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Effect of Chronic Endometritis Treatment on Pregnancy Rate in Unexplained Infertility: A Review Article

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ABSTRACT

Background: Changes in the endometrial microenvironment seen in chronic endometritis (CE) might impair endometrial receptivity, potentially leading to female infertility. Studies indicate that chronic endometritis is often identified in women experiencing infertility, especially those with recurrent in vitro fertilization failures, with prevalence rates reaching up to 57.55%. Interestingly, as many as 30% of couples facing difficulties in conceiving are found to have unexplained infertility. Recent research indicates a link between chronic endometritis (CE) and issues related to unexplained infertility, as well as complications during pregnancy and childbirth.

Objective: This review seeks to enhance understanding of the epidemiology, causes, pathophysiology and diagnosis of CE, its impact on reproductive outcomes, and the effect of its treatment on pregnancy rate

Method: We conducted a search on Google Scholar and PubMed to investigate the effect of chronic endometritis treatment on pregnancy rate in unexplained infertility. Our review included only the most comprehensive studies published between January 2003 and 2019. **Conclusion:** chronic endometritis is commonly found in cases of unexplained infertility & its treatment improves the rate of spontaneous pregnancy.

Keywords: Antibiotic treatment, Chronic endometritis, Pregnancy rate, Infertility**.**

INTRODUCTION

Chronic endometritis (CE) is a long-term inflammatory condition characterized by infiltration of endometrial stroma by plasma cells. This condition can be quite subtle and may be overlooked by healthcare providers because of its mild symptoms, which may include vaginal bleeding, pelvic discomfort, pain during intercourse, and leucorrhea **(1)**.

Diagnosing CE can be difficult because clinical and radiological findings are often non-specific, and pathological analysis may result in a false diagnosis because leukocytes commonly appear in the endometrial lining, particularly before menstruation (2).

Fluid hysteroscopy can be useful in enhancing detection as it reveals specific features of CE including micro polyps, stroma swelling, and increased blood flow. Confirmation of CE is achieved through histological examination that identifies 1-5 plasma cells per high-power field **(3)**. Studies indicate that chronic endometritis is often determined in women experiencing infertility, especially those with recurrent in vitro fertilization failures, with prevalence rates reaching up to 57.55% (4).

Up to 30% of couples with infertility are classified as having unexplained infertility, a diagnosis typically made only when standard infertility tests do not identify any clear abnormalities. These initial tests should demonstrate ovulation, sufficient sperm production, and open fallopian tubes. However, even advanced diagnostic methods may not detect all potential issues (5).

This review aimed to enhance understanding of the epidemiology, pathophysiology & diagnosis of CE, its impact on reproductive outcomes, and the effect of its treatment on pregnancy rate.

INFERTILITY

The International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization define infertility as a reproductive health condition marked by the failure to attain a confirmed pregnancy after 12 months or more of regular unprotected intercourse (6).

Immunological infertility:

Autoimmune diseases impact up to 20% of individuals in developed countries. Initial concerns regarding a connection between peripheral blood natural killer (NK) cells and IVF results has not been established. Women with peripheral NK cell levels up to 12% do not show a greater incidence of previous abortions or lower pregnancy rates. However, some studies suggest that heightened NK cell activity in patients with unexplained infertility may be a potential risk factor for pregnancy failure (7).

Unexplained infertility:

In 15–30% of infertility cases, standard investigations fail to identify a cause. This does not necessarily mean that there is no underlying issue, but rather that it remains undetected(8).

Anovulatory infertility:

Referring to the inability to conceive, this condition arises from the lack of ovulation. Several factors can contribute to this issue, including hormonal imbalances, polycystic ovary syndrome (PCOS), thyroid disorders, and various medical or lifestyle-related influences (9).

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CLASSIFICATION

World Health Organization (WHO) categorizes ovulation disorders into three groups [10]**.**

1. **Hypothalamic–pituitary failure:** This category encompasses disorders like hypothalamic amenorrhea and hypogonadotropic hypogonadism.
2. **Hypothalamic–pituitary dysfunction:** This category includes women with amenorrhea or oligomenorrhea, with or without hyperandrogenism, as polycystic ovary syndrome (PCOS). These women generally have normal levels of FSH, estrogen, and prolactin, but exhibit variable serum LH and testosterone levels.
3. **Ovarian failure:** This group includes women who experience amenorrhea along with elevated serum levels of FSH and LH.

