REVIEW
https://doi.org/10.5653/cerm.2016.43.4.185
pISSN 2233-8233 · eISSN 2233-8241
Clin Exp Reprod Med 2016;43(4):185-192

CERM

Chronic endometritis and infertility

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Chronic endometritis (CE) is a condition involving the breakdown of the peaceful co-existence between microorganisms and the host immune system in the endometrium. A majority of CE cases produce no noticeable signs or mild symptoms, and the prevalence rate of CE has been found to be approximately 10%. Gynecologists and pathologists often do not focus much clinical attention on CE due to the time-consuming microscopic examinations necessary to diagnose CE, its mild clinical manifestations, and the benign nature of the disease. However, the relationship between CE and infertility-related conditions such as repeated implantation failure and recurrent miscarriage has recently emerged as an area of inquiry. In this study, we reviewed the literature on the pathophysiology of CE and how it may be associated with infertility, as well as the literature regarding the diagnosis and treatment of CE. In addition, we discuss the value of hysteroscopic procedures in the diagnosis and treatment of CE.

Keywords: Chronic endometritis; Endometrium; Fertilization *in vitro*; Hysteroscopy; Repeated implantation failure

Introduction

Chronic endometritis (CE) is generally asymptomatic or has vague symptoms, such as abnormal uterine bleeding, pelvic pain, and leukorrhea [1]. The research has shown the prevalence rate of CE to be approximately 10% to 11% based on biopsies of patients who underwent hysterectomies due to benign gynecologic conditions [2,3]. Gynecologists and pathologists often do not focus much clinical attention on CE due to the time-consuming microscopic examinations necessary to diagnose CE, its mild clinical manifestations, and the benign nature of the disease [4,5]. However, the possible relationship of CE with infertility and/or perinatal complications has recently emerged as an area of ongoing research [6].

In fact, Romero et al. [7] reported that 15% of infertile women who underwent *in vitro* fertilization (IVF) cycles had CE, and the prevalence rate of CE was as high as 42% in patients with recurrent implantation failure (RIF). Zolghadri et al. [8] also reported CE findings on hysteroscopy in 57.8% of women with a past history of three or more recurrent pregnancy losses (RPLs). According to a recent prospective study of patients with RIF or RPL, the CE prevalence rate in the RIF group was 14% (six of 43) and 27% in the RPL group (14 of 51) [9]. Considering these results, CE may be a gynecologic condition that must not be ignored in the context of assisted reproductive treatment (ART). In this study, we reviewed the literature on the relationship between CE and infertility-related conditions, such as RPL, RIF and other reproductive outcomes, that had been published on PubMed as of January 2016.

Diagnosis of CE

Usually, CE is diagnosed by endometrial biopsy, and the presence of plasma cells in the endometrial stroma is the generally accepted histological diagnostic criterion for CE [2,10]. However, the accuracy of histological diagnoses can be compromised by conditions such as mononuclear inflammatory cell infiltration, stromal cell proliferation, a plasmacytoid appearance of stromal cells, or a pronounced pre-decidual reaction in the late secretory endometrium (EM). Therefore, the rate of misdiagnosis may be higher than ideal [1,11-13]. Furthermore,

Received: May 19, 2016 · Revised: Jun 9, 2016 · Accepted: Jun 30, 2016
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the histological detection of CE is time-consuming and difficult.

Hematoxylin and eosin (H&E) staining in women with infertility and patients with a history of repeated spontaneous miscarriages had a low diagnostic rate (< 10%) [10,14]. Recently, an immunohistochemical (IHC) stain capable of detecting CD38 and CD138 plasma cell-specific surface antigens was introduced for the confirmation of the presence of plasma cells inside the EM [15]. In women with a history of RPL, IHC staining for CD138 showed a dramatically higher sensitivity for diagnosing CE, with values as high as 56%, as compared to a 13% sensitivity for H&E staining [16]. Furthermore, additional IHC staining for CD138 in H&E-stained tissue specimens increased the diagnostic concordance between pathologists [11].

The diagnostic difficulties posed by CE as well as the relatively low clinical effectiveness of pathological diagnoses of CE have been considered problems. In fact, plasma cell endometritis was found to have no correlation with bacterial colonization of the EM or the clinical presentation of pelvic inflammatory disease (PID) [17,18]. In actual cases, plasma cell endometritis was histologically diagnosed in 39% of women who underwent an endometrial biopsy, but as many as 82% of women had positive findings in microbial cultures of EM biopsy samples. Haggerty et al. [19] reported that histologic endometritis showed no association with reproductive morbidity in randomized controlled trials (RCTs) of antibiotics in patients with clinical PID symptoms. These findings suggested that the histological diagnosis of CE could not determine which patients could benefit from further antibiotic treatment in terms of fertility-related outcomes.

