CHRONIC ENDOMETRITIS AND INFERTILITY

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ABSTRACT

Background: Chronic endometritis is a persistent inflammatory condition of the endometrium characterized by the infiltration of plasma cells into the endometrial tissue. It does not receive much attention in clinical practice because chronic endometritis is frequently asymptomatic or has mild symptoms such as abnormal uterine bleeding, pelvic discomfort, dyspareunia, and leukorrhea. On the other hand, the current diagnostic standards for chronic endometritis are ambiguous and frequently require an endometrial biopsy. **Methods:** The published articles were reviewed. **Results:** The gold standard for diagnosing chronic endometritis is immunohistochemical staining (CD138) on endometrial biopsy specimens. In addition, hysteroscopy could be used as an effective screening method. The relationship between chronic endometritis and infertility has recently emerged as a significant clinical challenge. In fact, several studies have found that chronic endometritis is diagnosed among women with infertility (from 2.8% to 56.8%), recurrent implantation failures (from 14 to 67.6%), and recurrent pregnancy loss (from 9.3 to 67.6%). After chronic endometritis was diagnosed, treatment included a first round of doxycycline administration followed by a second round of ofloxacin plus metronidazole for 14 days in cases of chronic endometritis persistence. As a result, Assisted Reproductive Technologies centers need to pay attention to the diagnosis and treatment of chronic endometritis. **Conclusion:** The gold standard for diagnosing chronic endometritis is immunohistochemical staining CD138 of biopsied endometrium. In cases of recurrent implantation failure owing to chronic endometritis, antibiotic therapy is useful in chronic endometritis treatment and increasing in vitro fertilisationoutcomes.

Keywords: Chronic endometritis; ART; Infertility; Immunohistochemical staining (CD138); Hysteroscopy

INTRODUCTION

According to ESHRE data in 2018, it is estimated that over 8 million babies have been born through in vitro fertilization (IVF) around the world since Louise Brown's birth in 1978[1]. Embryo transfer is an important part of IVF treatment, determining whether or not the treatment is successful. The success rate of embryo transfer depends on various factors, the two most crucial of which are embryo quality and endometrium, as well as embryo-endometrial interaction and synchronization[2]. Approximately one-third of implantation failure is due to the embryo and two-thirds to endometrial factors[3], and 10% of these are recurrent implantation failure (RIF)[4].

In the study by Shaulov et al., 2020, the definition of recurrent implantation failure (RIF) is inconsistent. RIF is a case of two previous implantation failures with no precision on the number of embryos (Lensen et al., 2019). However, another opinion is that three failed IVF or intracytoplasmic sperm injection (ICSI) treatments, each with at least one fresh good-quality embryo per transfer, or failure to achieve pregnancy after the transfer of 10 good-quality embryos (Koot et al., 2019)[5]. By 2023, the ESHRE good practice recommendations paper defines RIF as cases in which there is no successful implantation by a certain number of embryo transfers and the cumulative predicted chance of implantation associated with that number is greater than 60%[6]. Currently, RIF is still a challenge in infertility treatment. It was discovered that 30% of RIF patients had chronic endometritis (CE), and CE had to be determined in those circumstances[7].

MATERIAL AND METHODS

We looked at the diagnostic methods and standards that researchers looking into chronic endometritis employed. To find pertinent research, a search of PubMed and Embase was conducted, limiting the results to publications written in English. Three keywords and their combinations were used: "diagnostic criteria", "chronic endometritis" and "infertility." Supplementary queries encompassed citations from recognized works.

DEFINITION AND EPIDEMIOLOGY

CE is a persistent inflammation of the endometrial mucosa caused by bacterial pathogens such as Enterobacteriaceae, Enterococcus, Streptococcus, Staphylococcus, Mycoplasma, and Ureaplasma. Although chronic endometritis can be asymptomatic, it is found in up to 40% of infertile patients and is responsible for repeated implantation failure and recurrent miscarriage[8]. Meanwhile, CE is diagnosed among women with infertility (from 2.8% to 56.8%), recurrent implantation failures (from 14 to 67.6%), and recurrent pregnancy loss (from 9.3 to 67.6%) (Murtinger et al., 2022)[9]. Especially in cases of uterine polyps, 92.6% of infertile patients had combined CE (Kuroda et al., 2020)[10].

