furthermore, among different studies, various approaches have been used to quantify plasma cells and define chronic endometritis, ranging from a single plasma cell in the whole tissue section to several per randomly chosen high-power field (*Liu et al., 2018*). The latter explains the inconsistency in the reported prevalences of chronic endometritis in the current literature and further questions whether histology (alone) can be used to guide clinical decision making.

Besides endometrial histology, macroscopic inspection of the uterine cavity via hysteroscopy and microbial culture/microbiota analysis are also used for the diagnosis of chronic endometritis (*Cicinelli et al., 2019*; *Moreno et al., 2018*). The concordance between these approaches, on the other hand, has been shown to be as low as 20% (*Moreno et al., 2018*). Cicellini and colleagues proposed a consensus on the diagnostic criteria for chronic endometritis during hysteroscopy (more specifically mucosal oedema, focal or diffuse endometrial hyperaemia and micropolyps). The authors found a substantial agreement among the observers (*Cicinelli et al., 2019*), but again the physicians' experience is of the utmost importance.

Microbial culture is an interesting method for detecting chronic endometritis as it allows for a germ-targeted treatment. However, the technique can yield false-negative results due to bacteria that are not culturable in standard laboratory settings (*Cicinelli et al., 2018*). More recently developed molecular techniques might hold promise for the future to assist in the diagnosis of chronic endometritis (*Moreno et al., 2018*). The advantage of microbial analysis based on next-generation sequencing of

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the 16S ribosomal subunit and/or focused real-time polymerase chain reaction is that both culturable and non-culturable pathogenic microorganisms associated with chronic endometritis could be identified (*Kitaya et al., 2018*; *Moreno et al., 2018*). Nevertheless, additional research is needed as false-positive results due to contamination in these typically low biomass endometrial tissue analyses is a potential problem.

It is furthermore important to mention that the uterine cavity is no longer considered sterile, and that the interaction between infectious agents and the endometrial environment is the most important factor in defining pathology.

CAN WE EFFECTIVELY TREAT CHRONIC ENDOMETRITIS?

Data on the optimal treatment regimen for chronic endometritis are scarce. Although broad-spectrum antibiotics are the conventional treatment, various regimens have been applied across studies. The overall cure rates range between 64% and 100%, potentially as a result of different regimens and repeated courses of treatment, and because the definition of a cure differs between the studies (*Espinós et al., 2021*). In some studies women were considered to be cured when a plasma cell-negative histology/immunohistochemistry was reached (*Kitaya et al., 2018*), while others considered a normalization of the hysteroscopy findings to define a woman as cured (*Cicinelli et al., 2021*). Other studies have investigated adjuvant therapies such as anti-inflammatory drugs, probiotics to regulate the female reproductive tract microbiome, or progestogens as alternative treatment options; however, the current evidence is insufficient to apply them in daily practice (*Espinós et al., 2021*).

DOES THE DIAGNOSIS AND TREATMENT OF CHRONIC ENDOMETRITIS HAVE AN IMPACT ON IVF SUCCESS RATES?

There are no robust published data on this, and hence no guidelines to direct who and/or when to screen which women for the potential presence of chronic endometritis along an assisted reproductive technology (ART) trajectory. A recent Strengths, Weaknesses, Opportunities and Threats analysis by Espinos and colleagues reported the highest evidence level of current publications to be 2a and thus concluded that no high-quality studies have yet been performed (*Espinós et al., 2021*). Given the hurdles, as discussed above, that are hampering a consistent and adequate diagnosis and treatment of chronic endometritis, routine screening prior to ART should be avoided outside a research setting. If a consensus can be reached on a uniform diagnosis, future multicentric, randomized trials could aim to investigate the effect of antibiotic treatment regimens, not only on endometrial histology and the disappearance of plasma cells as a surrogate outcome parameter, but also on the actual reproductive success following ART treatment.

The limited data currently available suggest that patients who probably benefit mostly from screening and treatment are women suffering from recurrent early pregnancy loss (*Pirtea et al., 2021*) and recurrent implantation failure (*Cicinelli et al., 2018*). Future studies should, however, try to take into account the pivotal role of the embryo in implantation in both of these conditions, as chromosomal abnormalities are confirmed to explain the majority of cases (*Finley et al., 2022*; *Pirtea et al., 2021*). Excluding aneuploid miscarriages and implantation failures will increase the likelihood of finally unravelling whether or not there is an impact of chronic endometritis in the case of failed implantation.

CONCLUSION

Despite the increasing number of publications on chronic endometritis in ART, essential questions of daily clinical practice are not being resolved. As a first step, the community needs to work towards and establish a uniform definition of the pathology, which will probably need to rely on and take into account a combination of several diagnostic methods. Once fertility specialists as well as pathologists are able to examine for chronic endometritis in a standardized way, interventions of cure should be tested in a randomized design, focused on specific patient populations (euploid failed implantation) and with reproductive success (and not the histological disappearance of plasma cells) as the primary outcome parameter. Until then, the evidence for the screening and treatment of chronic endometritis along the course of an ART treatment is very debatable, even in women who have had a failed embryo implantation (*Pirtea et al., 2021*). A substantial delay in the initiation of subsequent reproductive treatments, the disruption of healthy uterine bacterial microbiomes with blind, cumulative antibiotic use, antibiotic resistance, additional expenses for any healthcare system, and the complications associated with the invasive nature of endometrial biopsy and hysteroscopy should not be neglected.

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