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Carolina Bandeira Domiciano

Carolina Bandeira Institute of Minimally Invasive Surgery, Brazil
ORCID: <https://orcid.org/0000-0001-6653-9795>
E-mail: bandeiracarolina@hotmail.com

Aníbal Costa Filho

Unineves College, Brazil
ORCID: <https://orcid.org/0000-0001-7388-9638>
E-mail: costafilhomd@yahoo.com.br

Geraldo Camilo Neto

Carolina Bandeira Institute of Minimally Invasive Surgery, Brazil
ORCID: <https://orcid.org/0000-0003-2336-2285>
E-mail: geraldocamiloneto@hotmail.com

Daniel Hortiz de Carvalho Nobre Felipe

Carolina Bandeira Institute of Minimally Invasive Surgery, Brazil
ORCID: <https://orcid.org/0000-0002-2227-8244>
E-mail: danielhortiz@gmail.com

Ana Cecília Maia

Carolina Bandeira Institute of Minimally Invasive Surgery, Brazil
ORCID: <https://orcid.org/0000-0003-2869-3534>
E-mail: ceciliamaia85@gmail.com

Deborah Cristina Nascimento de Oliveira

Nova Nova Esperança Medical School, Brazil
ORCID: <https://orcid.org/0000-0002-0285-8890>
E-mail: debmedfamene@outlook.com

Bianca Vasconcelos Braga Cavalcante

Nova Esperança Medical School, Brazil
ORCID: <https://orcid.org/0000-0001-9324-8301>
E-mail: biancavbraga@gmail.com

Priscila Coutinho Ferreira

Nova Esperança Medical School, Brazil
ORCID: <https://orcid.org/0000-0002-3722-0985>
E-mail: priscila_coutinho@hotmail.com

Ana Livia Gadelha Xavier da Nóbrega Pereira

Nova Esperança Medical School, Brazil
ORCID: <https://orcid.org/0000-0003-1065-190X>
E-mail: analivianobre8@gmail.com

ABSTRACT

Introduction: Chronic endometritis (EC) is a disease of continuous inflammation caused by bacterial pathogens such as Enterobacteriaceae, Enterococcus, Streptococcus, Staphylococcus, Mycoplasma, and Ureaplasma. In addition to being poorly investigated, it can be found in up to 40% of infertile patients. EC has been linked to adverse reproductive outcomes such as repeated implantation failure (RIF) and recurrent miscarriage. **Objective:** The objective of our study is to evaluate the impact of antibiotic treatment on the obstetric prognosis of patients. **Methodology:** This is a literature review on the use of antibiotics as therapy for chronic endometritis, elaborated through consultations in the main scientific databases. **Results:** Patients with cured chronic endometritis had a higher pregnancy rate and live birth rate compared to women with persistent disease. In this bias, current studies show that treatment with oral antibiotics against EC may be a promising therapeutic option for infertile women with RIF. **Conclusion:** It is concluded that antibiotic treatment improves RIF and decreases the miscarriage rate, although they have a failure rate of 10% and there is a lack of well-designed prospective studies that corroborate this finding. Finally, research on associations with corticosteroids and local administration is necessary, as some studies have brought positive results.

Keywords: Anti-Bacterial agents, Endometriosis, Diagnostic techniques, obstetrical and gynecological.

1 INTRODUCTION

Chronic endometritis (CE) is a chronic endometrial inflammation, characterized by the infiltration of plasma cells in the endometrial stroma area. It was believed that the uterine cavity was

sterile under normal conditions, but in recent studies, microorganisms have been detected even in patients considered healthy (Kimura, et al., 2019). Thus, one of the main causes of EC is a microbial infection in the uterine cavity, and some pathogens, such as *Escherichia coli*, *Streptococcus* spp, *Enterococcus faecalis*, *Ureaplasma* spp, are related to this disease (Xu, et al., 2020).

EC has a varied and nonspecific clinical presentation, some patients may be asymptomatic, while others may develop abnormal uterine bleeding, chronic pelvic pain, dyspareunia, and leukorrhea (Xu, et al., 2020). Despite being little investigated, some studies show negative results regarding endometrial receptivity, which can lead to implantation failures and recurrent miscarriages (Grando, 2021).

It is known that for the diagnosis of EC, histological confirmation with the presence of plasmocytes in the endometrial stroma in hematoxylin and eosin staining is the gold standard. Furthermore, one can observe the proliferation of stromal cells, dissociated maturation between the epithelium and the stroma, and the deep pre-decidual reaction (Kimura, et al., 2019). As diagnostic complementation, immunohistochemical staining of CD138, which is a specific antigen on the cell surface of plasmocytes, can be performed. McQueen reports that in his study the prevalence of CE rose from 6% to 52% in women with abnormal uterine bleeding (McQueen, et al., 2015).

