https://doi.org/10.25207/1608-6228-2023-30-5-15-40

UDC: 618.145-007.415:618.177-089.888.11

Chronic endometritis and infertility — *in vitro* fertilization outcomes: systematic review and meta-analysis

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ABSTRACT

Background. The relevance of the problem is related to the high prevalence of chronic endometritis (CE); its role in female infertility, implantation failures during assisted reproductive technology procedures, and recurrent miscarriage; as well as the lack of a unified strategy in the diagnosis and treatment of this pathology. The present systematic review with a meta-analysis focuses on evaluating the impact of CE and its therapy on the outcome of in vitro fertilization. In addition, the effect of CE of various severity on the outcomes of assisted reproductive technologies is analyzed. **Objective.** To analyze the effect of CE of varying severity and its treatment on the outcomes of in vitro fertilization. **Methods.** Using PubMed, Medline, Scopus, Embase, ELibrary, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry, and Russian Science Citation Index, a systematic search was conducted for articles published over the past 12 years that met the following criteria: randomized controlled trial examining the effect of CE of varying severity on fertility and ways to treat it. The following indicators were calculated: ongoing pregnancy/live birth, clinical pregnancy, and miscarriage rates. A total of 4145 patients (from ten studies) were included. A meta-analysis was performed using Stata 11.0 software (The Cochrane Collaboration, Oxford, UK). The heterogeneity was considered low at I^2 <30%, moderate at 30–50%, and high at >50%. **Results.** Women with CE exhibited lower ongoing pregnancy/live birth (OR 1.97; $p < 0.02$) and clinical pregnancy rates (OR 2.28; $p < 0.002$) as compared to women without it. CE treatment increased the ongoing pregnancy/live birth (OR 5.33; $p < 0.0001$) and clinical pregnancy rates (OR 3.64; $p < 0.0001$). In vitro fertilization outcomes were comparable in women treated for CE and women without CE (ongoing pregnancy/live birth rate, clinical pregnancy rate, and miscarriage rate: $p <$ ns). Women with severe CE exhibited lower ongoing pregnancy/live birth (OR 0.43; $p < 0.003$) and clinical pregnancy rates (OR 0.40; $p < 0.0007$). Mild CE showed no significant effect on in vitro fertilization outcomes (ongoing pregnancy/live birth rate, clinical pregnancy rate, and miscarriage rate: $p <$ ns). **Conclusion.** The conducted meta-analysis showed that CE significantly reduces the ongoing pregnancy/live birth and clinical pregnancy rates in infertile women undergoing in vitro fertilization. Noteworthy is that antimicrobial therapy in such patients improves the results of assisted reproductive technologies, which are comparable to those of patients without CE. The negative impact of this pathology on the implantation capacity of the endometrium is most often observed in the severe form, while its mild form has virtually no effect on the in vitro fertilization outcome.

KEYWORDS: Chronic endometritis; infertility; recurrent implantation failure; in vitro fertilization; plasma cells; immunohistochemistry; hysteroscopy

FOR CITATION: Lokshin V.N., Kutsenko I.I., Borovikov I.O., Bulgakova V.P, Kravtsova E.I., Biryukova M.I., Borovikova O.I., Nikogda Ju.V. Chronic endometritis and infertility — in vitro fertilization outcomes: systematic review and meta-analysis. *Kuban Scientific Medical Bulletin*. 2023; 30(5): 15–40. https://doi.org/10.25207/1608-6228-2023-30-5-15-40

CONFLICT OF INTEREST: One of the authors (Prof. Kutsenko, Dr. Sci. (Med.)) is an editorial board member of the Kuban Scientific Medical Bulletin. The authors are unaware of any other potential conflict of interest associated with this manuscript.

DATA AVAILABILITY STATEMENT: Data presented in the study are the result of analyzing already existing scientific literature that is publicly available and in the public domain. To get acquainted with the original data, please refer to the list of references at the end of this publication.

FUNDING: No funding support was obtained for the research.

COMPLIANCE WITH ETHICAL STANDARDS: The study complies with the Helsinki Declaration standards and is approved by the Independent Committee for Ethics (Minutes No. 19 as of September 20, 2021) of the Kuban State Medical University (Mitrofana Sedina str., 4, Krasnodar, Russia).

AUTHOR CONTRIBUTIONS: V.N. Lokshin, I.I. Kutsenko, I.O. Borovikov, V.P. Bulgakova, E.I. Kravtsova, M.I. Biryukova, O.I. Borovikova, Ju.V. Nikogda — concept formulation and study design; I.O. Borovikov, E.I. Kravtsova — data collection; V.N. Lokshin, I.I. Kutsenko, I.O. Borovikov, M.I. Biryukova, O.I. Borovikova, Ju.V. Nikogda — analysis and interpretation of the obtained results; I.O. Borovikov, E.I. Kravtsova, M.I. Biryukova, O.I. Borovikova — literature review and statistical analysis; I.O. Borovikov, E.I. Kravtsova, Ju.V. Nikogda — drafting of the manuscript and preparation of its final version; V.N. Lokshin, I.I. Kutsenko, V.P. Bulgakova, M.I. Biryukova, O.I. Borovikova — critical revision of the manuscript for valuable intellectual content. All the authors approved the final version of the manuscript prior to publication, agreeing to be accountable for all aspects of the work, meaning that issues related to the accuracy and integrity of any part of the work are appropriately examined and resolved.

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Received: 15.02.2022 / **Received after revision:** 27.07.2023 / **Accepted:** 01.09.2023

Хронический эндометрит и инфертильность — исходы экстракорпорального оплодотворения (систематический обзор и метаанализ)

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АННОТАЦИЯ

Введение. Актуальность проблемы связана с высокой распространенностью хронического эндометрита, его ролью в женской инфертильности, неудачах имплантации при проведении процедур вспомогательных репродуктивных технологий и привычном невынашивании беременности, а также отсутствии единой стратегии в диагностике и лечении данной патологии. Этот систематический обзор с метаанализом посвящен оценке влияния хронического эндометрита и его терапии на исход экстракорпорального оплодотворения. Также был проведен анализ влияния хронического эндометрита различных степеней тяжести на исходы вспомогательных репродуктивных технологий. **Цель исследования** — анализ влияния хронического эндометрита различной степени тяжести и его лечения на исходы экстракорпорального оплодотворения. **Методы.** С помощью поисковых систем PubMed, Medline, Scopus, Embase, ELibrary, Cochrane Central Register of Controlled Trials (CENTRAL), Международного реестра клинических испытаний Всемирной организации здравоохранения, национальной библиографической базы данных научного цитирования был проведен систематический литературный поиск за последние 12 лет статей, отвечающих следующим критериям: рандомизированное контролируемое исследование влияния хронического эндометрита различной степени тяжести на фертильность и способы его лечения. Рассчитаны показатели: частота продолжающейся беременности/рождаемости, частота клинической беременности и частота выкидышей. Включено в общей сложности 4145 пациентов (из десяти исследований). Метаанализ выполнялся с помощью прикладных программ Stata 11.0 (The Cochrane Collaboration, Оксфорд, Великобритания). Оценка степени неоднородности: считалась низкой при $I^2 < 30\%$, умеренной — 30–50%, высокой — >50%. **Результаты.** Женщины с хроническим эндометритом имели более низкую частоту продолжающейся беременности/рождаемости (OR 1,97; $p = 0,02$) и частоту клинической беременности (OR 2,28; $p = 0,002$) по сравнению с женщинами без него. Излечение хронического эндометрита увеличило частоту продолжающейся беременности/рождаемости (OR 5,33; $p < 0,0001$) и частоту клинической беременности (OR 3,64; $p = 0,0001$). Результаты экстракорпорального оплодотворения были сопоставимы между женщинами после терапии хронического эндометрита и женщинами без него (частота продолжающейся беременности/рождаемости, частота клинической беременности и частота выкидышей: p = ns). Женщины с тяжелой степенью хронического эндометрита имели более низкую частоту продолжающейся беременности/рождаемости (OR 0,43; $p = 0,003$) и частоту клинической беременности (OR 0,40; $p = 0,0007$). Легкая степень хронического эндометрита не демонстрировала существенного влияния на исходы экстракорпорального оплодотворения (частота продолжающейся беременности/рождаемости, частота клинической беременности и частота выкидышей: p = ns). **Заключение.** Проведенный метаанализ показал, что хронический эндометрит значительно снижает частоту продолжающейся беременности/рождаемости и частоту клинической беременности у инфертильных женщин, проходящих процедуру экстракорпорального оплодотворения. Важно отметить, что антибактериальная терапия таких пациенток способствует улучшению результатов вспомогательных репродуктивных технологий, сопоставимых с результатами пациенток без хронического эндометрита. Негативное влияние этой патологии на имплантационные свойства эндометрия наиболее часто проявляется при ее тяжелом течении, тогда как легкая форма практически не влияет на успех экстракорпорального оплодотворения.

КЛЮЧЕВЫЕ СЛОВА: хронический эндометрит, бесплодие, повторные неудачи имплантации, экстракорпоральное оплодотворение, плазматические клетки, иммуногистохимия, гистероскопия

ДЛЯ ЦИТИРОВАНИЯ: Локшин В. Н., Куценко И. И., Боровиков И. О., Булгакова В. П., Кравцова Е. И., Бирюкова М. И., Боровикова О. И., Никогда Ю. В. Хронический эндометрит и инфертильность — исходы экстракорпорального оплодотворения (систематический обзор и метаанализ). *Кубанский научный медицинский вестник.* 2023; 30(5): 15–40. https://doi.org/10.25207/1608-6228-2023-30-5-15-40

КОНФЛИКТ ИНТЕРЕСОВ: один из авторов — профессор, доктор медицинских наук Куценко И. И. является членом редакционного совета журнала «Кубанский научный медицинский вестник». Авторам неизвестно о каком-либо другом потенциальном конфликте интересов, связанном с этой рукописью.

ДЕКЛАРАЦИЯ О НАЛИЧИИ ДАННЫХ: данные, представленные в исследовании, являются результатом анализа уже существующей научной литературы, которая общедоступна и находится в открытом доступе. Ознакомиться с исходными данными можно через список литературы, представленный в конце данной публикации.

ИСТОЧНИК ФИНАНСИРОВАНИЯ: авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

СООТВЕТСТВИЕ ПРИНЦИПАМ ЭТИКИ: проведенное исследование соответствует стандартам Хельсинкской декларации, одобрено Независимым этическим комитетом федерального государственного бюджетного образовательного учреждения высшего образования «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации (ул. им. Митрофана Седина, д. 4, г. Краснодар, Россия), протокол № 19 от 20.09.2021 г.

