Endometriosis as an Infectious Disease: Association with Chronic Endometritis

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Abstract

Objectives: Recent studies focus on immunological, infectious, and inflammatory aspects of endometriosis. Meanwhile, chronic endometritis (CE) is an immunological, infectious, and inflammatory disorder of the eutopic endometrium with unusual stromal plasmacyte infiltration. Mechanism: In this review article, we aimed to gain a better understanding of the relationships between endometriosis and CE. Findings in Brief: Accumulating evidence supports the idea that CE is associated with infertility of unknown etiology, repeated implantation failure in an in vitro fertilization-embryo transfer program, recurrent pregnancy loss, as well as several perinatal/neonatal complications. Endometrial biopsy/histopathologic examinations and/or hysteroscopy are required to make a definitive diagnosis of CE. Conclusions: While endometriosis has been long considered a cause of infertility, CE is also an emerging issue that may reduce fecundity in women of reproductive age. Endometriosis and CE share characteristics of endometrial proliferative nature. The potential relationships between these two diseases of the uterine lining warrant future studies.

Keywords: antibiotic treatment; chronic endometritis; endometriosis; microbiota; progesterone resistance

1. Introduction

Chronic endometritis (CE) is an endometrial inflammatory disorder, which is characterized by asymptomatic nature and unusual Cluster of Differentiation 138(+) (CD138(+)) endometrial stromal plasmacyte (ESPC) infiltration [1]. The major cause of CE is thought to be intrauterine infection represented by common bacteria (such as Escherichia coli, Enterococcus faecalis, Streptococcus, and Staphylococcus), Mycoplasma/Ureaplasma, and Mycobacterium [2,3], as antibiotic treatments against these microorganisms are effective for the elimination of ESPCs in the affected patients [4,5]. Other causes such as local dysbiosis, however, may be involved in the pathogenesis of CE [6]. Accumulating evidence support that CE is associated with infertility of unknown etiology (28%), repeated implantation failure in an in vitro fertilization-embryo transfer program (14%–31%), recurrent pregnancy loss (9%–13%), as well as several perinatal/neonatal complications [6–10].

Endometriosis involves endocrinological, genetic, and epigenetic factors in its etiology and pathogenesis [11]. Recent studies focus on immunological, infectious, and inflammatory aspects of endometriosis and demonstrate the common characteristics between endometriosis and CE. This review aimed to gain a better understanding of the relationships between these two infertility-associated diseases.

2. Prevalence of CE in Women with Endometriosis

Studies reported that CE is identified in 3%–53% of patients with endometriosis (Table 1, Ref. [12–17]). These interstudy variances are due to the differences in the diagnostic criteria (ESPC density and microscopic fields observed) and methodology to detect CD138(+) ESPCs (the clones, concentrations, incubation temperatures, and duration of the primary antibody as well as specimen conditions) between the studies.

In 2011, we first investigated the prevalence of CE in the archival full-thickness eutopic endometrial tissues of women undergoing hysterectomy due to benign uterine corpus diseases, such as leiomyoma, adenomyosis, and endometriosis. Histopathologic CE (defined as five CD138(+) ESPCs in 10 high power fields (HPFs), 400 magnification) was detected in 5.0% of the endometriosis group and 11.7% of the non-endometriosis group [12], although the results were inconclusive due to the small sample size.

In 2014, Takebayashi et al. [13], retrospectively searched for CE using a larger number of the eutopic endometrium obtained from the hysterectomized specimens. In contrast to 27.0% of the non-endometriosis group, CE was detected in 52.9% of the endometriosis group (p = 0.031), which is the highest number among the studies published so far. There were no relationships between CE and age, body mass index (BMI), gravidity, and parity. They further compared the prevalence of CE in women with leiomyoma and adenomyosis. According to stepwise logistic regression analysis, there were no significant associations between CE and these two frequent uterine benign diseases, along with carcinoma in situ of the uterine cervix. Additionally, CE was unrelated to the stage of endometriosis (according to the revised American Society for Repro-
Table 1. Studies on the prevalence of histopathologic CE in women with endometriosis.

