The Role of Chronic Endometritis in Infertility and Recurrent Miscarriage: A Comprehensive Review

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Authors

Vida Shafti[1], Alireza Azarboo[2*]

1. School of Medicine, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran.
2. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Authors:
Alireza Azarboo, MD
School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: alirezaazarboo52@gmail.com

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ABSTRACT

The diagnosis of chronic endometritis presents a challenge in patients with infertility issues and recurrent miscarriages. It not only poses problems before pregnancy but also manifests complications during pregnancy. Issues such as recurrent miscarriages, repeated implantation failure, endometriosis, cervical insufficiency, second-trimester miscarriages, and a decrease in the number of live births are associated with it.

There is still no consensus on the diagnosis and treatment of endometritis. Diagnosis is typically done through biopsy, which is relatively expensive and invasive, and relies on histological examination and the presence of plasma cells. There are many conflicting reports on this matter.

In recent years, the uterine microbiome has garnered attention. This study reviews recent literature to explore the causes, pathophysiology, diagnostic methods, and treatments for this disease.

Keywords: chronic endometritis, recurrent miscarriage, repeated implantation failure, infertility, endometriosis.

Introduction

Chronic endometritis (CE) is characterized as a specific inflammation detected by the presence of bacteria in the endometrial stroma. It has negative impacts on human reproductive processes, including recurrent implantation failure (RIF), endometriosis (1), recurrent miscarriage (2), mid trimester loss due to cervical incompetency (3), and reduced live birth rate (4). The topic of chronic endometritis is currently of great interest in research on recurrent pregnancy loss and recurrent implantation failure. Physiologically, the endometrium has a diverse range of immune system cells such as natural killer cells (NK), macrophages, T cells, and neutrophils, with its makeup and concentration changing regularly throughout the menstrual cycle (5).

Human microbiota

The Human Microbiome Project (HMP) has discovered that approximately 9% of the human microbiota resides in the female genital tract in recent years (6). Nevertheless, increasing evidence indicates that the female reproductive system is an open entity. The uterine cavity has a small number of bacterial communities, referred to as low biomass microbiota (6, 7). Increasing data suggests that the makeup of microbiota could impact endometrial receptivity, crucial for immune acceptance of fetal antigens and accurate control of inflammatory agents (8). New data indicates that there is a constant interaction between the microorganisms in the endometrium and the immune system, indicating that an imbalance in these microorganisms could affect pregnancy results (9).

Etiology & Symptoms

CE is characterized by enduring inflammation of the endometrium due to infectious organisms, namely Escherichia coli, Enterococcus faecalis, Streptococcus agalactiae, Mycoplasma, Ureaplasma, Chlamydia, Mycobacterium tuberculosis (10), and several viruses (11). The cause of CE can result from foreign objects or abnormal structure in the endometrial cavity, such as an intrauterine device (IUD), submucous myomas, polyps, leftover conception products, incomplete abortion, or infections.

Chronic endometritis may show no symptoms but can lead to various uterine changes, such as pain, bleeding, leukorrhea, dyspareunia, and other issues. The occurrence of the condition greatly changes and relies on different factors such as uterine inflammation and the existence of infectious bacteria in the endometrial stroma. Several studies show that the occurrence varies between 10% and around 57% (12).

Pathophysiology

A concise overview of the pathophysiology of CE would involve mentioning the diverse bacteria impacting the endometrial microenvironment, along with cytokine secretions triggering leukocyte recruitment, which affects conditions like vascularity, uterine contractility, and endometrial function necessary for successful implantation post in vitro fertilization (IVF) (13, 14). While the proliferative and early secretory phases have leucocytes making up less than 10% of stromal cells, their population significantly rises during the mid-secretory phase, continuing to increase in the late secretory phase and early pregnancy (5). The cycle-dependent variations of these subpopulations are essential for implantation. High numbers of uterine natural killer (uNK) cells and plasma cells in the endometrial stroma have been linked to recurrent miscarriage (RM) and RIF (15). The use of CD138+ cells in immunohistochemical analysis is a dependable way to identify CE, characterized by ≥5 plasma cells in a minimum of one out of 30 HPF (16). Confirmation of diagnosis requires an endometrial biopsy stained with Syndecan-1 for plasma cells (CD138) immunohistochemically. The use of MUM1 and CD138 immunohistochemical expression is becoming more popular as a secondary method for identifying plasma cells in chronic endometritis (17).

