Gynecopathology in the Diagnosis and Assessment of Chronic Endometritis

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Abstract

Objectives: To summarize the gynecopathology findings in the diagnosis and assessment of chronic endometritis (CE) and provide insights into the therapeutics of CE. Mechanism: Chronic endometritis (CE) refers to the inflammatory state of the endometrium, which might alter endometrial receptivity and impact embryo implantation. As a relatively asymptomatic disease, the diagnosis and assessment of CE mainly lies in endometrial biopsy and further morphological and functional examinations. The authors searched the electronic database with a combination of key terms including chronic endometritis, histopathology, hysteroscopy, microbiota, inflammation, vascularization, decidualization as well as autophagy and summarized the current findings in the diagnosis and assessment of CE. Findings in Brief: Plasma cell infiltration with immune staining, hysteroscopic manifestations including swelling, hyperemia and micropolyps, and pathogenic diagnosis were the main criteria for diagnosing CE. Further assessment of CE revealed the release of proinflammatory cytokines, leukocyte infiltration, enhanced vascularization and autophagy. These factors all contribute to an inflammatory state of the endometrium and decreased flow reserve supplying the embryo, which lead to the pathway explaining implantation failure in CE patients. Conclusions: Gynecopathology plays an essential role in the diagnosis and assessment of CE. Understanding such methods can help to screen out asymptomatic patients and initiate proper treatment, which eventually promotes better knowledge of the relationship between CE and embryo implantation and a higher successful implantation rate.

Keywords: chronic endometritis; gynecopathology; histopathology; hysteroscopy; inflammation; autophagy

1. Introduction

Chronic endometritis (CE) is a persistent inflammatory state of the endometrium characterized by endometrial edema, increased stromal cell density, plasma cell infiltration, and altered vascularization and contractility [1]. Triggered by pathogenic infections, these morphological and functional changes collaboratively contribute to the development of endometrium receptivity, which negatively impacts the implantation success of embryos [2]. Unlike acute endometritis, CE is usually mild and asymptomatic, with some patients complaining of pelvic pain, abnormal uterine bleeding and leukorrhea [3]. For these reasons, CE is often overlooked in previous clinical practices.

With the recent detection of uterine cavity microbiota and evidence of its physiological role in maintaining immunological stability, the diagnosis and treatment of CE as well as its correlation with implantation success were given increasing clinical concerns [1]. However, the diagnosis and treatment of CE still lack a unified gold standard or biomarker with distinguished sensitivity and specificity, which results in the overestimation or underestimation of its effect on pregnancy outcomes [4].

Gynecopathology refers to the application of histopathology to determine the pathological changes and expression of certain molecules at cellular or tissue level, which might help to define morphological and functional abnormalities of the endometrium [5]. Therefore, this article intends to review the gynecological findings in promoting the diagnosis and assessment of chronic endometritis.

2. Methods

This is a comprehensive literature review focusing on the pathology, pathophysiology mechanism of CE and how they impact on the diagnosis, assessment and treatment. Electronic databases including PubMed, Embase and the Cochrane Library were searched for the related articles. The key terms applied included chronic endometritis, histopathology, hysteroscopy, microbiota, inflammation, vascularization, decidualization and autophagy. No restrictions on the year of publication were applied, while only studies with full text available in the English language...
were included. All studies relevant to our topic were carefully examined with gynecological methods used in diagnosing and assessing CE summarized in our study.

3. Diagnosis of Chronic Endometritis

3.1 Histopathological Diagnosis of CE

Histopathological diagnosis of CE with the detection of plasma cells within the endometrial stroma is the current gold standard [1,6]. Endometrial biopsy was first obtained and stained for plasma cell-specific biomarkers. Conventional staining methods, such as hematoxylin and eosin (HE) staining, identify plasma cells simply with their monocentric nucleus, basophilic cytoplasm and comparably large cell body, which morphologically resemble fibroblasts and monocytes and thus can be easily missed or overestimated without sufficient experience [7] (Fig. 1A,B).

Therefore, an alternative method uses immunohistochemistry (IHC) staining for CD138, where a proteoglycan found on the cell surface of plasma cells and keratinocytes that symbolizes the differentiation from B cells to plasma cells [4,7] (Fig. 1C,D). Prior studies have shown that IHC staining for CD138 may enhance the recognition of chronic endometritis from 14.9% to 42.6% [8]. However, the threshold value for the number of plasma cells per sample or per microscopic field to diagnose CE varies as >1/10 high power fields (HPF), >1/section, >5/10 HPF or density above the established reference range (95th percentile) despite the quantification method being used as the diagnostic criteria for E [7].

