REVIEW ARTICLE

Unraveling Chronic Endometritis: A Review

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Abstract

Chronic endometritis (CE) is a pathology associated with persistent inflammation of the endometrial lining. The symptomatology of CE is usually mild or absent. CE is emerging as one of the main causative factors for altering the endometrial receptivity, which negatively impacts the process of implantation. It is mainly associated with unexplained infertility, recurrent miscarriages, and recurrent implantation failures. While immunohistochemical CD 138 staining is the gold standard for the diagnosis of CE, conventional tissue staining, hysteroscopy, transvaginal color Doppler, and culture sensitivity are other useful diagnostic modalities. Targeted or empirical antimicrobial therapy is effective for treatment in women with CE. Reproductive outcomes may improve following treatment with antimicrobial agents.

Keywords: Recurrent implantation failure, Recurrent pregnancy loss, Unexplained infertility, Transvaginal sonography

International Journal of Infertility and Fetal Medicine (2022): 10.5005/jp-journals-10016-1279

Introduction

Assisted reproductive technologies (ARTs) are continuously evolving to optimize the reproductive outcomes. Despite the various changes introduced in ART practice, one of the rate-limiting steps for ART success is the stage of embryo implantation. The ongoing pregnancy rate with euploid embryo transfer is approximately 45% and 60% among autologous ART population and donor oocyte recipient women, respectively. Thus, the endometrial factors account for more than half of the failed embryo implantation. Chronic endometritis (CE) exerts a negative effect on implantation by altering the endometrial receptivity. CE has received less focus as a gynecological disease compared to acute endometritis. Acute endometritis commonly manifests with fever, vaginal discharge, and pelvic pain. In contrast, the minor symptoms of CE are usually ignored by both the patient and gynecologist.[1] Dana B and McQueen defined CE as the presence of 1–5 plasma cells per high-power field (HPF) or isolated clusters of <20 plasma cells identified by CD 138 staining.[2,3]

Prevalence

The prevalence of CE in the general population is not clearly defined and varies widely from 2.8 to 72%, whereas CE in the infertile group varies between 22 and 28%.[4] The prevalence of CE in women with unexplained infertility is 56.8%.[5] While, the prevalence of CE in women with recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) varies from 30.3 to 55.7% and 52.7 to 57.8%, respectively.[2,4-6]

Women with RIF diagnosed with CE have a significantly lower implantation rate (15% vs. 46%) than those women without CE.[7] Likewise, the live birth rate in women with a history of RPL and untreated CE is very low (7%).[6] The prevalence of CE varies significantly in the studies due to the different diagnostic methods used and the time of menstrual cycle in which endometrial sample was obtained.

Chronic Endometritis and Reproductive Outcome

Implantation is a physiological process involving several inflammatory markers such as leukocytes, cytokines, chemokines, and other endometrial factors. CE alters the receptivity of the endometrium. Recent data by Wu et al. suggests that in one-third of infertile women with CE, the endometrium exhibits a high level of estrogen, progesterone receptor, and Ki-67 nuclear marker of cell proliferation, in addition to the increased expression of anti-apoptosis genes, i.e., *BCL-2*, *BCL-6*, and *BCL-XL*.[8] These represent proliferative changes in the endometrium even during the secretory phase of the menstrual cycle. One-third of the endometrial samples obtained from infertile women with CE demonstrate such "out-of-phase" endometrial morphology.[9] Additionally, the plasma cells (PCs) and immunoglobulin (Ig) involved in inflammatory reactions exert a negative influence on endometrial receptivity.

The uterine contraction pattern also changes in CE. Physiologically, during the proliferative phase, there are antegrade contractions from the fundus to the cervix, which are preceded by retrograde contractions in the periovulatory and luteal phases of the menstrual cycle. It favors the migration of the spermatozoa to the fallopian tubes. Conversely, during CE, there is "altered peristalsis," which may partially affect the fertility and also contribute to some of the symptoms of pelvic pain and dysmenorrhea.[10,11]

Diagnosis of Chronic Endometritis

Patients with CE are usually asymptomatic or present with vague symptoms such as pelvic discomfort, spotting, and leukorrhea. Systemic inflammatory markers such as peripheral blood leukocytosis and raised serum C-reactive protein are usually negative in women with CE.[3]

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How to cite this article: Sarkar S, Aleyamma TK, Kamath MS. Unraveling Chronic Endometritis: A Review. Int J Infertil Fetal Med 2022;13(2):82–86.