ВКЛАД АВТОРОВ: В. Н. Локшин, И. И. Куценко, И. О. Боровиков, В. П. Булгакова, Е. И. Кравцова, М. И. Бирюкова, О. И. Боровикова, Ю. В. Никогда — разработка концепции и дизайна исследования; И. О. Боровиков, Е. И. Кравцова, — сбор данных; В. Н. Локшин, И. И. Куценко, И. О. Боровиков, М. И. Бирюкова, О. И. Боровикова, Ю. В. Никогда — анализ и интерпретация результатов; И. О. Боровиков, Е. И. Кравцова, М. И. Бирюкова, О. И. Боровикова — обзор литературы, проведение статистического анализа; И. О. Боровиков, Е. И. Кравцова, Ю. В. Никогда — составление черновика рукописи и формирование его окончательного варианта; В. Н. Локшин, И. И. Куценко, В. П. Булгакова, М. И. Бирюкова, О. И. Боровикова — критический пересмотр черновика рукописи с внесением ценного замечания интеллектуального содержания. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью и добросовестностью любой части работы.

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Получена: 15.12.2022 / **Получена после доработки**: 27.07.2023 / **Принята к публикации**: 01.09.2023

INTRODUCTION

The currently accepted definition of chronic endometritis (CE) was given in 2018 by I. Moreno, E. Cicinelli, et al.: a chronic inflammation of the endometrium caused by its abnormal microbiome [1]. Recent years have seen an increasing interest in this pathology, primarily due to its presumed role in infertility, recurrent miscarriage, and recurrent implantation failure (RIF) during in vitro fertilization (IVF) procedures [2–10]. It is noted that the prevalence of CE exceeds 30% in these conditions [11–14].

A variety of theories are available to explain the CE-related reduction in the implantation capacity of the endometrium [15–20] — activation of local inflammatory processes with altered secretion of cytokines and chemokines [19, 21–25]; abnormal leukocytic infiltration, decidualization, and vascularization in the uterine cavity mucosa [13, 19, 23, 24, 26, 27, 29, 30]; altered uterine contractility [16, 28]. Although these theories clearly reflect some features of CE pathogenesis, the current evidence for a correlation between this pathology and implantation defects is often based on data from studies that are not without their limitations, such as heterogeneous sampling and questionable diagnostic criteria for CE [31, 32]. Therefore, the scientific community remains divided between those who are for and against recognizing CE as the real cause of female infertility.

One of the most frequently asked questions regarding CE is the methodology used to diagnose it. Hysteroscopy has sufficient sensitivity; however, it is highly dependent on the technician [33–35]. Therefore, the current gold standard for CE diagnosis is the detection of plasma cells (PCs) in endometrial biopsy material [36–38]. The number of PCs required to diagnose CE remains a matter of discussion [38, 39].

In this systematic review involving a meta-analysis, we examined scientific and clinical studies of infertile women with repeated IVF failures; specifically, we studied the role of CE in reducing IVF effectiveness, evaluated the impact of CE treatment on IVF outcomes, and analyzed the propensity to implantation impairment depending on CE severity (determined by plasma cell infiltration).

The article **aims** to analyze the effect of chronic endometritis of varying severity and its treatment on the outcomes of in vitro fertilization.

METHODS

Study design

The systematic review with meta-analysis was reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [40].

Eligibility criteria

The evaluation of studies for compliance with the inclusion criteria was conducted in three stages: evaluation of the title, abstract, and full text of the article.

Inclusion criteria

All studies (experimental and observational) evaluating the impact of chronic endometritis on the outcome of in vitro fertilization.

Exclusion criteria

Studies that include patients with recurrent miscarriage; evaluate spontaneous conception rate in women with CE; evaluate other types of endometrial inflammation (acute, subacute, or tuberculous endometritis).

Diagnostic criteria

Chronic endometritis was defined as the presence of at least one endometrial stromal plasma cell in the entire section; immunohistochemical analysis was used as an evaluation method for CD138+ cells (syndecan-1 staining). Severe CE was defined as the presence of ≥5 PCs in the endometrial tissue per HPF, while the mild form was defined as the presence of 1–4 PCs per HPF.

The following comparisons were made: 1) CE patients vs non-CE patients (with normal endometrial histology); 2) patients with CE (untreated or persistent after antibiotic therapy) vs treated CE, i.e., following antibiotic therapy (endometrial biopsy showed no CE); 3) treated CE patients (following antibiotic therapy) vs non-CE patients (with normal endometrial histology).

Also, a comparison was conducted between CE patients, which was defined by the number of PCs in endometrial tissue: ≥5 PCs per HPF (severe CE) vs 1–4 PCs (mild CE). Also,

a subgroup of patients with 1–4 PCs was compared with non-CE patients.

Information sources

Two authors conducted an independent search for publications in all languages across electronic databases (PubMed, Medline, Scopus, Embase, ELibrary, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry, and RSCI) that were published between January 2010 and January 2022.

Search strategy

The search query included the following words: chronic endometritis; infertility; endometrial plasma cells (EPC); endometrial CD-138; hysteroscopy; in vitro fertilization (IVF); assisted reproductive technology (ART); embryo transfer; recurrent implantation failure (RIF). For domestic databases, Russian equivalents for these terms were used.

Study selection

Initially, the title and abstract of potential studies were examined, and in case of insufficient information, the full text of the article was studied. Reviews, case histories, comments, and letters were excluded. In order to increase the transparency of the method, we selected only randomized controlled trials (RCTs) in human beings. The references of all found studies were examined to identify additional, previously undiscovered publications. Duplicate results obtained in the search across different databases were also excluded.

Data collection

Two researchers independently examined databases and found potentially relevant studies. Then, another reviewer assessed whether the full text of the articles met the inclusion criteria. Points at issue were resolved through discussion. For the sake of transparency and complete reporting of the meta-analysis, the search for studies was presented as a PRISMA block diagram.

Data and generalized effect size

With the aim to establish the relationship between chronic endometritis and in vitro fertilization outcomes, the meta-analysis used the following indicators as primary endpoints: ongoing pregnancy or live birth rate (per patient — OPR/LBR), clinical pregnancy rate (per patient — CPR), and miscarriage rate (per clinical pregnancy — MR). OPR/LBR ("ongoing pregnancy") — after 12 weeks of gestation; "live birth" — birth of one or more viable children; CPR — presence of an intrauterine gestational sac as indicated by transvaginal ultrasound or other reliable clinical signs; MR — fetal loss before 20 weeks of gestation expressed as mean values (M) ± standard deviations (SD).

Data retrieval and quality assessment

RCT data meeting inclusion and exclusion criteria were obtained by the reviewers according to the predefined criteria. Special attention was paid to data concerning severity, diagnostic criteria for chronic endometritis, its therapy methods, and treatment outcomes (biochemical pregnancy, clinical pregnancy, live birth rate, and miscarriage rate). All authors independently assessed the risk of systematic error in each study using guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (www.handbook.cochran.org). In the course of the study, reviewers also evaluated the randomization method; the degree of blinding of patients, medical staff, and researchers, as well as the availability and completeness of data on outcomes presented by the authors.

Statistical analysis

The meta-analysis was performed using Stata 11.0 and Review Manager (version 5.4, The Cochrane Collaboration, 2020, Oxford, UK). The study results were expressed using an odds ratio (OR) with a 95% confidence interval (95% CI); values of $p < 0.05$ were considered statistically significant.

Synthesis of results

The heterogeneity was considered low at I^2 <30%, moderate at 30–50%, and high at >50%. The relation I^2>50% indicated significant heterogeneity between studies and prevented reliance on a combination of study results, so a random effects model was used to summarize the effects. The random effects model (DerSimonian & Laird method) was applied in the meta-analysis [41]. The analysis of subgroups and sensitivity was used to examine the sources of heterogeneity in the studies. The condition was to follow the Cochrane Handbook recommendations for assessing publication bias [42].

Risk of bias in individual studies

The recommendations provided in the Cochrane Handbook for Systematic Reviews were used to assess the risk of bias in RCTs. The following criteria were assessed: presence of randomization; allocation concealment; blinding of participants and staff; blinding of the researcher evaluating outcomes; presence of incomplete data on outcomes; selective reporting of data; and other risks of bias. The systematic error risk assessment was denoted as follows: low risk — "+"; questionable risk of bias, as well as incompletely reported data — "?"; high risk of bias — "–."

Additional analyses

No additional analyses were planned for this study.

RESULTS

Selection of studies

We conducted a search for papers published between January 2010 and January 2022 that met the inclusion criteria. The search scheme is presented in Fig. 1.

After removing duplicate publications, the search yielded 1905 relevant studies; of these, 19 full-text articles that met the eligibility criteria for this meta-analysis were selected. After evaluating the full text, a total of ten studies in the English language were included in this meta-analysis [6, 9, 11, 12, 14, 17, 18, 44, 45, 46]. The most important data from the ten RCTs included in the analysis are summarized in Table 1.

Characteristics of studies included in the meta-analysis

The studies included a total of 4145 patients. All studies were observational: five prospective [9, 18, 43, 44, 46], five retrospective [6, 12, 14, 17, 45], and one crossover study [11].

