Antibiotic therapy for chronic endometritis and its reproductive implications: a step forward, with some uncertainties

During the last 2 decades, there has been growing interest in the study of endometrial pathologies and their reproductive implications. Chronic endometritis (CE), defined as the abnormal invasion of plasma cells within the endometrial stroma, has been one of the most investigated conditions (1–5).

Recent studies based on molecular biology-based methods and endometrial culture showed that CE was often associated with an abnormal endometrial microbiome, with the local proliferation of common gram-positive (i.e., streptococci, staphylococci) or gram-negative (i.e., *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*) or less common intracellular (*Mycoplasmi*, *Ureaplasmi*, Chlamydiae) or anaerobic (bifidobacteria, *Prevotella*) bacteria (2).

In this issue of *Fertility and Sterility*, the randomized controlled trial by Song et al. (3) brings to light the potential effectiveness of empiric double-regimen oral antibiotic therapy (i.e., levofloxacin 500 mg and tinidazole 1,000 mg daily for 14 days) for CE cure. To the credit of the investigators, this is the first study on antibiotic therapy for CE with rigorous methodology, including blinding of the pathologists. Interestingly, the investigators found that the CE test negative rate was 89.3% after a single course of antibiotics in the treatment arm compared with 12.7% in the control group. Such a difference between comparators was statistically significant (relative risk [RR] = 7.06; 95% confidence interval [CI], 3.51–14.72) and suggested a promising effect of broad-spectrum antibiotic therapy based on oral quinolones and nitroimidazoles against pathogens involved in CE. In particular, levofloxacin would be active against most gram-positive and gram-negative bacteria including streptococci, staphylococci, and Enterobacteriaceae. Tinidazole would provide coverage for most intracellular and anaerobic bacteria including *Ureaplasma*, *Mycoplasma*, and bifidobacteria. On this basis, the combination of levofloxacin and tinidazole may offer appropriate antibiotic coverage against most pathogens involved in CE.

While this therapeutic strategy seems effective for CE, someone may perceive the indiscriminate administration of broad-spectrum antibiotics as potentially conducive to the development of antibiotic resistance. This phenomenon, which results from changes in the genes encoding the proteins that are targeted by antibiotics, is increasingly common with respect to quinolones and represents a major public health concern. In order to avoid this situation, a recent retrospective case-control study evaluated the effectiveness of a personalized, antibiogram-guided antibiotic treatment for CE (4). This approach led to a cumulative cure rate of 81.3% after 3 antibiotic cycles, which was inferior to the success rate of empiric therapy in the study by Song et al. (89.3% after a single antibiotic cycle). These divergent results between the studies can be because of different study design, methodology, and diagnostic techniques as well as ethnic diversity (with potential implications on the type of infectious agents involved in CE and their antibiotic sensitivity). With respect to diagnostics, Song et al. reported a markedly lower sensitivity of hysteroscopy for CE diagnosis (n = 48/114, sensitivity 42.1%) as compared with previous studies (1). This point is worthy of reflection and highlights once again the current criticisms in the diagnosis of CE, especially by hysteroscopy, in which the recognition of endometrial features of CE is influenced by the physician's expertise. In spite of those methodological differences between the studies, the fresh insights reinforce the "old theory" regarding CE as a curable, infectious disease.

On the other hand, after Song's study, doubts persist about the impact of CE and its cure on the reproductive outcome of women with a desire for pregnancy. In the study by Song et al. (3), the treatment arm did not experience a significant improvement in the conception rate at 12 months follow-up (48.6% vs. 40%; RR 1.22; 95% CI, 0.72–2.05). Additionally, among subjects who attempted pregnancy, the investigators found no difference between groups in terms of ongoing pregnancy rate (43.2% vs. 25.7%; RR 1.68; 95% CI, 0.86–3.30) and miscarriage rate (5.4% vs. 14.3%; RR 0.31; 95% CI, 0.08–1.83). These interesting results need cautious interpretation for several reasons. First, the reproductive outcomes were conceptualized as secondary end points in this study. As a consequence, the study was not sufficiently powered to find a statistically significant effect in large absolute differences between the groups in the reproductive outcomes (+17.5% ongoing pregnancy rate and −8.9% miscarriage rate in the treatment arm vs. controls). Second, the diagnosis of CE relied on the immunohistochemical detection of plasma cells in endometrial biopsy specimens. Given the blind nature of the endometrial sampling in the study by Song et al. (3) (i.e., endometrial curettage), a certain bias in the estimates of CE cure was implicit. Third, Song et al. (3) found a low percentage of women with CE signs at hysteroscopy in the treatment arm (25/59, 42.4%). Previous studies found a significant correlation between the disappearance of CE signs at hysteroscopy and improvement of the patients' reproductive outcome (5). In this respect, the number of women in whom a relation between disappearance of hysteroscopic signs and enhancement of fertility could be evaluated was too small for significant results (3) enrolled patients with heterogeneous characteristics (i.e., suffering from infertility, repeated implantation failure, recurrent miscarriage, abnormal uterine bleeding, or cervical incompetence), potentially leading to miscellaneous estimates of the reproductive outcomes. In this respect, several previous studies on patients with selected reproductive disorders (5) conversely concluded that CE therapy significantly improved the clinical pregnancy rate and ongoing pregnancy rate in women suffering from unexplained infertility, repeated in vitro fertilization failure, and recurrent miscarriage. However, all those studies suffered from certain methodological issues and were nonrandomized, controlled trials.

In conclusion, Song et al. (3) provide new evidence from a randomized, controlled trial about the effectiveness of empiric, broad-spectrum antibiotic therapy for CE cure.

Nonetheless, some issues within the study limit the conclusions that can be drawn about the impact of CE and its treatment on female fertility. While appropriate antibiotic regimens may definitely cure CE, the understanding of the relationship between CE therapy and female fertility appears a more challenging matter.

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