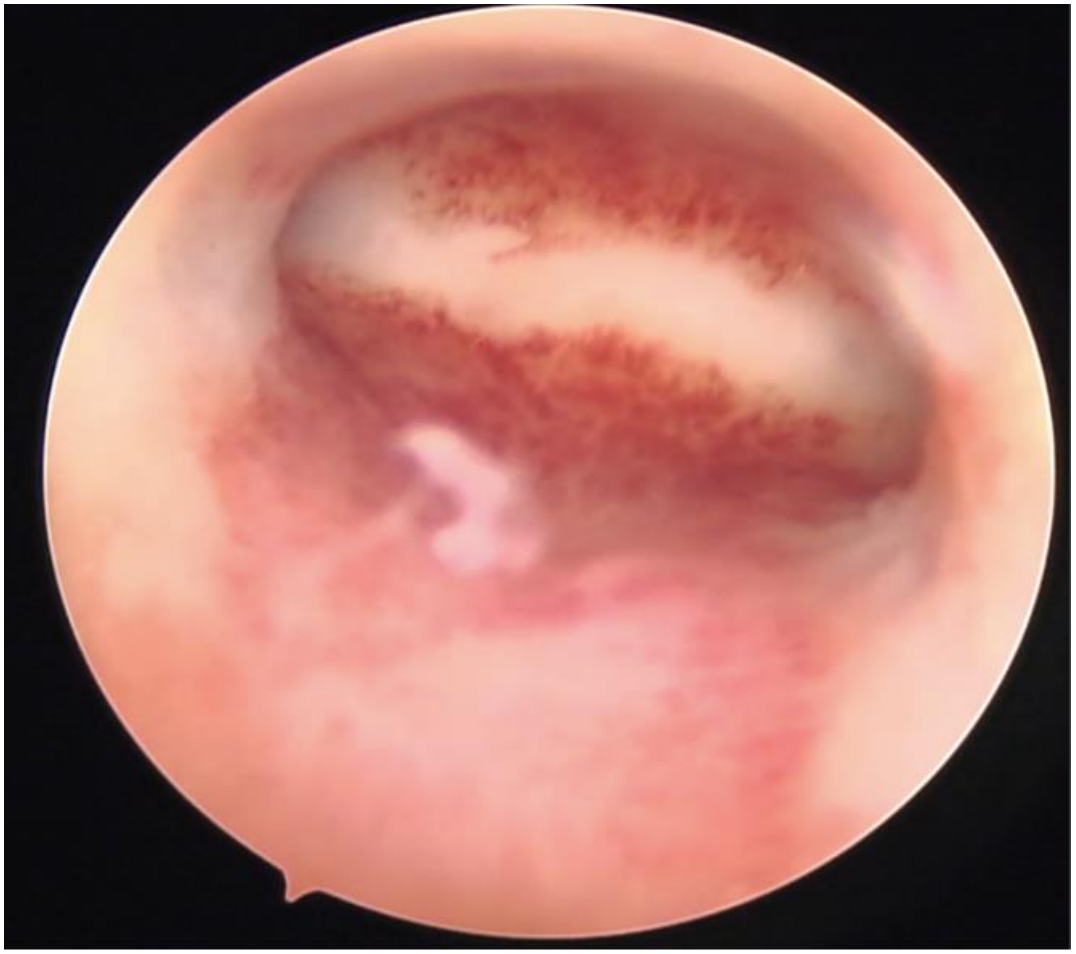


Image 1. Chronic endometritis (strawberry sign) on office hysteroscopy at Tam Anh Hospital

SYMPTOMS AND MECHANISMS

In most cases, women with CE are asymptomatic or display mild disturbances, such as abnormal uterine bleeding (AUB), dyspareunia, pelvic discomfort, and leukorrhea. Moreover, CE cannot be identified by ultrasound examination due to a lack of specific ultrasound markers. For these reasons, CE is often overlooked or diagnosed incidentally during the diagnostic workup of different gynecological disorders, including AUB, infertility, or chronic pelvic pain[11].

In the view of Amerigo Vitagliano et al. (2022), there are four major pathways of CE impacting embryo implantation: (1) The activation of local inflammatory processes with altered cytokine and chemokine secretion; (2) Abnormal leukocyte infiltration within the endometrium; (3) Altered uterine contractility; (4) Defective decidualization and defective endometrial vascularization[12].

DIAGNOSIS

Clinical symptoms of CE have little positive predictive value. The overall accuracy of hysteroscopic examination with regard to the diagnosis of CE is only 67% with strawberry spots. So, hysteroscopy shouldn't be used to replace histology; and endometrial biopsy should be obtained at the same time to confirm or refute the diagnosis when CE is suspected on hysteroscopy[13]. The current gold standard for CE diagnosis is immunohistochemical staining (CD138) on endometrial tissue sections. Yet, the amount of plasma cells per sample/area or microscope field for diagnosing CE remains controversial[12].

The immunohistochemical staining for CD138 was associated with lower intra- and interobserver variability between pathologists in the detection of plasma cells and has now become the reference standard technique for diagnosing CE[11]. Despite the number of reports, there is still no consensus as to the number of CD138-stained cells that are needed for making a definitive diagnosis of CE in endometrial biopsies[14]. In addition, the timing and method of endometrial sampling are also major issues for

accurate assessment of CE, and the prevalence of CE diagnosis in the proliferative phase is higher than in the secretory phase (Kitaya et al., 2018)[15].

