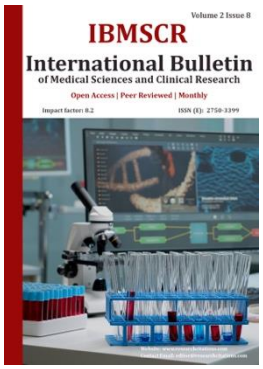


# DIAGNOSTIC PERSPECTIVES OF CHRONIC ENDOMETRITIS

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**Annotation.** Chronic endometritis is an understudied pathology associated with adverse reproductive outcomes such as implantation disorders and recurrent miscarriages. We provide summary information from the current literature, summarizing information obtained by searching computer databases. It is more common in infertile patients. With effective antibiotic therapy, SE improves pregnancy, live birth rates in patients with recurrent miscarriages during pregnancy and increases the miscarriage rate in patients with recurrent implantation failure. In addition to traditional histology, immunohistochemistry is recommended to improve diagnostic accuracy. In addition, hysteroscopy can be considered as an effective diagnostic standard, given its high correlation with histologic findings. Bacterial interaction with the endometrial microenvironment contributes to alterations in leukocyte population, cytokine and growth factor production, which enhances its negative impact on endometrial susceptibility. Nevertheless, it is important to define the standardization of histopathological diagnostic criteria and immunohistochemistry methods.

**Keywords:** endometritis, hysteroscopy, immunochemistry, reproductive outcomes

Endometritis is an inflammation localized in the endometrium, the inner lining of the uterus, usually of infectious etiology. An infection that spreads to the fallopian tubes, ovaries or pelvic peritoneum is called pelvic inflammatory disease. Endometritis is conventionally divided into 2 types: acute and chronic. Postpartum endometritis is a subtype of acute endometritis associated with pregnancy. Non-pregnancy-related acute endometritis refers to endometrial infection that has been present for ≥30 days. It is usually caused by a sexually transmitted infection or bacterial vaginosis. Common symptoms are similar to those of TCDD (e.g., fever, pelvic pain, vaginal discharge) and can range from mild to severe. Because of the similar symptoms, some physicians consider acute endometritis to be synonymous with TCDD. It is histologically characterized by microabscess formation and invasion of neutrophils into the endometrium. In addition, although acute salpingitis, which often accompanies acute endometritis in TCDD, is associated with infertility due to tubal scarring, acute endometritis per se is not associated with decreased fertility. Chronic endometritis is a mild inflammation of the endometrium, usually caused by microbial colonization unrelated to pregnancy, and lasting about 30 days. It is characterized by the presence of plasma cells in the endometrial stroma and other signs of chronic inflammation. Patients are often asymptomatic; however, the most common symptoms are abnormal uterine bleeding, dyspareunia, and pelvic pain. Chronic endometritis is often the cause of recurrent pregnancy loss and infertility. This disease can be difficult to diagnose because, unlike acute endometritis, most studies lack accurate diagnostic parameters other than endometrial stromal plasmacytes, which are considered sensitive histologic findings.

Postpartum endometritis is the most common cause of postpartum infection. Most cases of postpartum endometritis are polymicrobial, contain aerobic and anaerobic bacteria, and are associated with movement of normal vaginal flora into the uterine cavity during labor and delivery. Endometritis is 5 to 20 times more common in patients undergoing cesarean section than in vaginal delivery. Postpartum endometritis is the most common cause of postpartum infection. Most cases of postpartum endometritis are polymicrobial, contain aerobic and anaerobic bacteria, and are associated with movement of normal vaginal flora into the uterine cavity during labor and delivery. Endometritis is 5-20 times more common in patients undergoing cesarean section than in vaginal delivery. In this article, we aim to provide an overview of the diagnosis, etiology, pathophysiology and treatment, its effect on the endometrial microenvironment and its association with infertility. We will give an overview of the current literature, summarizing the results of computer database searches. It is more common in infertile patients.