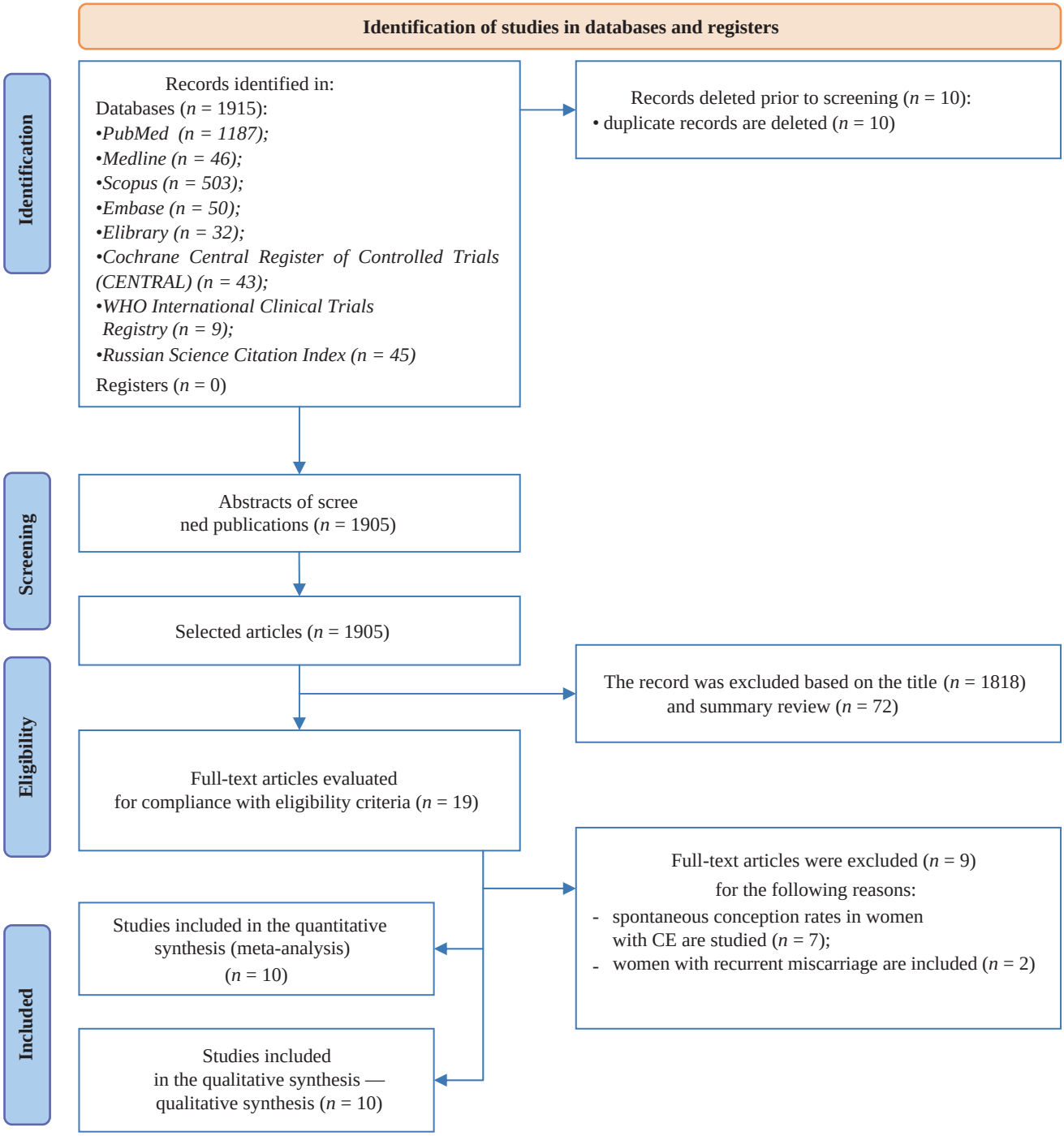

Fig. 1. Block diagram of the study design
Note. The block diagram was created by the authors (as per PRISMA recommendations).
Рис. 1. Блок-схема дизайна проведенного исследования
Примечание: блок-схема выполнена авторами (согласно рекомендациям PRISMA).

Two studies compared non-CE patients with treated CE and recurrent CE patients [18, 46]; one study compared women with treated and recurrent CE [6]; and two studies compared non-CE, treated CE, and infertile patients who were not tested for CE [9, 17]. Three studies compared CE and non-CE patients [43, 44, 45], and one compared CE, non-CE, and treated CE patients [11]. Y. Li, S. Xu et al. (2021) divided patients into groups according to the number of plasma cells (0, 1, 3, 4, and ≥5 per HPF) and compared pregnancy outcomes in women with <5 and ≥5 CD138+ cells [12]. Also on the basis of PC count, Y. Xiong et al. (2021) compared pregnancy outcomes in patients with different CD138+ counts and recurrent CE following antibiotic therapy [14]. As the main criteria of CE recovery, T.M. Motovilova et al. chose sonographic markers—increase in endometrial thickness and blood flow change (resistance index, RI) in radial, spiral, and basal uterine arteries [43].

Table 1. Characteristics of the studies
Таблица 1. Характеристика исследований

Authors and year	Design, period, country	Participants, main inclusion criteria	IVF cycle	Procedure	Diagnostic criteria for CE	Groups	Results
Cicinelli et al. 2015 [6]	prospective, 2009–2012, Italy	106 RIF patients undergoing an IVF cycle - unexplained infertility; - age of <40 years	oocyte retrieval 34 h following ovulation induction; - ≤3 embryos; - transfer at day 3	hysteroscopy, biopsy, morphological examination, and endometrial culture - antibiotics - IVF cycle monitoring	1–5 CD138+ cells or discrete <20 PC clusters	Group A: treated CE patients (n = 46); Group B: recurrent CE patients (n = 15)	- clinical pregnancy rate - ongoing pregnancy/live birth rate - miscarriage rate
Demirdag et al. 2021 [17]	retrospective, 2016–2019, Turkey	1164 patients undergoing an IVF cycle (232 RIF) - age of <40 years	- oocyte retrieval 36 h following ovulation induction; - 1–2 embryos; - transfer at days 3–5	biopsy and morphological examination - antibiotic therapy - IVF cycle monitoring	≥1 CD138+ cell per HPF	Group 1: treated CE patients (n = 129); Group 2: no-CE patients (n = 103); Group 3: first IVF cycle (n = 932)	- implantation rate - clinical pregnancy rate - live birth rate
Fan et al. 2019 [45]	retrospective, 2016–2018, China	141 patients aged 20–38 years undergoing the 1st IVF cycle	–	biopsy and morphological examination - IVF cycle monitoring	≥1 CD138+ cell per HPF or mm^2	Group 1: <1 CD138 cells (n = 97) Group 2: ≥1 CD138 cells (n = 44)	- implantation rate - clinical pregnancy rate
Hirata et al. 2021 [44]	prospective, 2014–2017, Japan	53 patients undergoing an IVF cycle - unexplained infertility; - age of <41 years	oocyte retrieval and freezing - transfer within 90 days of endometrial biopsy	hysteroscopy, biopsy, and morphological examination	four criteria: - ≥1 CD138+ cell / 10 HPF. - ≥2 - ≥3 - ≥4	according to the criterion: (≥1; 2; 3, 4) Group A: CE patients (26; 19; 14; 11) Group B: non-CE patients (27; 34; 39; 42)	- clinical pregnancy rate - live birth rate - miscarriage rate
Johnston-Mac Ananny et al. 2010 [**9**]	prospective, 2001–2007, US	518 RIF patients undergoing an ART cycle: 33 patients with endometrial biopsy and 485 patients without biopsy	oocyte retrieval 35 h following ovulation induction	biopsy and morphological examination - antibiotic therapy - IVF cycle monitoring	≥1 CD138+ cell per HPF	Group 1: treated CE patients (n = 10); Group 2: non-CE patients (n = 23); Group 3: RIF patients, no endometrial biopsy (n = 485)	- clinical pregnancy rate - ongoing pregnancy rate

Table 1. Continuation
Таблица 1. Продолжение

Kitaya et al. 2017 [**18**]	prospective cohort, 2011–2014, Japan	421 RIF patients who underwent up to three IVF cycles	–	hysteroscopy, biopsy, and morphological examination - antibiotic therapy - IVF cycle monitoring	endometrial stromal plasmacyte density index (ESPDI) of ≥0.25 (stromal PCs / total number of PCs)	Group A: treated CE patients (n = 116); Group B: recurrent CE patients (n = 4); Group C: non-CE patients (n = 226)	- clinical pregnancy rate - ongoing pregnancy/ live birth rate - miscarriage rate
Kuroda et al. 2020 [11]	crossover study, 2018–2020, Japan	88 infertile women	ovulation stimulation (follicle size of ≥17 mm); - oocyte retrieval 35 h following ovulation induction - IVF and vitrification	biopsy and morphological examination - ERA - antibiotic therapy - IVF cycle monitoring	≥5 CD138+ cells per ten random stromal areas	Group A: non-CE patients (n = 33); Group B: CE patients (n = 19), ERA; Group C: treated CE patients (n = 36)	- hCG+ - clinical pregnancy rate - miscarriage rate - ongoing pregnancy rate
Li et al. 2021 [**12**]	retrospective, 2017–2018, China	716 infertile patients undergoing an IVF cycle - age of <45 years; - previous antibiotic treatment for CE	–	- endometrial scratching - biopsy and morphological examination - IVF cycle monitoring	six diagnostic criteria - 0–4 PCs per 30 HPF; - ≥5 PCs per 30 HPF	Group A: 0 PCs (n = 433); Group B: 1 PC (n = 178); Group C: 2 PCs (n = 33); Group D: 3 PCs (n = 18); Group E: 4 PCs (n = 6); Group F: ≥5 PCs (n = 38)	- clinical pregnancy rate - live birth rate - miscarriage rate

Table 1. Continuation
Таблица 1. Продолжение

Xiong et al. 2021 [14]	retrospective, 2017–2018 China	640 patients undergoing an IVF cycle - without antibiotics prior to hysteroscopy - age of <40 years; - BMI of <30 kg/m^2 - transfer cycles within six months following antibiotics	ovulation stimulation at a follicle size of 18 mm; - oocyte retrieval 36 h following hCG administration	hysteroscopy, biopsy, and morphological examination - antibiotic therapy - IVF cycle monitoring	≥1 PC per HPF	Group 1: 0 PCs (n = 88); Group 2: 1–4 PCs with antibiotic treatment (n = 116); Group 3: 1–4 PCs without antibiotic treatment (n = 199). ------- Group 1: 0–4 PCs (n = 403); Group 2: treated CE (n = 211); ------- Group 1: 0–4 PCs (n = 403); Group 2: recurrent CE (n = 26)	- implantation rate - clinical pregnancy rate - live birth rate - early pregnancy loss rate - cumulative live birth rate
Zhang et al. 2019 [46]	prospective cohort, 2015–2017, China	298 RIF patients undergoing the 1st IVF cycle - age of <35 years; - ≥3 failed IVF cycles	ovulation stimulation at a follicle size of 17 mm - oocyte retrieval 36 h following ovulation induction	hysteroscopy, biopsy, and morphological examination - intrauterine antibiotic therapy - IVF cycle monitoring	≥1 PC per HPF	Group 1: non-CE patients (n = 126); Group 2: treated CE patients (n = 85); Group 3: recurrent CE patients (n = 24)	- implantation rate - clinical pregnancy rate - live birth rate - clinical losses

Note. The table was compiled by the authors; Abbreviations: CD — Cluster of Differentiation; ERA — Endometrial Receptivity Analysis; ESPDI — endometrial stromal plasmacyte density index; RIF — Recurent Implantation Failure; BMI — body mass index; PC — plasma cells; hCG — human chorionic gonadotropin; CE — chronic endometritis; IVF — in vitro fertilization.

Примечание: таблица составлена авторами. Сокращения: CD — Cluster of Differentiation; ERA — Endometrial Reciptivity Analysis; ESPDI — индекс плотности стромальных плазмоцитов эндометрия (endometrial stromal plasmacyte density index); RIF — Reccurent Implantation Failure; ИМТ — индекс массы тела; ПК — плазматические клетки; ХГЧ — хорионический гонадотропин человека; ХЭ — хронический эндометрит; ЭКО — экстракорпоральное оплодотворение.

