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Review: Chronic endometritis and its effect on reproduction

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Abstract

Aim: Chronic endometritis (CE) is a disease of continuous and subtle inflammation characterized by the infiltration of plasma cells in the endometrial stromal area. Although the clinical significance of CE has been thought in clinical practice for a long time because it is either asymptomatic or presents with subtle symptoms, recent studies have shown the potential adverse effects of CE on fertility. In the present review, we focus on the concept, diagnosis, etiology, pathophysiology, diagnosis, impact on reproduction and treatment for it to understand CE.

Methods: The published articles were reviewed.

Results: The prevalence of CE has been found to be 2.8–56.8% in infertile women, 14–67.5% in women with recurrent implantation failure (RIF), and 9.3–67.6% in women with recurrent pregnancy loss. Microorganisms are thought to be a main cause of CE, since antibiotic treatment has been reported to be an effective therapy for CE. Common bacteria are frequently detected in the uterine cavity of CE patients by microbial culture. In CE endometrium, the prevalence of immune cells and decidualization has been reported to be modified, and these modifications are thought to adversely affect fertility. The gold standard for the diagnosis of CE is the histological detection of plasma cells in the stromal area of the endometrium in endometrial specimens, although universally accepted criteria for the diagnosis of CE have not been determined. The treatment currently thought to be most effective for the recovery of fertility in CE is administration of oral antibiotics. Patients whose CE has been cured have been reported to have a higher ongoing pregnancy rate, clinical pregnancy rate, and implantation rate compared with patients with persistent CE.

Conclusion: CE greatly affects implantation and impairs fertility. Antibiotic administration is an effective therapeutic option. Pregnancy rate in in vitro fertilization is improved when CE is cured by antibiotic.

Key words: chronic endometritis, infertility, repeated implantation failure.

Introduction

Chronic endometritis (CE) is a disease of continuous and subtle inflammation characterized by the infiltration of plasma cells into the endometrial stromal area, where they are not typically present except just before and during menstruation.[1] The clinical significance of CE has not traditionally been a concern in clinical practice because it is usually asymptomatic or presents only with subtle symptoms, such as abnormal uterine bleeding, pelvic pain, dyspareunia, and leucorrhea.[2,3] Thus, it was thought to be a benign condition for which the purpose of diagnosis and treatment were not clear and would require endometrial specimens, which can burden the patient.[4] However, recent research has suggested that CE adversely affects

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fertility, proposing a pathological role for CE.[5–8] In the present review, the aim was to clarify the concept of CE, with a particular focus on its etiology, epidemiology, clinical features, pathophysiology, diagnosis and treatment of CE involved in reproduction.

Concept of CE

In general, endometritis refers to acute endometritis. Patients with acute endometritis usually present with clinical symptoms of pelvic inflammatory disease (PID) due to infection.[9] Patients with acute endometritis usually have a history of fever and lower abdominal pain with leukocytosis and/or elevated serum inflammatory markers. However, if the disease is in the early phase or the infection is not severe, it may be hard to diagnose based on clinical features. Endometritis may be, therefore, diagnosed by histology.[10] The histologic diagnosis of acute endometritis is made when a large number of neutrophils are present in the endometrial stroma.[10] Neutrophils can be aggregated with or without edema, hemorrhage, venule ectasia, microabscesses and pus-filled glands.[10]

The endometrium is shed during menstruation in women of reproductive age and subsequently regenerates during the next cycle. Therefore, it is unclear whether chronic inflammation can occur in the endometrium that periodically sheds. Asherman's syndrome is a morphological change in which fibrosis occurs in the endometrium.[11] Although the mechanism underlying the occurrence of Asherman's syndrome is not well understood, in that status, the inflammation destroys the endometrial functional layer and induces morphological changes such as fibrosis and adhesion between the upper and lower endometrial walls in the whole or in parts of the uterine cavity. This indicates that there is at least one state of persistent inflammation in the endometrium histologically. In addition to Asherman's syndrome, another state of persistent inflammation in the endometrium that exists across menstrual cycles is known as CE.

