Review Article

Endometritis in infertility

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Abstract Chronic endometritis is an asymptomatic condition. It results from persistent inflammation of the endometrial lining caused by the presence of microorganisms in the uterine cavity. It is often associated with infertility and poor reproductive outcome. The pathogenesis of chronic endometritis and its association with infertility has been reviewed. Diagnostic modalities and treatment for chronic endometritis are also discussed.

Keywords: Chronic endometritis, endometrium, hysteroscopy

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INTRODUCTION

A good healthy endometrium is necessary for successful implantation and continuation of pregnancy. Endometritis is an infection or inflammation of the endometrium. It is grouped as acute and chronic.

Acute endometritis is symptomatic and characterized by acute inflammations of the endometrium caused by bacteria. Neutrophils are seen invading the superficial epithelium, endometrial glands, and uterine cavity. It lasts for a short duration, responds well to treatment, and only rarely is associated with long-standing infertility.

Chronic endometritis is usually silent and characterized by the presence of plasma cells in the endometrial stroma. It is caused by a variety of agents such as bacteria, viruses, and parasites. It is often associated with infertility. However, in majority of cases the etiology cannot be determined. Chronic inflammation in long-standing endometritis can lead to formation of intrauterine adhesions or synechiae. This review aims to discuss the effect of chronic endometritis in infertility.

PREVALENCE

Chronic endometritis is asymptomatic or has nonspecific symptoms like atypical uterine bleeding, pelvic pain, and leukorrhea. In addition, the diagnosis of endometritis is not a simple one and depends on clinical and various diagnostic modalities used. Depending on the patient population and diagnostic method used, the prevalence of chronic endometritis has been reported to be between 2.8% and 30.3% in studies.[1,2]

PATHOGENS

The uterine cavity is thought to be sterile, but studies have shown the presence of microorganisms in it.[3,4] This may be because the microorganism present in the lower genital tract ascends upward and colonizes the uterine cavity. Uterus has its own defense mechanisms to prevent infections. The cervical mucus plug present acts as a

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gatekeeper because of its physical and immunological properties.[5,6] The endometrium also possesses innate immune defense system that produces natural antimicrobial peptides to protect it from microorganisms. These natural antimicrobial peptides are expressed by both, the epithelial cells and the endometrial leukocytes.[7] The expression of the peptides is modulated by hormonal and pro-inflammatory factors.[8] The immune responses of endometrium thus play an important role in limiting the microbial invasions.

Chronic endometritis is the persistent inflammation of the endometrial mucosa caused by the presence of microorganisms in the uterine cavity. Earlier studies suggested that *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were the main causative agents of endometritis.[9] A randomized clinical trial, however, demonstrated a low detection rate of *C. trachomatis* (7%) and *N. gonorrhoeae* (8%) in women with endometritis.[10] Antibiotic intervention therapies which target *C. trachomatis* and *N. gonorrhoeae* such as cefixime and azithromycin also failed to treat infertility in women with chronic endometritis.[10] Cicinelli *et al.* in their study observed that the most frequent microorganism detected in the endometrial cavity were common bacteria (58% of cases).[11] *Ureaplasma urealyticum* was detected in 10% and Chlamydia in only 2.7% of positive endometrial cultures. They also compared the results of vaginal and intrauterine cultures obtained from the study population and found that in only 143 (32.6%) cases the same infectious agents were isolated in the endometrial and vaginal cultures. In an another study, it was seen that in 69% cases common bacteria were found in the endometrial culture, of which streptococci were seen in 27% of cases and bacteria from intestinal flora (*Enterococcus faecalis* and *Escherichia coli*) were recovered in 31% of cases. *U. urealyticum* was detected in 10% and Mycoplasma in only one patient (0.2% of cases). No cases of *N. gonorrhoeae* were found.[12]

In developing countries, *Mycobacterium tuberculosis* is one of the commonest causes of endometritis leading to infertility in women.[13] Although *M. tuberculosis* has been the main causative agent, recent studies show an increasing incidence of *M. bovis* infection in humans.[14,15,16] Diagnostic tests available can differentiate between the M. *tuberculosis* and *M. bovis*. Differentiation is essential for epidemiological purposes and also from treatment purposes since *M. bovis* is intrinsically resistant to pyrazinamide, a first-line antitubercular drug.

A possible relationship between human immunodeficiency viruses (HIV) infection and endometritis has been suggested by a case report.[17] It has been observed that cytomegalovirus (CMV) infection can also cause chronic endometritis in nonimmunocompromised patients.[18] CMV infection should be considered in the differential diagnosis of granulomatous endometritis.