Four studies included patients with recurrent implantation failures (defined as failure of at least two or three previous IVF attempts (fresh or frozen/thawed embryos), including at least one high-quality cleavage-stage embryo or blastocyst transferred per cycle) [6, 9, 17, 18, 44]. One study included patients with only one previous embryo transfer failure [45], while four studies analyzed infertile patients with previous non-elective embryo transfers [11, 12, 14, 44].

All of the women underwent IVF. Information on IVF protocols was missing in four studies [11, 17, 43, 44], while the remaining seven provided adequate information on the protocols of assisted reproductive technologies (ART). Ovarian stimulation was conducted by administering recombinant FSH alone or in combination with human menopausal gonadotropin using GnRH. The administration of hCG was performed following visualization (transvaginal ultrasound) of at least two preovulatory (17 mm) follicles; oocyte retrieval was conducted 34–36 h following ovulation induction (transfer of no more than three embryos or two blastocysts): two studies transferred only cleavage-stage embryos (up to three) [6, 46]; two studies transferred only blastocysts [11, 44]; and two studies transferred both cleavage-stage embryos and blastocysts [14, 17].

Two studies provided no data on the embryo stage [9, 43]. Gestagen luteal phase support was carried out in all studies providing data on IVF protocols.

Risk of bias

All RCTs used randomization without allocation concealment—blinding of study participants and staff was not conducted due to patient specificity (infertility, in vitro fertilization protocol). Three studies had adequate sample representativeness [6, 17, 45], while the rest had a high risk of systematic error. Three studies reported an adequate (consistent) sampling strategy [11, 17, 18], whereas most studies provided no accurate data. In the diagnosis of chronic endometritis, all studies had a low risk of bias (≥3 points) (Table 2).

Two studies failed to clearly describe the study population or did not fully report descriptive statistics [18, 46], while the others had a low risk of bias for this domain. Three studies provided incomplete data on outcomes [17, 18, 45]. According to the assigned points, all studies have a low risk of bias.

Results of individual studies and their synthesis

Results of the meta-analysis of primary endpoints

Diagnosis of chronic endometritis

Plasma cell identification was achieved via hematoxylin and eosin (H&E) staining alone or in combination with immunohistochemical analysis of CD138+ cells, with the exception of the study that only provided an immunohistochemical analysis of PCs [43]. Six studies collected endometrial samples during the follicular phase in [6, 14, 18, 44, 45, 46]; one study performed endometrial biopsies either in the follicular or mid-luteal phase (cycle days 21–23) [17]; two studies collected samples in the mid-luteal phase [11, 12].

CE therapy

The first-line antibiotic therapy for CE was microbe-specific, with a microbiological culture assessment of the endometrium [6, 11, 46] or empiric (doxycycline [9, 14, 1, 43] or ciprofloxacin and metronidazole for 14 days [18]).

Summary of the results

CE patients vs non-CE patients

Data from eight studies [9, 11, 12, 14, 17, 18, 44, 46] showed significantly lower OPR/LBR (OR 1.97; 95% CI 1.11–3.48; I^2=64%; $p < 0.02$) and CPR (OR 2.28; 95% CI 1.34–3.86; I^2=70%; $p < 0.002$) in CE patients as compared to non-CE patients, with no difference in the MR ($p <$ ns) (Tables 3–5; Figs. 2–4).

The sequential exclusion of each study from the meta-analysis provided no significant changes in the pooled results in terms of OPR/LBR, CPR, and MR.

CE patients vs treated CE patients

Four studies revealed higher OPR/LBR (OR 5.33; 95% CI 2.41–11.79; I^2=0%; $p < 0.0001$) and CPR (OR 3.64; 95% CI 1.89–7.04; I^2=0; $p < 0.0001$) in patients with treated CE as compared to patients with untreated/recurrent CE [6, 11, 18, 46], with a borderline significance in terms of MR ($p < 0.05$) (Tables 6–8; Figs. 5–7). The sequential exclusion of individual

Table 2. Risk of bias assessment
Таблица 2. Оценка риска смещения

Authors and year	Sample representativeness	Sampling procedure	Quality of patient descriptions	Incomplete data on outcomes	Total score	Risk of bias
Cicinelli et al. 2015 [6]	*	-	*	*	****	low
Demirdag et al. 2021 [17]	*	*	*	-	****	low
Fan et al. 2019 [45]	*	-	*	-	***	low
Hirata et al. 2021 [44]	-	-	*	*	***	low
John.-MacAnanny et al. 2010 [9]	-	-	*	*	***	low
Kitaya et al. 2017 [18]	*	*	-	-	***	low
Kuroda et al. 2020 [11]	-	*	*	*	****	low
Li et al. 2021 [12]	*	-	*	*	****	low
Xiong et al. 2021 [14]	*	-	*	*	****	low
Zhang et al. 2019 [46]	*	-	-	*	***	low

Note. The table was compiled by the authors.

Примечание: таблица составлена авторами.

Table 3. Ongoing pregnancy / live birth rate (CE patients vs. non-CE patients)
Таблица 3. Коэффициент частоты продолжающейся беременности/рождаемости (хронический эндометрит и нехронический эндометрит)

	non-CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	31	103	36	129	20.2	1.11 (0.63, 1.97)
J.-MacAnanny 2010 [9]	12	23	1	10	5.2	9.82 (1.06, 9.59)
Kitaya 2017 [18]	50	226	0	4	3.3	2.58 (1.14, 8.63)
Zhang 2019 [46]	22	126	3	24	11.0	1.48 (0.41, 5.40)
Hirata 2021 [44]	14	27	6	26	12.1	3.59 (1.10, 11.73)
Kuroda 2020 [11]	18	27	3	18	9.4	10.00 (2.29, 4.73)
Li 2021 [12]	221	443	142	273	23.7	0.92 (0.68, 1.24)
Xiong 2021 [14]	42	83	8	26	15.1	2.05 (0.81, 5.22)
Total (95% CI)		1063		510	100.0	1.96 (1.11, 3.68)
Total No. of cases	410		199			
Heterogeneity: *tau²=0.33; Chi²=15.43; df=7 (P < 0.007); I²=64%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.
Table 4 . Clinical pregnancy rate (CE patients vs. non-CE patients)
Таблица 4. Коэффициент частоты клинической беременности (хронический эндометрит и нехронический эндометрит)

	non-CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	39	103	47	129	16.4	1.06 (0.62, 1.82)
Fan 2019 [45]	78	97	23	44	13.8	3.75 (1.73, 8.14)
J.-MacAnanny 2010 [9]	12	23	2	10	6.2	4.36 (0.76, 25.17)
Kitaya 2017 [18]	61	226	0	4	2.8	3.34 (0.18, 63.03)
Zhang 2019 [46]	40	126	6	24	11.6	1.40 (0.51, 3.78)
Hirata 2021 [44]	17	27	8	26	10.2	3.83 (1.22, 11.98)
Kuroda 2020 [11]	21	27	4	18	8.0	12.25 (2.92, 51.42)
Li 2021 [12]	283	443	172	273	18.4	1.04 (0.76, 1.42)
Xiong 2021 [14]	58	88	11	26	12.6	2.64 (1.08, 6.45)
Total (95% CI)		1160		554	100.0	2.28 (1.34, 3.86)
Total No. of cases	609		273			
Heterogeneity: *tau²=0.37; Chi²=26.24; df=8 (P < 0.0010); I²=70%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

studies from the meta-analysis provided no significant changes in the pooled results for OPR/LBR and CPR (sensitivity analysis was impossible for MR).

Treated CE patients vs non-CE patients

An analysis of 609 patients from three studies [11, 18, 46] showed no difference between the groups in terms of OPR/LBR, CPR, and MR (p < ns) (Tables 9–11; Figs. 8–10).

A sensitivity analysis was not possible due to the small number of studies included in the meta-analysis (n = 3).

CE patients vs patients who were not tested for this pathology

A pooled analysis of data on 1,556 patients from two studies [9, 17] showed lower OPR/LBR (OR 0.55; 95% CI 0.37–0.82; I^2=0%; p < 0.003) and CPR (OR 0.59; 95% CI 0.41–0.85; I^2=0%; p < 0.005) in untreated CE patients as compared to those who was not tested for CE. No differences in miscarriage rates (p < ns) were found (Tables 12–14; Figs. 11–13).

A sensitivity analysis was not possible due to the small number of studies included in the meta-analysis (n = 2).

Severe CE patients vs mild CE patients

Two studies [12, 14] showed that severe CE (≥5 PCs per HPF) was associated with significantly lower OPR/LBR (OR 0.43; 95% CI 0.25–0.74; I^2=0%; p < 0.003) and CPR (OR 0.40; 95% CI 0.24–0.68; I^2=0%; p < 0.0007) as compared to mild CE (1–4 PCs per HPF), with no difference in the miscarriage rate (Table 15–17; Figs. 14–16).

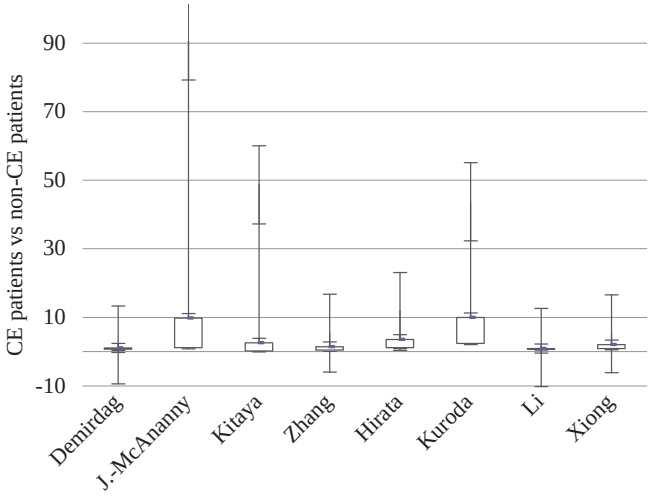

Fig. 2: Odds ratio (95% CI) (ongoing pregnancy / live birth rate)

Note: The figure was created by the authors. Abbreviations: ХЭ — chronic endometritis; CI — confidence interval.