A definitive diagnosis of CE can only be made histologically and is noted by the existence of plasma cell in the stromal area of the endometrium.[12–16] In addition to plasma cell, high stromal cell proliferation, dissociated maturation between the epithelium and stroma, and a pronounced predecidual reaction may be present.[12,16] If the role of plasma cell (i.e., secreting large concentrations of antibodies) is taken into account, CE may describe the condition in which immune cells monitor some aberrant pathogens, which reside in the uterine cavity for a long period, and regulate them to prevent the progression to intense inflammation.[17,18] It is possible that CE is a state with old inflammation after acute endometritis. However, the relationship between acute endometritis and CE remains to be determined.

There is no unified diagnostic criterion for CE accepted worldwide. However, the histological confirmation of multiple plasma cells in the endometrial stromal area is considered to be the most reliable diagnostic method.[12–18]

Etiology

For almost a century, the consensus was that the uterine cavity is sterile under normal conditions.[19,20] This sterility was thought to be maintained by the cervical mucosal system, which provides an impermeable barrier against bacterial ascension from the vagina.[21] However, this hypothesis was refuted, and recent research has shown microorganisms detected even in the endometrial cavity of healthy asymptomatic women.[22–25] Furthermore, the uterine mucus plug has been shown to incompletely block bacterial ascension by vaginal bacteria.[26,27] Additionally, particles can translocate from the vagina to the uterus through the cervical canal within minutes by the function of the uterine peristaltic pump.[27,28] Thus, the existence of microorganisms in the uterus has come to be accepted, and they are thought to be a main cause of CE, since antibiotic treatment has been reported to be an effective therapy for CE.[29–32] Because acute endometritis and PID are caused by microorganisms ascending from the lower genital tract,[9] *Chlamydia trachomatis* and *Neisseria gonorrhoeae* may be considered the main pathogenic microorganisms of CE. However, a lower detection rate of these bacteria has been reported in CE patients.[24,33,34] Within the uterine cavity of CE, common bacteria are usually present,[24,33,34] such as *Streptococcus* spp., *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Staphylococcus* spp., *Corynebacterium* and *Mycoplasma/Ureaplasma* spp., which are frequently detected in microbial cultures or polymerase chain reaction tests for *Mycoplasma/Ureaplasma* DNA (Tables 1–2).[24,35,36] Thus, these bacteria obtained as a result of these cultures or PCR are currently thought to be the causal organisms of CE.

Therefore, the question arises as to the origin of the bacteria in the intrauterine cavity. Cicinelli *et al*.[24] performed bacterial cultures of endometrial tissue in 438 CE patients and found pathogens in only 73% of

Table 1 Specific etiological agents of chronic endometritis in endometrial specimens of women undergoing hysteroscopy for different indications (n = 438)

Escherichia coli	50
Streptococci	122
Staphylococci	20
Enterococcus faecalis	62
Chlamydia	12
Ureaplasma	44
Yeast	10
Total	320

Reproduced from Cicinelli *et al*.[24] with permission.

Table 2 Specific etiological agents of chronic endometritis in endometrial specimens of infertile women with repeated implantation failure

Corynebacterium	10/142 (7.0)
Enterococcus	15/142 (10.6)
Escherichia coli	14/142 (9.9)
Klebsiella pneumoniae	2/142 (1.4)
Streptococcus spp.	11/142 (7.7)
Staphylococcus spp.	12/142 (8.4)
Chlamydia trachomatis	2/142 (1.4)
Neisseria gonorrhoeae	0/142 (0)
Mycoplasma	12/46 (26.1)
Ureaplasma	20/46 (43.4)

The values in parenthesis are in percentages. Reproduced from Kitaya *et al*.[35] with permission.

their cohort. Moreover, in patients positive for pathogenic bacteria in both vaginal secretions and endometrial tissue, only 32.6% cultured the same bacterial species. These results suggest that the results of bacterial cultures of the vaginal cavity cannot predict the endometrial microbiome in CE patients. Additionally, the cause of CE may not necessarily be ascending infection from the intravaginal bacterial flora, or the progression of intrauterine bacterial colonization is independent of the vaginal bacterial flora once it is formed.