In addition to identifying plasma cells, other microscopic morphological features were also considered valid reference standards. McQueen et al. [9] suggested that plasma cells themselves were insufficient in identifying all CE patients and that other endometrial stromal changes, such as spindling of cells, edema, breakdown, pigment deposition, areas of hypercellularity, and the presence of inflammatory cells other than plasma cells, might aid the diagnosis of CE with higher sensitivity. However, consensus has not been reached on whether endometrial stromal changes alone are capable of diagnosing CE and whether such pathological changes should be strictly required when plasma cells are already detected [10].

Histopathological diagnosis with IHC staining for CD138 is the current gold standard for diagnosing CE. However, determining the presence of CD138-positive plasma cells is often influenced by the subjective judgment of pathologists. In addition, the density threshold of plasma cells in diagnosing CE also differs among pathologists and healthcare professionals, making it difficult to build unified yet accurate criteria for the histopathological diagnosis of CE.

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Fig. 1. Histopathological and Hysteroscopical diagnosis of CE. (A,B) Detection of endometrial plasma cells through HE staining. (C,D) Immunohistochemical identification of CD138. (E,F) Hysteroscopical manifestation of endometrial edema and hyperemia.
3.2 Hysteroscopic Diagnosis of CE

Hysteroscopy is a definite method that can be used for direct observation and evaluation of the uterine cavity. Unlike ultrasonography or hystero-salpingography, hysteroscopy was able to identify small lesions of the endometrium that might be easily missed by the former two methods. Diagnostic criteria include endometrial stromal edema, focal or diffuse endometrial hyperemia, and the presence of micropolyps (<1 mm) [11] (Fig. 1E,F). Song et al. [12] included 1189 infertile women undergoing hysteroscopy and endometrial biopsy in a cross-sectional study and suggested that hyperemia, micropolyps (<1 mm), and interstitial edema were found in 39.5%, 53.5%, and 51.9% of CE patients, respectively, whereas 64.0% of CE patients showed more than 2 hysteroscopic features. Prior studies have also shown that the degree of hysteroscopic features were in parallel with plasma cell count, as Song et al. [12] reported that 31.1% of patients with microscopic findings of 0 plasma cell count showed hysteroscopic features of CE, while such features were seen in 56.4% and 61.1% of patients with 1–4 and >5 plasma cell count/HPF, respectively. In general, hysteroscopic criteria for diagnosing CE showed high specificity and negative predictive value, while sensitivity and positive predictive value were relatively low and varied in different study populations [13–15]. Recent studies also established a scoring system setting points for each positive hysteroscopic feature, which was proven to be of considerably high predictive value (Area Under the Curve (AUC) = 0.823) toward diagnosing clinical CE [16]. However, controversies lie in the diagnostic value of hysteroscopy as some studies have noted that hysteroscopy itself is not useful or powerful enough in screening CE in symptomatic patients and that discrepant conclusions have been reached between histopathological and hysteroscopic standards [17,18].

In summary, the hysteroscopic diagnosis of CE highly relies on the surgeon’s recognition of the inflammatory morphological changes of the endometrium, which might also be affected by subjectivity when performing hysteroscopy. Additionally, endometrial biopsy when performing hysteroscopy cannot fully reflect the pathological changes of the entire endometrium given that certain parts of the endometrium with symbolic morphological manifestation can possibly be missed due to sampling location.

3.3 Pathogenic Diagnosis of CE

The uterine cavity was once thought to be sterile until recent studies confirmed the presence of endometrial microbiota through microbial culture and RNA sequencing [19]. The normal uterine microbiota is dominated by Lactobacillus and fluctuates throughout the menstrual cycle to guarantee the anti-inflammatory response of the female upper genital tract and sustain proper endometrial receptivity [20].

Prior studies have shown that Phyllobacterium and Sphingomonas are significantly highly infiltrated in CE patients. The dysbiosis of endometrial microbiota subsequently regulates immune cells by interfering with the process of carbohydrate metabolism and/or fat metabolism in the endometrium, which results in reduced endometrial receptivity and eventually implantation failure [21]. Liu et al. [22] reported a decreased abundance of Bifidobacterium spp. and increased abundance of Atopobium, Gardnerella and Anaerobacillus spp. in patients with recurrent spontaneous abortion, with specific dysbiosis in endometrial samples with detection of CD138-positive plasma cells, indicating the possible pathogenesis of CE. Other studies proposed that CE patients showed a non-Lactobacillus-dominated pattern of endometrial microbiota with the presence of Ralstonia and Gardnerella spp. identified through abundance analysis [23]. Such pathogenic features of CE patients promoted the pathogenic diagnostic criteria for asymptomatic chronic endometritis.

