

# Chronic endometritis and assisted reproduction: a systematic review and meta-analysis

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## INTRODUCTION

Chronic endometritis (CE) is defined as a localized inflammation signaled by the infiltration of bacteria in the endometrial stroma. It has adverse implications in human reproduction, including recurrent implantation failure (RIF) and recurrent miscarriage<sup>1-3</sup>.

Chronic endometritis can be asymptomatic, and it can cause several changes in the uterus, namely, pain, bleeding, leukorrhea, and other complications. Its prevalence significantly varies and is dependent on several factors, including inflammation of the uterus and the presence of infectious bacteria in the endometrial stroma. The incidence ranges from 10% to approximately 57% according to several studies<sup>4-10</sup>.

A brief summary of the pathophysiology of CE would include not only various bacteria that influence the entire endometrial microenvironment but also cytokine secretions that can induce leukocyte recruitment, which in turn influences the conditions (e.g., vascularity, uterine contractility, and endometrial function) for successful implantation after *in vitro* fertilization (IVF)<sup>11,12</sup>.

Women with chronic endometritis have fertilization difficulties in assisted reproduction; therefore, treating the pathology is essential for improving the results of infertility and assisted reproduction treatments<sup>13-15</sup>.

The objective of this study was to carry out a systematic review and meta-analysis of the literature on the subject of chronic endometritis and reproductive outcomes.

## METHODS

For the systematic reviews, we used examples and guidelines by Arya et al.<sup>16</sup>, Hennessy et al.<sup>17</sup>, Berstock et al.<sup>18</sup>,

and Page et al.<sup>19</sup>. The meta-analysis was conducted in accordance with the study by Dettori et al.<sup>20</sup>.

## Search strategy

To identify the studies for inclusion in this review, we selected articles indexed in PubMed, Google Scholar, and SciELO and published from January 2012 to February 2023. First, we chose keywords from the related articles and used MeSH international data lines to find more related keywords with closer meanings, which included (“endometritis”) [MeSH Terms] [All Fields] AND (“assisted reproductive technologies”) [MeSH Terms] OR (“Infertility”) [MeSH Terms] [All Fields]. The search was carried out in the three databases. In PubMed, we found 91 articles with titles and abstracts worth reading. From SciELO, we extracted 15 articles, and from Google Scholar, we retrieved 47 (Figure 1).

This review was conducted according to the recommendations established by Preferred Reporting Items for Systematic Reviews and Meta-Analysis Page et al.<sup>19</sup>.

## Inclusion and exclusion criteria

Studies were included if they met the following criteria: English or Spanish or Portuguese language, *in vitro* models, theme relevance, and objectives consistent with those of this study (see the flowchart in Figure 1). There were 14 articles that met the inclusion criteria (Figure 1). The eligibility steps shown in Figure 1 were independently tracked by two different authors (ECAV and JMSJ). In case of a disagreement or contradiction, a third author (MS) stepped in and repeated the search strategy.

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Five meta-analyses were conducted comparing women diagnosed with chronic endometritis (group CE) and control women (women without the presence of the disease) (group NO CE).

### Statistical analysis

For descriptive statistics, the means, standard deviations, mean differences, and odds ratios with 95% of confidence interval were calculated. Meta-analysis was carried out with the Review Manager 5.4.1 software program (Cochrane Collaboration, Oxford, UK). For the values of 95%CI and “test for overall effect size,” values of  $p \leq 0.05$  were assumed for significant differences<sup>20</sup>.