<table>
<thead>
<tr>
<th>Article/Ethnicity/Study period/design</th>
<th>Prevalence of histopathologic CE in endometriosis vs control group (p-value)</th>
<th>Age (years) in endometriosis vs control group</th>
<th>BMI (kg/m²) (endometriosis group vs control group)</th>
<th>Samples and preparations</th>
<th>Detection system for ESPC/clone, concentration, incubation time, and temperature of primary antibody against CD138</th>
<th>Diagnostic criteria for CE</th>
<th>Stage of endometriosis (Revised American Society for Reproductive Medicine classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitaya K et al. [12]/Japan/January 2002–December 2010/retrospective</td>
<td>5.00% (1/20) vs 11.68% (25/214) (non-endometriosis, endometrial benign diseases) (p = 0.7072)</td>
<td>Information unavailable</td>
<td>Information unavailable</td>
<td>Hysterectomy specimens</td>
<td>Immunohistochemistry, paraffin-embedded 4-µm sections /B-A38 (Nichirei Corp., Tokyo, Japan), stock solution, 60 min, room temperature</td>
<td>5 or more ESPCs in 10 high power fields (HPFs)</td>
<td>Information unavailable</td>
</tr>
<tr>
<td>Takebayashi A et al. [13]/Japan/April 2001–December 2012/retrospective</td>
<td>52.94% (18/34) vs 27.02% (10/37) (non-endometriosis, endometrial benign diseases) (p = 0.0311)</td>
<td>44.15, 3.65 vs 43.15, 2.75 (mean and SD) (p = 0.711)</td>
<td>22.08, 4.83 vs 21.60, 3.14 (mean and SD) (p = 0.940)</td>
<td>Hysterectomy specimens</td>
<td>Immunohistochemistry, paraffin-embedded 4-µm sections/stock solution (Nichirei Corp., Tokyo, Japan), 60 min, room temperature</td>
<td>1 or more ESPCs in 10 HPFs (400-fold magnification)</td>
<td>Stage I–IV No relationship between the prevalence of CE and stage</td>
</tr>
<tr>
<td>Khan KN et al. [14]/Japan/June 2012–December 2013/retrospective</td>
<td>3.08% (2/65) vs 0% (0/55) (non-endometriosis, infertility/dysmenorrhea) (p = 0.4993)</td>
<td>21–51 (range) vs 22–51 (range)</td>
<td>Information unavailable</td>
<td>Curettage specimens</td>
<td>Immunohistochemistry, paraffin-embedded 5-µm sections/stock solution (Nichirei Corp., Tokyo, Japan), 60 min, room temperature</td>
<td>1 or more ESPCs in 15 HPFs (100-fold magnification) in 3 or more sections</td>
<td>Information unavailable</td>
</tr>
<tr>
<td>Cicinelli E et al. [16]/Italy/January 2010–June 2016/retrospective</td>
<td>38.46% (30/78) vs 14.10% (11/78) (non-endometriosis, endometrial benign diseases) (p = 0.001)</td>
<td>44.3, 2.8 vs 44.0, 2.3 (mean and SD) (p &lt; 0.05)</td>
<td>27.3, 4.2 vs 27.2, 4.3 (mean and SD) (p &lt; 0.05)</td>
<td>Hysterectomy specimens</td>
<td>Immunohistochemistry, paraffin-embedded 4-µm sections /ab34164, 1:200, overnight, 4 °C</td>
<td>1 or more ESPCs in 10 HPFs (100-fold magnification)</td>
<td>Stage IV</td>
</tr>
<tr>
<td>Freitag N et al. [17]/Germany (&gt;90% Caucasian)/January 2013–February 2017/retrospective</td>
<td>12.90% (8/62) vs 10.00% (5/50) (non-endometriosis, infertility) (p = 0.634)</td>
<td>26–48 (range)</td>
<td>Information unavailable</td>
<td>Pipelle suction specimens</td>
<td>Immunohistochemistry, paraffin-embedded/Other information not available (sent to laboratory)</td>
<td>5 or more ESPCs per mm² section</td>
<td>Information unavailable</td>
</tr>
<tr>
<td>Khan KN et al. [15]/Japan/April 2015–February 2017/Prospective, non-randomized</td>
<td>≥22.6% (≥12/53) Not examined prior to treatment 33.4% (7/21) (Untreated endometriosis) vs ≥23.4% (≥11/47) Not examined prior to treatment 27.3% (3/11) (Untreated endometriosis)</td>
<td>18–51 vs 26–51 (range)</td>
<td>Information unavailable</td>
<td>Curettage specimens</td>
<td>Immunohistochemistry, paraffin-embedded 5-µm sections /ab34164, 1:200, overnight, 4 °C</td>
<td>1 or more ESPCs in 5 HPFs (200-fold magnification)</td>
<td>Stage I–IV No relationship between the prevalence of CE and stage</td>
</tr>
</tbody>
</table>
ductive Medicine classification) [11]. The higher prevalence of CE in this study is due to the diagnostic criteria (defined as one CD138(+) ESPCs in 10 HPFs, 400 magnification). When the researchers adopted the cut-off index of 6 ESPCs in one HPF, the overall prevalence was still higher in the endometriosis group than in the non-endometriosis group (29.41% vs 5.4%, \( p = 0.0101 \)). Additionally, they found that all women with endometriosis enrolled had more than 11 ESPCs in one HPF.