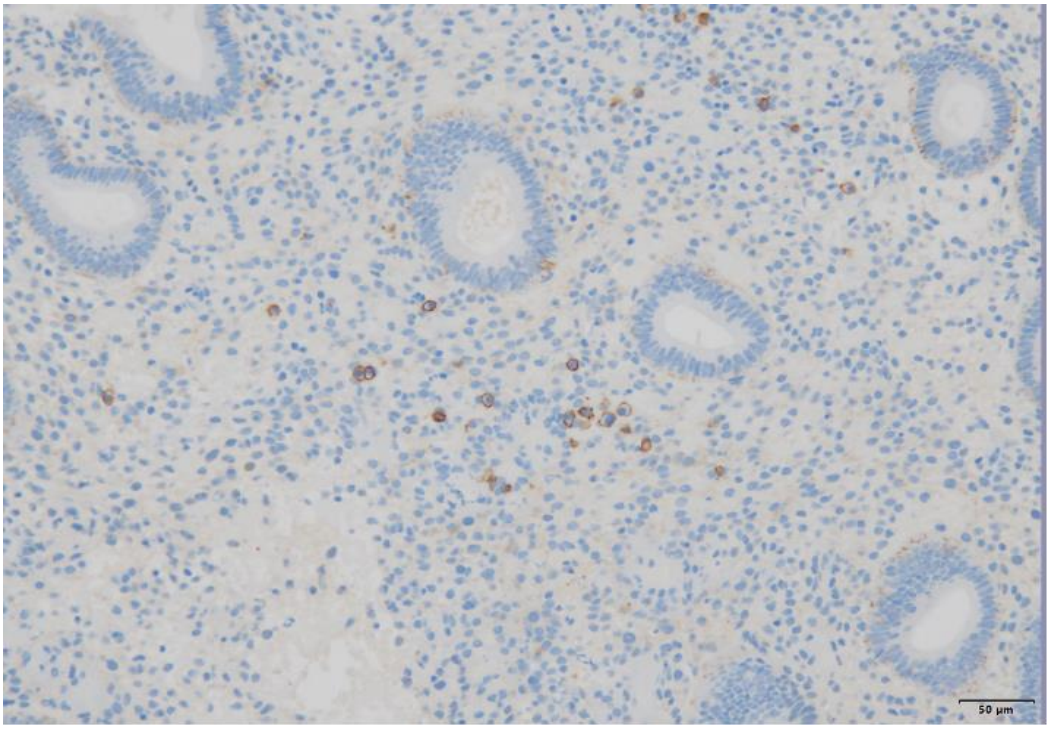


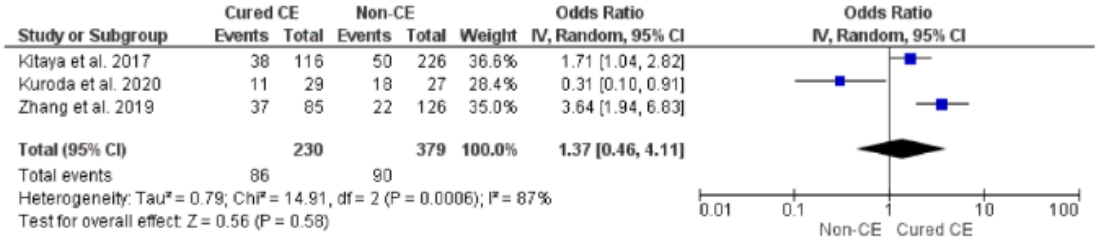
Image 2. Plasma cells when using immunohistochemical staining at Tam Anh Hospital

TREATMENT

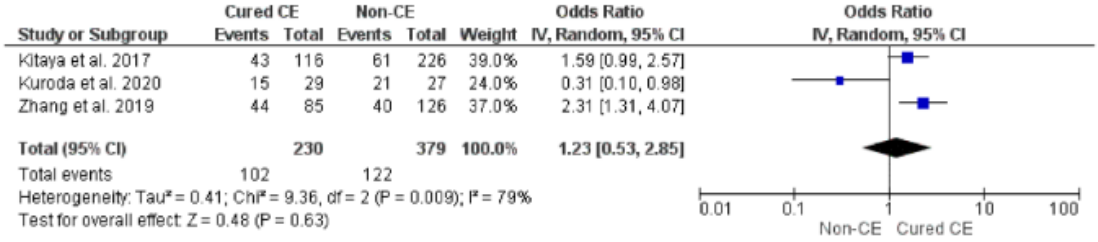
After chronic endometritis was diagnosed, treatment included a first round of doxycycline administration (i.e., 100 mg twice daily for 14 days) followed by a second round of ofloxacin (400 mg orally twice a day) plus metronidazole (500 mg orally twice a day) for 14 days in cases of CE persistence, with 93% of patients achieving cure after first-line antibiotic therapy[15,16] The ALICE test findings not only identify the microorganisms causing CE but also recommend relevant antibiotics for treatment[17]. However, the cost of performing the ALICE test remains an obstacle to prescribing it.