Effective antibiotic therapy with SE improves the miscarriage and live birth rates in patients with unexplained recurrent pregnancy loss (ppb) and increases the miscarriage rate in patients with recurrent implantation failure. In addition to traditional histology, immunohistochemistry is recommended to improve diagnostic accuracy. In addition, hysteroscopy can be considered the gold standard of diagnosis, given its high correlation with the results of histologic examination. It, as a chronic inflammation of the endometrium, is usually asymptomatic and probably underestimated. Bacterial interaction with the endometrial microenvironment contributes to alterations in leukocyte population, cytokine and growth factor production, which supports its negative impact on endometrial susceptibility. Nevertheless, criteria for histopathological diagnosis and standardization of immunohistochemistry methods need to be defined.

Chronic endometritis is a delicate condition that is difficult to diagnose. Clinically, it is rarely suspected because chronic endometritis is usually asymptomatic. In addition, the diagnosis is often doubtful or unnoticeable if the endometrial surface is seen directly on hysteroscopy (5). It has been suggested that endometrial biopsy under hysteroscopy guidance is the preferred method to ensure the integrity of the uterine cavity prior to IVF (6). Although infiltration of the endometrium with lymphocytes and eosinophils is associated with chronic endometritis, the diagnosis is ultimately based on the presence of plasma cells 7, 8, 9, 10 in the endometrial stroma. The search for plasma cells can be hampered by many factors such as adequate staining, maintenance of endometrial tissue, or mimicry of plasma cells by plasmacytoid cells in the stroma 7, 8, 11. Therefore, histologic diagnosis is also difficult. Assisted reproductive technologies have undergone significant changes, including improved tissue culture facilities, updated embryo selection criteria, and expanded blastocyst culture, resulting in an increased pregnancy rate of up to 66% in selected patients (1-4). However, many factors involved in implantation are not yet fully understood, and the endometrium plays a much more important role than other recognized factors (5-7).

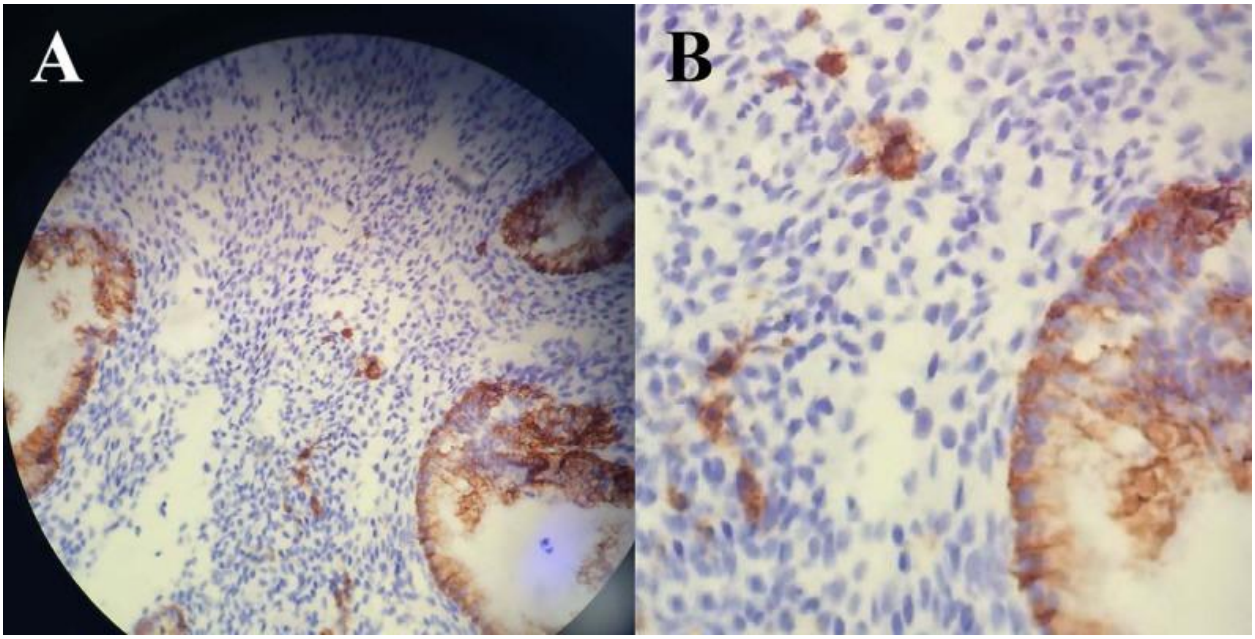
The endometrium is a unique tissue that undergoes monthly cyclic changes under the influence of ovarian steroids that lead to menstruation, reproduction, secretion and decidualization. The endometrium contains large numbers of immunocompetent cells, natural killer (NK) cells, macrophages, T cells, and neutrophils, whose composition and density change periodically (8). Cycle-dependent changes in these leukocyte subpopulations and their mediators may play a crucial role in implantation. In contrast, B-lymphocytes and antibody-