Unexplained infertility:

Unexplained infertility affects 30-40% of couples, where routine investigations do not reveal any identifiable abnormalities. The causes of this condition are diverse and may include factors related to endocrinology, immunology, genetics, and reproductive physiology. Couples with unexplained infertility often face reduced and delayed fertility. This condition is more accurately described as subfertility, as some couples may still achieve pregnancy without medical intervention. In a randomized study with 253 cases experiencing unexplained infertility, the ongoing pregnancy rate for those receiving expectant management was 27%, 13% for those awaiting IVF, and only 5.9% for the untreated group waiting for IVF over 12 months [11].

ENDOMETRIOSIS

The prevalence of endometriosis in cases with infertility is still a topic of debate, with estimates varying from 5-10% to as much as 30-50%. Diagnosing endometriosis can be challenging even for skilled laparoscopists due to its often microscopic nature and the presence of atypical lesions. Research has indicated that women with mild endometriosis may share similar profiles with those experiencing unexplained infertility (UI). This has led to suggestions that endometriosis might be underdiagnosed, with UI potentially representing an early, undetectable, or microscopic form of endometriosis in many instances [12].

Mild tubal disease:

The tubal function can be compromised even when tubal patency is present, as has been well documented. Research indicates that routine hysterosalpingography (HSG) fails to identify one anatomical or physiological tubal abnormality in 84% of infertile cases. Furthermore, abnormalities in physiological function, like elevated tubal perfusion pressure, are frequently linked to endometriosis confirmed via laparoscopy, occurring in 85% of instances [13].

Premature ovarian aging:

The number of ovarian follicles declines continuously from birth. **Baerwald *et al.* [14]** observed that subfertility typically emerges around the age of 30–31 years, as the quantity of remaining follicles significantly declines from their initial count. By the age of 37–38 years, the follicle count drops to about 25,000, marking a critical stage where follicular loss accelerates as one nears menopause. Menopause occurs when approximately 1,000 follicles remain, generally around the age of 51 years. Women with premature ovarian aging (POA) can be accurately diagnosed by thoroughly investigating signs of POA in patients with unexplained infertility (UI). Key indicators include age-inappropriate resistance to ovarian stimulation with gonadotropins, elevated baseline FSH levels, irregular ovarian function tests, low antral follicle counts, and a family history of early menopause [15].

Subclinical autoimmune disease:

Autoimmune diseases impact up to 20% of individuals in industrialized nations. There has been considerable focus on the influence of immunological factors on reproductive outcomes, with some evidence suggesting that autoimmune factors may contribute to female infertility [16].

Treatment of un-explained infertility:

In cases of unexplained infertility where no correctable abnormalities are identified, treatment typically involves empirical approaches. Recommended treatment options include intrauterine insemination (IUI), ovarian stimulation with oral or injectable medications, a combination of IUI and ovarian stimulation, and in vitro fertilization (IVF) [17].

Clomiphene citrate treatment:

Clomiphene citrate is frequently used to treat unexplained infertility. However, It has been proposed that the application of clomiphene citrate in cases who are already ovulating may disrupt the normal hormonal regulation of ovulation [18].

Gonadotropin therapy: A few trials have compared different stimulation regimens, with one randomized clinical trial indicating that gonadotropin/IUI treatment is more effective than clomiphene citrate/IUI. Specifically, the cycle fecundity was 0.19 with gonadotropins/IUI compared to 0.04 with clomiphene citrate/IUI ($P<.05$) [19].

Intra-uterine insemination (IUI): Intrauterine insemination (IUI) entails inserting prepared sperm directly into the uterine cavity during the ovulation period. This procedure can be carried out with natural ovulation monitored using an LH kit, or in conjunction with ovarian stimulation through clomiphene citrate or injectable gonadotropins. Evidence regarding the effectiveness of IUI without ovulation induction is limited. A recent cochrane review indicated that combining IUI with ovulation induction results in a higher

rate of successful live births compared to IUI alone [20]. Consequently, IUI without supplementary treatments like clomiphene citrate or gonadotropins is generally not recommended for cases facing unexplained infertility.

Assisted reproductive technology: Assisted reproductive technology (ART) is widely supported by physicians, drawing on evidence from retrospective and uncontrolled studies. According to a 2003 report by the Centers for Disease Control and Prevention (CDC), the American Society for Reproductive Medicine (ASRM), and the Society for Assisted Reproductive Technology (SART) reported that the live birth rate for cases suffering from unexplained infertility was 30.4% (Control and f47 2010). In trials comparing IVF with other treatments for unexplained infertility, the European Society for Human Reproduction and Embryology Multicenter Trial reported pregnancy rates per cycle of 15.2% for gonadotropin-only cycles, 27.4% for gonadotropin combined with IUI cycles, and 25.7% for IVF cycles [21].