Bacterial culture is a frequently used and conventional method for determining pathogenic microbes of CE. With the identification of pathogens through microbial culture, antimicrobial therapy is able to precisely target specific pathogens. Nonetheless, endometrial culture is not a routine diagnostic criterion due to its long turnaround time and because a number of pathogens are not culturable [24]. In 2008, Cicinelli et al. [25] included 438 women with hysteroscopically confirmed CE as well as 100 non-CE patients and suggested that positive cultural tests for common pathogens were found in more than 70% of CE patients, while only 5% of control cases showed positive endometrial culture results. Similar findings in 2014 implied that uncommon pathogens, including Mycoplasma and Ureaplasma, were found in 25.3% of CE patients, and Chlamydia was found in 12.7% of CE patients [26].

With the development of polymerase chain reaction and RNA sequencing, the molecular diagnosis of CE has compensated for the shortcomings of conventional microbial culture methods for difficult-to-culture bacteria. In 2018, Moreno et al. [24] compared the validity of 16S RNA sequencing and its consistency with other methods on endometrial samples from 65 patients. A study showed that the most commonly identified bacteria of endometrial samples from CE patients through 16S RNA sequencing was Streptococcus species. Moreover, the molecular diagnosis of CE showed matching rates of 46.15%, 58.46% and 66.15% when compared with histology, hysteroscopy and bacterial culture diagnosis, respectively. The sensitivity of molecular diagnosis was higher than that of histology diagnosis but lower than that of hysteroscopy diagnosis and was more sensitive at screening out G. vaginalis, which is a common pathogen of CE but seldomly cultured bacteria [24].

Notably, the limitation of pathogenic diagnosis of CE lies in the fact that the microbiota concentration of the female genital tract, especially the uterine cavity, is relatively
low, making it difficult to determine the concentration of targeted species. The distribution of microbiota varies in the upper and lower genital tract, the distinction of which can lead to certain fluctuations in the microbiome of the acquired samples. With the underlying mechanism of dysbiosis causing CE still unclear, high-quality clinical trials with large sample sizes are still needed to further illustrate the relationship between uterine microbiota, endometritis and implantation failure.

To sum up, the summarized diagnostic algorithm varies among different medical centers, whereas a combination of histopathological, histological and pathogenic diagnostic criteria were applied. Clinical symptoms and risk factors may also aid in the diagnosis of CE (Fig. 2).

### 4. Assessment of Chronic Endometritis

In prior studies, infection was widely believed to be a trigger of CE, as histology, hysteroscopy and pathogenic diagnosis favored inflammation features, and the development of inflammation at both the morphological and functional levels is seen as a clear pathway of CE [1]. Therefore, in addition to the primary diagnosis of CE, further assessment of CE regarding inflammation and its influence on angiogenesis, vascularization, decidualization and autophagy is also worth noting. Gynecopathology plays an important role in assessing the onset and development of CE and provides references for subsequent treatment.

#### 4.1 Cytokine and Chemokine Dysregulation

Cytokines are important mediators of inflammation and symbols for the aberrant local microenvironment of the uterine cavity. Gynecology methods assessing the synthesis and secretion of cytokines include immunofluorescence and immunohistochemistry assays. In 2019, Wang et al. [27] included 75 CE patients and 75 patients with male factor infertility in a case–control study and suggested that the expression of interleukin 17 (IL-17) was higher in CE patients, while transforming growth factor-β (TGF-β) and interleukin 10 (IL-10) were downregulated in CE patients. The alterations in TGF-β and IL-10 indicate a deficiency or absence of regulatory T cells (Tregs), and with lower quantity or functional defects of Tregs, inflammation and fibrosis may occur [28,29]. It may also disturb maternal-fetus immune tolerance and cause maternal alloreactive immune responses against paternal antigens in trophoblasts [30]. The literature also emphasizes the downregulation of IL-11 and upregulation of IL-6 in CE patients, which might lead to an altered inflammatory response, decidualization of human endometrial stromal cells, endometrial vascularization and remodeling of the maternal vasculature [1,31].