PATHOGENESIS

Chronic endometritis is considered to be an infectious or a reactive process. Endotoxins[19] produced by bacteria may induce a more predominant type 1 immune response (TH1) at the deciduas and stimulate pro-inflammatory cytokine production. This results in the formation of abnormal patterns of lymphocytes in the endometrium and induces the secretion of paracrine factors that ultimately may reduce the receptivity of endometrium.[20] A large number of B lymphocyte cells are seen infiltrating the endometrial tissue, including the glandular epithelial areas and lumen. Aberrant expression of CXCL1, a chemokine involved in B-cell migration,[21] is also seen in endometrial glandular epithelial cells of this endometrium. This massive B-cell invasion into the endometrium in severe chronic endometritis results in higher level of expression of IgM (immunoglobulin), IgA, and IgG in the endometrium of the infertile women with recurrent implantation failure (RIF) than that without chronic endometritis as seen in a study done by Kitaya *et al.* This study showed that the density of IgG_2+ stromal cells were significantly higher than that of any other Ig subclass-positive cells ($P<0.045$) in women having RIF with chronic endometritis.[22]

In women with chronic endometritis, the endometrial expression of some genes is also significantly altered. In particular, insulin-like growth factor-binding protein (IGFBP1), BCL2, and BAX were up-regulated, whereas interleukin 11 (IL11), CCL4, insulin-like growth factor 1 (IGF1), and CASP8 were down-regulated.[23] Increase in IGFBP1 gene expression and reduction in IGF1 gene expression in endometrium with chronic endometritis results in unfavorable conditions for implantation and embryo development. IL11 is a cytokine with anti-inflammatory properties, and its production is greatest during decidualization.[24] Down regulation of IL11 alters trophoblast invasion and leads to infertility. Also in the early stage of pregnancy, trophoblasts recruit natural killer (NK) cells and macrophages into the endometrium through chemokines such as CCL4. Down-regulated CCL4

activity due to chronic endometritis could result in the failure of implantation or abnormal placental formation. The altered gene endometrial expression may explain the impaired endometrial receptivity and the finding of endometrial hyperplastic lesions in women affected by chronic endometritis.

Implantation refers to a physiological inflammation process that involves inflammatory mediators, such as leukocytes, cytokines, chemokines, and other endometrial factors. These cells and their inflammatory mediators are important in the regulation of immune responses and trophoblast growth. As already seen, in chronic endometritis there is an imbalance in this process that leads to infertility and implantation failure.

A recent study has reported that women with chronic endometritis have altered endometrial wave patterns in both the periovulatory and midluteal phases. This altered uterine contractility seen in chronic endometritis may also contribute to infertility.[25]

Infertility in patients with genital tuberculosis may be because of the implantation failure caused by immune modulation of the endometrium resulting from hormonal imbalance and release of antiphospholipid antibodies.[26]

IMPLICATIONS IN INFERTILITY

Current evidence suggests that chronic endometritis is associated with infertility and poor reproductive outcome. Kitaya *et al.*[27] have reviewed the association of chronic endometritis with infertility and obstetric and neonatal complications. They stated that chronic intervillositis and decidual plasma cell infiltration leads to chronic deciduitis at the fetal–maternal interface. This results in pregnancy loss, preterm labor, and neonatal periventricular leukomalacia/cerebral palsy. Chronic deciduitis may even lead to rejection of the conceptus by the maternal immune system.

The changes in the endometrial milieu seen in chronic endometritis may hamper endometrial receptivity. Studies[28,29] conducted have shown that chronic endometritis leads to implantation failure. Restoration of normal endometrial histology improves the implantation rate in such patients. A retrospective study demonstrated that chronic endometritis is frequently associated with RIF. The study adds further evidence to the relationship between chronic endometritis and impaired endometrial receptivity. It states that normalization of both hysteroscopic and histologic endometrial pattern improves the reproductive outcome at *in vitro* fertilization (IVF) in these women.

Study done by Cicinelli *et al.* has shown an association between chronic endometritis and unexplained infertility.[30]

The subtle inflammation of chronic endometritis is found to be even associated with recurrent miscarriage (RM). A study[31] was conducted to evaluate the relationships between chronic endometritis and RM. Data from hysteroscopy, endometrial histology, endometrial culture, and polymerase chain reaction (PCR) for Chlamydia, performed before and after antibiotic treatment for chronic endometritis in 360 women with unexplained RM, were analyzed. 208 (57.8%) women with RM showed chronic endometritis at hysteroscopy of which 190 (91.3%) had positive histology, and 142 (68.3%) had positive cultures. Successful antibiotic treatment showed a significantly higher number of pregnancies (78.4%) compared to other groups (17.5%; $P<0.001$) and in treatment group (15.3%; $P=0.005$).

DIAGNOSIS

Diagnosis of endometritis is challenging. It is usually an asymptomatic condition. At times, it may present with symptoms such as atypical uterine bleeding, pelvic pain, and leukorrhea. Ultrasound examinations are also nonspecific. The triage of hysteroscopy, histopathology, and microbiology is often used to diagnose endometritis.