Adverse effects: Clomiphene citrate (CC) has been widely used for the past three decades, has well-documented side effects. The most common include multiple pregnancies in 8% to 10% of cases and ovarian cysts in 5% to 10% [18].

Gonadotropin therapy carries a higher risk of multiple pregnancies and ovarian hyperstimulation syndrome. In a large multicenter trial in the United States, 33% of live births resulted in multiple pregnancies, including 3 quadruplets, 4 triplets, and 17 twins. Among the 72 live births observed, there were 5 triplet births and 19 twin births [19]. Severe ovarian hyperstimulation occurred in 1.3% of women treated with follicle-stimulating hormone (FSH), with 6 out of 465 requiring hospitalization [22].

Chronic endometritis: Chronic endometritis (CE) often goes unnoticed or manifests with vague symptoms. These can include pelvic pain, irregular bleeding, painful intercourse, vaginal discharge, vaginitis, recurrent urinary tract infections, and mild gastrointestinal issues [23]. The non-specific nature of these symptoms and the necessity of endometrial biopsy for accurate diagnosis complicate the assessment of CE prevalence.

Epidemiology and clinical features: The prevalence of CE in females of reproductive age varies widely, ranging from 8% to 72%. This broad range is attributed to factors such as the relatively small sample sizes in studies and differing diagnostic criteria. For infertile patients, prevalence rates vary significantly based on the biopsy methods used and the populations studied. For example, a prospective study by **Cicinelli *et al.*** [24] involved 2,190 diagnostic hysteroscopies for various reasons and found a 20% prevalence of chronic endometritis (CE) among 438 patients, with 37% of those also experiencing infertility. In contrast, a study by **Kasius *et al.*** [25] indicated a significantly lower prevalence of 2.8% among 678 women. Various risk factors have been linked to CE including intrauterine devices (IUDs), which can induce CE even with short-term use, and the condition may persist after the IUD is removed. Additionally, certain patient characteristics, such as a history of multiple births and abnormal uterine bleeding, have been identified as risk factors for chronic endometritis [26].

Pathophysiology of CE:

B cells, though a small part of the immune cells in a healthy endometrium, usually cluster in the stromal region and may enter the glandular lumina. In chronic endometritis (CE), gram-negative bacteria trigger an atypical immune response, which causes circulating B lymphocytes to migrate into the endometrial stromal area. This response results in the expression of various immunoglobulins at the endometrial level, which can adversely impact embryonic implantation. Women with chronic endometritis (CE) frequently show changes in uterine contractility, which can result in symptoms like pelvic pain, spotting, and difficulties with implantation. Studies indicate that chronic endometritis (CE) significantly alters the expression of specific genes in the endometrium, such as insulin-like growth factor binding protein 1 (IGFBP1), B-cell CLL/Lymphoma 2 (BCL2), and BCL2-associated X protein (BAX). These changes may impact embryonic implantation and contribute to the development of endometrial hyperplastic lesions [27].

ETIOLOGY

Acute endometritis and pelvic inflammatory disease (PID) usually result from microorganisms that migrate from the lower genital tract. Chlamydia trachomatis and Neisseria gonorrhoeae are often regarded as primary pathogens associated with CE. Instead, common bacteria found in the uterine cavity of CE patients include Streptococcus spp., Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, Staphylococcus spp., Corynebacterium, and Mycoplasma/Ureaplasma spp., typically identified through microbiological cultures or PCR tests for Mycoplasma/Ureaplasma DNA [28]. Therefore, these bacteria are currently regarded as the primary causal agents of CE.

DIAGNOSIS

Histopathology of chronic endometritis: The definitive diagnosis of chronic endometritis (CE) is established through histological examination, specifically by identifying plasma cells in the stromal area of endometrial tissue samples as in figure 1. In addition to the presence of plasma cells, histopathological characteristics of chronic endometritis (CE) may feature significant stromal cell proliferation, disrupted maturation between the epithelial and stromal layers, and a marked pre-decidual reaction (Figure 1) [29].

