Consistent evidence on the detrimental role of severe chronic endometritis on in vitro fertilization outcome and the reproductive improvement after antibiotic therapy: on the other hand, mild chronic endometritis appears a more intricate matter

In the last decade, different studies demonstrated a detrimental impact of chronic endometritis (CE) on the success of spontaneous conception and assisted reproduction technologies, as well as an improvement in reproductive outcomes after CE cure (1, 2). Studies based on endometrial cultures and biomolecular techniques found variable alterations of the endometrial microbiome in CE, with the local proliferation of common gram-positive (i.e., streptococci, staphylococci), gram-negative (i.e., *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*) or less commonly intracellular (*Mycoplasma*, *Ureaplasma*, *Chlamydiae*) or anaerobic bacteria (*Bifidobacteria*, *Prevotella*) (2).

Notwithstanding the growing attention from the scientific community, CE still represents an "uncertain matter" in terms of diagnosis, treatment, and reproductive implications. In this issue of *Fertility and Sterility*, a large retrospective study by Xiong et al. (3) (including 640 women undergoing frozen-thawed embryo transfer cycles) shed new light on this controversial topic. In particular, through the analysis of their large single-center study cohort, Xiong et al. (3) add new evidence about the negative effects of CE on in vitro fertilization (IVF) outcomes and show the potential benefits of a standard oral antibiotic regimen for CE on embryo implantation. Interestingly, the investigators evaluated whether CE entity, as determined based on the number of endometrial plasma cells per high power field (HPF) identified through CD-138 immunohistochemistry, had an incremental impact on IVF outcome.

The entity of CE was classified into three categories, namely no CE (0 plasma cells/HPF), mild CE (1–4 plasma cells/HPF), and severe CE ($\geq$5 plasma cells/HPF). Antibiotic therapy (i.e., doxycycline 100 mg orally twice a day for 14 days; oral levofloxacin lactate 200 mg twice daily plus oral metronidazole 500 mg three times daily for 14 days) was administered to all patients with severe CE and to some women with mild CE. Interestingly, no significant difference in IVF outcomes was found between women with no and those with mild CE. Alternatively, women with $\geq$5 plasma cells/HPF experienced lower implantation (32.3% vs. 51.6%), clinical pregnancy (42.3% vs. 65.7%), and live birth (30.7% vs. 52.1%) rates when compared with women with mild CE. These results led the investigators to conclude that mild CE had no negative impact on IVF outcomes, while antibiotic treatment was an effective way to improve reproductive outcomes in women with severe CE.

The study by Xiong et al. (3) had several strengths, including originality and a large sample size. On the other hand, their choice to classify CE exclusively based on plasma cell counts was a possible study limitation. Given the blind nature of endometrial biopsy (i.e., with the use of aspiration catheters), the reliability of the CE diagnosis mainly depended on the amount of endometrial tissue captured.

Moreover, in case of focal disease, CE entity could have been underestimated because of the collection of endometrial tissue from random (potentially healthy) areas of the uterine cavity. Additionally, as acknowledged by the investigators, false-positive reactions may occur with CD138 staining in endocervical and glandular cells. This implies that some women with CD138+/HPF 1–4 actually could be unaffected by CE. Finally, antibiotic treatment was administered arbitrarily in mild cases, potentially leading to biased estimates of the treatment effects.

According to recent data, hysteroscopy might have been a helpful add-on technique for narrowing the "gray area" of those cases classified as mild CE conditions (4). Through a visual inspection of the entire uterine cavity, hysteroscopy may have allowed the identification of specific endometrial features consistent with severe CE (e.g. micropolyps, focal/diffuse hyperemia, hemorrhagic spots). In this respect, we previously had found considerable inconsistency between the diagnoses of CE achieved by CD-138 immunohistochemistry and those obtained by hysteroscopy (4).

Specifically, the total number of women with CE signs at hysteroscopy was higher when compared with CD-138 immunohistochemistry, even after repeated antibiotic cycles. Our results were in line with those by other investigators showing higher prognostic value of CE diagnosis at hysteroscopy compared with CD-138 immunohistochemistry in patients undergoing IVF cycles (i.e., those women in whom hysteroscopy showed restoration of a normal endometrium had higher success rates than women in whom endometrial plasma cells had vanished after CE treatment) (5). Based on our previous experience, hysteroscopy may improve the accuracy of CD-138 immunohistochemistry and this may be true, especially in what is here defined as "mild cases."

In conclusion, the study by Xiong et al. (3) opens new cues of reflection about the potential relevance of CE diagnosis (and treatment) on the success rates of assisted reproductive technologies, particularly in the case of intense plasma cells infiltration. On the other hand, when a few plasma cells/HPF are detected within endometrial tissue (1–4 plasma cells/HPF), the optimal management remains to be defined. Probably, those situations may require a cautious assessment on a case-by-case basis with the aid of hysteroscopy. However, future studies evaluating the extra value of hysteroscopy in the management of mild CE must be undertaken.

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