In the same year, Khan et al. [14] also retrospectively compared the prevalence of CE in women with and without endometriosis using endometrial curettage biopsy specimens collected during laparoscopy. They defined CE as the presence of one or more CD138(+) ESPCs (without neutrophils) in five non-overlapping power fields (×100 magnification) in three or more 5-μm thickness sections. CE was detected in 3.1% (2/65 patients) with endometriosis, but not in any non-endometriosis patients (no statistical difference). However, the prevalence is much different from another prospective non-randomized study published in 2021 (endometriosis group 22.6%– and non-endometriosis group 23.4%–) [15], even with the same sample preparation and examination methods. The discrepancies between the two studies may be due to the presence or absence of (i) histopathologic examinations for CE before laparoscopy, (ii) preoperative administration of the oral antibiotic agents (levofloxacin, 500 mg, once), and/or intramuscular gonadotropin-releasing hormone agonist (1.88 mg per month, three times), and (iii) the difference in age of the women enrolled in the study. Again, no relationship was found between the prevalence of CE and the stage of endometriosis.

In 2017, Cicinelli et al. [16] retrospectively compared the prevalence of CE in the endometrial tissues in the hysterectomized specimens of patients with and without endometriosis. Histopathologic CE was significantly more frequent in the stage IV endometriosis group than in the non-endometriosis group (38.5% vs 14.1%, \( p < 0.001 \)). The concomitance of CE and endometriosis was observed in more than one-third of women. There were no significant associations between CE and age, BMI, and the presence of uterine leiomyoma/adenomyosis, but multiparity was found as a factor lowering the prevalence of CE in women with endometriosis.

As many of these studies enrolled women undergoing pelvic surgery (hysterectomy or laparoscopy) and diagnosed with endometriosis during the operation, the prevalence of CE in women with suspected endometriosis (so-called “clinical endometriosis”) remains unknown and thus awaits further studies.

### 3. Microbiota in Reproductive Tract in Endometriosis and CE

While there are three major theories underlying the onset of endometriosis (i.e., retrograde menstrual blood flow, coelomic metaplasia, and Mullerian remnants), a single one is unable to explain the whole entity of the disease. Given the immunological and inflammatory natures of endometriosis, it is conceivable that bacterial infection and their metabolites are involved in this pathology [18].