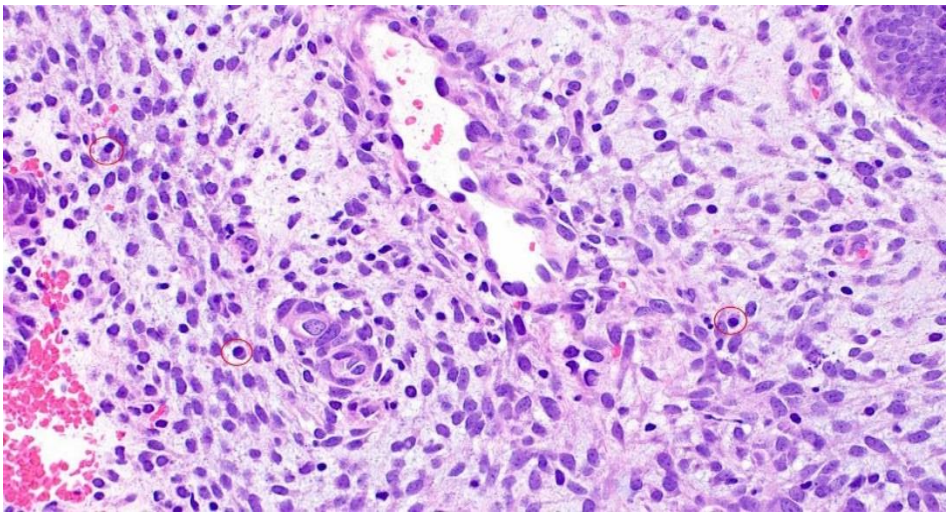

Figure (1): Chronic endometritis, spindled endometrial stroma with scattered plasma cells (circled), which may be challenging to differentiate from pre-decidualized stromal cells [(29)].

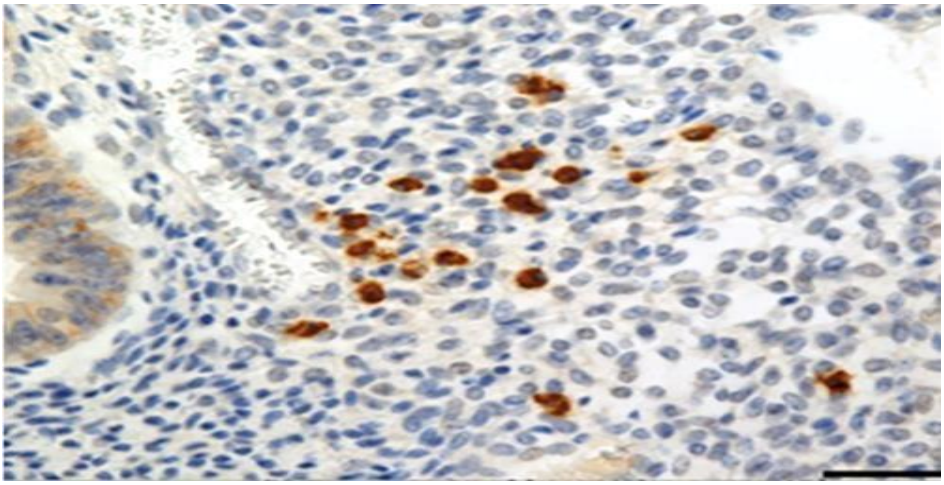

Figure (2): Immunohistochemistry for plasma cell detection with CD138. CD138 staining highlights the surface of plasma cells within the stromal compartment of chronic endometritis. Plasma cells may show occasional accumulation. Scale bar = 100 μm (Reproduced from **Takebayashi *et al.*** [(30)] with permission).

Although pathological features of CE can be identified using stains like hematoxylin and eosin (HE), detecting plasma cells in the endometrium remains challenging even for skilled pathologists. This difficulty arises due to the presence of monocyte infiltration, stromal mitosis, the plasmacytoid appearance of stromal cells, and pre-decidual reactions. All of which can be morphologically similar and hard to differentiate. Consequently, immunohistochemistry (IHC) employing the plasma cell marker CD138 (also known as syndecan-1) is used to diagnose CE, as CD138 effectively labels the surface of plasma cells. In CE patients, plasma cells are typically found in the functional layers near the basal layer of the endometrium and may sometimes form aggregates as in figure (2) [(30)].