Fluid hysteroscopy is another powerful tool for diagnosing CE [20,21]. The diagnostic findings of CE from fluid hysteroscopy include micropolyps, stromal edema, and focal or diffuse hyperemia (Figure 1). The hysteroscopic evaluation of endometrial inflammatory disease showed a much greater sensitivity for detecting CE than endometrial cultures [22]. Even when compared with the histologic diagnosis of CE, fluid hysteroscopy showed a very high diagnostic accuracy (93.4%) [20,21,23]. Discrepancies between hysteroscopic findings and histologic observations may be due to the many limitations involved in the histologic diagnosis of CE [13].

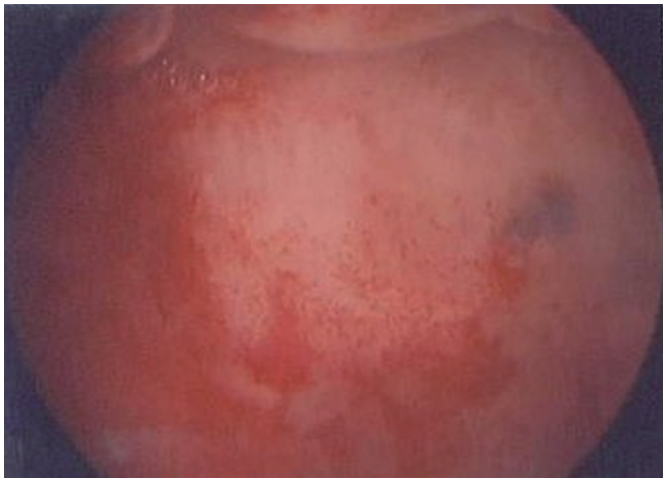

Figure 1. Hysteroscopic finding of chronic endometritis. The focal hyperemic area allowed chronic endometritis to be diagnosed in a woman with a history of repeated implantation failure (photo courtesy of HJ Park, MD).

A normal EM pattern observed in hysteroscopy was a relatively accurate predictor of successful pregnancy after ART [22]. In a retrospective study including patients with unexplained RPL, the patients in whom hysteroscopic findings normalized after antibiotic treatment for CE, regardless of the results of endometrial cultures, showed a significantly higher incidence of successful pregnancy than the patients who did not show normalization [24]. Considering the link between hysteroscopic CE findings and poor reproductive outcomes, the difficulties involved in the pathological diagnosis of CE, and the discrepancy between pathological and hysteroscopic findings, hysteroscopic evaluation of the endometrial cavity should be considered as a regular test in clinical practice in the assessment of patients with RIF or RPL [24,25].

Pathophysiology of CE

1. Host and microorganisms

Conventionally, the uterine cavity is assumed to be sterile, but in fact, microorganisms have been detected in the endometrial cavity of non-pregnant women [26-29].

It has been proposed that microorganisms ascending from the lower genital tract could colonize the uterine cavity; however, host mechanisms have been expected to restrict bacterial proliferation and invasion [26-30]. These mechanisms involve the cervical mucus plug [31-34], the endometrial epithelium and its immune cellular components (neutrophils, macrophages, and natural killer cells), and elements of the innate immune system, including natural antimicrobial peptides present in the EM [32,35-37]. An appropriate and balanced acute inflammatory process has been shown to play a major role in the eradication of microbial invasions [38].

Microorganisms form biofilms (i.e., matrices of polymeric compounds) as strategies against host immune mechanisms as well as against natural and synthetic antibiotics [39,40]. In fact, chronic infections such as valvular endocarditis, otitis media, chronic bacterial prostatitis, and periodontitis have been associated with the presence of bacterial biofilms, which contribute to subclinical colonization of the uterine cavity [41-47].

Interactions between infectious agents and the endometrial environment are a major concern in the treatment of infertility, miscarriage, and preterm labor [48]. In septic conditions, microorganisms

https://doi.org/10.5653/cerm.2016.43.4.185

are only a part of the problem; sepsis also involves problems in inflammatory control and/or the anti-inflammatory response of the host [49]. In a study of the mechanisms involved in preterm labor, the microorganisms present on the endometrial surface were not found to induce a pro-inflammatory response, and maintained peaceful co-existence with the host during the course of normal pregnancies [40,50-54]. However, if the host (mother, embryo/fetus, or both) became aware of the microorganisms via pattern-recognition receptors and initiated a pro-inflammatory response, peaceful co-existence was no longer possible. Changes in virulence patterns, such as planktonic bacteria released from biofilms, also caused a change in the balance between microorganisms and the host, resulting in inflammation-induced preterm parturition.