Hysteroscopy

Fluid hysteroscopy is a useful tool to detect endometritis. It is usually done in the follicular phase of menstrual cycle. The presence of micropolyps, less than 1 mm in size, polypoid endometrium, stromal edema, and focal or diffuse hyperemia on hysteroscopy, is highly diagnostic of endometritis.[32,33] The diagnostic accuracy of hysteroscopy was 93.4% in a study.[11]

Hysteroscopy is also a useful method in diagnosing endometrial tuberculosis. Kumar[34] used high resolution images and videos on hysteroscopy to demonstrate the differences between hysteroscopic markers in chronic endometritis and endometrial tuberculosis. He said that the classical hysteroscopic finding of endometrial tuberculosis is a rough dirty looking bizarre pale-looking endometrium with gland openings not seen and with overlying whitish deposits and adhesions. At times, the white deposits do not overlie the endometrium, and instead they are anchored to flimsy adhesions by being impregnated in the same. On staining with methylene blue the unstained caseous deposit reflects white light in contrast to the surrounding dark

blue endometrium, thereby giving a starry sky appearance.[35]

Histological diagnosis

For histopathological examination (HPE), endometrial specimen is collected through a 3-mm Novak curette connected to a 20-mL syringe. To prevent contamination it is inserted under visual control into the uterine cavity avoiding any contact with the vaginal walls. The presence of 1–5 plasma cells/ HPF or discrete clusters of plasma cells is generally accepted as the histological diagnostic criterion for chronic endometritis.[1]

In histological examination cells are stained with hematoxylin–eosin. The inflammatory status of the endometrium is graded based on the presence of stromal infiltrate dominated by lymphocytes and plasma cells, and a spindle cell change of stromal cells. However, it has a low diagnostic rate (<10%) as mononuclear inflammatory cell infiltration, stromal cell proliferation, or a plasmacytoid appearance of stromal cells can alter accuracy.[1]

Addition of an immunohistochemical (IHC) stain[36] capable of detecting CD38 and CD138 plasma cell specific surface antigens has increased the sensitivity for diagnosing chronic endometritis. The detection rate with IHC is as high as 56%, as compared to 13% sensitivity for hematoxylin–eosin staining.[37]

Cicinelli *et al.* in a study[38] have shown a significant correlation between focal hyperemia and isolated micropolyps with Grade 1 inflammation and between generalized hyperemia, the presence of diffuse micropolyps, and polypoid endometrium with Grade 2 inflammation. They said that hysteroscopic and histologic grading show good agreement (kappa index = 0.62).

Diagnosis of tuberculosis is based on the identification of acid-fast bacilli (AFB) in smears stained by Ziehl–Neelsen technique. However, in paucibacillary, extrapulmonary endometrial samples, AFB smears are negative at times. HPE of tissue sections in tuberculosis shows typical caseous granulomas with giant epithelioid cells. Ideal time for the endometrial sampling is the late secretory phase of the menstrual cycle as during this period there is increased probability of isolating the classic giant cells and tubercles.

Microbial culture

Microbiological culture of endometrial samples detects the presence of culturable microorganisms (*E. faecalis*, *E. coli*, *Staphylococcus epidermidis*, *S. aureus*, *Streptococcus agalactiae*, *S. mitis*, and yeasts). The endometrial samples are inoculated onto culture media either directly or after enrichment in brain heart infusion medium. To detect tuberculosis Lowenstein–Jensen (LJ) medium or agar-based Middlebrook 7H10 medium and the liquid culture are used. Liquid cultures require at least 9–10 days for positive results and 6 weeks for being considered negative and, in LJ medium cultures, the minimum time to positivity is 4–8 weeks.[39]

Microbial culture, the most reliable of the three classic methods, has few limitations like contamination of the microbial culture with skin or environmental bacteria (i.e., *S. epidermidis*) and the inability to grow and isolate nonculturable bacteria.

Molecular diagnosis

Reverse transcription polymerase chain reaction (RT-PCR) test can be used for the molecular diagnosis of chronic endometritis in endometrial samples using a comprehensive panel of primers to detect the most common microorganisms involved. *C. trachomatis*, *N. gonorrhoeae*, *U. urealyticum*, *U. parvum*, and *Mycoplasma hominis* are few noncultivable strains for which this method can be used.[11]

The molecular analysis has a degree of agreement of 76.92% when endometrial samples showed concordant results by all three classic methods.[11] It is highly sensitive and can identify and quantify very small amounts of bacterial DNA (deoxyribonucleic acid) even in frozen or fixed samples.

The main limitation of molecular microbiology is the relatively low negative predictive value, estimated at 25%,[11] compared to concordant histology + hysteroscopy + microbiology. Also, since DNA can even be from nonviable bacteria the presence of such DNA would not discriminate between acute and chronic endometritis.