## RESULTS

### Results of meta-analyses

The live birth rates of the two study groups were significantly different ( $p=0.004$ ), meaning that women with no chronic

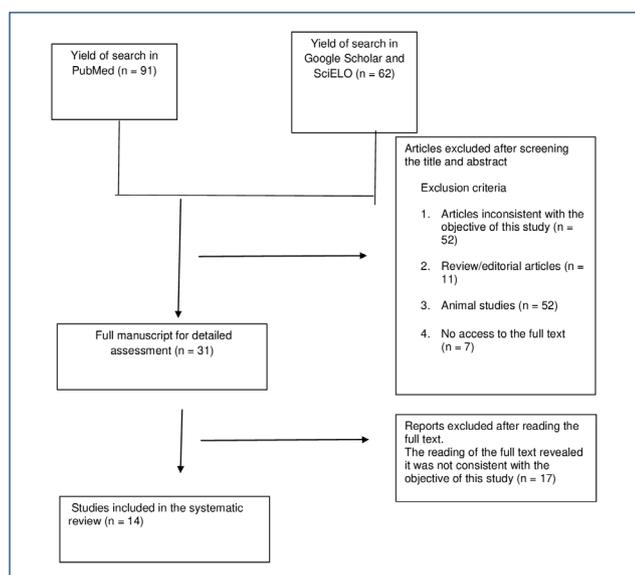


Figure 1. Flowchart of the study.

endometritis had a higher rate of live births (Figure 2). In other words, women who underwent IVF and were treated for their endometritis, thus falling into the NO CE group (without endometritis), had a higher rate of healthy live births than pregnant women with endometritis.

The clinical pregnancy rates of the two groups also differed statistically ( $p \leq 0.00001$ ), that is, the group of women without endometritis had a higher pregnancy rate than women with inflammatory endometrium who availed themselves of assisted reproduction techniques (Figure 3). Women with chronic endometritis had a higher rate of miscarriage and were statistically significant ( $p=0.0002$ ) than the control participants. Hence, women with endometritis were found to have a greater number of miscarriages than women without comorbidity. As for maternal age, there was no statistical difference between the groups ( $p=0.66$ ).

All studies selected for this systematic review were at risk for bias and the details are shown in Supplementary Figure 1. It was demonstrated that close to half of the seven domains recommended for analysis by Cochrane had an unclear risk of bias, that is, the study did not mention whether the risk of bias was present or not in the work; therefore, we regarded the lack of analysis of the risk of bias as a limitation of the study<sup>21</sup>.

## DISCUSSION

The main findings were that women without endometritis have improved rates of clinical pregnancy and live birth.

Our meta-analysis showed a significant improvement in the rates of live birth and clinical pregnancy in the group without chronic endometritis to be consistent with the literature. In the study by Cicinelli et al.<sup>22</sup>, the live birth rate was 60% in the group treated with a CE antibiotic compared with 13% in the group that went untreated after the IVF procedures, and the clinical pregnancy rate doubled when comparing the CE and the NO CE groups<sup>22</sup>. Other studies that

