Hysteroscopic criteria for the diagnosis of chronic endometritis: a systematic review and diagnostic test accuracy meta-analysis

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OBJECTIVE: To assess the diagnostic accuracy of current hysteroscopic criteria compared with histopathological analysis (with or without additional immunohistochemistry) for the detection of chronic endometritis.

DATA SOURCES: MEDLINE, Scopus, SciELO, Embase, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, LILACS, conference proceedings, and international controlled trials registries were searched without date limit or language restrictions.

STUDY ELIGIBILITY CRITERIA: Studies were selected if they were randomized, prospective, or retrospective and estimated the diagnostic accuracy of hysteroscopy for chronic endometritis by comparing hysteroscopic criteria with histopathological (with or without immunohistochemistry) diagnosis. Primary outcomes were the diagnostic odds ratio, area under the summary receiver operating characteristic curve, sensitivity, and specificity. Positive and negative likelihood ratios were secondary outcomes.

METHODS: Diagnostic accuracy meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Synthesizing Evidence from Diagnostic Accuracy Tests recommendations and Synthesizing Evidence from Diagnostic Accuracy Tests methodological guidelines. Quality assessment was conducted using the Quality Assessment Tool for Diagnostic Accuracy Studies 2. Publication bias was evaluated with Deeks funnel plot asymmetry test.

RESULTS: Thirteen studies compared available hysteroscopic criteria (stromal edema, diffuse or focal hyperemia, "strawberry aspect," micropolyposis) with subsequent histopathological analysis of endometrial sampling. After pooling all the studies, the diagnostic odds ratio was 40 (95% confidence interval, 12—133). The evaluated area under summary receiver operating characteristic curve was 0.93 (95% confidence interval, 0.90—0.95), correlating with very high diagnostic accuracy. Sensitivity and specificity were 84% (95% confidence interval, 0.68—0.93) and 89% (95% confidence interval, 0.75—0.95), respectively. In addition, the positive and negative likelihood ratios were 7.4 (95% confidence interval 3.2—17.0) and 0.19 (95% confidence interval, 0.09—0.39), respectively.

CONCLUSION: Hysteroscopic diagnostic criteria are highly accurate and sensitive for detecting chronic endometritis. Absence of hysteroscopic suspicion might be sufficient to exclude disease. However, in cases in which hysteroscopic diagnostic findings of chronic endometritis are present, performing endometrial biopsy is recommended to confirm the diagnosis due to risk of false positives with hysteroscopy alone.

Key words: chronic endometritis, histopathology, hysteroscopic criteria, hysteroscopy, infertility

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Introduction

Persistent inflammation of the endometrial mucosa is known as chronic endometritis (CE).[1] This condition is characterized by the microscopic identification of plasma cells in the endometrial stroma. Numerous bacteria, primarily gram-negative and intracellular (such as *Enterococcus faecalis, Mycoplasma, ureaplasma Chlamydia, Escherichia coli,* and *Streptococcus* spp.), have been associated with the development of CE,[2,3] but some cases of abacterial CE are described. Although frequently asymptomatic, women with CE often complain of vaginal discharge, dyspareunia, pelvic pain, and abnormal uterine bleeding.[4] Furthermore, multiple studies have shown women with primary infertility, recurrent implantation failure (RIF), and

AJOG at a Glance

Why was this study conducted?

This study aimed to assess the diagnostic accuracy of the primary suggested hysteroscopic criteria—stromal edema, diffuse or focal hyperemia, "strawberry aspect," endometrial micropolyposis—considered suggestive of chronic endometritis (CE).

Key findings

Current hysteroscopic criteria yield high accuracy for diagnosing CE, showing a receiver operating characteristic under the curve of 0.93. Therefore, high pooled sensitivity and specificity (84% and 89%, respectively) were achieved, with pooled positive and negative likelihood ratios of 7.4 and 0.19.

What does this add to what is known?

