ORIGINAL ARTICLE: INFERTILITY

Effects of chronic endometritis therapy on in vitro fertilization outcome in women with repeated implantation failure: a systematic review and meta-analysis

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Objective: To evaluate the impact of antibiotic therapy for chronic endometritis (CE) on IVF outcome.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Infertile women with history of recurrent implantation failure, defined as two or more failed ETs, undergoing one or more IVF cycle(s).
Intervention(s): The review was registered in PROSPERO (CRD42017062494) before the start of the literature search. Observational studies were identified by searching electronic databases. The following comparators were included: women with CE receiving antibiotics vs. untreated controls; women with cured CE vs. women with persistent CE; and women with cured CE vs. women with normal endometrial histology (negative for CE). The summary measures were reported as odds ratio (OR) with 95% confidence interval (CI).
Main Outcome Measure(s): Clinical pregnancy rate (CPR), ongoing pregnancy rate/live birth rate (OPR/LBR), implantation rate (IR), miscarriage rate.
Result(s): A total of 796 patients (from five studies) were included. Women receiving antibiotic therapy (without the histologic confirmation of CE cure) did not show any advantage in comparison with untreated controls (OPR/LBR, CPR, and IR). Patients with cured CE showed higher OPR/LBR (OR 6.81), CPR (OR 4.02), and IR (OR 3.24) in comparison with patients with persistent CE. In vitro fertilization outcome was comparable between women with cured CE and those without CE (OPR/LBR, CPR, and IR). Miscarriage rate was not significantly different between groups.
Conclusion(s): Chronic endometritis therapy may improve IVF outcome in patients suffering from recurrent implantation failure. A control biopsy should always confirm CE resolution before proceeding with IVF. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Antibiotic therapy, chronic endometritis, infertility, live birth rate, pregnancy rate

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Chronic endometritis (CE) is a chronic infectious disease characterized by a persistent inflammation of the endometrial lining, whose prevalence in the general population is still unclear. Women with intrauterine pathologies, such as submucosal uterine fibroids and endometrial hyperplasia, were recently showed to be at higher risk of suffering from CE (1, 2).

Chronic endometritis has subtle symptomatology, such as dysfunctional uterine bleeding, pelvic discomfort, and leukorrhea. For this reason it is often overlooked in clinical practice (3, 4).

The diagnostic gold standard for CE is endometrial biopsy with histologic analysis, in which the detection of endometrial stromal plasma cells represents the histologic diagnostic marker (1–4).

Different authors have recently demonstrated that CE is highly prevalent in infertile women, especially in those with recurrent implantation failure (RIF) at IVF (5–7). Interestingly, specific antibiotics (against Gram-negative or intracellular bacteria) can cure CE in the majority of patients (cure rate up to 80% after a single antibiotic cycle) (7). Nevertheless, it is still unclear whether CE cure results in a better chance to achieve clinical pregnancy and live birth in subsequent IVF-ET attempts (7, 8).

Thus, the aim of the present study was to summarize the evidence regarding the impact of CE treatment on IVF outcome in women with a history of RIF.

MATERIALS AND METHODS

Study Design

This was a systematic review of published and unpublished data. The study protocol was registered in PROSPERO (in the context of a review project entitled "Systematic review and meta-analysis of prevalence and reproductive implications of chronic endometritis in women affected by infertility or recurrent pregnancy loss," CRD42017062494). Review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (9).

Ethical Approval

Because this study was a systematic review and meta-analysis, formal ethical approval was not required.

Search Strategy

Electronic databases (ScienceDirect, MEDLINE, Scopus, Embase, the Cochrane Library, Clinicaltrials.gov, EU Clinical Trials Register, and the World Health Organization International Clinical Trials Registry) were searched until November 8, 2017 (without date restriction).

Key search terms were as follows: chronic endometritis OR endometrial inflammation OR endometrial plasma cells OR antibiotic therapy AND IVF OR ICSI OR embryo transfer OR embryo implantation AND failure OR impairment OR defect OR deficiency. The electronic search and the eligibility of the studies were independently assessed by two of the authors (A.V. and M.N.).

Inclusion Criteria

We included all studies evaluating the effects of CE therapy on IVF-ET outcome in patients with RIF (defined as at least two previous failed IVF-ET attempts). All studies (experimental and observational) reported in the English language were eligible. Chronic endometritis was defined as the histologic presence (demonstrated by conventional staining and/or by immunohistochemistry) of at least one endometrial stromal plasma cell in the entire section. Studies evaluating other types of endometrial inflammation (such as acute, subacute, or tubercular endometritis) were excluded.

Comparators. Comparators were as follows. [1] Patients with treated CE vs. untreated CE: defined as patients receiving antibiotic therapy for CE vs. patients with CE not receiving antibiotics. Control biopsy was not performed. [2] Patients with cured CE vs. persistent CE: defined as patients in whom (after antibiotic therapy) a control biopsy showed the resolution of CE vs. those in which CE was still present. [3] Patients with cured CE vs. non-CE: defined as women with CE resolution (after antibiotic therapy) vs. women negative for CE (with normal endometrial histology).

Outcomes. Outcomes were ongoing pregnancy or live birth rate (per patient [OPR/LBR]): "ongoing pregnancy" defined as a pregnancy beyond 12 weeks' gestation, "live birth" defined as the delivery of one or more living infants; clinical pregnancy rate (per patient [CPR]): defined as the presence of a gestational sac on transvaginal ultrasound or other definitive clinical signs; implantation rate (per embyo [IR]): defined as the number of gestational sacs on transvaginal ultrasound divided by the number of embryos transferred; and miscarriage rate (per clinical pregnancy [MR]): defined as fetal loss before the 20 weeks' gestation.

Study Selection and Data Extraction

Two authors (A.V. and M.N.) independently assessed the inclusion criteria and study selection. Disagreements were discussed with a third reviewer (C.S.).

Data extraction was performed by two independent investigators (A.V. and C.S.). When studies involved a control group considered negligible for the endpoints of the meta-analysis, authors provided only a qualitative data extraction. A manual search of reference lists of studies was performed to avoid missing relevant publications. One author (A.D.S.S.) reviewed the selection and data extraction process. The results were then compared and any disagreement discussed and resolved by consensus. Additional data and details about included studies were obtained by contacting study authors by e-mail.

Risk of Bias

Two reviewers (A.V. and M.N.) independently judged the methodological quality of studies included in the meta-analysis using a modified version of the "Newcastle-Ottawa Scale" (10). Quality of studies was evaluated in five different domains: "sample representativeness," "sampling technique," "ascertainment of chronic endometritis diagnosis," "quality