Source of support: Nil

Conflict of interest: None

Conventional Tissue Staining

Endometrial sampling with histopathologic detection using hematoxylin and eosin (H and E) staining of multiple endometrial stromal plasmacytes (ESPCs) is important for the diagnosis of CE.[12] Chronic endometritis can be diagnosed as the presence of ≥ 1 plasma cells in 10 HPFs with sensitivity of 87.5% and specificity of 64.9 %.[13] Other histological features of CE are superficial edematous change in the endometrium, high-stromal cell density, the differential rate of maturation between epithelium and stroma, as well as glandular-stromal asynchrony and eosinophil infiltration.[14]

A wide variety of immunocompetent cells such as macrophages, natural killer cells, and T lymphocytes infiltrate the endometrium. The changes in the composition and density of endometrial immunocompetent cells influence the endometrial receptivity.[12] Under physiologic conditions, B cells comprise <1% of all endometrial leukocytes and are mainly limited to the basal layer of the endometrium. Microbial antigens, i.e., lipopolysaccharides, cause a vast number of peripheral B cells to extravasate and accumulate into the stroma of the endometrium.[15] Additionally in CE, endometrial epithelial cells express several adhesion molecules and chemokines such as Selectin E, CD62E, and CXCL1, which are involved in B cell extravasation and accumulation into the stromal compartment.[15] There is also increased levels of interleukin-6 (IL-6), IL 1β, tumor necrosis factor-α (TNF-α), and Ig subclasses with a predominance of IgG2. The upregulation of anti-apoptotic genes results in the formation of micropolyps, affecting the endometrial receptivity.[9,15,16] A fraction of the accumulated endometrial B cells differentiates into ESPCs. Thus, plasmacytes (PCs) develop from antigen-activated B lymphocytes. Typical PCs have a large cell body with basophilic cytoplasm, with high nuclei/cytoplasm ratio and nuclei with heterochromatin arranged in a "spoke-wheel" or "clock-face" pattern.[17]

Immunohistochemical CD138 Staining

CD-138 (Syndecan 1) is a type I transmembrane heparan sulfate proteoglycan. Antibodies (i.e., clone B-B4 and B-A38) can selectively recognize CD138 antigens on the PCs and, therefore, can be used for its detection. Histopathological evaluation using IHC is currently the most reliable and rapid method for diagnosing CE. In contrast to conventional staining, there is no significant intraobserver and interobserver variability in immunohistochemical (IHC).[11] Plasma cells are identified brown by IHC staining.[18] In a previous study, the sensitivity and specificity of CD-138 for detection of plasma cells in endometrial biopsy was 66.7% and 48.9%, respectively, when hysteroscopy is taken as reference test for detection of CE.[19]

Hysteroscopy

Hysteroscopy is a useful modality in diagnosing CE. Some of the hysteroscopic findings, which suggest CE, are the presence of local or diffuse hyperemia, edematous stroma, and the presence of micropolyps.[8] Micropolyps are small pedunculated and vascularized protrusions of the uterine mucosa measuring <1 mm in size.[20] Studies have reported a correlation of up to 86.5–93.4% between hysteroscopy and histology for detection of CE.[21] The detection of hysteroscopic features in CE depends largely on the expertise of performing clinicians and can be subjective. The overall accuracy of hysteroscopic examination with regard to the diagnosis of CE is only 67%. Studies suggest that hysteroscopy cannot replace IHC as the diagnostic tool of choice. The sensitivity, specificity, positive predictive value, and negative predictive value of hysteroscopy in the diagnosis of CE were found to be 98.4%, 56.23%, 63.5%, and 97.82% respectively, when the reference test was histological diagnosis.[22]

Ultrasound in Chronic Endometritis

During transvaginal color Doppler examination, CE can be suspected when there is persistently thin hypovascular endometrium with an altered junctional zone in preovulatory as well as secretory phases.[23] The persistence of focal or diffuse endometrial thickening postmenstrual is known as endometrial shreds. These endometrial shreds may either result from the inflammatory process or due to inability of the uterus to evacuate during menses efficiently. The endometrial focal thickening or echogenicity can predict CE with sensitivity and specificity of 94.9% and 81.3% respectively, when hysteroscopy is taken as the reference diagnostic test.[24]