In general, the potential reasons for RM and RIF include abnormalities in the uterus, changes in the parents' genetic structure, and blood clotting disorders like protein C deficiency, factor V Leiden mutation, and antiphospholipid syndrome (18, 19). Nevertheless, roughly half of women experiencing recurrent miscarriage and recurrent implantation failure still have an unknown cause, which may be linked to chronic endometritis (20). From a histological perspective, CE is identified by the existence of inflammatory cells in the endometrial stroma, such as plasma cells, lymphocytes, eosinophils, and even lymphoid follicles (21, 22). Additional histopathologic features of CE consist of shallow swelling, heightened stromal thickness, and asynchronous maturation of endometrial epithelium and stroma (23).

Diagnosis

Transvaginal 2D and 3D ultrasound with Doppler assessment is essential for assessing chronic endometritis during both the initial evaluation and follow-up. Several specific ultrasound indicators associated with chronic endometritis include ongoing thickening of the endometrium post-menstruation, echogenic remnants of menstrual blood or tissues post-menses, and focal echogenic foci or minimal thickening in the triple-line endometrium during

certain phases. Other signs include disturbances in endometrial ultrasonic structure, gas bubbles, acoustic effects, fibrosis, sclerosis, calcinosis, alterations in blood flow patterns in various arteries, and changes in uterine artery blood flow assessed through Doppler ultrasound (24-26). Ultrasound assessments are usually done right after menstruation ends (cycle days 5-8) and halfway through the cycle (cycle days 14-20) for women with regular periods (25).

Hysteroscopy with an endometrial biopsy of the endometrium is the most reliable method for diagnosing CE (27). Endometrial micro-polyps, a characteristic observed in hysteroscopy, are small growths in the endometrial mucosa that develop due to excessive growth of glands and stroma surrounding a vascular core (28). Medical professionals associate increased blood flow and swelling of the uterine lining with chronic endometritis, with over 50% considering the presence of small growths as a defining characteristic of this hidden medical issue. According to the literature, micro-polyps, stromal edema, hemorrhagic spots, strawberry appearance, and hyperemia are suggested as appropriate indicators of hysteroscopic evidence of CE (29). In women before menopause, there may be a link between CE and endometrial micro-polyps, which could be seen as two sequential stages of the same disease process (30). One issue with diagnosing CE hysteroscopically is that gynecologists often interpret findings subjectively (31). CADx systems using deep learning models are being actively implemented in gynecologic practice, along with other medical fields, in order to reduce human biases and errors (32).

Management & Treatment

Certain articles propose that giving oral antibiotics may enhance reproductive results (33, 34). Significantly, resolving CE after antibiotic treatment appears to enhance the reproductive results in these women, resulting in IVF outcomes similar to those of unaffected patients (13). However, women who have successfully treated CE see a significant increase in clinical pregnancy and live birth rates compared to those with untreated CE. Therefore, we have concluded that it is necessary to conduct a follow-up biopsy to evaluate patients for resolution of their CE (35).

The typical treatment protocol for CE is Doxycycline 100 mg twice daily for 14 days is a common first-line empiric treatment. Clindamycin and gentamicin, administered intravenously every 8 hours, are considered the standard treatment for more severe cases. Broad-spectrum antibiotics like cephalosporins, extended-spectrum penicillin, or fluoroquinolones may be used as monotherapy in 80-90% of patients. A second or third-generation cephalosporin with metronidazole is another popular choice. Oral antibiotics are typically given for 14 days. For inpatient treatment, parenteral therapy is continued until the patient has been afebrile for over 24 hours (35-37). Adjuvant therapies, including anti-inflammatory medications or probiotics, might directly address the inflammation process or assist in managing the endometrial microbiome (38). A systematic review proved that oral antibiotic treatment did not improve pregnancy outcomes in patients with chronic endometritis (39). Therefore, additional research is required to determine effective treatments for improving pregnancy outcomes.

Conclusion

Chronic endometritis is frequently asymptomatic but can adversely affect women's fertility. While there are numerous outstanding problems, incorporating hysteroscopy into the diagnostic procedure is crucial for clinical practice; nevertheless, hysteroscopy, when paired with histological examination of the endometrium, frequently does not lead to a definitive diagnosis of chronic endometritis. In summary, it is crucial to reach an agreement on the diagnostic standards for chronic endometritis. This is the sole method to improve global collaboration and establish properly planned multicenter research to demonstrate the impact of this endometrial condition on fertility concerns.

Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

Author's ORCID

Vida Shafti
https://orcid.org/0000-0002-5345-2188

Alireza Azarboo
https://orcid.org/0000-0003-3399-2360

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