2. Normal-pattern pregnancies and other background information

Inflammatory mediators in the EM, including leukocytes, immunoglobulins, and cytokines, have been found to play very important roles in regulating the immune response and trophoblast growth in implantation [7]. The EM was found to be physiologically colonized by a pleiotrophic population of immune-competent cells [55]. These immune-competent cells controlled local defenses and modulated the host reaction to the embryo, ultimately assisting in the implantation of the embryo and the maintenance of pregnancy. Successful implantation of the embryo and maintenance of the pregnancy were the result of a delicate balance between the embryo and the EM, reflecting the prevalence of a TH2 versus a TH1 cytokine profile in the EM. Therefore, any conditions that disturb this balance could damage endometrial receptivity.

Various immune-competent cells of the EM have been found to secrete chemokines, attracting natural killer (NK) cells and macrophages from the circulating peripheral blood toward the EM [56-59]. In addition, trophoblasts facilitated pro-inflammatory cytokine production from the recruited monocytes and macrophages, which had a significant role in implantation and placental formation [58].

An increase in the amount of NK cells in peripheral blood drove the cytokine balance to favor the TH1 pathway [55,60]. This is likely to have negative effects on trophoblast invasion and implantation, consequently increasing the possibility for early pregnancy loss.

3. Chronic endometritis

In CE, endometrial receptivity decreases through mechanisms other than an increase in the percentage of NK cells. In fact, the secretory EM of patients with CE was found to show significantly lower percentages of CD56+ CD16– cells and CD56 bright CD16– cells than was observed in patients without CE (47.8% vs. 30.1% and 79.5% vs. 67.3%, $p < 0.01$) [60]. The secretory EM of the CE group showed a significantly higher percentage of CD3+ cells than the secretory EM of patients without CE (25% vs. 10.5%, $p < 0.01$). Additionally, in micropolypoid EM samples in patients with CE, the low endometrial NK cell density facilitated the survival of residual endometrial cells, possibly resulting in the development of mucosal polyps [61]. Kitaya and Yasuo [2] reported that lymphocyte B cell levels were elevated in the EM of patients with CE, as well as observing the abnormal expression of paracrine mediators such as adhesion molecules and chemokines. In fact, the menstrual effluent of women with CE showed elevated pro-inflammatory cytokine levels, including interleukin (IL)-6, IL-1β, and tumor necrosis factor α, in comparison to women without CE; these findings were argued to reflect a TH1/TH2 cytokine imbalance at the EM level [62].

Infection is the basis of CE. Cicinelli et al. [21] analyzed 438 cases of hysteroscopically diagnosed CE, and reported that 73.1% exhibited ≥1 positive pathogen finding. Most endometrial infections were common bacterial infections (58%), including Gram-negative bacteria, and *Ureaplasma urealyticum* was found in 10% of cases. Chlamydia was found in 2.7% of cases. Gram-negative bacterial colonization of the EM may lower the implantation rate of embryos while increasing the rate of miscarriage. The endotoxins of Gram-negative bacteria may induce a more predominant TH1 response at the decidua in order to stimulate pro-inflammatory cytokine production, thereby creating an endometrial paracrine milieu that could cause embryo damage, implantation failure, or spontaneous abortion [62,63]. Female genital tuberculosis can cause CE and infertility. It is uncommon in developed countries, and is associated with predisposing factors such as poverty, ill health, and immune suppression [64]. In addition, it is a secondary form of tuberculosis, mainly originating from pulmonary tuberculosis, so rare cases of solitary tuberculous endometritis may have occurred due to female genital tuberculosis spreading to the neighboring viscus [65]. We excluded tuberculous endometritis from the discussion of this article.

In EM with CE, the *IGFBP1* gene was upregulated, whereas genes such as *IGF1, IL-11,* and *CCL4* were downregulated [66]. *IGF1* mediated the effect of estrogen on endometrial proliferation, while *IGF2* mediated the effect of progesterone during the secretory phase by facilitating the implantation and invasion of embryos [59,67,68]. *IGFBP1* was secreted from endometrial stromal cells during the process of decidualization, exerting negative effects on the implantation process of the embryo and counteracting the effect of *IGF2*. Increased *IGFBP1* gene expression and reduction in *IGF1* gene expression in EM with CE resulted in unfavorable conditions for implantation and embryo development.

IL-11 is a cytokine with anti-inflammatory properties. Its production was found to be greatest during decidualization [69,70]. Inappropriate *IL-11* signaling resulted in dysregulation with respect to trophoblast

invasion [56,71,72]; therefore, *IL-11* downregulation in EM with CE at the implantation window was strongly associated with infertility.

During the early stage of pregnancy, trophoblasts were found to recruit NK cells and macrophages into the EM through chemokines such as *CCL4* and to stimulate them to produce pro-inflammatory cytokines [56-59]. Downregulated *CCL4* activity due to CE could result in the failure of implantation or abnormal placental formation.