Recent advances in next-generation sequencing methods enabled us to analyze the local microbiota in various tissues and organs. In 2011, Human Microbiome Project revealed that the microbiota in the human vagina is dominated by four Lactobacillus species (L. iners, L. crispatus, L. gasseri, and L. jensenii), along with lower proportions of lactic acid bacteria, indicating the essential role of lactate in the integrity of this organ [19,20]. However, it remained undetermined if these results go for the whole female reproductive tract. In 2017, Chen et al. [21] comprehensively investigated the microbiota throughout the female reproductive tract in Chinese women of reproductive age. They demonstrated that each reproductive organ has its unique microbiota, and the local microbiota is affected by multiple factors, such as age, body temperature, menstrual cycle, fecundability/infertility, and anemia.

Studies have demonstrated conflicting findings on the microbiota in the reproductive tract, particularly on Lactobacillus, in women with endometriosis. While some researchers reported a decrease in Lactobacillus in the endometrial and vaginal microbiota [22,23], others claimed the opposite result [24–26]. Interestingly, Khan et al. [22] found that the administration of gonadotropin-releasing hormone agonist, one of the therapeutic agents against endometriosis, changed the microbiota in the uterine cavity, resulting in a further decrease in Lactobacillus. Additionally, Le et al. [25], and Chang et al. [26] reported that surgical intervention and hormonal therapy altered the abundance of vaginal bacterial communities in the affected women with endometriosis. For example, the proportion of Lactobacillus in the vaginal microbiota was lower in patients using monophasic oral contraceptives than in the non-users. The mechanisms underlying these medical interventions that affected the local microbiota in women with endometriosis remain unelucidated. Regarding other bacterial genera/species, the consequences are quite inconsistent among the studies [22–28]. These discrepancies are likely to result from the conditions for examinations such as types of local disinfectants, sampling device, and route. Taken together, the bacterial genera/species and/or microbial communities in the female reproductive tract that are unique to endometriosis remains open so far and further studies are required.

Meanwhile, studies on CE share some common findings on the microbiota in the reproductive tract in the affected women. For example, bacterial taxa such as Bifidobacterium, Gardnerella, Lactobacillus, Prevotella, and Streptococcus were found to be predominant in the endometrial microbiota in women with CE [29–35]. By contrast, a number of studies failed to find unique bacterial gen-
era/species and microbial communities and/or differences in diversity and taxonomical composition in the endometrial and vaginal microbiota between women with and without CE [36–38]. The results of the endometrial microbiome analysis must be interpreted with precautions, as the estimated bacterial load in the vaginal cavity is shown to be 100- to 10,000-fold more than those in the uterine cavity [21]. No matter how local cleansing and disinfection are well performed before sampling, the contamination of the vaginal bacteria into endometrial bacteria is inevitable in the course of the transvaginal procedure. Indeed, studies using the samples obtained via the transperitoneo-myometrial route (laparoscopy or laparotomy) and transvaginal route disclosed quite different findings on endometrial microbiota, particularly about the compositions of Lactobacillus species [21,39,40]. We recently reported that the vaginal microbiota in infertile women with CE is characterized by the reduction of lactic-acid-producing bacteria other than Lactobacillus, such as Streptococcus, Enterococcus, Atopobium, and Bifidobacterium [41]. The vaginal microbiome analysis should be noticed in future studies in this field.

4. Inflammatory Profiling of CE in Women with Endometriosis

Non-pathological human endometrium contains a wide variety of leukocyte subsets. One of the physiological roles of these local leukocytes is the clearance of endometrial cell debris shed over the course of the menstrual period. The density and proportion of endometrial leukocytes significantly fluctuate throughout the menstrual cycle. After ovulation, the subpopulations of macrophages, natural killer cells, and neutrophils increase in density in the endometrium [42].