Variations in non-standardized protocols result in inconsistent measurements of plasma cell density, while differing diagnostic criteria can lead to disparities in prevalence rates among similar studies. For example, a prevalence rate of 2.8% for CE was detected in asymptomatic infertile women before in vitro fertilization (IVF), which starkly contrasts with the 30.3% prevalence noted by **Johnston-MacAnanny *et al.*** [(31)] and 10% seen in patients with recurrent abortion. Therefore, establishing a universally accepted definition of 'true CE' based on reliable pathological significance is crucial for accurate diagnosis and consistent prevalence reporting.

Hysteroscopic findings of chronic endometritis:

Hysteroscopy is used to assess signs of inflammation in the endometrium and has been investigated as a diagnostic method for CE. According to one study, CE is diagnosed when at least one characteristic is present, this study indicated that hysteroscopic diagnosis for CE demonstrated high sensitivity and specificity, achieving a 93.4% correlation

between hysteroscopy and histological confirmation for detecting CE. However, following research has shown that office hysteroscopy has low sensitivity for detecting histological CE. The effectiveness of hysteroscopic diagnosis may vary based on the clinician's skill. Fluid hysteroscopy can detect micro polyps, linked to high positive and negative predictive values of 93.7% and 89.2%, respectively. In one study, micro polyps were identified in 96 cases, representing 11.7% of all hysteroscopies, with 90 (93.7%) were confirmed histologically as CE. In contrast, when micro polyps were absent, CE occurred in only 78 cases, yielding a 10.8% negative predictive value [(32)]. The Identification of micro polyps is relatively straightforward and accessible for clinicians, making it a practical tool in clinical settings. In conclusion, while hysteroscopy can be useful in diagnosing CE, it should not replace histological examination. Instead, hysteroscopy should be used to complement histological diagnosis to improve accuracy.

Chronic endometritis and its impact on reproductive outcomes:

The implantation depends on various inflammatory mediators, including leukocytes, cytokines, chemokines, and other endometrial factors. These components play vital roles in regulating immune responses and facilitating trophoblast growth. CE can affect endometrial receptivity, resulting in a less favorable microenvironment that negatively affects normal implantation [(1)].

Implantation failure after IVF and chronic endometritis:

The effect of CE on implantation success, particularly after IVF, remains controversial. Although numerous studies indicate that CE adversely impacts endometrial receptivity—attributed to plasma cell infiltration, alterations in immunoglobulin levels (IgM, IgG, and IgA), and changes in genes related to inflammation, proliferation, and apoptosis—the results remain mixed. For instance, **Cicinelli *et al.* [(33)]** reported a live birth rate of 61% among cases who responded to antibiotic treatment, compared to only 13% in those who did not respond. On the other hand, **Johnston-MacAnanny *et al.*** [(31)] found that although CE patients showed an improved pregnancy rate following effective antibiotic therapy, their pregnancy rate remained lower than that of the non-CE group, even with successful treatment. These discrepancies may be attributed to the presence of other undetected endometrial abnormalities that are not addressed by antibiotic therapy.

Treatment for CE reproductive outcomes

Research has explored how treating CE influences IVF outcomes, with doxycycline frequently utilized as the standard treatment. Doxycycline, a broad-spectrum antibiotic, has been employed globally for many years to prevent intrauterine infections following procedures like abortion, and it is also used in the treatment of CE. **Johnston-MacAnanny *et al.* [(31)]** reported that doxycycline (200 mg/day for 14 days) successfully cured 66.7% of CE cases confirmed by immunohistochemistry (IHC) for plasma cells. In their study, 6 out of 9 treated CE patients achieved a cure, while a second-line treatment using ciprofloxacin and metronidazole (500 mg each per day for 14 days) proved effective for those who did not respond to doxycycline.

McQueen *et al.* [(34)] investigated CE in patients with recurrent early pregnancy loss and/or fetal demise, treating 26 out of 35 patients with ofloxacin (800 mg) and metronidazole (1000 mg) for two weeks. The other 9 patients received various regimens, including doxycycline alone or in combination with metronidazole, and ciprofloxacin with metronidazole. Among the 35 patients, 31 had repeat endometrial biopsies to assess treatment success, revealing persistent CE in 7 patients, all treated with ofloxacin and metronidazole. In contrast, those who received alternative treatments were all cured. Two of the seven with persistent CE underwent a second antibiotic course and were successfully treated, while the remaining five, who opted out of further treatment, showed resolution in follow-up biopsies. Overall, the cure rate after one course of antibiotics was 94% (29 out of 31), and it reached 100% (31 out of 31) after up to two courses.

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