In summary, chronic endometrial inflammation can alter endometrial cytokine production, damage endometrial function [73], result in the formation of abnormal patterns of lymphocyte subsets in the EM, and induce the altered secretion of paracrine factors, which ultimately may reduce the receptivity of embryos in the EM [60,66]. In fact, delayed differentiation of the EM in the mid-secretory phase (out-of-phase morphology) was observed in cases of CE [74]. The proliferative phenotype of the EM was found in cases of CE even during the secretory phase, due to an increase in estrogen receptors and cell proliferation-associated nuclear marker *Ki-67* expression [75,76].

Treatment of CE

Doxycycline, a broad-spectrum antibiotic effective against organisms ranging from common bacteria to mycoplasma, is often used to treat CE [77]. Antibiotic treatment has been found to be relatively effective for CE. Johnston-MacAnanny et al. [78] showed that 70% of cases of CE demonstrated in EM biopsies were cured by a regimen of 100 mg of doxycycline twice per day for 14 days. Kitaya et al. [79] also reported that the histological clearance rate of CD138+ plasma cells on the EM of RIF patients with CE was up to 96% using the above doxycycline-only regimen. The histopathologic cure rate of CE 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% [14].

Antibiotic treatment may attenuate the effect of CE on infertility. In a retrospective analysis of patients with unexplained RPL and CE findings on diagnostic hysteroscopy, Cicinelli et al. [24] reported that the clinical pregnancy rate of the group whose hysteroscopic findings normalized 1 year after antibiotic treatment was significantly higher than that of the non-normalized group (74.8% [88 of 118] vs. 24.4% [22 of 90]). The prospective study of McQueen et al. [14] showed that the per-pregnancy live birth rate in RPL patients with CE significantly increased to as high as 56% after antibiotic treatment, compared to 7% before treatment.

Studies have been carried out on RIF patients with CE undergoing *in vitro* fertilization-embryo transfer (IVF-ET) cycles. According to the retrospective study of Yang et al. [25], the implantation rate (18.6% [18 of 97] vs. 4.9% [3 of 61]) and the ongoing pregnancy rate (29.3% [12 of 41] vs. 7.4% [2/27]) in IVF-ET cycles significantly increased after antibiotic treatment, in comparison to pre-treatment outcomes. Cicinelli et al. [22] conducted a retrospective study of RIF patients undergoing fresh IVF-ET 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 CE findings (65% vs. 33% and 60.8% vs. 13.3%, respectively). The above results suggest that CE plays a significant role in infertility.

In this article, we discussed the value of diagnostic hysteroscopy in the treatment of CE. Some studies have proposed that endometrial scratching or injury, as is involved in diagnostic hysteroscopy, could increase the implantation rate and the clinical pregnancy rate in women with previous IVF-ET failures [80-85]. The hypothetical biological basis for this proposal is as follows [86]. First, a topical injury in the EM could increase the implantation rate, leading to decidualization. Second, cytokines and growth hormone secreted during the recovery process after an artificial injury to the EM could have good effects on the embryo implantation. Third, an artificial injury to the EM could delay the earlier maturation of the EM attributable to hyperstimulated ovaries in the next IVF-ET cycle.

In this article, we would like to propose an additional hypothesis regarding CE. Hysteroscopy may be a powerful tool for physically removing bacterial biofilms in the EM that contribute to the pathophysiology of CE. Finally, as latent CE in patients with RIF can improve after hysteroscopy, reproductive outcomes in subsequent IVF-ET cycles may also improve. Currently, limited evidence supports this proposal. Recent meta-analyses [87,88] concerning hysteroscopy or artificial endometrial injuries in ART have reported significant improvements in the clinical pregnancy rate. However, this possibility has yet to be supported by well-designed RCTs, so this proposal must remain hypothetical for the time being.

Conclusions

So far, CE has been considered insignificant in gynecologic clinical practice. However, it is has been associated with poor reproductive outcomes in the context of ART. In cases of CE, the peaceful co-existence between the host immunity and microorganisms breaks down, the distribution of lymphocytes involved in the implantation of embryos is altered, and ultimately, EM receptivity is reduced due to the inadequate secretion of various cytokines. Recent clinical studies in patients with RPL or RIF showed that antibiotic treatment for CE could produce dramatic changes in future pregnancy outcomes [14,22,24,25]. Our review article attempted to evaluate the benefits of hysteroscopic procedures in the diagnosis and treatment of latent CE as an addition to extant theories. However, due to the lack of high-quality evidence in the published literature, such proposals must remain hypothetical. Therefore, well-designed prospective

https://doi.org/10.5653/cerm.2016.43.4.185

studies or RCTs should be conducted in order to clarify possible correlations between CE and poor reproductive outcomes as well as the efficacy of endometrial interventions.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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https://doi.org/10.5653/cerm.2016.43.4.185