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

of description of the population," and "incomplete outcome data" (Supplemental Table 1, available online). According to the total number of points assigned, each study was judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any discrepancies concerning authors' judgements were referred to a third reviewer (A.D.S.S.) and resolved by consensus.

Statistical Analysis and Publication Bias Assessment

Data analysis was performed independently by two authors (A.V. and C.S.) with Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration). All results were compared, and any differences were discussed. Study outcomes were expressed using odds ratio (OR) with 95% confidence interval (95% CI). A P value of $<.05$ was considered statistically significant. Higgins I^2 was used to assess heterogeneity (defined as high when I^2 was ≥50% and low when I^2 was <50%). When heterogeneity was high, we evaluated "random" outcomes. Subgroup and sensitivity analyses were also planned to explore the sources of inconsistency among studies (when at least three studies were included in meta-analysis).

We followed Cochrane Handbook recommendations for the assessment of publication bias (Cochrane Handbook, 10.4.3.1, "Recommendations on testing for funnel plot asymmetry"). However, not enough studies (fewer than ten) were included in the pooled analysis.

RESULTS

Study Selection

After the evaluation of full text, 12 studies were excluded (8, 11–21) (characteristics of studies and reasons for exclusion are reported in Supplemental Table 2). Finally, a total of five studies (22–26) were included in the present meta-analysis (Supplemental Fig. 1).

Included Studies

The studies included a total number of 796 patients. All studies were observational (three prospective (23, 25, 26) and two retrospective (22, 24) studies). Yang et al. (23) reported two different studies in their article (with prospective and retrospective design, respectively). The retrospective one (investigating the prevalence of CE in 60 patients, of whom 30 got pregnant and 30 did not) was excluded. In addition, a group of patients from the Johnston-MacAnanny et al. study (22) (in which CE was not investigated) was excluded.

Two studies compared patients with cured CE vs. patients with persistent CE. Three studies included patients with cured CE and patients not affected by CE. Yang et al. (23) compared patients receiving antibiotic therapy for CE vs. patients not receiving therapy for CE. Characteristics of included studies are summarized in Table 1.

Patients. All trials included patients with RIF. Recurrent implantation failure was defined as the failure of at least two (22, 25) or three (23, 24, 26) previous (fresh or frozen–thawed) IVF-ET attempts, including at least one good-quality cleavage-stage embryo or blastocyst transferred per cycle. Patients had heterogeneous causes of infertility (i.e., male factor, tubal factor, diminished ovarian reserve), except in the Cicinelli et al. study (24) (which included only patients with unexplained infertility).

IVF-ET cycle. All patients underwent homologous IVF-ET cycles, except in the study by Tersoglio et al. (25) (oocyte donation program). Three studies evaluated a single IVF-ET attempt (23–25), whereas other studies evaluated two or fewer (22) or three or fewer (26) IVF-ET cycles.

Only three studies reported adequate information about IVF-ET protocols (22, 24, 25). Ovarian stimulation was performed through the daily administration of recombinant FSH alone (24) or in combination with hMG, using GnRH antagonist (fixed or flexible protocol) or GnRH agonist (long protocol) for pituitary desensitization. Urinary hCG (5,000–10,000 IU) was administered when at least two preovulatory (17-mm) follicles were identified on transvaginal ultrasound scan. Egg retrieval was performed 34–35 hours after ovulation induction, and no more than three (22–24, 26) embryos or two blastocysts (25, 26) per cycle were transferred. Specifically, in two studies (22, 24) only cleavage-stage embryos (up to three) were transferred, whereas in the study by Tersoglio et al. (25) only blastocysts (up to two) were transferred. In another study (26), embryo transfer was performed at cleavage stage or blastocyst stage (up to two blastocysts or three cleavage-stage embryos transferred). No data were available on embryo stage for the study by Yang et al. (23). Preimplantation genetic testing was not used (information not available about two studies (23, 25)). Vaginal P was administered (22, 24, 25) from the day of ET. In the study by Tersoglio et al. (25), recipient preparation was achieved with oral E_2 valerate (and GnRH agonist depot for pituitary block).