Рис. 2. Отношение шансов (95% ДИ) (частота продолжающейся беременности/рождаемости)

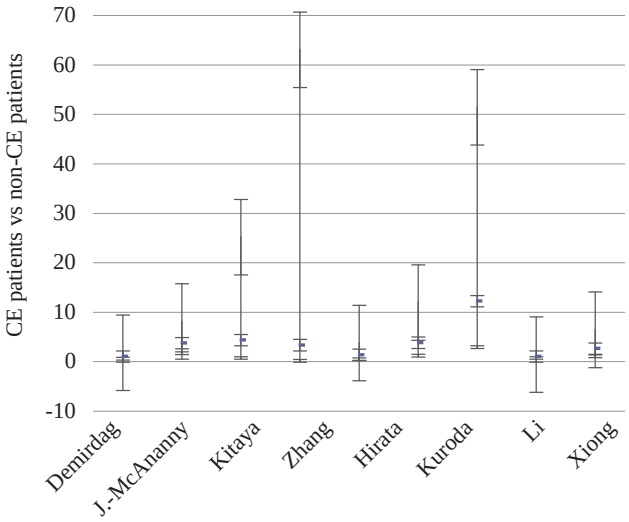

Fig. 3. Odds ratio (95% CI) (clinical pregnancy rate)

Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.

Рис. 3. Отношение шансов (95% ДИ) (частота клинической беременности)

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 5. Miscarriage rate (CE patients vs non-CE patients)

Таблица 5. Коэффициент частоты выкидышей (хронический эндометрит и нехронический эндометрит)

	non-CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	8	39	11	47	18.9	0.84 (0.30, 2.36)
J.-MacAnanny 2010 [9]	0	12	1	2	1.5	0.04 (0.00, 1.50)
Zhang 2019 [46]	18	40	3	6	6.8	0.82 (0.15, 4.56)
Hirata 2021 [44]	3	17	2	8	4.9	0.64 (0.08, 4.89)
Kuroda 2020 [11]	3	21	1	4	3.0	0.50 (0.04, 6.55)
Li 2021 [12]	36	283	18	172	55.4	1.25 (0.68, 2.27)
Xiong 2021 [14]	16	58	3	11	9.6	1.02 (0.24, 4.32)
Total (95% CI)		470		250	100.0	0.99 (0.63, 1.54)
Total No. of cases	84		39			
Heterogeneity: *tau²=0.00; Chi²=4.17; df=6 (P < 0.065); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

A sensitivity analysis was not possible due to the small number of studies included in the meta-analysis (n = 2).

Mild CE patients vs patients untested for CE

No differences were found between the groups [12, 14] in terms of OPR/LBR, CPR, and MR (p < ns) (Tables 18–20; Figs. 17–19).

A sensitivity analysis was not possible due to the small number of studies included in the meta-analysis (n = 2).

Risk of bias in all studies

Due to the limited number of included studies, publication bias could not be effectively represented using a funnel chart.

Additional analyses

No additional analyses were planned for this study.

DISCUSSION

Interpretation of results

The present systematic review summarizes the available data on the impact of chronic endometritis, its therapy, and its severity on the outcome of assisted reproductive technologies. The analysis included a total of 4,145 infertile patients from 11 studies [6, 9, 11, 12, 14, 17, 18, 43, 44, 45, 46]; of these, 1,716 were women with recurrent implantation failures. The overall quality of the included studies was considered satisfactory (no study had a high risk of bias).

Noteworthy is that non-CE women showed a significantly higher live birth rate (OPR/LBR) (OR 1.97; 95% CI 1.11–3.48) and clinical pregnancy rate (CPR) (OR 2.28; 95% CI

Table 6. Ongoing pregnancy / live birth rate (CE patients vs treated CE patients)
Таблица 6. Коэффициент частоты продолжающейся беременности/рождаемости (хронический эндометрит и пролеченный хронический эндометрит)

	Treated CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Cicinelli 2015 [6]	28	46	2	15	24.5	10.11 (2.04, 50.19)
Kitaya 2017 [18]	25	116	0	4	7.3	5.73 (0.30, 98.91)
Kuroda 2020 [11]	11	29	3	18	30.0	3.06 (0.72, 13.01)
Zhang 2019 [46]	37	85	3	24	38.2	5.40 (1.50, 19.47)
Total (95% CI)		276		61	100.0	5.33 (2.41, 11.79)
Total No. of cases	121		8			
Heterogeneity: *tau²=0.00; Chi²=1.18; df=3 (P < 0.76); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 7. Clinical pregnancy rate (CE patients vs treated CE patients)
Таблица 7. Коэффициент частоты клинической беременности (хронический эндометрит и пролеченный хронический эндометрит)

	Treated CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Cicinelli 2015 [6]	30	46	5	15	28.5	3.75 (1.09, 12.87)
Kitaya 2017 [18]	53	116	0	4	5.0	7.58 (0.40, 94.05)
Kuroda 2020 [11]	15	29	4	18	24.6	3.75 (0.99, 14.16)
Zhang 2019 [46]	44	85	6	24	41.9	3.22 (1.16, 8.90)
Total (95% CI)		276		61	100.0	3.64 (1.89, 7.04)
Total No. of cases	142		15			
Heterogeneity: *tau²=0.00; Chi²=0.30; df=3 (P < 0.96); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.

Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 8. Miscarriage rate (CE patients vs treated CE patients)
Таблица 8. Коэффициент частоты выкидышей (хронический эндометрит и пролеченный хронический эндометрит)

	Treated CE		CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Cicinelli 2015 [6]	2	30	3	5	31.2	0.05 (0.00, 0.47)
Kuroda 2020 [11]	4	15	1	4	27.3	1.09 (0.09, 13.78)
Zhang 2019 [46]	7	44	3	6	41.6	0.19 (0.03, 1.14)
Total (95% CI)		89		15	100.0	0.20 (0.04, 0.98)
Total No. of cases	13		7			
Heterogeneity: *tau²=0.76; Chi²=3.22; df=2 (P < 0.20); I²=38%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.

Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

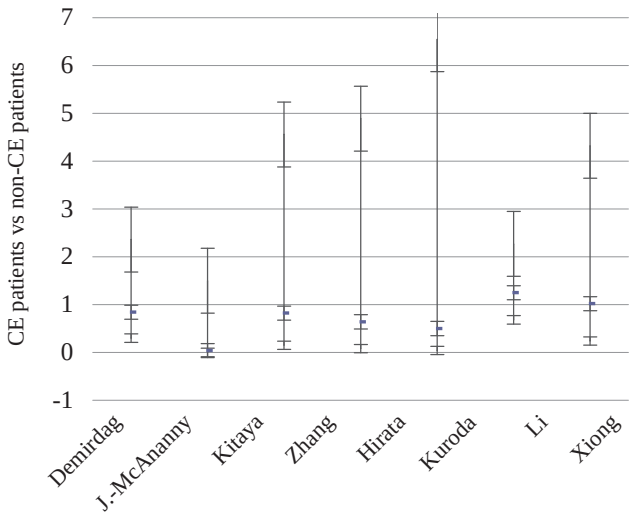

Fig. 4. Odds ratio (95% CI) (miscarriage rate)
Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.
Рис. 4. Отношение шансов (95% ДИ) (коэффициент частоты выкидышей)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

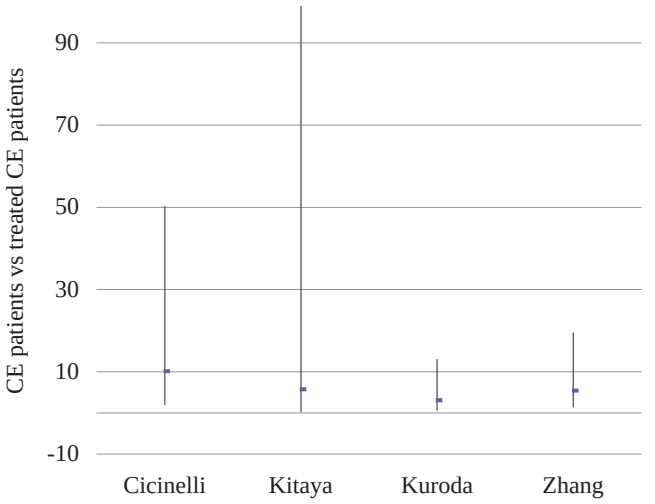

Fig. 5. Odds ratio (95% CI) (ongoing pregnancy / live birth rate)
Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.
Рис. 5. Отношение шансов (95% ДИ) (Коэффициент частоты продолжающейся беременности/рождаемости)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

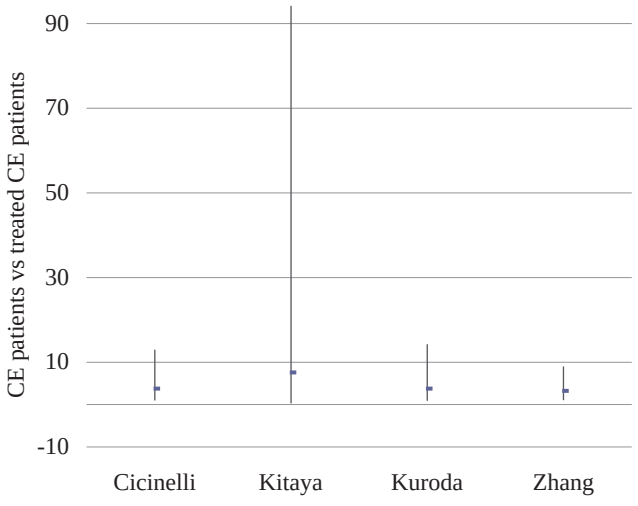

Fig. 6. Odds ratio (95% CI) (clinical pregnancy rate)
Note: The figure was created by the authors. Abbreviations: ХЭ — chronic endometritis; CI — confidence interval.
Рис. 6. Отношение шансов (95% ДИ) (коэффициент частоты клинической беременности)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

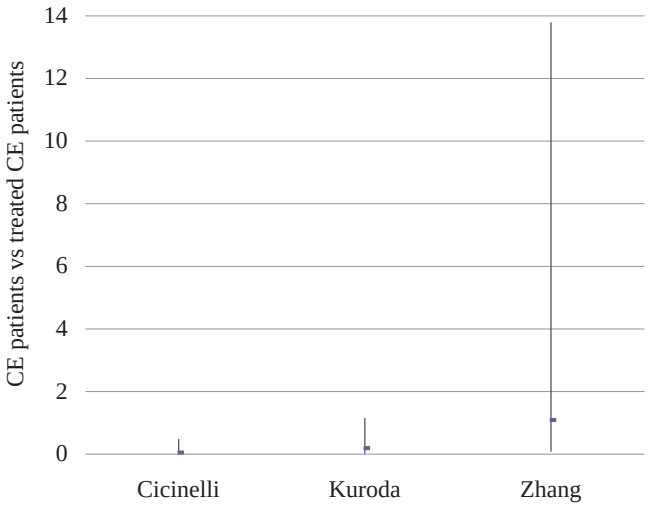

Fig. 7. Odds ratio (95% CI) (miscarriage rate)
Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.
Рис. 7. Отношение шансов (95% ДИ) (коэффициент частоты выкидышей)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 9. Ongoing pregnancy / live birth rate (non-CE patients vs treated CE patients)
Таблица 9. Коэффициент частоты продолжающейся беременности/рождаемости (не-хронический эндометрит против пролеченного хронического эндометрита)