Microbial Culture for Chronic Endometritis Diagnosis

The microorganisms detected frequently in the endometrium with CE are *Streptococcus*, *Escherichia coli*, *Enterococcus, Staphylococcus, Mycoplasma,* Ureaplasma, *Proteus, Klebsiella, Gardnerella, Pseudomonas,* and yeasts.[25,26] *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the principal pathogens responsible for acute endometritis, are rarely detected in CE.[27,28]

Newer Diagnostic Methods

In a study by Moreno I et al., investigators demonstrated that compared to the conventional diagnostic methods such as hysteroscopy, histology or microbial culture, and real-time polymerase chain reaction (RT-PCR) are more effective in detecting CE. With RT-PCR as a reference diagnostic test, the single use of conventional diagnostic tests (histology, hysteroscopy, or microbial culture) showed poor diagnostic accuracies (46.15%, 58.46%, and 66.15%, respectively). The sensitivity and specificity for histology, hysteroscopy, and microbial culture were 56% and 40%, 58.73% and 50%, 71.43% and 56.67%, respectively. Additionally, the sensitivity and specificity of combination of histology and hysteroscopy with concordant results and combination of histology, hysteroscopy, and microbial culture with concordant results were 56% and 50%, 75% and 100%, respectively. RT-PCR is a low cost and less time-consuming diagnostic method. It can identify and quantify very small amounts of bacterial DNA, irrespective of their culturable or nonculturable nature. Furthermore, the microbiome results using next-generation sequencing (NGS) are concordant with RT-PCR in 91.67% of cases and correlates with the microbial culture in 75% of cases.[29]

Limitations of Diagnostic Tests

Identification of ESPCs by conventional tissue staining alone is difficult. The classical appearance of PCs is not always detectable in conventional tissue staining. The PCs resemble stromal fibroblasts and mononuclear cells of the endometrium. Furthermore, the edematous changes and increase in cellular density seen frequently in the secretory phase of endometrium interfere with the identification of stromal PC.[30]

Although detection of PCs by IHC is a gold standard diagnostic method, the results should be interpreted cautiously. Many of the monoclonal antibodies targeting CD138 on PCs are also reactive to the epitope of this antigen expressed normally on endometrial epithelial cells. This may lead to inaccuracy in detection of PC infiltration.[31] Furthermore, its diagnosis may be affected by other technical factors such as antibody selection and dilution, incubation time, the thickness of tissue section obtained, ambient temperature, and number of sections examined. CE may involve the partial or full thickness of the endometrium. CE is detected more often in the proliferative phase than in the secretory phase of the menstrual cycle.[7,8,9,12]

The traditional methods of microbial examinations in the diagnosis of CE have limited clinical relevance as culture methods and conventional PCR are not able to identify microorganisms in more than half of infertile women with CE.[26]

Proposed Treatment and Response to Treatment

Treatment is indicated for women with a history of unexplained infertility, RPL, and RIF with the diagnosis of CE. Targeted antimicrobial therapy is appropriate when the causative agent is identified. Empirical antimicrobial therapy with doxycycline is preferred treatment of CE.[19] In a retrospective study, Johnston–MacAnanny et al. prescribed oral doxycycline (200 mg per day for 14 days) in 33 CE women with a history of RIF undergoing ART. There was clearance of CD138 positive ESPCs in 70% of these women after therapy. In remaining women resistant to doxycycline, a combination of ciprofloxacin and metronidazole (500 mg of each per day for 14 days) was found to be effective.[7]

In another cohort study, McQueen et al. treated 395 CE women with a history of early RPL and/or fetal demise. After the first course of antibiotics [combination of ofloxacin (800 mg per day for 14 days) and metronidazole (1,000 mg per day for 14 days)], there was an adequate response in 94% of the cases, rising to 100% after administration of two courses of antibiotics. Women who were resistant to the first-line regimen were cured with the second-line regimens using doxycycline alone, doxycycline and metronidazole, or metronidazole and ciprofloxacin. They also reported an increase in live birth rate from 7% before treatment to 56% after receiving antibiotic treatment for 2 weeks.[2] Few studies have also explored the effectiveness of progestogens as a treatment option for CE, but the data remains inconclusive.[19]