Diagnosis of chronic endometritis. Plasma cells identification was achieved with hematoxilin and eosin staining alone (24, 25) or in combination with immunohistochemical examination for CD-138 (22, 23, 26) and CD-38 (23). Endometrial specimens were collected during the follicular phase, except in the Tersoglio et al. study (25) (day LH+5). The diagnosis of CE was made by a single expert pathologist in three studies (22, 24, 26). No information was obtained about two studies (23, 25).

Therapy of chronic endometritis. First-line antibiotic therapy for CE was germ-specific (when endometrial culture was performed (24, 25) or empiric (doxycycline 200 mg/d for 14 days (22, 26), 1 g/d ciprofloxacin and metronidazole for 14 days (23)). In all studies, except Yang et al (23), a control biopsy was performed to evaluate the rate of cure.

Assessment of the Risk of Study Bias

Sample representativeness. Only two studies (24, 26) were judged at low risk of bias for sample representativeness. Other studies were judged at high risk of bias.

Sampling technique. Two studies (23, 26) had adequate sampling strategy (random or consecutive). Other studies did not provide data.

TABLE 1

General features of the included studies.

Authors and year (reference)	Study design, country, and time of realization	Participants and main inclusion criteria	IVF-ET cycle	Methods	Groups	Outcomes
Johnston-MacAnanny et al. 2010 (22)	Retrospective study, United States, January 2001–December 2007	518 patients undergoing up to two IVF-ET cycles At least two failed IVF-ET cycles (with ≥1 good-quality embryo transferred per cycle) Normal karyotypes Negative testing for antiphospholipid antibodies Normal uterine cavity	Short GnRH-ant or long GnRH-a protocol rFSH alone or rFSH plus hMG U-hCG (5,000–10,000 UI) at follicle size 17 mm (≥2) Egg retrieval 35 h after ovulation induction Luteal phase support with 50 mg IM P	EB HIS examination Antibiotic therapy (if necessary) Control EB (if necessary) IVF cycle	Group A: patients with cured CE (n = 10) Group B: patients without CE (n = 23)	Clinical pregnancy rate Miscarriage rate Live birth rate
Yang et al. 2014 (23)	Prospective cohort study, China, May 2010–April 2012	202 patients undergoing IVF-ET cycle Three failed IVF-ET cycles or ≥6 high-quality embryo transferred Normal uterine cavity	–	Diagnostic HSC EB HIS examination Antibiotic therapy (when appropriate) IVF cycle	Group A: patients with treated CE (n = 68) Group B: patients with untreated CE (n = 20)	Clinical pregnancy rate Ongoing pregnancy/live birth rate Miscarriage rate
Cicinelli et al. 2015 (24)	Retrospective study, Italy, January 2009–June 2012	106 patients undergoing IVF-ET cycle Unexplained infertility Age <40 y At least 6 good-quality embryos transferred in ≥3 previous IVF/ICSI cycles Normal karyotype FSH on day 3 ≤10 mUI/mL BMI ≤30 kg/m^2 No previous surgery for myoma and/or endometriosis No condition interfering with immune system No antiphospholipid syndrome or thrombophilic condition No antisperm antibodies	GnRH-ant with flexible or fixed scheme rFSH (175–225 IU/d) U-hCG (10,000 IU) at follicle size 17 mm (≥2) Egg retrieval 34 h after ovulation induction ≤3 embryos transferred (of which at least one with good quality) Luteal phase support with vaginal P	Diagnostic HSC EB HIS examination Endometrial culture Antibiotic therapy (if necessary) Control EB IVF cycle	Group A: patients with cured CE (n = 46) Group B: patients with persistent CE (n = 15)	Clinical pregnancy rate Ongoing pregnancy/live birth rate Miscarriage rate
Tersoglio et al. 2015 (25)	Prospective cohort study, Argentina, 2010–2013	30 patients undergoing one heterologous IVF-ET cycle At least two IVF-ET cycles failed with two or more blastocysts transferred No uterine malformation No autoimmune thyroid disease No antiphospholipid syndrome Normal uterine cavity Good embryo quality	Recipient preparation with GnRH-a depot and oral E_2 valerate	EB HIS examination Flow cytometry Endometrial culture Antibiotic treatment Control EB OD cycle	Group A: patients with cured CE (n = 9) Group B: patients with persistent CE (n = 5) Group C: patients without CE (n = 16)	Clinical pregnancy rate Ongoing pregnancy/live birth rate Miscarriage rate

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TABLE 1

Continued.