On the basis of the final hysteroscopy examination and histological results, 61 CE patients received treatment and were

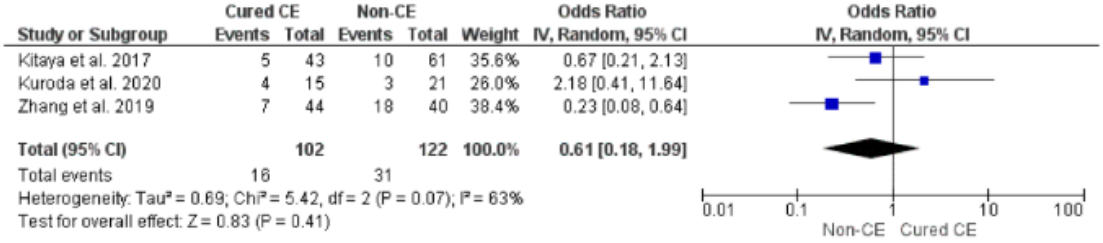
divided into two groups (Cicinelli et al., 2015). Group 1 consisted of 46 patients with hysteroscopy and normal histology. Group 2 consisted of 15 patients who had persistent CE on hysteroscopy and histology. Clinical pregnancy and live birth rates were significantly higher in patients in group 1 compared to group 2 (65.2% vs. 33.0%, p = 0.039; 60.8% vs. 13.3%, p = 0.02, respectively)[18]. On the other hand, CE is divided into two types: mild CE (1–4 plasma cells/HPF) and severe CE (≥5 plasma cells/HPF). Antibiotic treatment is used for all severe and some mild cases of CE. The authors found no statistically significant difference between women without and with mild CE in terms of IVF outcomes. Compared to mild CE, severe CE had lower implantation (32.3% vs. 51.6%), clinical pregnancy (42.3% vs. 65.7%), and live birth rates (30.7% vs. 52.1%). Therefore, the authors believe that mild CE has no detrimental effect on IVF outcomes (Cicinelli et al., 2021)[19]. However, in the study by Haixia Duan et al., 2022, 7,218 patients underwent embryo transfer, with 330 in the cured CE group and 6,888 in the non-CE group, from January 1, 2019 to December 31, 2020. CE was diagnosed by hysteroscopy and histology (CD138). The authors found that women with cured CE had a higher rate of spontaneous abortion than did those without CE (11.8% vs. 9.2%; crude odds ratio [OR], 1.32 [0.94, 1.86]), and this difference was statistically significant after adjusting for confounding variables (adjusted OR, 1.49 [1.01, 2.19]). The live birth rate was 43.9% in the cured CE group and 50.5% in the non-CE group (crude OR, 0.77 [0.62, 0.96]; adjusted OR, 0.73 [0.59, 0.92]). The incidence of clinical pregnancy did not differ significantly between the two groups (56.1% vs. 60.0%; crude OR, 0.85 [0.68, 1.06]; adjusted OR, 0.83 [0.66, 1.03])[20]. Based on ten studies and 4145 patients, the authors found that CE significantly reduces clinical pregnancy rates, ongoing pregnancy rates, and live birth rates in women undergoing IVF. Importantly, CE resolution following antibiotic therapy may improve IVF outcomes in those patients, leading to similar IVF outcomes as compared to unaffected patients (Amerigo Vitagliano et al., 2022)[12].



(a)



(b)



(c)

Image 3. Pooled data analysis comparing CE versus non-CE[12]:

(a) ongoing pregnancy rate/live birth rate;

(b) clinical pregnancy rate;

(c) miscarriage rate.

Despite this, empiric antibiotic treatment of suspected chronic endometritis does not improve pregnancy outcomes for patients with a prior failed euploid transfer[21].

CONCLUSION

Chronic endometritis is a disease that has no obvious clinical manifestations but affects reproduction. Chronic endometritis is a cause of recurrent implantation failure and hysteroscopy is an effective screening method. The gold standard for diagnosing

Chronic endometritis is immunohistochemical staining CD138 of biopsied endometrium. In cases of recurrent implantation failure owing to Chronic endometritis, antibiotic therapy is useful in Chronic endometritis treatment and increasing in vitro fertilisationoutcomes.

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