The presence of a uterine microbiome has also been reported in animal models. Specific bacterial species, such as *Fusobacterium*, have been reported to colonize both mouse and cow uteri.[37,38] Colonization with this particular bacterium in mice has been reported to occur by transmission through the hematogenous route (bloodstream).[38] Moreover, epithelial barrier breach (e.g., gingivitis and leaky barrier) triggers hematogenous spread of oral or gut bacteria,[39,40] allowing resident bacteria in mucosal sites of the oral cavity and the gastrointestinal tract to colonize distal mucosal sites.[20,38,41,42]

Recent research has also shown microorganisms in the peritoneum.[25,43] It may be possible that peritoneal microorganisms from the gastrointestinal tract reach the uterus via the fallopian tube. Future investigation is necessary to elucidate the origin and pathway of colonized microorganisms causing CE.

Recently, new techniques have been developed, in which small number of bacteria can be detected with high sensitivity. Studies using these new techniques have reported intrauterine bacterial colonization occurs even in the normal physiological condition.[20,25,44–46] Previously, the detection of bacterial colonization was dependent on the cultivation technique used, which typically did not enable the characterization of small colonies.[20] However, recently, low biomass microbiota can be characterized, with advances in the technology, by quantitative polymerase chain reaction and next-generation sequencing of the 16S rRNA gene.[25,44–46] With these techniques, lactobacilli have been found to dominate the endometrium of healthy women, as well as the normal vaginal cavity. However, non-lactobacilli are also predominant in healthy fertile women, suggesting that the presence of microorganisms other than lactobacilli could be considered normal.[25,44,46] In contrast, Fang *et al*. reported a higher detection rate of *Lactobacillus* in patients with endometrial polyps or with endometrial polyps and CE (38.6% and 33.2%, respectively) compared to healthy controls (6.2%), although *Lactobacillus* dominancy is generally accepted as the healthy state in the vaginal cavity.[45] Moreover, the presence of nine pathogens was evaluated by real-time PCR in endometrial samples from patients assessed for CE by CD138 immunostaining. Similar detection rates of the pathogens were observed in CE and non-CE patients (24/40 vs 14/25).[47] These results suggest inconsistency in the detection of the microorganisms inside the uterine cavity in CE. Therefore, the main issue of CE is thought to be the interaction between microorganisms and endometrial immunity rather than just the presence of microorganisms in the endometrium.

The results of these studies suggest that the involvement of microorganisms inside the uterine cavity in the occurrence of CE and the mechanism of its progression require further study.

Although it has been reported that herpes simplex virus and cytomegalovirus can cause endometritis,[48,49] the relationship between viral infection and the occurrence of CE remains unknown.

Pathophysiology

The levels of proinflammatory cytokines, for example, interleukin-6, interleukin-1β and tumor necrosis factor α, are increased in menstrual effluents of women

with CE.[50] This elevation of proinflammatory cytokines may affect cell migration, proliferation and apoptosis. Thus, similar to other chronic inflammatory diseases, CE modifies the distribution and function of endometrial cells including immune cells, epithelial cells and stromal cells.

B cells are found throughout the menstrual cycle and reside mainly in the basal layer, although they comprise only a small component (<1%) of all immune cells in the normal endometrium.[51,52] In CE, a number of B cells not only infiltrate and aggregate in the stromal area of the functional layer, but they also rush into the glandular lumina by passing through glandular epithelial cells.[53] This phenomenon is related to aberrant expression of adhesion molecules and cytokines such as E-selectin, CXCL1 and CXCL13, with a role in the extravasation of B cells.[53] B cell infiltration may be related to the presence of plasma cells in the stromal field of the functional layer.