On the other hand, chemokines are chemotactic cytokines involved in leukocyte activation and migration, which take part in inflammation regulation and the acquisition of endometrium receptivity [31]. In 2010, Kitaya et al. [32] recruited 22 CE patients and 54 non-CE controls in a study and reported that aberrant expression of selectin E, CXCL1, and CXCL13 was observed in CE patients. Immunohistochemistry showed that CE enhances the immunoreactivity of the microvascular endothelial layer to adhesion molecule selectin E and chemokine C-X-C motif ligand 13 (CXCL-13) and that of the glandular epithelial layer to CXCL1, which plays a key role in the circulation of stromal B cells in the endometrium. Other studies also reported upregulation of insulin-like growth factor bind-

![Fig. 2. Diagnostic algorithm for chronic endometritis.](image-url)
ing protein-1 (IGFBP-1) and downregulation of insulin-like growth factor-1 (IGF-1), which participated in endometrial decidualization and the reactivity of the endometrium toward estrogen and progesterone. However, contradictory findings have indicated that cytokine and chemokine levels cannot be used as indicators for CE [33].

4.2 Leukocyte Aggregation and Infiltration

After cytokine and chemokine hypersynthesis and secretion, the targeted leukocytes aggregated in the endometrial microenvironment through chemotaxis. In prior studies, it has been proven that the profile of immune cells of both the peripheral blood and the uterine cavity are altered by CE. In 2019, Li et al. [34] included 634 non-CE patients and 74 CE patients for immune status analysis. Using IHC staining for CD56+ NK cells, CD68+ macrophages, CD163+ M2 macrophages, CD1a+ immature dendritic cells (iDCs), and CD83+ mature dendritic cells, researchers have suggested that CD68+ macrophages and CD83+ mature dendritic cells tend to be more induced in CE patients. The proportions of leukocytes demonstrated the inflammatory trend of CE, and after antibiotic treatment, the percentages of CD68+ macrophages and CD83+ mature dendritic cells were reduced in cured CE patients [34].

Another gynecopathological feature of CE is marked B-cell infiltration into the endometrium. Kitaya et al. [32] applied IHC staining to assess the focal aggregation of CD20+ B cells and reported that in CE patients, dense B-cell aggregates were found in the functional layer, along with single cell infiltration with the epithelium and the gland lumina. However, few CD20+ B cells were detected in the nonpathological endometrium. These findings were in agreement with the infiltration of neutrophils in acute endometritis (AE) patients, as both CE and AE were triggered by infection and thus shared a similar pathway for accumulating and spreading inflammation [35].

Aside from being a marker of infection and inflammation, the infiltration of leukocytes may also serve as a predictor for endometrial decidualization. For example, uterine NK cells (uNK cells) are commonly detected in the stromal decidualization area and might express certain immune modulatory proteins to promote an endometrial re-action to progesterone and remodeling of uterine spiral arteries [36,37]. Matteo M et al. [38] recruited 23 infertility patients with 9 hysteroscopically diagnosed CE and 14 non-CE patients and suggested that the percentage of leukocytes in CE patients was lower than that in non-CE patients. These findings provide an explanation of altered implantation in CE patients and a way to assess the immune status as well as the immunomodulatory effect of the endometrium.

4.3 Angiogenesis and Vascularization

Angiogenesis and altered vascularization are associated with CE as symbols for inflammation and morphological features of functional polyps [1]. Carvalho et al. [39] reported in 2013 that approximately 85.7% of CE patients showed vascular changes, including endothelial proliferation, tissue edema, luminal occlusion and small vessel thrombosis, all implying the onset of inflammation and infection. These changes that occur in the inflammation procedure might result in implantation failure and pregnancy loss owing to either increased or decreased vessel density. On the one hand, an excessive inflammatory response may result in a higher expression of vessel epithelial growth factor (VEGF), as suggested by Praderio et al. [40] which promotes angiogenesis. By applying immunostaining, researchers have shown that VEGF could also be a marker for assessing CE, as CE patients showed higher expression and intensity of VEGF in the endometrium.

Angiogenesis and altered vascularization may also affect the synthesis and secretion of reactive oxygen species (ROS), changing the hypoxic environment during implantation [41]. On the other hand, swelling and tissue edema from inflammation might damage the flow reserve of the endometrium, causing microcirculation abnormalities and luminal impairment [42], which could be responsible for the lack of embryo blood supply.