Reproductive Outcome Following Treatment

In a retrospective analysis on pregnancy outcomes after antibiotic treatment in CE patients with a history of RIF, the live birth rate following fresh ET was significantly increased in the cured CE group compared with the persistent CE group (60.9% vs. 13.3%). But, no difference was found in the live birth rate between the women undergoing a single course or multiple courses of antibiotic treatment.[5]

Cicinelli et al. performed a retrospective study of 360 women with RPL, they found a higher live birth rate in women responding to antibiotic treatment, compared to nonresponder women.[32]

In cases of unexplained infertility with CE, the cumulative live birth rate per women during the course of a 12-month follow-up period was significantly higher in the cured CE group (65.8%) than in the persistent CE group (6.6%) for spontaneous conception.[33]

Overall, studies suggest that CE has a negative impact on endometrial receptivity, and adequate response to antibiotic therapy may significantly improve reproductive outcomes.[34] Nevertheless, diagnostic hysteroscopy and endometrial biopsy itself may have a beneficial effect on reproductive outcomes. Hysteroscopy may remove the bacterial biofilms involved in the pathophysiology of CE, whereas endometrial biopsy may induce secretion of cytokines and growth factors in the endometrium-enhancing embryo implantation.

Indian Scenario with Tuberculosis

Worldwide, 5–10% of infertile women have genital tuberculosis, which varies from <1% in the United States to approximately 18% in India.[35] *Mycobacterium tuberculosis* is highly prevalent in India. The endometrium is affected in 50–80% of women with female genital tract tuberculosis patients (FGTB). It causes implantation failure due to alterations in the immune response mechanisms, change in the hormonal milieu, and the release of antiphospholipid antibodies. In early phase, the uterine changes may be seen as "collar–stud abscess," later the typical lesions can be focal or multiple ulcers, caseous necrosis, and hemorrhagic areas. Chronic infection may lead to extensive destruction of the endometrium and myometrium resulting in complete narrowing of uterine cavity. The sequelae of endometrial tuberculosis result in varying levels of uterine synechiae which are otherwise known as Asherman's syndrome.[36] On microscopy, poorly developed caseating epithelioid granulomas with surrounding lymphocyte infiltrates including ESPCs are diagnostic of chronic tubercular endometritis.[37,38] N-PCR, histopathology, and culture are other diagnostic methods. Certain ultrasound features associated with tubercular endometritis are persistently thin endometrium, disrupted endomyometrial junction, vertically oriented interstitial part of the tube, echogenic flecks in the endometrium, vascular myometrial cysts, fluid in the endometrial cavity in the mid-proliferative phase, an echogenic inner layer of endometrium and micropolyps.[23]

For infertile women with chronic granulomatous endometritis, anti-tubercular therapy (ATT) for 9–12 months is effective. In a study by Bahadur et al., on repeat hysteroscopy after completion of ATT, there was a significant improvement in grade I and II adhesions, but major adhesions (grade III onwards) persisted.[39,40] Parikh et al. observed a 16.6% pregnancy rate per embryo transfer after completion of ATT in patients with normal endometrium.[41] However, in cases with endometrial TB causing damage to the endometrium like in Asherman's syndrome, adoption or gestational surrogacy can be advised.

Conclusion

- There has been renewed focus on association of chronic endometritis with unexplained infertility, and repeated reproductive failures.
- It is important to determine the diagnostic criteria and define chronic endometritis by a universally accepted method which will help in assessing the effectiveness of proposed treatments.
- Histopathological evaluation using IHC is currently the gold standard diagnostic test for chronic endometritis but there is a need to standardize the test.
- Diagnosis by hysteroscopic assessment of uterine cavity can be easily incorporated in evaluation of cases of unexplained infertility and repeated reproductive failure, but is clinician dependent and cannot replace IHC.
- Real-time transvaginal ultrasound can be used as first-line screening test for CE.
- With advancing technologies, newer and more effective diagnostic tests for CE are microbiome detection using NGS and RT-PCR
- Diagnosis and treatment of CE may result in an increase of spontaneous conceptions in couples with unexplained infertility and repeated reproductive failures.
- In certain regions across the world, endometrial TB is one of the important causes of chronic endometritis.
- Large placebo-controlled trials are required to determine if treatment of CE helps in improving reproductive outcomes, in women with unexplained infertility and recurrent IVF failures.

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