Authors and year (reference)	Study design, country, and time of realization	Participants and main inclusion criteria	IVF-ET cycle	Methods	Groups	Outcomes
Kitaya et al. 2017 (26) [UMIN-CTR000006536][a]	Prospective cohort study, Japan, November 2011–July 2014	421 patients undergoing up to three IVF-ET cycles IVF failure with three or more morphologically good cleavage-stage embryos and/or blastocysts transferred No intrauterine pathology	–	Diagnostic HSC EB HIS examination Endometrial culture Antibiotic therapy (if necessary) Control EB IVF cycle	Group A: patients with cured CE (n = 116) Group B: patients with persistent CE (n = 4) Group C: patients without CE (n = 226)	Clinical pregnancy rate Ongoing pregnancy/ live birth rate Miscarriage rate

Note: EB = endometrial biopsy; GnRH-a = GnRH agonist; GnRH-ant = GnRH antagonist; HIS = histology; HSC = hysteroscopy; nr = not reported; OD = oocyte donation; rFSH = recombinant FSH; rhCG = recombinant hCG; U-hCG = urinary hCG.
[a] Registered trial: identification code in square brackets.

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TABLE 2

Authors' judgement of study quality according to the "Modified Newcastle-Ottawa Risk of Bias Scoring System."

Authors and year (reference)	Sample representativeness	Sampling technique	Ascertainment of CE diagnosis	Quality of description of the population	Incomplete outcome data	Total score	Risk of bias
Johnston-MacAnanny et al. 2010 (22)	–	–	★	★	★	★★★	Low
Yang et al. 2014 (23)	–	★	★	–	–	★★	High
Cicinelli et al. 2015 (24)	★	–	★	★	★	★★★★	Low
Tersoglio et al. 2015 (25)	–	–	–	★	★	★★	High
Kitaya et al. 2017 (26)	★	★	★	–	★	★★★★	Low

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Ascertainment of chronic endometritis diagnosis. One study (25) was judged at high risk of bias in CE detection (endometrial biopsy performed during luteal phase). Other studies were at low risk of bias.

Quality of description of the population. Two studies (23, 26) were judged at high risk of bias owing to lack of information about IVF-ET protocols. Other studies provided adequate information.

Incomplete outcome data. One study provided incomplete outcome data (23) (Table 2).

Synthesis of Results

Treated CE vs. untreated CE (test of cure not performed). Data from one study (23) did not show a significant difference in OPR/LBR (P=.70), CPR (P=.66), IR (P=.82), and MR (P=1.00) in patients with CE receiving antibiotics vs. patients with CE not receiving therapy.

Cured CE vs. persistent CE. We found a significantly higher OPR/LBR (OR 6.81, 95% CI 2.08–22.24, I^2 = 0%, P=.001), CPR (OR 4.98, 95% CI 1.72–14.43, I^2 = 0%, P=.003), and IR (OR 3.24, 95% CI 1.33–7.88, I^2 = 0%, P=.01) in patients with cured CE in comparison with those with persistent CE, with no difference in terms of MR (P=.30) (Fig. 1A–1C). The exclusion of egg donation cycles (from the Tersoglio et al. study (25)) from pooled analysis did not provide statistical changes to OPR/LBR (OR 8.66, 95% CI 2.07–36.14, I^2 = 0%, P=.003), CPR (OR 3.42, 95% CI 1.07–10.94, I^2 = 0%, P=.04), IR (OR 2.95, 95% CI 1.10–7.95, I^2 = 0%, P=.03), and MR (P=.20). Sensitivity analysis was not performed owing to minimal inconsistency (I^2 = 0%).