Endometrial polyps are abnormal endometrial growths containing glands, stroma and blood vessels projecting from the lining of the uterus, which have also been considered common hysteroscopic manifestations of CE in prior studies. In 2021, Vitagliano et al. [43] included 8 observational studies in their systematic review and concluded that patients with hysteroscopically confirmed endometrial polyps had a higher prevalence of CE and that patients with multiple (≥3) polyps were at higher risk of CE than those with a single polyp. Similar results were seen in Guo’s study, reporting a twofold risk of CE in patients with multiple polyps compared with single polyps and that multiple polyps were considered an independent risk factor for CE [44]. Moreover, patients with CD138+ endometrial polyps were more likely to be diagnosed with CE than those with CD138− polyps, as reported by Nomiyama et al. [45], who applied immunohistochemical staining methods. Therefore, morphological analysis of vascular pathology and molecular biomarkers determining vessel density (e.g., VEGF and its receptors) can be used as valid parameters for the severity and prognosis of CE.

4.4 Decidualization

Decidualization is the process during which the endometrium undergoes both morphological and functional changes to prepare for embryo implantation. Generated by endometrial stromal cells (ESCs), decidualization is viewed as a process involving genetic, environmental, immune and endocrine factors [46]. Considering the association between chronic endometritis and recurrent implantation failure and early pregnancy loss, increasing evidence has shown relevance between defective decidualization and CE.
The decidua undergoes transformation under the regulation of estrogen and progesterone and subsequently secretes hormones and growth factors such as prolactin (PRL) and IGFBP-1 [47]. By applying PRL and IGFBP-1 as biomarkers for decidualization and modulators for hormonal regulation of the endometrium, studies have demonstrated decreased expression of IGFBP-1 and decreased PRL and IGFBP-1 mRNA in CE patients, while the number of ESCs was thought to increase compared to non-CE patients [48]. Additionally, since sex hormones are essential inducers of the transformation and differentiation of decidua, their binding receptors can also be used as a parameter for CE assessment. Wu et al. [48] suggested that both estrogen and progesterone receptors (PRA, PRB, ERα and ERβ) were found to have higher expression levels in endometrial stromal cells, whereas only ERα and ERβ were higher in the glandular cells of CE patients [49]. Taken together, a possible explanation could be that the chronic inflammatory status of CE inhibits or slows down the maturation of decidua through certain sexual-steroid resistance and that proliferation of the endometrium is promoted, whereas differentiation into the secretory phase is otherwise downregulated [1,48]. As a result, the lack of decidualization potential leads to difficulty in maintaining endometrial receptivity and preparing for embryo implantation. This also hints that the detection of sex hormones and their binding receptors as well as other biomarkers for decidualization that are capable of determining CE and predicting its effect on embryo implantation.

4.5 Autophagy

Autophagy is an intracellular lysosome-mediated protein degradation process by which cytoplasmic materials are delivered and degraded to maintain cellular homeostasis [49,50]. It has also been proven that autophagy plays a key role in the regulation of inflammation in that it improves host defense through the direct elimination of invading pathogens and the upregulation of innate adaptive immunity, which includes leukocyte recruitment and cytokine secretion [51]. Considering that CE is also a continuous state of inflammation, the role of autophagy in assessing CE has been widely studied. Wang et al. [27] included 75 CE patients with implantation failure and 75 patients with male factor infertility in their case control study. Using gynecopathology methods, including immunohistochemical and immunofluorescence assays, researchers have shown increased expression of microtubule-associated protein 1A/1B-light chain 3 (LC3-II) and decreased expression of mechanistic target of rapamycin (mTOR) in CE patients. Both molecules are essential components in cellular autophagy in regulating inflammation and metabolism, impacting embryo implantation [27]. LC3-II is a protein inserted into both the inner and outer membranes of the growing autophagosome, which is seen as a marker for autophagy considering its role in autophagosome genesis [52]. An increase in LC3-II might activate autophagosome formation and clearance and therefore unlock the inflammatory cascade, inducing cell apoptosis and unprogrammed cell death. Such cellular injuries lead to impairment of the endometrium, causing detrimental effects on endometrial receptivity and eventually disturbing implantation success [53]. It has also been reported that the changes in LC3-II paralleled inflammatory cytokines, as CE patients showed increased transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) levels, as well as decreased IL-
17 levels. These findings supported the idea that the inflammatory response was upregulated, while regulatory T cells (Tregs) were downregulated, the dysfunction of which might alter immune tolerance of the maternal-fetal interface and cause implantation failure [54,55]. On the other hand, mTOR is a member of the phosphatidylinositol-3-OH-kinase-related kinase (P13KK) family that participates in cell metabolism. It also modifies host defense and the innate immune response by modulating immunoproteasomal degradation and suppressing lipopolysaccharide (LPS)-induced inflammation [56]. Hence, the downregulation of mTOR might exaggerate the inflammation status of the endometrium in CE patients. The collaborative effect of LC3-II and mTOR contributes to enhanced autophagy in CE patients and might cause an imbalance between proteins being recycled and those being discharged, eventually leading to a suboptimal environment for embryo implantation.