Since there is a polymicrobial culture in the uterine cavity, the use of oral antibiotics restores normality and improves the quality of life of patients with a decrease in symptoms and resolution of infertility (Grando, 2021). Doxycycline is the standard therapy for the prevention of post-abortion uterine infection and, according to some studies, this drug is already included in the treatment of EC. The use of ciprofloxacin and metronidazole can also help in the cure rates of these patients (Cicineli, et al., 2014).

2 METHODOLOGY

The study was carried out using the integrative review (IR) methodology. Through databases such as PubMed; Virtual Health Library (VHL); Scientific Electronic Library Online (SciELO) and Google Scholar, published in the last 10 years.

The website Descritores em Saúde (DeSC) in Portuguese “Antibacterials” was used; “Endometriosis”; “Obstetric and Gynecological Diagnosis Techniques” in a single or combined form.

Articles not available for free, in other languages (except Portuguese and English), and publications with dates before 2018 were excluded. In addition, selection criteria, namely: articles in Portuguese and English; full texts available free of charge; were adopted to add and delimit only those articles that fall within the scope of this article.

3 RESULTS AND DISCUSSION

Chronic Endometritis (CE) is the infiltration of plasma cells into the stromal compartment of the endometrium. Thus, a localized inflammation of the endometrial mucosa is caused, defined by the presence of edema, increased density of stromal cells, and dissociated maturation between epithelial cells. These factors can affect endometrial receptivity, leading to infertility (Barcelos, et al., 2021).

Currently, it is known that there are microorganisms in the uterine cavity, which does not necessarily mean infection. Inflammation occurs depending on the interaction between infectious agents and the endometrial environment because biofilms can form due to the action of microorganisms that hinder the action of host defense mechanisms (Barcelos, et al., 2021). Subclinical endometrial infection can lead to miscarriages, premature labor, and implantation failures after IVF (In Vitro Fertilization) as inflammatory mediators can cause trophoblast apoptosis (Crosera, et al., 2012)

The main infectious agents responsible for Chronic Endometritis are *Enterococcus faecalis*, *Enterobacteriaceae*, *Streptococcus* species, *Staphylococcus* species, *Gardnerella vaginalis*, and *Mycoplasma* species. Also, some causes of STDs, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (Barcelos, et al., 2021).

It was also observed that an altered distribution of Natural Killer cells can be found, with a decrease in CD56 lymphocytes and an increase in CD16 lymphocytes in the endometrial mucosa of infertile patients suffering from chronic endometritis, an altered maternal immune tolerance is assumed about the embryo, along with adverse effects on implantation mechanisms and a faulty trophoblastic invasion

The prevalence of the disease is not known for sure due to a lack of information about the disease, the difficulty of diagnosis, and the high statistics of asymptomatic patients or nonspecific symptoms, but estimates vary from 0.8% to 19.0%. (Polisseni, et al., 2003) up to 72% in patients with a history of genital infections according to Paavonen. (Cicinelli, 2018); (Paavonen, et al., 1985). In their study, Féghali et al. (2003) found pathological findings in 45% of diagnostic hysteroscopies before IVF; 17.2% of these alterations were represented by EC. In addition, Di Pinetti (2019) concludes in his study that chronic endometritis was present in 19 (7.2%) of the hysteroscopic reports confirmed by the anatomopathological result (Di Pinetti, 2019). Regarding the age range, it was observed that in infertile women with chronic endometritis diagnosed by hysteroscopy and anatomopathological examination (n=19), a higher prevalence of CE was observed from 35 years of age, with 63.10% over 30 years (Di Pinetti, 2019).

Evidence shows that CE is associated with infertility because it modifies the endometrial

microenvironment, promoting changes in the population of immunocompetent cells in the endometrium, affecting the production of inflammatory cytokines, which generate a local immune response in the first months of pregnancy, favoring implantation. In addition, it promotes endometrial proliferation, decreases apoptosis, and modifies the expression of sex steroid receptors (Puentes, et al., 2020).

Clinical diagnosis is difficult because about 25% of patients are asymptomatic and, when symptomatic, have nonspecific pelvic pain, abnormal uterine bleeding, dyspareunia, vaginal discharge, vaginitis, and recurrent cystitis (Puentes, et al., 2020). Thus, it is currently consensus, the association of conventional histology (HE) and immunohistochemistry through the detection of CD138 - specific antigen of the cell surface of plasmocytes - as diagnostic criteria for EC (Grando, 2021). The search for the etiological agent is performed by the culture of the endometrial tissue and is frequently indicated. However, the causative microorganism is not identified in approximately one-third of patients, since it - not necessarily - ascends through the vagina.