T cells are distributed mainly in the basal lymphoid aggregates and scattered in the stroma and epithelial sites. In contrast to T cells in the peripheral blood, two-thirds of endometrial T cells are $CD8^+$ cells in the endometrium.[51,52] The effect of CE on the composition of T cell subpopulations remains unknown. The major phenotype of endometrial natural killer (NK) cells is $CD56^{bright}CD16^-$, which are distinguished from $CD56^{dim}CD16^+$ NK cells in the peripheral blood.[54,55] Since $CD56^{bright}CD16^-$ NK cells have low cytotoxicity and the number of NK cells increases up to 30–40% of cells in the stromal compartment in the late secretory phase, these cells are thought to play an important role for successful pregnancy.[54] Recent research showed that a subpopulation of $CD56^{bright}CD16^-$ or $CD56^+CD16^-$ NK cells is decreased with the increase of $CD3^+$ cells in the uterine endometrium of CE patients.[56] This fact is strongly related to the disturbance of uterine receptivity in CE patients.

It has been reported that women with CE showed altered uterine contractility in both the periovulatory and midluteal phases.[57] This alteration may be associated with symptoms related to CE, such as pelvic pain, spotting and implantation failure. The authors speculate that CE could influence contractility, since abnormal lymphocyte subpopulations and the altered pattern of paracrine factors in the endometrium could affect the synchronized movement of the endometrium and myometrium, including the junctional zone.

For successful implantation and establishment of pregnancy, appropriate proliferation and differentiation regulated by sex steroid hormones in the endometrium is necessary. In CE, these processes and expressions of related molecules are aberrant. The expressions of Ki-67 (nuclear marker for cell proliferation), BCL2 and BAX (regulator of apoptosis) are upregulated.[58,59] Recently, our group showed that CE modifies decidualization via aberrant expression of estrogen and progesterone receptors. In that study, the endometrial stromal cells (ESC) in CE patients had significantly lower secretion of prolactin and insulin-like growth factor binding protein-1 *in vitro* after the induction of decidualization compared with the ESC in patients without CE.[60] Moreover, the number of ESC after the induction of decidualization with estradiol and progesterone for 13 days was significantly higher in CE patients. CE disturbs decidualization *in vitro* and weakens the action of progesterone on ESC (induction of progesterone resistance), resulting in less potential to differentiate and greater potential to proliferate. Our results may provide fundamental evidence for understanding how CE disturbs the decidualization process and consequently affects implantation and the establishment of pregnancy.

Epidemiology and Clinical Features

The prevalence of CE ranges from 8% to 72% in women of reproductive age.[4,15,61–63] This large variance among studies is thought to be caused by the relatively small number of patients and differences in the diagnostic criteria applied.

Several factors have been reported to be associated with CE. It has long been known that insertion of an intrauterine device (IUD),[14,64] even short-term insertion, causes CE, and CE persists even after IUD removal.[64] Several patient characteristics related to obstetric history and gynecological symptoms, such as multiparity and atypical uterine bleeding, have been reported to be risk factors for CE.[14]

Bacterial vaginosis, endometrial polyps and endometriosis are gynecological diseases that have been reported to be associated with CE.[65–68] We considered the characteristics of eutopic endometrium in endometriosis and reported the association between endometriosis and CE in patients with benign gynecologic disease for the first time. This association was also shown in infertile patients.[69]

The relationship between CE and infertility has recently emerged as an important clinical challenge. In fact, 2.8–56.8% of infertile women,[15,70–72] 14–67.5%

of women with RIF,[8,30,72–75] and 9.3–67.6% of women with recurrent pregnancy loss are diagnosed with CE.[76–78] Considering these high prevalence rates, CE is a condition that must not be ignored during fertility treatment. Several reports have investigated the effect of CE on subsequent conception after the diagnosis of CE, as well as the prevalence of CE.

Kasius *et al*. evaluated a total of 678 asymptomatic infertile women before the first *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment cycle and compared the live birth rates (LBR, including spontaneous pregnancies) between CE and non-CE patients within 3 years after initiation of their randomized, controlled trial.[21] They showed a low prevalence of CE (2.8%) and no difference in the cumulative LBR (including spontaneous pregnancies) and clinical pregnancy rate (CPR) per embryo transfer. In contrast, Johnston-MacAnanny *et al*. showed that histologically confirmed CE patients suffering from RIF had a lower implantation rate with IVF compared with RIF patients without CE (11.5% vs 32.7%).[30] Based on these recent studies, the effect of CE on infertility remains unclear. However, CE treatment may also affect fertility. This potential relationship will be discussed in detail later.

