Endometritis, new time, new concepts

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Endometritis is subdivided into two categories. Acute endometritis is symptomatic and characterized by microabscess formation and neutrophil invasion in the endometrial superficial epithelium, gland lumina, and uterine cavity. Chronic endometritis is rather silent and recognized as unusual plasmacyte infiltration in the endometrial stromal areas. Over the last decade, studies have disclosed the potential association between poor reproductive outcomes and endometritis, particularly chronic endometritis. The aim of this review is to address the current literature surrounding chronic endometritis and highlight recent advances in the research of this long-neglected gynecologic disease. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)

Key Words: Chronic endometritis, infertility, obstetric and neonatal complications, recurrent pregnancy loss, repeated implantation failure

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Under physiological conditions, human cycling endometrium is infiltrated by a wide variety of immunocompetent cells, including macrophages, natural killer cells, and T lymphocyte subsets. The composition and density of endometrial immunocompetent cells vary periodically across the menstrual cycle. Such timed fluctuation in local leukocyte subpopulations is thought to play a role in the tissue remodeling required to obtain endometrial receptivity (1).

Endometritis is an infectious and inflammatory disorder of the endometrium. Endometritis is histopathologically subdivided into two categories (2). One is acute endometritis, which is characterized by microabscess formation and neutrophil invasion in the endometrial superficial epithelium, gland lumina, and uterine cavity. The results of randomized controlled trials have demonstrated that acute endometritis is not associated with reduced pregnancy or elevated infertility (3). The other is chronic endometritis (CE), the histopathologic features of which are endometrial superficial edematous change, high stromal cell density, dissociated maturation between epithelium and stroma, and infiltration of endometrial stromal plasmacytes (ESPCs) (2, 4). There are currently no universally accepted standardized definitions or established diagnostic guidelines for CE, although experts agree that the presence of multiple ESPCs is the most specific and sensitive finding in this pathology (5–7).

In sharp contrast to acute endometritis being manifested with fever, pelvic pain, and vaginal discharge, the subtle and nondescript symptoms (pelvic discomfort, spotting, and leucorrhea) of CE are often unnoticed by patients and ignored by gynecologists (5). As a benign disease, interventional endometrial biopsy and arduous histopathologic examinations for CE are not favored in gynecologic practice. Accurate histopathologic diagnosis of CE has been demanding and time-consuming until recently (5). Increasing attention, however, has been focused on the potential association between poor reproductive outcomes and CE.

Here we aim to address the current literature surrounding CE and highlight recent advances in research of this long-neglected gynecologic disease. The following databases were searched for articles regarding CE until February 2018: PubMed, Embase, ScienceDirect, Wiley-Blackwell, Lippincott Williams & Wilkins, Highwire, and Google Scholar. Each database was searched using the following terms: “endometritis”, “deciduitis”, “subclinical pelvic inflammatory diseases”, and “upper female tract infection”.

MICROORGANISMS IN CE

The major cause of CE is microbial infection in the uterine cavity. This is supported by the fact that some antibiotic therapies are effective to eliminate ESPCs in the affected patients (8–12). The microorganisms detected frequently in endometrium with CE are common bacteria (streptococcus species, *Escherichia coli*, *Enterococcus*

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faecalis, and staphylococcus species), mycoplasma/ureaplasma species (*Mycoplasma genitalium*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*), proteus species, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Gardnerella vaginalis, Corynebacterium*, and yeasts (*Saccharomyces cerevisiae* and candida species) (13–15). In some developing countries, *Mycobacterium tuberculosis* is a microorganism causing chronic granulomatous endometritis, a subtype of CE characterized by poorly developed caseating granuloma and surrounding lymphocyte infiltrates including ESPCs (16).

By contrast, accumulating studies found that the detection rate of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the principal pathogens causing acute endometritis, are very low in patients with CE (2%–7% and 0%–8%, respectively) (13, 17, 18). Moreover, administration of azithromycin or cefixime, the antibiotics targeting *C. trachomatis* and *N. gonorrhoeae*, failed to preserve future fertility in women with CE (19). *C. trachomatis* and *N. gonorrhoeae* are thereby unlikely to be the major pathogens in CE. Although their cause-effect relationship remains undetermined, such differences in the microbial profiles suggest that acute endometritis and CE are distinct pathologic entities (20).