In the assessment of CE, IHC and immunofluorescence assay were the main methods applied in clinical settings and the scientific research field. We here summarized the biomarkers being used in the assessment of CE in Fig. 3.

5. Treatment of Chronic Endometritis

To guarantee the comprehensive administration of CE, proper therapeutic methods were vital for refining gestational outcome and enhancing implantation rate. Moreover, experimental treatment might also aid the diagnosis and assessment of therapeutic effect of CE.

Oral antibiotics are the most commonly used treatment for CE, with doxycycline, ofloxacin and metronidazole being the first line therapy. Mcqueen et al. [57] applied an ofloxacin and metronidazole combined therapy as the first-line treatment for infertility women with repeated pregnancy loss and found that the overall curing rate was 94%, while the curing rate reached 100% after substituted therapy of doxycycline was added to patients showing no response to the first-line dual therapy. Kitaya et al. [58] reported a 92.3% rate of endometrial plasma elimination. On the other hand, Cicinelli et al. [59] selected oral antibiotics based on the bacterial culture of endometrial biopsies and it turned out that 75% of the recruited patients showed no hysteroscopy manifestation of CE after 3 cycles of oral antibiotic treatment. For gestational outcomes, Xiong et al. [60] demonstrated higher implantation rate, clinical pregnancy risk and live birth rate in CE patients after antibiotic treatment than those with persistent CE. Vitagliano et al. [61] Systematically reviewed 5 studies featuring on the therapeutic effect of antibiotic treatment of CE and found that patients with cured CE had higher rate of implantation, live birth and ongoing pregnancy. However, controversies lie in existing literature as Liu et al. [62] found that antibiotic therapy didn’t bring statistical significance to CE patients in terms of implantation rate, ongoing pregnancy rate and live birth rate, while patients with cured CE did show lower miscarriage rate.

Other treatment including uterine mechanical stimulus and uterine perfusion might also be of help in curing CE. Mitter et al. [63] demonstrated that diagnostic endometrial biopsy can enhance live birth rate and ongoing pregnancy rate after both natural conception and embryo transfer. Seval et al. [64] also reported higher implantation rate after endometrial scratching. Compared with oral antibiotics that directly target on pathogenic microbes, endometrial scratching or diagnostic hysteroscopic biopsy promote endometrial blood flow, stimulate the secretion of growth hormone and facilitates endometrial decidualization, which subsequently ensure the establishment of endometrial receptivity and guarantee success embryo implantation. On the other hand, intrauterine delivery of antibiotics and hormone have also proved to be effective in treating CE as implantation, clinical pregnancy and live birth rate [65].

6. Conclusions

In this review, we summarized the role of several gynecopathological methods in both diagnosing and assessing the severity of CE. In summary, gynecopathology has advantages in visualizing and quantifying the pathological changes and molecular expression of specific biomarkers in the endometrium of CE patients. For diagnosing CE, histopathological, hysteroscopic and pathogenic methods are the most commonly used tools. Gynecopathological methods help with determining the infiltration of plasma cells, morphological changes within the endometrium, including edema, polyps and hyperemia, and the presence of CE-related bacteria. Furthermore, it also promotes assessing the severity, pathological and pathophysiological changes of CE with regard to altered inflammatory status, leukocyte infiltration, decidualization and autophagy, the findings of which help to uncover the mechanism of CE and its relationship with implantation failure. However, the establishment of a gold standard for diagnosing CE and a comprehensive mechanism for assessing CE is still needed through well-designed epidemiological studies so that the correlation between CE and implantation can be fully understood. It might also benefit the therapeutics of CE (i.e., oral antibiotics, endometrial scratching and intrauterine perfusion) and refine endometrium preparation for successful embryo implantation.

Author Contributions

Study design and concept—YG, SY, YY, RL; Data collection and analysis—YG, SY, YL; Interpretation of data and critical revision of the manuscript—YG, SY and RL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.
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Conflict of Interest

The authors declare no conflict of interest.

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