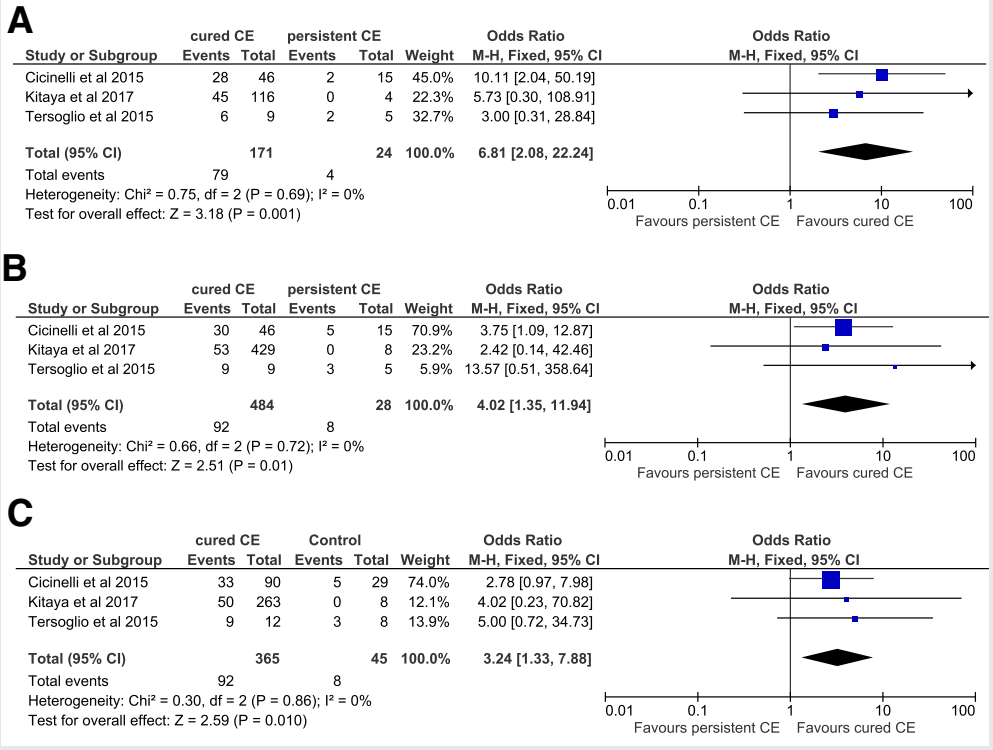
Cured CE vs. non-CE. Analysis of 389 patients did not show any difference between groups in terms of CPR (P=.90), OPR/LBR (P=.75), IR (P=.93) (Fig. 2A–2C), and MR (P=.75). The exclusion of the study by Tersoglio et al. (25) from aggregate analysis did not modify OPR/LBR (P=.54), CPR (P=.81), IR (P=.78), and MR (P=.62). Sensitivity analysis (with the exclusion of Johnston MacAnanny et al. study (22)) yielded significant changes in pooled results, with a significant advantage in patients with cured CE in terms of OPR/LBR (OR 1.68, 95% CI 1.06–2.67, I^2 = 0%, P=.03), CPR (OR 1.67, 95% CI 1.06–2.62, I^2 = 0%, P=.03), and IR (OR 1.78, 95% CI 1.21–2.63, I^2 = 0%, P=.004), with no difference in MR (P=.27).

DISCUSSION

Main Findings

The present systematic review and meta-analysis included a total of 796 RIF patients from five observational studies (22–26). Although patients with cured CE showed higher OPR/LBR (OR 6.81, P=.001), CPR (OR 4.98, P=.003), and IR

FIGURE 1



Persistent CE vs. cured CE. (**A**) Ongoing pregnancy/live birth rate; (**B**) clinical pregnancy rate; (**C**) implantation rate. M-H = Mantel-Haenszel.