	Treated CE		non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Kitaya 2017 [18]	38	116	50	226	36.6	1.71 (1.04, 2.82)
Kuroda 2020 [11]	11	29	18	27	28.4	0.31 (0.10, 0.91)
Zhang 2019 [46]	37	85	22	126	35.0	3.64 (1.94, 6.83)
Total (95% CI)		230		379	100.0	1.37 (0.46, 4.11)
Total No. of cases	86		90			
Heterogeneity: *tau²=0.79; Chi²=14.91; df=2 (P < 0.0006); I²=87%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 10. Clinical pregnancy rate (non-CE patients vs treated CE patients)
Таблица 10. Коэффициент частоты клинической беременности (не-хронический эндометрит против пролеченного хронического эндометрита)

	Treated CE		Non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Kitaya 2017 [18]	43	116	61	226	39.0	1.59 (0.99, 2.57)
Kuroda 2020 [11]	15	29	21	27	24.0	0.31 (0.10, 0.98)
Zhang 2019 [46]	44	85	40	126	37.0	2.31 (1.31, 4.07)
Total (95% CI)		230		379	100.0	1.23 (0.53, 2.85)
Total No. of cases	102		122			
Heterogeneity: *tau²=0.41; Chi²=9.36; df=2 (P < 0.009); I²=79%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 11. Miscarriage rate (non-CE patients vs treated CE patients)
Таблица 11. Коэффициент частоты выкидышей (нехронический эндометрит против пролеченного хронического эндометрита)

	Treated CE		Non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Kitaya 2017 [18]	5	43	10	61	35.6	0.67 (0.21, 2.13)
Kuroda 2020 [11]	4	15	3	21	26.0	2.18 (0.41, 11.64)
Zhang 2019 [46]	7	44	18	40	38.4	0.23 (0.08, 0.64)
Total (95% CI)		102		122	100.0	0.61 (0.18, 1.99)
Total No. of cases	16		31			
Heterogeneity: *tau²=0.69; Chi²=5.42; df=2 (P < 0.007); I²=63%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

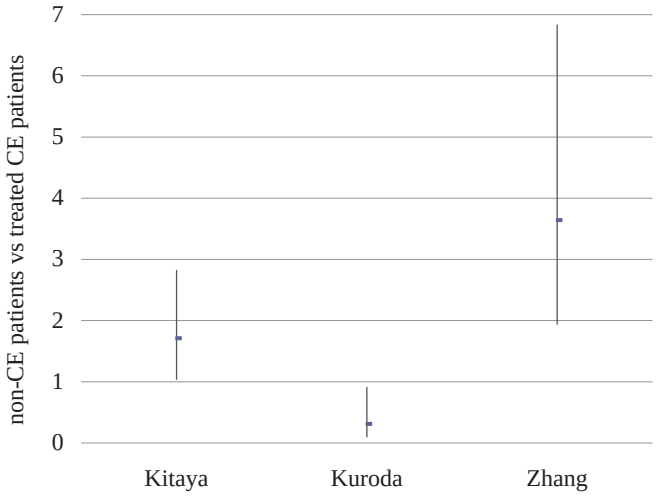

Fig. 8. Odds ratio (95% CI) (ongoing pregnancy / live birth rate)

Note: The figure was created by the authors. Abbreviations: ХЭ — chronic endometritis; CI — confidence interval.

Рис. 8. Отношение шансов (95 % ДИ) (коэффициент частоты продолжающейся беременности/рождаемости)

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

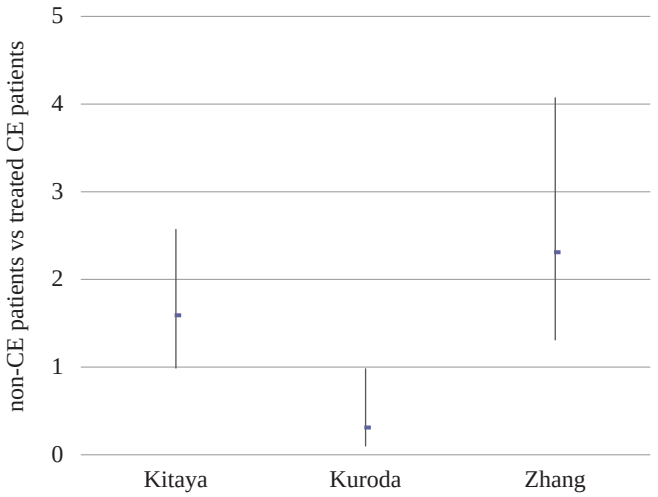

Fig. 9. Odds ratio (95% CI) (clinical pregnancy rate)

Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.

Рис. 9. Отношение шансов (95 % ДИ) (коэффициент частоты клинической беременности)

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

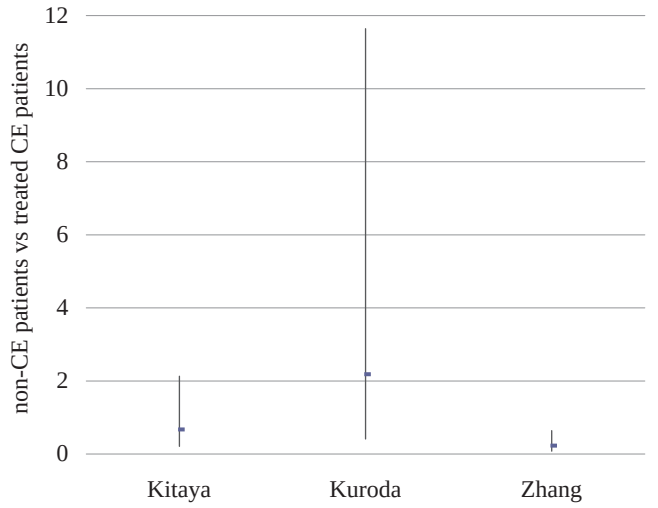

Fig. 10. Odds ratio (95% CI) (miscarriage rate)

Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.

Рис. 10. Отношение шансов (95 % ДИ) (коэффициент частоты выкидышей)

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

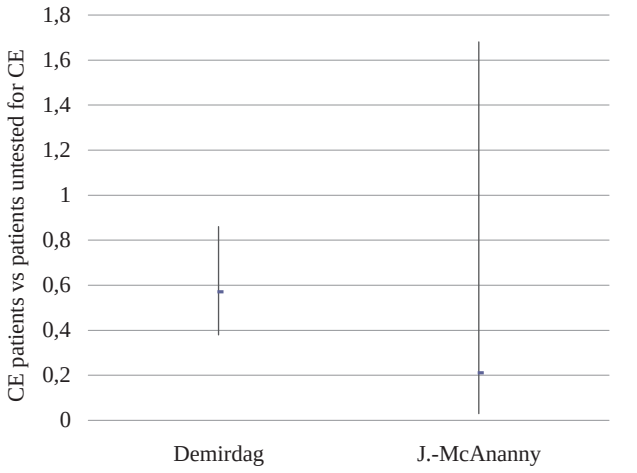

Fig. 11. Odds ratio (95% CI) (ongoing pregnancy / live birth rate)

Note: The figure was created by the authors. Abbreviations: ХЭ — chronic endometritis; CI — confidence interval.

Рис. 11. Отношение шансов (95 % ДИ) (коэффициент частоты продолжающейся беременности/рождаемости)

Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 12. Ongoing pregnancy / live birth rate (CE patients vs patients untested for CE)
Таблица 12. Коэффициент частоты продолжающейся беременности/рождаемости (хронический эндометрит против нетестированного хронического эндометрита)

	CE		Untested for CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	36	129	377	932	96.3	0.57 (0.38, 0.86)
J.-MacAnanny 2010 [9]	1	10	157	485	3.7	0.21 (0.03, 1.68)
Total (95% CI)		139		1417	100.0	0.55 (0.37, 0.82)
Total No. of cases	37		544			
Heterogeneity: *tau²=0.00; Chi²=0.84; df=1 (P < 0.036); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 13. Clinical pregnancy rate (CE patients vs. patients untested for CE)
Таблица 13. Коэффициент частоты клинической беременности (ХЭ против нетестированного ХЭ)

	CE		Untested for CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	47	129	453	932	94.4	0.61 (0.38, 0.89)
J.-MacAnanny 2010 [9]	2	10	197	485	5.6	0.37 (0.08, 1.74)
Total (95% CI)		139		1417	100.0	0.59 (0.41, 0.85)
Total No. of cases	49		650			
Heterogeneity: *tau²=0.00; Chi²=0.38; df=1 (P < 0.54); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 14. Miscarriage rate (CE patients vs patients untested for CE)
Таблица 14. Коэффициент частоты выкидышей (хронический эндометрит против нетестированного хронического эндометрита)

	CE		Untested for CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Demirdag 2021 [17]	11	47	76	453	93.8	1.52 (0.74, 3.11)
J.-MacAnanny 2010 [9]	1	2	20	197	6.2	5.57 (0.34, 91.44)
Total (95% CI)		49		650	100.0	1.64 (0.82, 3.30)
Total No. of cases	12		106			
Heterogeneity: *tau²=0.00; Chi²=0.78; df=1 (P < 0.38); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

Table 15. Ongoing pregnancy/live birth rate (severe CE patients vs. mild CE patients)
Таблица 15. Коэффициент частоты продолжающейся беременности/рождаемости (тяжелая степень хронического эндометрита против легкой степени хронического эндометрита)

	CE, ≥5 PCs		CE, 1–4 PCs		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	15	36	127	206	58.6	0.44 (0.22, 0.91)
Xiong 2021 [14]	8	26	210	403	41.4	0.41 (0.17, 0.96)
Total (95% CI)		62		609	100.0	0.43 (0.25, 0.74)
Total No. of cases	23		377			
Heterogeneity: *tau²=0.00; Chi²=0.02; df=1 (P < 0.88); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

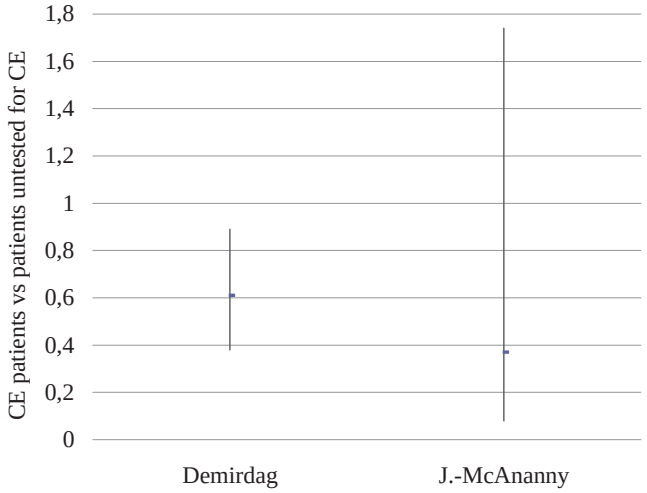

Fig. 12. Odds ratio (95% CI) (miscarriage rate)
Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.