Molecular techniques are increasingly being used for the detection of tuberculosis. The nucleic-acid amplification tests (NAAT) provide results in a few hours. PCR is a rapid molecular method for identification of nucleic acid sequences specific to mycobacteria tuberculosis and other mycobacteria in tissue samples of patients with genital tuberculosis. PCR assays can detect <10 bacilli/mL including dead bacilli and has a testing time of 8–12 h.[40]

Sensitivity of PCR is higher than culture and histopathology, and specificity may be as high as 100%

in detecting genital tuberculosis.[41] A retrospective study by Goel *et al.*[42] compared different methods, i.e., HPE, smear microscopy, LJ culture, Bactec culture, and PCR-DNA for diagnosing endometrial tuberculosis in females with infertility. The study concluded that none of the available tests were sensitive enough to diagnose all cases of genital tuberculosis, but conventional methods such as HPE and LJ culture still have an important role in the diagnosis of endometrial tuberculosis in resource-limited settings. PCR has higher specificity and sensitivity, faster turnaround time, but limited by high false-positive rates. Recently, GeneXpert MTB/RIF assay[43] has been endorsed by the World health organization (WHO) for detection of *M. tuberculosis*.

The high sensitivity of molecular microbiology allows for the detection of endometrial colonization in patients without histological signs of chronic endometritis, providing additional information to improve the current detection of this invisible endometrial pathology in asymptomatic infertile patients.

Treatment

Antibiotic treatment has been found to be relatively effective for chronic endometritis. Johnston-MacAnanny *et al.*[2] showed that 70% of cases of chronic endometritis diagnosed by endometrial biopsies were cured by a regimen of 100 mg of doxycycline twice per day for 14 days. Kitaya *et al.*[28] also reported that the histological clearance rate of CD138+ plasma cells in patient with chronic endometritis and RIF patients was 96% using the doxycycline-only regimen.

In a retrospective analysis of patients with unexplained recurrent pregnancy loss (RPL) and chronic endometritis, Cicinelli *et al.* administered antibiotics by antibiogram results. For Gram-negative bacteria, ciprofloxacin 500 mg twice a day for 10 days was mostly used as the first-line therapy. In cases of Gram-positive bacteria, amoxicillin and clavulanate 1 g twice a day for 8 days was prescribed. Mycoplasma and *U. urealyticum* were treated with josamycine 1 g twice a day for 12 days, whereas minocycline 100 mg twice a day for 12 days was administered if infection persisted. Clinical pregnancy rate was found to be significantly higher in treated group.[29]

In another prospective study, McQueen *et al.*[37] showed that the per-pregnancy live birth rate in RPL patients with chronic endometritis significantly increased to 56% after antibiotic treatment, compared to 7% before treatment. The histopathologic cure rate of chronic endometritis using a combination of ofloxacin (400 mg twice per day for 14 days) and metronidazole (500 mg twice per day for 14 days) was 73%.

Cicinelli *et al.*[29] conducted a retrospective study of RIF patients undergoing fresh IVF cycles, and found that the clinical pregnancy rate and the live birth rate in the group with normal hysteroscopic findings after antibiotic treatment were significantly higher than in the group with consistent chronic endometritis findings (65% vs. 33% and 60.8% vs. 13.3%, respectively). The results suggest that chronic endometritis plays a significant role in infertility.

A study conducted has shown that the diagnosis and treatment of chronic endometritis in women with unexplained infertility improve spontaneous pregnancy rate and live birth rate in such patients.[30] In women newly diagnosed with tubercular endometritis, WHO[44] recommends a regimen containing rifampicin (R) for 6 months: intensive phase with isoniazid (H), R, ethambutol (E), and pyrazinamide (Z) for a duration of 2 months followed by continuation phase with HR for 4 months. Study conducted by Jindal *et al.* has shown that the treatment of latent tuberculosis infection in infertile women improved the IVF and positive pregnancy outcome.[45] In another study, it was seen that the antitubercular treatment improved hysteroscopy findings in women with thin or flimsy adhesions (Grade I), singular dense adhesions (Grade II), and occluding adhesions at the internal os (Grade IIa) ($P < 0.01$). Patients with extensive adhesions, extensive endometrial scarring, fibrosis, and a tubular cavity showed no improvement after antitubercular treatment. The mean endometrial thickness also increased in the treatment group from 6.8 mm to 8.1 mm after 6 months of treatment.[46]

CONCLUSION

Chronic endometritis though asymptomatic is associated with infertility and poor reproductive outcome. Diagnosis is usually done by hysteroscopy, histopathology, and microbial examination. Timely treatment of this chronic inflammatory condition improves fertility and pregnancy outcome in these patients.

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Conflicts of interest

There are no conflicts of interest.

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