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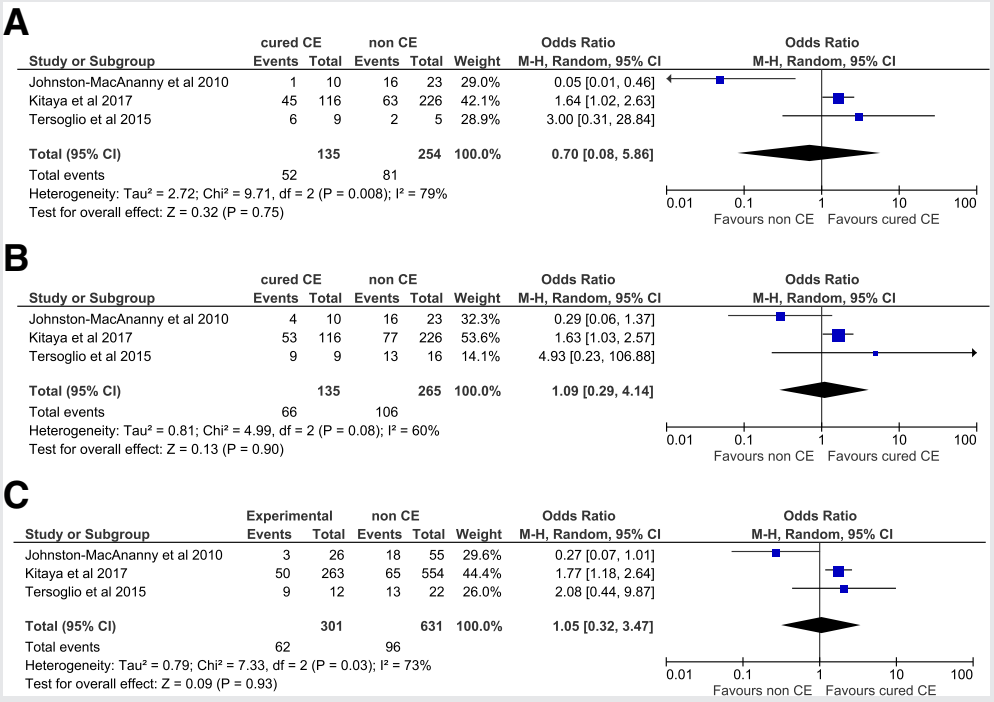
FIGURE 2



Cured CE vs. non-CE. (**A**) Ongoing pregnancy/live birth rate; (**B**) clinical pregnancy rate; (**C**) implantation rate.

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(OR 3.24, *P*=.01) in comparison with patients with persistent disease, the only study that compared patients with CE receiving antibiotics vs. patients not receiving antibiotics (23) did not observe any difference in terms of CPR, OPR/LBR, and IR (*P*=nonsignificant). Nevertheless, Yang et al. (23) did not perform a control biopsy after antibiotic therapy. Thus, the percentage of patients (among the antibiotic group) with persistent disease at the time of IVF was unknown, and this may represent a bias in the estimation of the benefits from CE treatment. Furthermore, Yang et al. (23) claimed that antibiotic therapy significantly improved OPR in patients with hysteroscopic signs of CE (such as mucous hyperemia, edema, and micropolyps). This may suggest the presence of methodological bias, because hysteroscopic and histologic findings are expected to be nearly correspondent in women with CE, according to other authors' experience (27).

Moreover, we found no difference in CPR, OPR/LBR, and IR in patients with cured CE vs. those without CE (*P*=nonsignificant), with high inconsistency (I^2 from 60% to 79%). The exclusion of egg donation cycles did not modify pooled results (CPR, OPR/LBR, IR, MR: *P*=nonsignificant). Data by Johnston-MacAnanny et al. (22) were the main source of statistical heterogeneity, potentially due to small sample size (n = 33 patients, of whom 10 with cured CE). As a matter of fact, other studies (25, 26) (including the study with better quality and larger size (26)) showed considerably higher CPR (*P*=.03), OPR/LBR (*P*=.03), and IR (*P*=.004) in patients with cured CE. These findings potentially suggest that CE is a reversible factor of infertility, whose recognition and therapy may provide better chances at subsequent IVF attempts.

Strength and Limitations

The present meta-analysis is the first evaluating the effects of CE therapy on IVF outcome. We planned sensitivity and subgroup analysis to reduce bias related to study heterogeneity, and we provided unpublished data and details about included studies. However, our results are considerably limited by the small number of patients included, heterogeneity in patient characteristics (including IVF cycles and days for ET [cleavage-stage vs. blastocyst-stage embryos]), poor methodological quality of original studies (no randomized controlled trial was included), and some concerns about the histologic diagnosis of CE in two studies (lack of information about the number and expertise of pathologists (23, 25)). Moreover, the inconsistent use of endometrial culture, as well as the variable antibiotic regimens used (type of drug and duration) may represent additional confounding factors in estimating the effects of CE therapy on IVF outcome. In addition, the timing of the first biopsy and of the test of cure varied among studies, potentially generating bias in the detection of CE. Finally, the lack of genetic testing of preimplantation embryos did not rule out embryo aneuploidy as cause for implantation failure.