producing plasma cells are rarely found in endometrial tissue (9). Chronic endometritis (SE) is defined as a localized inflammation of the endometrial mucosa characterized by edema, increased stromal cell density, dissociated maturation of epithelial cells and stromal fibroblasts, and the presence of a plasma cellulose infiltrate in the stroma (10). These changes at the level of the endometrial microenvironment may affect endometrial susceptibility (11). It is often asymptomatic and accompanied by nonspecific clinical symptoms such as pelvic pain, dysfunctional uterine bleeding, dyspareunia, vaginal discharge, vaginitis, recurrent cystitis and mild gastrointestinal discomfort (12). The nonspecificity of symptoms and the importance of endometrial biopsy to confirm the diagnosis make it difficult to assess the prevalence of this condition.

Figure 1: immunochemistry of chronic endometritis. A. endometrial biopsy fragment showing syndecan 1 immunoreactivity on the surface of glandular cells. Plasma cells were isolated by staining syndecan 1 in the center of the image (original magnification: ×400) and B. detailed illustration of plasma cell immunoreactivity with syndecan 1.

Histopathology of chronic endometritis. The generally accepted gold standard for the diagnosis of He is the presence of plasma cells in endometrial tissues. However, their histologic identification is sometimes complicated by infiltration of mononuclear cells, mitosis and proliferation of stromal cells, plasmacytoid type of stromal cells (fibroblasts and mononuclear cells), or decidual changes of the endometrium in the late secretory phase. Plasma cells are characterized by the presence of dial-shaped chromatin within an eccentric nucleus with a perinuclear halo (Fig.1) (15).

Syndecan 1 is a Heparansulfate-type transmembrane proteoglycan present on the surface of




plasma cells and keratinocytes but not expressed in mononuclear cells, lymphocytes and endometrial stromal cells. It is also known as cd138, which facilitates detection of plasma cells and the presence of TBE without affecting intrinsic and observer variability. It is recommended to include clinical immunohistochemistry and routine pathologic examination to improve the accuracy of diagnosis (15). In addition, it is important to achieve standardization of existing diagnostic methods, given that the diagnosis of KE may differ depending on the dilution of Syndecan 1. At a dilution of 1: 1000, a prevalence of he 2.8%

before in vitro fertilization (IVF) was initially reported (39) in women with asymptomatic infertility, which does not match the prevalence of 30.3% previously reported by Johnston-makananni et al. and the prevalence of 10% in patients with recurrent miscarriages. In addition, the phase of the menstrual cycle in which the biopsy is performed and the thickness of the biopsy are important: in particular, in 15% of the samples in the secretory phase, plasma cells are present only in the basal layer of the stroma and are missed if they are not included in the biopsy. Finally, it is important to determine the number of plasma cells required for the diagnosis of CE: although most authors consider that there should be two or more..

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