Diagnosis

The gold standard for diagnosis of CE is the histological detection of plasma cells in the stromal area of the endometrium in endometrial specimens. In addition to the detection of plasma cells, high stromal cell proliferation, dissociated maturation between the epithelium and stroma, and pronounced predecidual reaction may be observed.[12,16] Plasma cells are usually larger with an eccentric nucleus among abundant basophilic cytoplasm. The overall shape of the cell generally resembles a wedge or comet with thick chromatin expressed as a 'spoke wheel' or 'clockwork' pattern.[79,80] Although such pathological features can be confirmed with stains such as hematoxylin and eosin (HE), it is hard for even experienced pathologists to detect plasma cells in the endometrium because of monocyte infiltration, stromal mitosis, plasmacytoid appearance of stromal cells, and predecidual reaction, which are morphologically difficult to distinguish.[2,81–83] Thus, immunohistochemistry (IHC) for detection of the plasma cell marker CD138 (also known as syndecan-1) is used clinically to diagnose CE, since it stains well on the surface of plasma cells. Plasma cells are often found in functional layers near the basal layer of the endometrium and occasionally accumulate in CE patients (Fig. 1).

Bayer-Garner *et al*. found that, in 47 patients, seven cases of CE were detected by HE staining, whereas an additional 13 cases of CE were detected by IHC for CD138.[2] Moreover, McQueen *et al*. found a significantly higher CE detection rate by IHC for CD138 compared with diagnosis by HE staining and morphology alone (56% vs 13%, $P < 0.01$).[82] The false-positive rate could be decreased with IHC for CD138, since mononuclear and plasmacytoid stromal cells could be mistakenly counted as plasma cells with HE staining. IHC could also make it easy to enumerate the number of plasma cells, decreasing the pathologist's fatigue and/or amount of time required for diagnosis. Moreover, there is no significant inter- or intraobserver variability with IHC staining. Thus, IHC for CD138 is a more reliable method than HE staining with respect to plasma cell detection.

Despite the globally accepted recognition of plasma cell detection by IHC as the gold standard diagnostic method, international diagnostic criteria for CE have not yet been established. First, there is no standardized technique for CD138 immunostaining of endometrial specimens. IHC results can vary according to the experimental setting, for example, type and duration of antigen retrieval, antibody selection and concentration (dilution), incubation time, and temperature and area of the specimen. Second, there

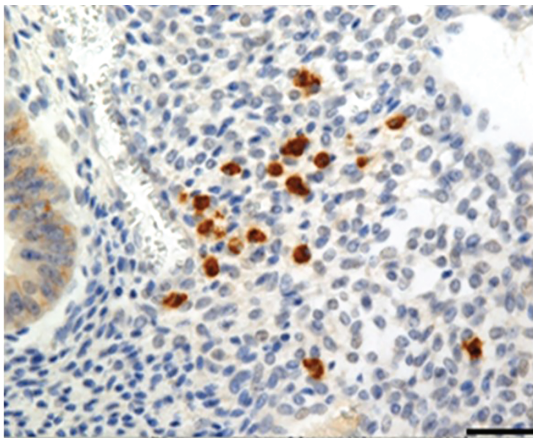

Figure 1 Immunohistochemistry for detection of plasma cells with CD138. CD138 is stained on the surface of plasma cells in the stromal compartment of chronic endometritis. Plasma cells occasionally accumulate. Scale bar = 100 μm (Reproduced from Takebayashi *et al*. [67] with permission.).