Implications

Despite recent innovations in ovarian stimulation protocols (28, 29), reproductive immunology (30, 31), and reproductive surgery (32, 33), implantation remains the main limiting factor of IVF success (34, 35). The implantation process encompasses different stages (endometrial decidualization, embryo apposition, adhesion, penetration, and trophoblast invasion) that are finely regulated by immune cells and cytokines (36–38). Recent in vitro studies showed that CE may exert a negative effect on implantation through impairing decidualization (39) and altering the expression of proteins involved in endometrial receptivity (such as cytokines, growth factors, and apoptotic proteins) (40–42). Accordingly, antibiotic therapy may eliminate the source of infection, restore normal endometrial histology, and improve endometrial receptivity (6, 20). In this respect, the present meta-analysis demonstrates that such an intriguing hypothesis is reasonable but still not supported by adequate evidence.

In our opinion, the clarification of the real impact of CE (and the potential advantages of CE therapy) on embryo implantation is of critical importance. If our results are confirmed, CE may represent a new therapeutic target for women suffering from RIF, with affordable access (diagnosed through a simple endometrial biopsy and treated by oral antibiotics). Nevertheless, future randomized controlled trials need to be undertaken to better understand whether CE therapy may really improve IVF outcome in women with RIF.

In conclusion, the present study demonstrates that CE therapy may improve IVF outcome in patients suffering from RIF. Notably, the resolution of CE should be confirmed (at histology) before proceeding with IVF. The body of evidence on this topic is still insufficient to recommend routine CE screening as intervention to improve CPR and OPR/LBR in such patients. Future randomized controlled trials are needed.

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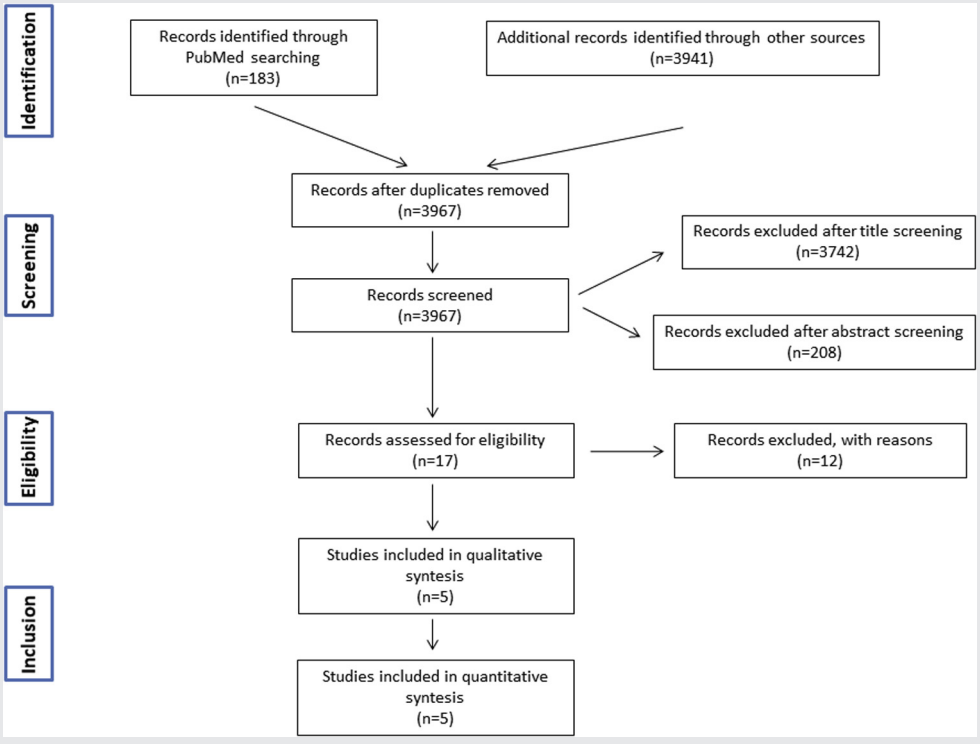
SUPPLEMENTAL FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Vitagliano. Antibiotics for chr endometritis. Fertil Steril 2018.