This postovulatory rise of macrophages, however, is not seen in the eutopic endometrium of women with endometriosis, whereas an unusual hormonal cycle-independent global augmentation of macrophages (in particular of M1 macrophages) is observed [43]. By contrast, in the ectopic endometrium of women with endometriosis, a large number of angiogenesis-supportive M2 macrophages are detectable in the endometriotic lesions [44]. These endometrial macrophages are thought to induce the proliferation of endometriotic cells. The postovulatory numerical increase of eutopic endometrial natural killer cells is maintained in women with endometriosis, but their cytolytic activity is impaired. In parallel, the lowered activity of cytotoxic T lymphocytes, as well as the expansion of eosinophils, neutrophils, and mast cells, are reported in the peritoneal fluid in women with endometriosis [45]. Such an aberrant local immunological microenvironment is thought to allow the proliferation and survival of ectopic endometrial tissues. Another immunological feature of the eutopic endometrium of women with endometriosis is the appearance of plasmacytes and CD20(+)CD5(+)HLA-DR(+) B cells, which are typical immunocompetent cells observed in CE, but are rare immunocompetent cells in the non-pathological eutopic endometrium [45]. On the contrary, endometrial immunoglobulin profiling remains undetailed. Early studies demonstrate a higher expression rate of IgG in eutopic endometrium with endometriosis compared with those without endometriosis, but subclass analysis has not been performed [46].

Meanwhile, the menstrual cycle-dependent fluctuation of the endometrial leukocyte subpopulations remains controversial in CE. Several studies did not find any differences [45,47], but others showed an increase in the proportion of local macrophages, M2 macrophages, and immature/mature dendritic cells [48]. Regarding mucosal immunoglobulin expression, the densities of endometrial IgM, IgA1, IgA2, IgG1, and IgG2 subclasses were shown to be higher in CE than in non-CE and healthy controls with the predominance of IgG2+ stromal cells [49].

We demonstrated that several pro-inflammatory molecules involved in the selective extravasation of B cells, such as chemokines (Chemokine (C-X-C motif) ligand (CXCL1) and CXCL13) and endothelial adhesion molecule 1 (ELAM1) are aberrantly expressed in endothelial and epithelial cells of the endometrium in women with CE [47]. These pro-inflammatory molecules are induced in endometrial cells by microbial antigens such as lipopolysaccharide. In addition, the concentration of interleukin (IL)-6 and tumor necrosis factor (TNF)-α is markedly higher in the menstrual effluents of women with CE compared with those without CE [49]. IL-6 is known as a differentiation factor of mature B cells in various tissues. TNF-α raises estrogen biosynthesis in endometrial glandular cells, which may drive the uterine lining to the proliferative phenotype that may cause the occurrence of endometrial micropolyposis, a hysteroscopic finding that is often seen in CE [50,51].