Hysteroscopy proved to be a reliable method in the diagnosis of chronic endometritis, where the agreement between the hysteroscopic and anatomopathological diagnosis of endometritis reaches 94.7% of cases. (GUO, 2013). Cicinelli et al (2014) published a randomized observational study with the following hysteroscopic diagnostic criteria: strawberry aspect; focal hyperemia; bleeding spots; micro polyps measuring less than 1mm; the pale and thickened appearance of the endometrium in the follicular phase (Cicinelli, et al., 2018).

There is a histological classification of CE, divided into 3 grades, namely: grade 1 (mild): mild and superficial inflammatory infiltrate, edema, and venular angiectasia; grade 2 (moderate): diffuse and glandular inflammatory infiltration; grade 3 (severe): massive and diffuse endo glandular infiltration (Resta et al., 2012)

Treatment with antibiotics becomes extremely important in chronic endometritis, as it recomposes the patient's normality clinically, hysteroscopic ally, and histologically. Some studies also suggest an improvement in the patient's fertility rates, since EC is a reversible cause of infertility, increasing implantation and live birth rates and decreasing miscarriage rates (Grando, 2021).

Studies by Patel, et al., (2018) and Cicinelli et al. (2018), in which patients diagnosed with EC were treated with antibiotics, suggest that EC hurts endometrial receptivity and adequate response to antibiotic therapy can significantly improve reproductive and clinical outcomes, as it improves the rates of implantation of embryos in infertile patients (Patel, et al., 2018); (Cicinelli, 2018); (Park, et al., 2016).

According to Cicinelli et al. (2018), the use of antibiotics resulted in CS resolution in 82.3% of patients, while in 17.6% the disease persisted. In addition, it helped with the infertility of these

women, as they had a higher pregnancy rate and live birth rate compared to women with persistent disease and women without a diagnosis of EC (Cicinelli, et al., 2018).

Cicinelli et al. (2018) carried out a retrospective study of 360 women under 40 years of age who had 03 (three) or more abortions before 20 weeks of gestation. The study confirmed that after treatment with antibiotics, the birth rate of women who responded to treatment was higher than that of non-responders. This suggests that the presence of infectious agents in the uterus has a potentially deleterious impact on the endometrial environment (Cicinelli, et al., 2018).

Also, in a work carried out by Francisco, in 2018, 211 patients who underwent investigation of infertility were studied, where 105 patients received prophylactic antibiotic therapy with doxycycline 100 mg, twice a day for 14 days and subsequently underwent assisted reproduction cycles. It is concluded that the group of patients with implantation failure had a higher prevalence of endometrial alterations observed at hysteroscopy. Finally, it suggested that the association of hysteroscopy with biopsy, associated with antibiotic therapy, is favorable in patients with implantation failure (Kitaya, et al., 2018).

In their retrospective analysis, Cicinelli et al. (2018) investigated pregnancy outcomes after antibiotic treatment in EC patients with a history of RIF (repeated implantation failure). In the 3-day cycle, the live birth rate was higher in the cured EC group (60.9%) than in the persistent EC group (13.3%) (Cicinelli, et al., 2018). No difference was found in the live birth rate between patients undergoing single-course antibiotic treatment and those undergoing multiple-course antibiotic treatment (Kitaya, et al., 2018).

The most empirically used drug, which is effective in curing CS, is doxycycline 100mg orally (VO), twice a day, for 10 to 14 days (Grando, 2021). According to Kitaya et al. (2018), the cure rate for a course of doxycycline was 92.3% and according to McQueen et al, the cure rate after a course was 94% cure. As a second option, ciprofloxacin and metronidazole have been used in combination, 500mg orally each day, for 14 days. As a third possibility, one can use ofloxacin 400mg, once a day, for 14 days associated with metronidazole 500mg, PO, for 14 days (Kitaya, et al., 2018). Research published by Cicinelli et al (2014) showed higher CS cure rates when the treatment was based on the antibiogram, concerning the treatment recommended by the CDC (78.4% vs. 50%) (Cicinelli, et al., 2014).

Partners are not usually treated (Grando, 2021). According to Bouet et al. (2016), hysteroscopy with biopsy after treatment is recommended to verify the effectiveness of antibiotics from a hysteroscopic and histological point of view (Bouet, et al., 2016). Better knowledge of the microbiome of the reproductive tract will allow the development of new therapies with the aim not only of eliminating the pathogenic microbiota but also of establishing the flora that favors

reproductive success (Grando, 2021).

4 CONCLUSION

Living with endometriosis interferes with the personal lives of patients, since there are a wide variety of symptoms related to this disease, making early diagnosis difficult, in addition to the delay in finding the best treatment for each affected individual.

In this way, it is concluded that treatment with antibiotics improves RIF (Repeated Implantation Failure) and decreases the abortion rate, although they present a failure rate of 10% and there is still a lack of well-designed prospective studies that corroborate this finding. Finally, research is needed on associations with corticosteroids and local administration, as some studies have yielded positive results.

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