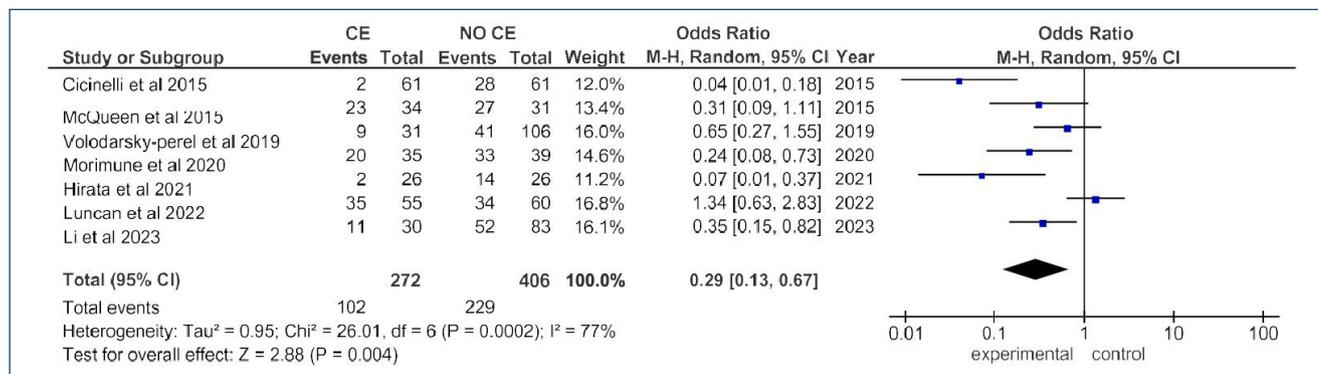
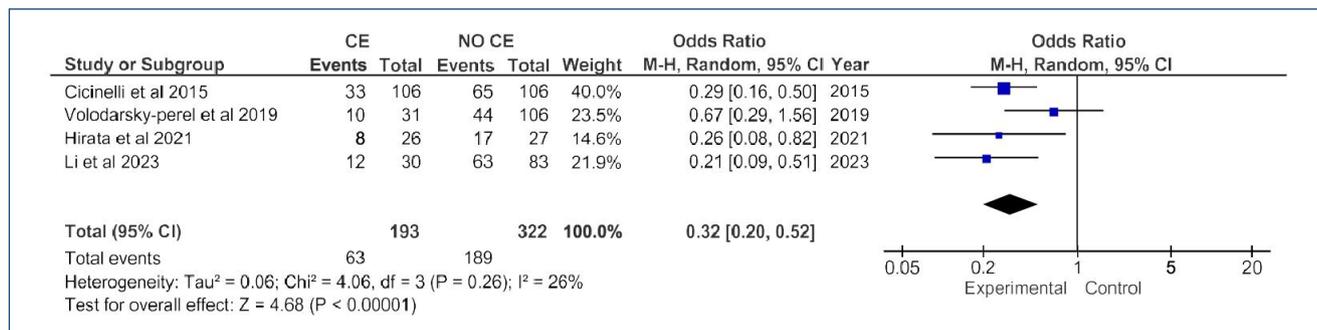


Figure 2. Comparison of the meta-analysis with the outcome live birth rate.



**Figure 3.** Meta-analyses comparing the group of women with chronic endometritis by the number of participants unit (events and total) with the group of women without chronic endometritis with respect to the clinical pregnancy rate.

corroborate our results include Yang et al.<sup>23</sup> and McQueen et al.<sup>24</sup>. More recent studies in the literature have also yielded similar results, including three meta-analyses, three analyses on women who suffered from RIF, and one study on a woman with recurrent pregnancy loss<sup>3,25-27</sup>.

Mitter et al.<sup>28</sup> observed long-term recurrent pregnancy loss, including miscarriage, and found that women with chronic endometritis, whom they observed for years, were more likely to have such losses. Despite the limitations imposed by the small number of studies and events and the lack of heterogeneity, the results of our meta-analyses showed that the NO CE group had fewer miscarriages.

In short, our results are in line with the literature in that CE therapy improves clinical pregnancy rate and the course of pregnancy of patients seeking IVF. Various studies are limited by methodological problems and lack of randomization<sup>29,30</sup>.

### Strengths and limitations of the study

The strength of this study definitely lies in the positive results of the meta-analyses of the live birth and pregnancy rates. A limitation of this study is that, from the perspective of Cochrane's methodology of the seven domains of risk of bias, which we followed, the authors' analyses in most studies were incomplete, for they did not clarify whether there were any of those

particular risks. In addition, the number of studies and the overall number of events and participants in the meta-analyses we performed were small.

## CONCLUSION

Our study showed that women who do not have chronic endometritis have better reproductive outcomes such as better rates of live birth and clinical pregnancy.

## AUTHORS' CONTRIBUTIONS

**ECAV:** Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **JMSJ:** Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **MS:** Visualization, Writing – review & editing. **FI:** Visualization, Writing – review & editing. **LSF:** Validation, Visualization, Writing – review & editing. **AS:** Validation, Visualization, Writing – review & editing. **LAMLU:** Visualization, Writing – review & editing. **ECB:** Visualization, Writing – review & editing. **JU:** Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

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