Although it remains fully elucidated if these hypotheses apply to the eutopic endometrium of endometriosis, studies suggest that these unusual plasmacytes and B cells are potentially involved in the proliferation and survival of the other endometrial cell components. For example, the endometrium with local polyps and micropolyps own proliferative nature and contains a larger number of ESCPs than the non-pathologic endometrium [52]. One of the histopathological characteristics of CE is delayed endometrial differentiation in the mid-secretory phase, when blastocysts start to implant in this mucosal tissue. We found that approximately one-third of the endometrium with CE exhibit “out-of-phase” morphology, such as pseudostratification and mitotic nuclei in both glandular and surface epithelial cells [47]. Additionally, the expression levels 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 unusually upregulated in the secretory phase endometri-
<table>
<thead>
<tr>
<th>Article/Ethnicity/Study period/Study design</th>
<th>Dose</th>
<th>Indications</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Samples/Detection system for ESPC/clone, dilution, incubation time, and temperature of primary antibody against CD138</th>
<th>Diagnostic criteria for CE</th>
<th>The cure rate of histopathologic CE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston-MacAnanny et al., [58] /United States/January 2001–December 2007/Retrospective</td>
<td>1000 mg/day, 14 days (500 mg, twice) in combination with ciprofloxacin 1000 mg/day, 14 days</td>
<td>RIF (two failed ET cycles), second-line against doxycycline-resistant CE</td>
<td>34.50, 3.27 (mean and SD)</td>
<td>Information unavailable</td>
<td>Pipelle suction specimens/Immunohistochemistry, paraffin-embedded sections/Mi15 Cell Marque (Biocare Medical, Concord, CA)/not available Biocare Medical, Concord, CA) /1:100 dilution/60 min/Romair?</td>
<td>1 or more ESPCs in 1 HPF observed</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>McQueen DB et al. [8] /United States (Caucasian and African-American)/July 2004–February 2012/Prospective</td>
<td>1000 mg/day, 14 days (500 mg, twice) in combination with ofloxacin 800 mg/day, 14 days</td>
<td>Recurrent pregnancy loss, first-line</td>
<td>22.08, 4.83 (mean and SD)</td>
<td>25.8, 6.4, 20–47 (mean, SD and range)</td>
<td>Not detailed</td>
<td>Not detailed</td>
<td>73.1% (19/26)</td>
</tr>
<tr>
<td>Yang R et al. [62] /Chinese/January 2009–January 2010/Prospective</td>
<td>1000 mg/day, 14 days (500 mg, twice) in combination with levofloxacian 500 mg/day, 14 days</td>
<td>RIF (three failed ET cycles or 6 or more high-quality transferred embryos), first-line</td>
<td>Not detailed (Two combined studies are reported in one article)</td>
<td>Not detailed (Two combined studies are reported in one article)</td>
<td>Pipelle suction specimens/Immunohistochemistry</td>
<td>1 or more ESPCs in the section observed</td>
<td>Not re-examined</td>
</tr>
<tr>
<td>Tersoglio AE et al. [59] /Argentina/2010–2013/Prospective</td>
<td>1000 mg/day, 14 days (500 mg, twice) in combination with ciprofloxacin 1000 mg/day, 14 days and precedent 200 mg/day doxycycline along with prednisone 4–8 mg/day</td>
<td>RIF (two or more failed ET cycles), first-line</td>
<td>36, 4.08 (mean and SD)</td>
<td>Information unavailable</td>
<td>Not detailed</td>
<td>Not detailed</td>
<td>64.3% (9/14)</td>
</tr>
<tr>
<td>Kitaya K et al. [10] /Japan/November 2011–July 2014/Prospective</td>
<td>500 mg/day, 14 days (250 mg, twice) in combination with ciprofloxacin 400 mg/day, 14 days</td>
<td>RIF (three or more 6 or more high-quality transferred embryos and/or blastocysts), second-line against doxycycline-resistant CE</td>
<td>38.1, 3.8 (mean and SD)</td>
<td>21.1, 1.9 (mean and SD)</td>
<td>Curette biopsy specimens/Immunohistochemistry, paraffin-embedded 4-µm sections /Bi-A38 (Nichirei Corp., Tokyo, Japan), stock solution, 60 min, room temperature</td>
<td>1 or more ESPCs in 1 HPF observed</td>
<td>88.9% (8/9)</td>
</tr>
<tr>
<td>Gay C et al. [63] /France/January 2013–January 2018/Retrospective</td>
<td>1000 mg/day, 14 days (500 mg, twice) in combination with doxycycline 200 mg/day, 14 days (Antibiotic was chosen according to antibiogram if bacteria were identified.)</td>
<td>Recurrent pregnancy loss, first-line</td>
<td>33 (9) median and (interquartile range)</td>
<td>24 (3) median and (interquartile range)</td>
<td>Pipelle suction specimens/Immunohistochemistry, not detailed</td>
<td>1 or more ESPCs in 1 HPF observed</td>
<td>Not detailed</td>
</tr>
</tbody>
</table>
ium with CE [53–56]. Meanwhile, the expression of the genes potentially associated with embryo receptivity (interleukin 11 (IL11), Chemokine Ligand 4 (CCL4), insulin-like growth factors 1 (IGF1), and caspase 8 (CASP8)) and decidualization (prolactin (PRL) and Insulin-like growth factor-binding protein 1 (IGFBP1)) are impaired in this period [53,56].

