Management of chronic endometritis before in vitro fertilization: lights and shadows

In the current issue of *Fertility and Sterility*, Duan et al. (1) report their 2-year, single center experience about in vitro fertilization (IVF) outcome in women with chronic endometritis (CE) after antibiotic therapy compared to negative controls. In their large prospective study, the entire study cohort ($n = 8,300$ women) underwent hysteroscopy plus endometrial biopsy. Women with signs of CE at hysteroscopy and endometrial biopsy were considered as CE positive. Endometrial biopsy was undertaken under hysteroscopic guidance with forceps, and revealed a 4.07% prevalence of CE. CE treatment included a first round of doxycycline administration (i.e., 100 mg twice daily for 14 days) followed by a second round of levofloxacin lactate (200 mg orally twice a day) plus metronidazole (500 mg orally twice a day) for 14 days in case of CE persistence, with a cumulative cure rate of 99.1% (of whom 93% achieved cure after first line antibiotic therapy). Chronic endometritis resolution was determined based on the disappearance of typical CE signs at hysteroscopy, without histologic confirmation. The primary outcome was to compare the miscarriage rate between groups (i.e., cured CE versus controls). Interestingly, women with cured CE showed higher miscarriage rate after adjusting for confounders (11.8% vs. 9.2%; odds ratio [OR], 1.49 [1.01–2.19]), whereas unadjusted comparison was not significant. Moreover, cured CE was associated with lower live birth rate compared to controls (43.9% vs. 50.5%; adjusted OR, 0.73 [0.59–0.92]), whereas clinical pregnancy rate was similar (56.1% vs. 60.0%; adjusted OR, 0.83 [0.66–1.03]).

This study throws new light and shadows on CE diagnosis and management, as well as on the effects of cured disease on IVF outcome. Regarding the "old dilemma" of CE diagnosis, there remains a lack of consensus on the minimum number of plasma cells to be identified within endometrial stroma (2). Duan et al. (1) adopted ≥ 1 plasma cells in 10 high power fields (HPF) as diagnostic criterion. Other studies found a detrimental effect of CE on the IVF outcome in untreated women with intense plasma cells infiltration (i.e., ≥ 5 plasma cells per HPF), but not in those with mild plasma cells infiltration (i.e., <5 plasma cells per HPF) (3). Therefore, the entity CE, as diagnosed on the basis of plasma cell count, may embrace a variety of histologic conditions with heterogeneous impact on female fertility.

Another long-standing problem is inherent to the optimal device for endometrial sampling in CE. Duan et al. (1) adopted hysteroscopic biopsy forceps, while other groups undertook blind endometrial biopsies with other devices, such as Novak curette or pipelle (4, 5). At the expense of greater patient discomfort, these latter tools reasonably allow greater biopsy depth and amount of tisse collected, potentially improving the chance to recognize deep and scattered stromal plasma cells infiltrates. On the other hand, hysteroscopy has the advantage of allowing the sampling of specific areas of the endometrium with macroscopic signs of disease, but the accuracy of this latter approach for CE diagnosis has been poorly investigated. Notably, the prevalence of CE in the study by Duan et al. (1) was 4.07%, namely considerably lower compared to the majority of previous studies on infertile women. In particular, the investigators reported no cases of disagreement between hysteroscopic and histologic diagnoses of CE. Namely, 338 women were diagnosed with CE at hysteroscopy and CD138 immunohistochemistry, while 7,962 women showed no sign of CE at both techniques. This finding was in contrast with several studies showing higher prevalence of CE at hysteroscopy compared to immunohistochemistry (4, 5).

Another important point of the study by Duan et al. (1) is about the "test of cure" for CE. Although they opted for avoiding a repeat biopsy when visual signs of CE were disappeared after antibiotic therapy, a previous meta-analysis concluded that CE treatment improves the IVF outcome only when a control biopsy confirms CE resolution (5). Therefore, the persistence of plasma cells in so-called cured patients by Duan et al. (1) cannot be excluded. Theoretically, incomplete restitutio ad integrum of the endometrium alone may justify poorer reproductive outcome in CE patients despite antibiotic treatment.

As a potential explanation of increased miscarriage rate in the CE group, a detrimental effect of antibiotic therapy with doxycycline and metronidazole on trophoblast invasion or endometrial decidualization is called into question by the investigators. Nevertheless, given the short half-life of those molecules (8 and 22 hours, respectively), and the long time elapsed between antibiotic therapy and embryo transfer (i.e., at least a complete menstrual cycle for performing the control biopsy), a direct embryotoxic effect of those molecules was unlikely. On the other hand, we may hypothesize that antibiotics alter endometrial microbiome homeostasis by destructing invaders and resident bacteria. Among resident bacteria, *Lactobacillus* spp. dominance (i.e., >90%) has been shown recently as a positive prognostic factor for IVF pregnancies. The time needed for restoration of *Lactobacillus* dominance in the uterine cavity after antibiotic therapy is unknown, and the putative usefulness of probiotics in reaching intrauterine eubiosis before IVF will be an intriguing matter of research. Nevertheless, cotreatment with probiotics was not included in the study protocol by Duan et al. (1).

From a statistical viewpoint, a separate discussion is needed regarding the intergroup difference in terms of miscarriage rate, which was slightly higher in the CE group (i.e., +2.6%; 11.8% vs. 9.2%). As recognized by the investigators themselves, this result should be interpreted with caution because of the risk of type II error. The total number of pregnancies in the CE group was $n = 185$ and +2.6% risk of miscarriage was consistent with a surplus of 9 miscarriages. Notably, with just 1 or 2 fewer miscarriages the data would no longer be statistically meaningful. Furthermore, the CE group had a higher prevalence of primary

infertility (60.4% vs. 49%), ovulatory disorders (19.5% vs. 12.8%), and male factor infertility (20.4% vs. 17.3%), as well as higher need for intracytoplasmic sperm injection compared to controls (26% vs. 23.9%). All these factors may potentially justify a slight increase in miscarriage rate in the CE group. However, as the mean age of the study population was close to 30 years, the miscarriage rate generally was acceptable in both groups according to data from the United States National Assisted Reproductive Technology Surveillance System (8.2%–12% in women <30 years old and 10%–13.1% in women aged 30–34 years after fresh/frozen embryo transfer).

In conclusion, the important study by Duan et al. (1) makes us open our eyes to the little that has been done to date to understand CE disease, and to all that it takes to have clear ideas. A precise definition of diagnostic criteria for CE, undertaking a control biopsy as a test of cure and a better knowledge on the microbiome are essential elements for allowing that shadows make room for light.

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