Рис. 12. Отношение шансов (95 % ДИ) (коэффициент частоты выкидышей)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

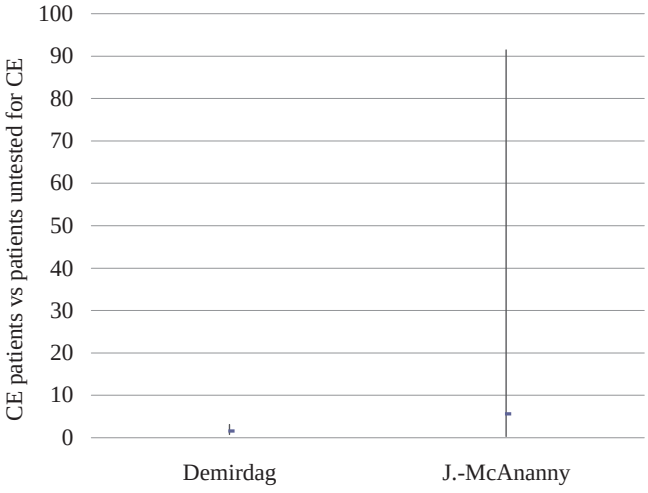

Fig. 13. Odds ratio (95% CI) (MR)
Note. The figure was created by the authors. Abbreviations: CE — chronic endometritis; CI — confidence interval.

Рис. 13. Отношение шансов (95 % ДИ) (ЧВ)
Примечание: рисунок выполнен авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал.

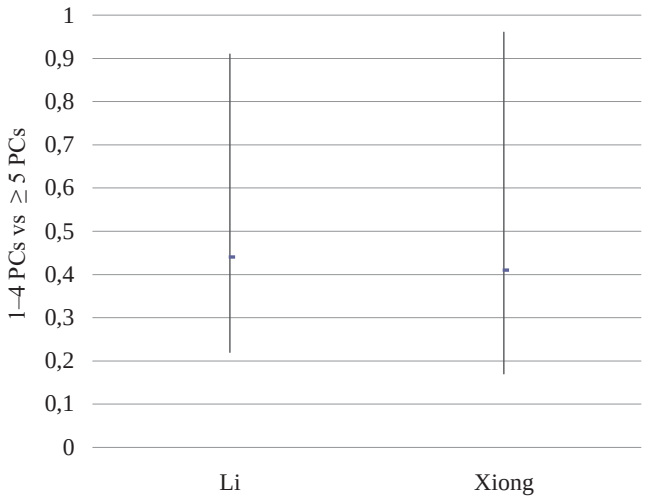

Fig. 14. Odds ratio (95% CI) (ongoing pregnancy/live birth rate)
Note: The figure was created by the authors. Abbreviations: ПК — plasma cells; CI — confidence interval.

Рис. 14. Отношение шансов (95 % ДИ) (коэффициент частоты продолжающейся беременности/рождаемости)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал.

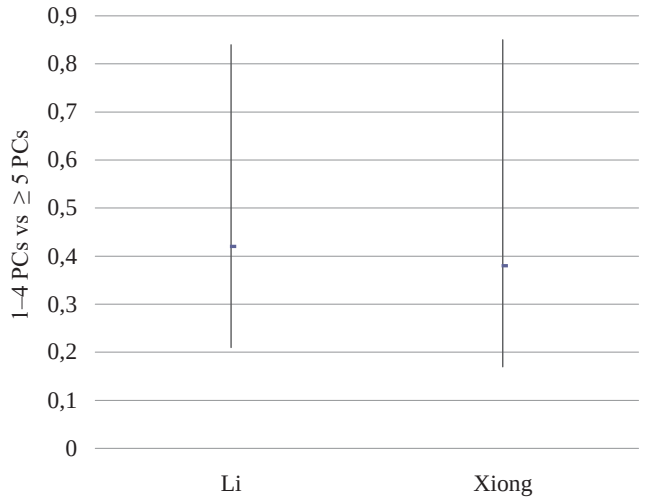

Fig. 15. Odds ratio (95% CI) (clinical pregnancy rate)
Note: The figure was created by the authors. Abbreviations: ПК — plasma cells; CI — confidence interval.

Рис. 15. Отношение шансов (95 % ДИ) (коэффициент частоты клинической беременности)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал

Table 16. Clinical pregnancy rate (severe CE patients vs mild CE patients)
Таблица 16. Коэффициент частоты клинической беременности (тяжелая степень хронического эндометрита против легкой степени хронического эндометрита)

	CE, ≥5 PCs		CE, 1–4 PCs		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	17	38	155	235	57.3	0.42 (0.21, 0.84)
Xiong 2021 [14]	11	26	265	403	42.7	0.38 (0.17, 0.85)
Total (95% CI)		64		638	100.0	0.40 (0.24, 0.68)
Total No. of cases	28		420			
Heterogeneity: *tau²=0.00; Chi²=0.03; df=1 (P < 0.87); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

Table 17. Miscarriage rate (severe CE patients vs. mild CE patients)
Таблица 17. Коэффициент частоты выкидышей (тяжелая степень хронического эндометрита против легкой степени хронического эндометрита)

	CE, ≥5 PCs		CE, 1–4 PCs		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	1	17	17	155	35.5	0.51 (0.06, 4.07)
Xiong 2021 [14]	3	11	38	265	64.5	2.24 (0.57, 8.82)
Total (95% CI)		28		420	100.0	1.32 (0.33, 5.32)
Total No. of cases	4		55			
Heterogeneity: *tau²=0.29; Chi²=1.36; df=1 (P < 0.24); I²=27%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

Table 18. Ongoing pregnancy / live birth rate (mild CE patients vs patients untested for CE)
Таблица 18. Коэффициент частоты продолжающейся беременности/рождаемости (легкая степень хронического эндометрита против нетестированного хронического эндометрита)

	CE, 1–4 PCs		Non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	210	403	221	381	62.7	0.79 (0.59, 1.04)
Xiong 2021 [14]	104	199	42	88	37.3	1.20 (0.73, 1.98)
Total (95% CI)		602		469	100.0	0.92 (0.62, 1.37)
Total No. of cases	314		263			
Heterogeneity: *tau²=0.05; Chi²=2.04; df=1 (P < 0.15); I²=51%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

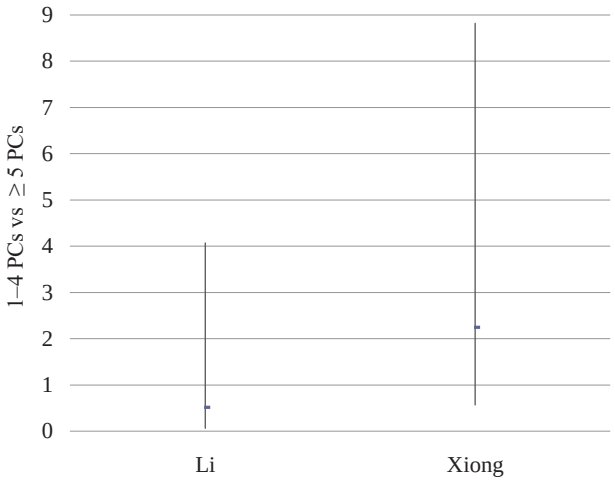

Fig. 16. Odds ratio (95% CI) (miscarriage rate)
Note: The figure was created by the authors. Abbreviations: ПК — plasma cells; CI — confidence interval.
Рис. 16. Отношение шансов (95 % ДИ) (коэффициент частоты выкидышей)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал.

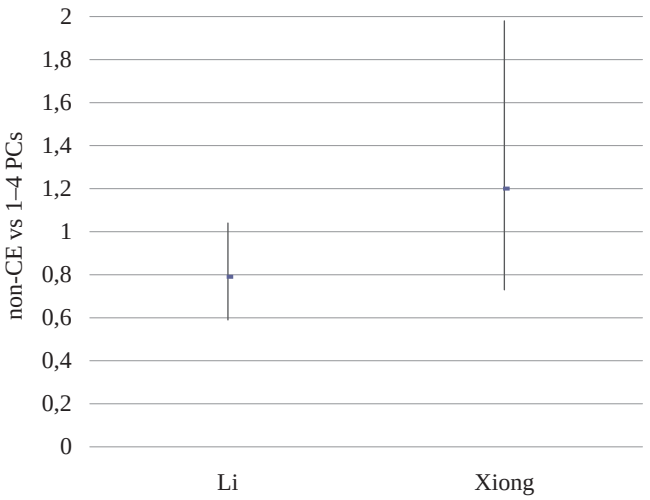

Fig. 17. Odds ratio (95% CI) (ongoing pregnancy / live birth rate)
Note. The figure was created by the authors. Abbreviations: PC — plasma cells; CI — confidence interval.
Рис. 17. Отношение шансов (95 % ДИ) (коэффициент частоты продолжающейся беременности/рождаемости)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал.

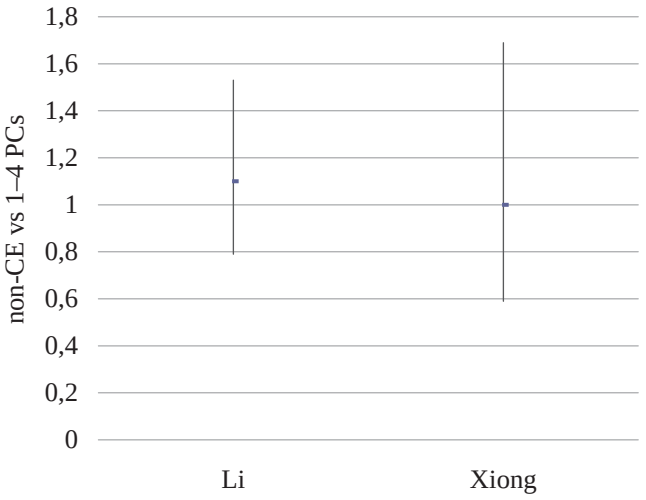

Fig. 18. Odds ratio (95% CI) (clinical pregnancy rate)
Note: The figure was created by the authors. Abbreviations: ПК — plasma cells; CI — confidence interval.
Рис. 18. Отношение шансов (95 % ДИ) (коэффициент частоты клинической беременности)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал.