are no unified diagnostic criteria regarding plasma cell density (plasma cell count in limited areas). Although, histologically, CE is generally defined as the presence of any plasma cell in the stroma, some argue that CE should not be diagnosed by only a few plasma cells, because the endometrial stroma can contain a limited number of plasma cells without an inflammatory process. In fact, some investigators consider finding one plasma cell in the endometrial stroma as sufficient for diagnosis, although other investigators stated that more than five plasma cells in at least one of three sections is required.[14,57,78,82] Third, the site of CE in the uterus is another concern. CE may occur throughout the endometrium or in only a part of the endometrium. Furthermore, plasma cells tend to aggregate around deeper stromal vessels rather than at the endometrial surface.[14] The site and amount of tissue collected may affect the detection of plasma cells. Non-standardized protocols cause inconsistent quantification of plasma cell density, and differences in CE criteria result in different prevalence rates, even in similar types of studies. This may be one of the primary causes of inconsistency in previous reports regarding the prevalence of CE in infertile patients. Therefore, it is critical to set the definition of 'true CE' by a universally accepted method that is reasonably based pathological significance.

Hysteroscopy is used to identify the visual signs of endometrial inflammation, and attempts have been made to diagnose CE using hysteroscopy. Cicinelli *et al*. have proposed the following hysteroscopic criteria: hyperemia (accentuated blood vessel accumulation at the periglandular level), strawberry aspect as a typical image of hyperemia (extensive hyperemic endometrium with a white central point that is localized and scattered throughout the cavity), stromal edema (pale and thickened endometrium in the proliferative phase) and micropolyps (small pedunculated, vascularized protrusions of the uterine mucosa measuring <1 mm).[59] This group's position is that CE is diagnosed by the presence of at least one feature, and they have reported high sensitivity and specificity of hysteroscopic diagnosis in the histologic confirmation of CE. Their prospective study reported a 93.4% correlation between hysteroscopy and histology for detection of CE.[59] In subsequent studies,[84] other groups reported that office hysteroscopy had low sensitivity for the detection of histological CE.[8,47,63,84] The sensitivity of hysteroscopic diagnosis may depend on the clinician's experience.

The presence of a micropolyp at fluid hysteroscopy has been reported to have high positive and negative predictive values (93.7% and 89.2%, respectively).[85] Micropolyps were reported in 96 cases (11.7% of all hysteroscopies), 90 (93.7%) of which had histologically confirmed CE. In women without micropolyps, a significantly lower frequency of CE was seen (78 cases, 10.8% negative predictive value).[85] The detection of micropolyps is simple even for beginners and is considered applicable to clinical practice.

According to these results, we conclude that hysteroscopic diagnosis of CE is not always consistent with histological diagnosis. Therefore, while hysteroscopy may be useful, it should only be used to assist the histological diagnosis of CE.

Treatment for CE and its Effect on Reproductive Outcomes

The effects of CE treatment and the outcomes of IVF have been studied. Doxycycline, a broad-spectrum antibiotic, is standard therapy for the prevention of intrauterine infection after abortion and has been used worldwide for a long time, was included for the treatment of CE. Johnston-MacAnanny *et al*. reported that 66.7% (6/9, 9/10 CE patients were enrolled and one patient was not treated) of CE cases confirmed by IHC for plasma cell detection were cured by the administration of doxycycline (200 mg/day for 14 days); a second-line regimen comprising ciprofloxacin and metronidazole (500 mg of each per day for 14 days) cured the remaining three patients.[30] Kitaya *et al*. also reported that 92.3% (108/117) of CE patients with RIF were cured by the same doxycycline regimen.[35] Additional treatment using a combination of ofloxacin (400 mg/day for 14 days) and metronidazole (500 mg/day for 14 days) cured the remaining 8 of 9 patients. Overall, the cure rate was 99.1% (116/117).

McQueen *et al*. treated CE patients with early recurrent early pregnancy loss and/or fetal demise. CE patients were mainly (26/35) treated by ofloxacin (800 mg) and metronidazole (1000 mg) for 2 weeks, and 9 of 35 were prescribed an alternative antibiotic, either doxycycline alone, doxycycline and metronidazole, or ciprofloxacin and metronidazole.[31] Thirty-one of all 35 patients underwent a repeat endometrial biopsy to assess them for CE cure. Seven of 31 patients were found to have persistent CE on the repeat endometrial biopsy. All seven patients had been treated with ofloxacin and metronidazole, although alternative

antibiotic treatment cured all patients. Two of the seven patients with persistent CE were treated by a second course of antibiotics and were cured. Although the other five patients declined further antibiotic treatment, subsequent biopsies after a longer period of time showed resolution of CE in all five patients. Therefore, the CE cure rate after a single course of antibiotics was 94% (29/31), and the overall cure rate after up to two courses of antibiotics was 100% (31/31).