Altered proportion in anaerobic lactobacilli species, the predominant bacteria in the female reproductive tracts (21–24), may be another characteristic of CE, although the results are conflicting between the studies. While the report employing conventional tissue culture showed a lower detection rate of lactobacilli in the endometrium of infertile women with CE than in those without CE, the others using barcoded sequencing demonstrated an increase of local lactobacilli in CE (15, 25). Further studies are required to confirm the change of lactobacilli species in the uterine cavity in CE.

A few reports implicate human immunodeficiency virus (26, 27) and cytomegalovirus (28) in CE. The association between these viral infections and CE remains uncertain.

Importantly, the microorganisms detected in the endometrial tissue are often inconsistent with those detected in the endocervical tissue or vaginal discharge (14), suggesting that the microbial examinations using lower genital tract samples cannot predict the pathogens of CE. In addition, endometrial tissue culture and conventional polymerase chain reaction were unable to identify microorganisms in more than half of infertile women with CE (15). These findings indicate the limitation of the traditional microbial examinations in the diagnosis of CE.

INFLAMMATION IN CE

B lymphocytes account for only less than 1% of entire leukocyte population in the nonpathological human endometrium. Endometrial B cells are mainly seen in the basal layer (the portion that persists across the menstrual cycle) as central cells in the unique lymphocyte aggregates surrounded by numerous CD8(+) T cells and macrophages (29). The role of B cells and lymphocyte aggregates in the human endometrium remains open to debate. In contrast, in CE, a large number of B cells infiltrate both the endometrial functional layer (the portion shed with the onset of menstruation) and the basal layer. These overpopulated B cells amass in the endometrial stromal compartment, trespass on the glandular epithelial areas, and invade further into the gland lumina (30, 31). Additionally, the secretory phase endometrium with CE was reported to contain a lower percentage of $CD16^{negative}$ $CD56^{positive/bright}$ natural killer cells compared with those without CE, along with an increase in T cells, indicating the aberrant mucosal leukocyte composition in this pathologic condition (32).

Several adhesion molecules and chemokines involved in B cell extravasation and migration (CD62E, CXCL1, and CXCL13) are aberrantly expressed in endometrial endothelial and epithelial cells with CE (31). The concentration of interleukin (IL)-6, a differentiation factor of mature B cells, is also markedly higher in the menstrual effluents of women with CE compared with those without CE (33). In vitro studies demonstrated that these proinflammatory molecules are induced in endometrial cells by microbial antigens such as lipopolysaccharide (31). These findings suggest that microbial infection in the uterine cavity triggers the immune responses unusual to human cycling endometrium. Such immune responses provide an abnormal microenvironment for the recruitment of circulating B cells into the endometrial stromal compartment and gravitation of these lymphocytes to the glandular areas. Furthermore, a fraction of accrued endometrial B cells may differentiate in situ into ESPCs.

Similar to other chronic inflammatory diseases, like rheumatoid arthritis and inflammatory bowel disease, the levels of IL-1β and tumor necrosis factor (TNF)-α are also elevated in the uterine cavity of CE (33). Exposure to TNF-α is known to raise estrogen biosynthesis in endometrial glandular cells (34), which may be associated with the occurrence of endometrial micropolyposis, a hysteroscopic finding that is often seen in CE (see below) (9, 35).

The ESPCs in CE legions express a high level of multiple immunoglobulin (Ig) subclasses (IgM, IgA_1, IgA_2, IgG_1, and IgG_2) with a predominance of IgG_2 (36). The excessive mucosal antibodies in CE potentially have a negative impact on the embryo implantation process. These local immune responses in CE rarely develop into systemic inflammation, as the values of the peripheral blood leukocyte counts, serum C-reactive protein, and fever index of the affected patients stay within the normal ranges (37, 38).

One of the histomorphological characteristics of CE is delayed differentiation of endometrium in the midsecretory phase. Approximately one-third of the endometrial samples with CE obtained from infertile women exhibit such "out-of-phase" morphology (37). The endometrium with CE obtained in the secretory phase often displays pseudostratification and mitotic nuclei in both glandular and surface epithelial cells. The expression of the antiapoptotic genes (*BCL2* and *BAX*), proliferation-associated nuclear marker (Ki-67), and ovarian steroid receptors (estrogen receptor-α, and -β, progesterone receptor-A, and -B) are also upregulated during the secretory phase in the endometrium with CE (39–42). By contrast, the expression of the genes potentially associated with embryo receptivity (*IL11, CCL4, IGF1*, and *CASP8*) and decidualization (*PRL* and *IGFBP1*) are downregulated in the endometrium with CE during this