These findings indicate that the endometrium with CE is unable to respond correctly to ovarian steroids and modulate its component cells into a receptive phenotype, implicating the potential relationship between progesterone resistance and CE, which is also seen in endometriosis [57].

5. Antibiotic Treatment against CE and Endometriosis

As a bacterial infectious disease, antibiotic treatments have been utilized in the treatment of CE. Indeed, recent studies demonstrated that antibiotic treatments are superior to follow-up observations in the cure rate of CE [4,5]. Additionally, some studies suggest an improved live birth rate in subsequent embryo transfer cycles after the cure of CE, although there are no published randomized controlled studies [7,9,58–60]. Considering the broad antibacterial spectrum covering from common bacteria to mycoplasma, the antibiotic agents such as oral doxycycline, fluoroquinolones (ofloxacin, levofloxacin, and ciprofloxacin), nitroimidazole (tinidazole and metronidazole) have been preferred in the treatment against CE [7,9,58–63]. Meanwhile, some studies adopted an antibiogram-oriented choice of antibiotic agents [6]. Antibiotic resistance is a global problem in the treatment of bacterial infectious diseases. CE is no exception anymore. We recently demonstrated the increase in multi-drug-resistant CE in infertile women with a history of repeated implantation failure (7.8% of whole CE cases), along with the effectiveness of azithromycin or moxifloxacin against multi-drug-resistant CE [37].

Although there is currently no literature that demonstrated the effectiveness and safety of antibiotic treatment against endometriosis in humans, animal studies suggest the potential of some antibiotic agents, particularly metronidazole, which has been utilized for the treatment of CE (Table 2, Ref. [8,10,58,59,62,63]), as a promising therapeutic drug against endometriosis.

Using a mouse model, Chadchan et al. [64] investigated the effect of 21-day oral water-solubilized administration of the broad-spectrum antibiotics (0.5 mg/mL vancomycin, 1 mg/mL neomycin, 1 mg/mL metronidazole, and 1 mg/mL ampicillin, Vancomycin, Neomycin, Metronidazole, and Ampicillin (VNMA)) on endometriosis lesions. Of them, metronidazole significantly reduced the volumes and weights of the ectopic endometriosis lesions, along with amelioration of pelvic inflammatory responses (suppression of macrophage proliferation and production of cytokines such as IL-1β, IL-6, and TNF-α). Interestingly, oral administration of feces from mice with endometriosis exacerbates the growth and inflammation of the endometriotic lesions in metronidazole-treated mice, indicating a key role of gut bacteria in the promotion and progression of endometriosis in these mice. Furthermore, Lu et al. [65] reported the effectiveness of the vaginal administration of the VNMA mixture (once every 3 days for 21 days) via an absorbable gel sponge on endometriosis lesions. While the disorder of the vaginal microbiota potentially promoted the progression of endometriosis, antibiotic treatment was capable of reducing the volume of the endometriotic lesions via regulation of the nuclear factor-kappa B signaling pathway.

Thus, antibiotic treatment can be a potential therapeutic option against endometriosis, although more basic studies are required prior to application to humans.

6. Conclusions

While endometriosis has been long considered a cause of infertility, CE is also an emerging issue that may reduce fecundity in women of reproductive age [66]. Endometriosis and CE share characteristics of endometrial proliferative nature. Like endometrial polyps being often seen in endometriosis, endometrial micropolyposis is frequently complicated with CE [17,67]. The potential relationships between these two diseases of the uterine lining warrant future studies.

Author Contributions

KK wrote the manuscript. TM and MM were involved in the discussion of the contents. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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