Cicinelli *et al*. treated infertile CE patients with RIF with systematic antibiotic regimens according to their endometrial microbial profiles.[32] Patients positive for Gram-negative and -positive bacteria were treated by ciprofloxacin (1000 mg/day for 10 days) and amoxicillin + clavulanate (2 g/day for 8 days), respectively. Patients with *Mycoplasma* and *Ureaplasma urealyticum* infections were treated with josamycin (2 g/day for 12 days), and minocycline (200 mg/day for 12 days) was administered for resistant cases. A combination of ceftriaxone (250 mg, single dose, intramuscular injection), doxycycline (200 mg/day for 14 days), and metronidazole (1000 mg/day for 14 days) was administered to patients with negative cultures according to the United States Centers for Disease Control and Prevention guidelines. Although 28% (17/61) of CE patients were histopathologically cured after the first course of antibiotics, 23% (14/61) and 25% (15/61) of patients recovered by the second and third course of antibiotics, respectively. Thus, CE persisted in 25% (15/61) of patients after three serial courses of antibiotic treatment. These results indicate the efficacy of oral antibiotic treatment for CE.

The efficacy of oral antibiotic treatment for fertility was also elucidated. Kitaya *et al*. conducted a prospective study and found that the LBR in the first ET cycle and three cumulative ET cycles in RIF patients cured by antibiotic treatment (32.8%, 38/116 and 38.8%, 45/116, respectively) was significantly higher than in RIF patients without CE (22.1%, 50/226 and 27.9%, 63/226, respectively).[35] In this study, the authors set RIF patients without CE as the controls, because almost all CE patients were cured by the antibiotic treatment.

Cicinelli *et al*. conducted a retrospective study and reported that the CPR and LBR in IVF patients normalized by antibiotic treatment were significantly higher than in patients with persistent CE (65% vs 33% and 60.8% vs 13.3%, respectively).[32] They also reported that the CPR of patients cured 1 year after antibiotic treatment was significantly higher than that of persistent patients (74.8%, 88/118 vs 24.4%, 22/90).[60] A prospective study by McQueen *et al*. showed that the LBR of next pregnancy in recurrent early pregnancy loss patients without CE was significantly higher (87.1%, 27/31) than that in patients with CE (67.6%, 23/34).[82]

Yang *et al*. showed that the implantation rate (IR, 18.6%, 18/97 vs 4.9%, 3/61) and the ongoing pregnancy rate (OPR, 29.3%, 12/41 vs 7.4%, 2/27) *in vitro* fertilization and embryo transfer (IVF-ET) cycles were significantly increased after antibiotic treatment when the diagnosis of CE was made by hysteroscopy, although these rates were not significantly increased when CE was diagnosed by IHC for plasma cell detection.[63]

Vitagliano *et al*. conducted a systematic review and meta-analysis of the effects of therapy for CE on the outcome of IVF in women with RIF.[86] They concluded that women receiving antibiotic therapy did not show any advantage in comparison with untreated controls on OPR/LBR, CPR and IR without histological confirmation of CE cure. Patients with cured CE showed higher OPR/LBR (OR, 6.81), CPR (OR, 4.02) and IR (OR, 3.24) than patients with persistent CE. The IVF outcome was comparable between women with cured CE and those without CE (OPR/LBR, CPR and IR). Additionally, the miscarriage rate was not significantly different between the two groups.

Taken together, these findings suggest that administration of oral antibiotics is a promising therapeutic option in infertile women with RIF due to CE.

Conclusion

CE may result in implantation failure. The etiology of CE is thought to be mainly microorganisms, but its origin has not been fully elucidated. CE causes immune abnormalities and impaired decidualization in the endometrium. In patients with CE, treatment with antibiotic therapy may improve uterine receptivity.

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Disclosure

None of the authors have any conflicts of interest to declare.

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