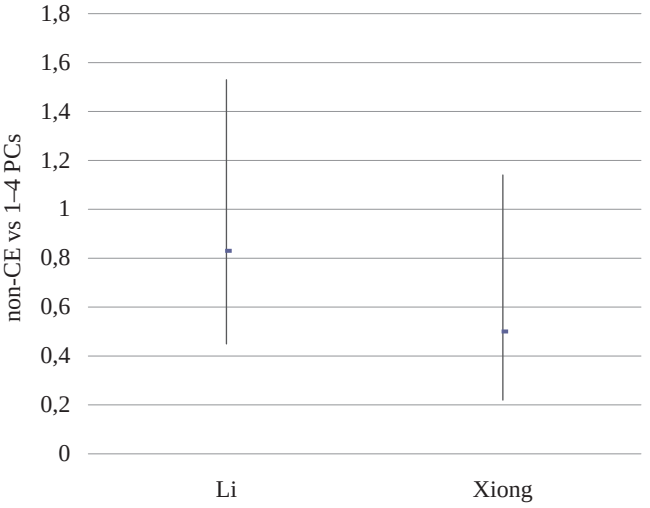

Fig. 19. Odds ratio (95% CI) (miscarriage rate)
Note: The figure was created by the authors. Abbreviations: ПК — plasma cells; CI — confidence interval.
Рис. 19. Отношение шансов (95 % ДИ) (коэффициент частоты выкидышей)
Примечание: рисунок выполнен авторами. Сокращения: ПК — плазматические клетки; ДИ — доверительный интервал.

Table 19. Clinical pregnancy rate (mild CE patients vs patients untested for CE)
Таблица 19. Коэффициент частоты клинической беременности (легкая степень хронического эндометрита против нетестированного хронического эндометрита)

	CE, 1–4 PCs		Non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	155	235	283	443	71.7	1.10 (0.79, 1.53)
Xiong 2021 [14]	131	199	58	88	28.3	1.00 (0.59, 1.69)
Total (95% CI)		434		531	100.0	0.40 (0.24, 0.68)
Total No. of cases	286		341			
Heterogeneity: *tau²=0.00; Chi²=0.09; df=1 (P < 0.77); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

Table 20. Miscarriage rate (mild CE patients vs patients untested for CE)
Таблица 20. Коэффициент частоты выкидышей (легкая степень хронического эндометрита против нетестированного хронического эндометрита)

	CE, 1–4 PCs		Non-CE		Study weight	Odds ratio
	No. of cases	Total No. of patients	No. of cases	Total No. of patients	%	95% CI
Li 2021 [12]	17	155	36	278	64.9	0.83 (0.45, 1.53)
Xiong 2021 [14]	15	131	12	58	35.2	0.50 (0.22, 1.14)
Total (95% CI)		286		336	100.0	0.69 (0.42, 1.13)
Total No. of cases	32		48			
Heterogeneity: *tau²=0.00; Chi²=0.95; df=1 (P < 0.33); I²=0%*						

Note. The table was compiled by the authors; Abbreviations: CE — chronic endometritis; CI — confidence interval; PC — plasma cells.
Примечание: таблица составлена авторами. Сокращения: ХЭ — хронический эндометрит; ДИ — доверительный интервал; ПК — плазматические клетки.

1.34–3.86) as compared to patients with diagnosed CE. This fact is consistent with the number of failed embryo transfers ($p < 0.05$) and supports the concept that CE has a negative effect on implantation [39], which is confirmed by a sufficiently large number of studies included in this meta-analysis, having equivalent approaches to CE diagnosis (i.e., CD138+ immunohistochemistry) [6, 9, 11, 12, 14, 17, 17, 18, 44, 45, 46].

Several major factors are currently considered responsible for reproductive dysfunction in CE [20]: this is primarily the abnormal uterine microbiome, as demonstrated by a sufficient number of microbiological studies [1, 47–50], the disruption of cytobiochemical and immune processes in the endometrium [28, 36, 51–54], and also confirmed by the improved fertility following antibacterial therapy in CE patients [34, 55, 56]. The abnormal uterine microbiome leads to immune deviations primarily affecting the leukocyte pool of immunocompetent cells with a change in the ratio of pro- and anti-inflammatory cytokines, which results in the reduced implantation capacity of the endometrium and prevents embryo invasion [19, 20, 22, 57]. In addition, prolonged activation of proliferation gene regulation with the downregulation of apoptotic genes (necessary for maintaining adequate endometrial responses) may contribute to the development of proliferative lesions such as polyps [25, 34, 55, 58, 61], whereas changes in the vascularization and decidualization of secretory endometrium in the presence of CE may additionally contribute to its receptivity impairment [9, 59, 60, 62].

On the basis of data from two studies (which somewhat limits the value of their interpretation), patients with diagnosed CE were found to have worse IVF outcomes as compared to a group of infertile women who were not tested for this pathology (OPR/LBR: OR 0.55; 95% CI 0.37–0.82; CPR: OR 0.59; 95% CI 0.41–0.85; $p < 0.05$) [9, 17]. If this result is confirmed by further studies, it could theoretically justify CE testing prior to IVF to identify (and treat) women with an expected poor reproductive prognosis. This is supported by the significant improvement in IVF outcomes following CE treatment that are presented in the review. It is true that the OPR/LBR and CPR were significantly higher following CE treatment as compared to those of patients with untreated or recurrent CE (OR 5.33; 95% CI 2.41–11.79; OR 3.64, 95% CI 1.89–7.04; $p < 0.05$). In addition, treated CE patients had similar IVF outcomes as women without this pathology ($p>0.05$), potentially indicating endometrial receptivity recovery after therapy.

Our conclusions for the MR seem to deviate from those for the other outcomes (OPR/LBR and CPR). The meta-analysis

found neither a significant effect of CE on the miscarriage rate nor improvements in pregnancy outcomes in treated patients ($p < 0.05$). It can be assumed that spontaneous abortion involves too many different etiopathogenetic factors related to both the mother and the embryo which in this case reduces the role of endometrial inflammation [63–66]. In particular, aneuploidy is considered to be the main factor behind miscarriage, while maternal age (≥35 years) constitutes a major risk factor [61, 67–70]. Most studies included in this meta-analysis had specific age limits: under 44 [12], 40 [44], 39 [6, 14, 17], and 38 years [45], while others (where age limits were not specified) reported mean patient ages close to [9] or above 35 years [11, 18]. None of the studies conducted preimplantation genetic testing for aneuploidies. The only study conducted in women aged under 35 years showed a trend toward a higher miscarriage rate in CE patients as compared to healthy women or treated CE patients [46]. Also, we should note statistical problems associated with the sample size of patients taking into account the realization of their reproductive function and a high risk of error, as any comparative studies of miscarriage rate (MR) are inadequate as compared to the population-based estimation of CPR or OPR/LBR.

Unambiguous results were obtained when comparing the effect of severe (≥5 PCs per HPF) and mild (1–4 PCs per HPF) CE on IVF outcomes. Two studies showed that severe CE is associated with lower OPR/LBR (OR 0.43; 95% CI 0.25–0.74) and CPR (OR 0.40; 95% CI 0.24–0.68; $p < 0.05$) [12, 14]. Of note is that mild CE patients exhibited similar results in terms of clinical pregnancy and live birth rates as women without this pathology (p>0.05). These data are consistent with the conclusions that a higher number of CD138+ cells determines a worse IVF outcome [12, 45]. Although the possibility of categorizing CE by severity is attractive from a practical point of view, the available evidence is insufficient to consider "mild CE" as a condition that does not pose a significant threat to the implantation capacity of the endometrium [37]. CE classification that is based solely on plasma cell counts, although practical, is potentially prone to clinical errors due to the ambiguity of sampling methods—blind endometrial biopsy (pipelle biopsy or curettage), where the diagnosis may depend on the amount of captured endometrial tissue, especially if the distribution of PCs is heterogeneous. In addition, the severity of the process may be underestimated in the case of focal CE due to the random nature of morphological material collection from the uterine cavity. An equally important issue is that if PC counts are based solely on CD138+ staining, there is a possibility of overdiagnosis due to the background reaction of adjacent cells [34].

One of the most promising additional methods for diagnosing CE is hysteroscopy [6, 16, 32, 34, 65, 71], especially in cases of diagnostic uncertainties [70, 72, 73]. Through visual evaluation of the entire endometrial surface, hysteroscopy can enable the identification of specific endometrial changes that are consistent with severe forms (e.g., micropolyps) [73, 74]. In this connection, some studies indicate inconsistency between the CE diagnosis made on the basis of plasma cell counts and those made via hysteroscopy [6, 22, 32]. Therefore, we cannot exclude that the combination of the two methods may provide a higher diagnostic and prognostic value than immunohistochemistry alone. For example, in a study by Yang R. et al. (2014), patients whose control hysteroscopy showed no CE signs exhibited better IVF outcomes as compared to women whose recovery was assessed via immunohistochemistry (no PCs) [75]. Also, hysteroscopy is a technique that enables endometrial material sampling under visual control [76–78]. However, despite the fact that the use of hysteroscopy with biopsy is mandatory in focal endometrial lesions, its effectiveness is yet to be evaluated in CE diagnosis [15, 79–83].

Study limitations

This meta-analysis has several limitations. The first is that the analysis is based on only ten RCTs and, therefore, a small number of women; thus, it is necessary to conduct more RCTs using a larger sample size. The second is the heterogeneity of patient characteristics (including IVF cycles and days of embryo transfer) included in the study—the variability of CE therapeutic regimens across studies and the inclusion of patients aged over 35 years without correction for the possibility of aneuploidy.

Meaning of the results

The evaluation of methods for diagnosing and treating chronic endometritis as one of the widespread factors in female infertility and, especially, implantation failures in assisted reproductive technologies, will help to promptly identify this pathology, conduct adequate therapy, and increase the effectiveness of in vitro fertilization programs.

CONCLUSION

Chronic endometritis can significantly reduce the effectiveness of in vitro fertilization in infertile women. Of note is that a rational antibacterial therapy of this pathology seems to improve the reproductive outcome, which becomes similar to that of women with no inflammatory changes in the endometrium.

The quality and number of studies on the limited negative impact of only severe CE (≥5 PCs per HPF) on IVF outcomes can currently be considered highly controversial, so further evidence is required.

Future RCTs are needed to check the effectiveness of the required CE tests in infertile patients prior to IVF in order to improve reproductive outcomes and increase live birth rates. In addition, further studies are recommended to evaluate the impact of chronic endometritis of varying severity on the IVF outcome and the feasibility of hysteroscopy in this pathology.

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