Hysteroscopic criteria have high accuracy for diagnosing CE even without histopathological confirmation. Accordingly, in the absence of hysteroscopic diagnostic criteria, an endometrial biopsy would not be required to confirm the diagnosis of CE. On the contrary, when the clinical suspicion is high, and/or hysteroscopic findings are unclear, or when evaluating antibiotic responsiveness, histologic confirmation with endometrial biopsy is recommended.

recurrent pregnancy loss (RPL) to have a higher prevalence of CE compared to the general population,[5–8] suggesting a potential correlation between CE and reproductive disorders.

The deleterious impact of CE on fertility is often attributed to the aberrant infiltration of plasma cells with the consequent release of antibodies and cytokines, but it is still subject to debate.[9] Notably, women with CE also display altered endometrial expression of genes encoding for proteins implicated in the inflammatory response, proliferation, and apoptosis.[10–12]

Hysteroscopy is the current gold standard technique for both the diagnosis and treatment of intracavitary and endocervical lesions.[13–15] Hysteroscopy has already been shown to have high diagnostic accuracy in women with endometrial polyps, submucosal fibroids, hyperplasia, and endometrial cancer.[13,16] As a result, hysteroscopy is considered as an effective first-line diagnostic technique for women with infertility, in whom the presence of endometrial pathology may negatively influence the endometrial receptivity for the embryo.[15] In this respect, a comprehensive examination of the endometrial cavity, including targeted biopsies if needed, is enabled through a hysteroscopic approach.[16]

Studies have shown that specific macroscopic changes in the endometrium, such as stromal edema and micropolyps, are suggestive of CE and can be detected using hysteroscopy.[17] However, the diagnostic accuracy of the macroscopic hysteroscopic criteria varies greatly amongst studies due to disagreements regarding the endometrial features of CE, creating controversy as to the precise role hysteroscopy should play in diagnosis.[18–20]

Objective

We performed this systematic review and meta-analysis to assess the diagnostic accuracy of the primary suggested hysteroscopic features—stromal edema, diffuse or focal hyperemia, "strawberry aspect," endometrial micropolyposis—which are thought suggestive of CE in the literature.

Methods

We conducted a systematic review and diagnostic test accuracy (DTA) meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies[21] and Synthesizing Evidence from Diagnostic Accuracy Tests guidelines.[22] The research protocol was designed and registered a priori in the International Prospective Register of Systematic Reviews database (CRD4 2024506030) on February 4th, 2024, defining methods for the literature screening, inclusion and exclusion criteria before article examination, data extraction, tabulation, and analysis.

Data sources and search strategy

Electronic databases (Medical Literature Analysis and Retrieval System Online, Scopus, SciELO, EMBASE, LILACS, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Allied and Complementary Medicine Database, Clinicaltrials.gov, the Cochrane Central Register of Controlled Trials, the World Health Organization International Clinical Trials Registry Platform) for articles and the gray literature (National Technical Information Service - National Technical Reports Library, PsycEXTRA) for abstracts of national and international conferences were searched in January 2024 from inception of each database without date, language, or geographical limits. Search terms used were the following text words and Medical Subject Headings: "hysteroscopy" and "chronic endometritis." The detailed search strategy, customized for each database, is reported in Appendix 1.

Further screening was done for research not found by computerized searches by looking through the reference lists of all eligible publications and relevant reviews. Commentaries, letters to the editor, editorials, and reviews were excluded from the search.

Study selection and data extraction

Randomized prospective or retrospective studies were considered. Studies inherently had a crossover design where individuals served as their own controls. Studies not reporting diagnostic accuracy data, but only risk and/or prevalence or treatment of CE were excluded.

The population of interest included women (both infertile and not infertile) who underwent hysteroscopy for evaluation of endometrial pathology suggestive for CE.

The index tests considered were the hysteroscopic criteria recorded prior to endometrial sampling. According to available literature, the following criteria (at least one) were considered: micropolyps (small intrauterine new polypoid endometrial growths, dispersed on focal areas, that are less than 1 mm in size and have a clear connective-vascular axis), focal hyperemia (small areas of hyperemic endometrium), stromal edema (the endometrium's thick and pale appearance during the follicular phase), and a "strawberry pattern" (wide areas of hyperemic endometrium flushed with white central points).

The reference comparator was the histopathological analysis of endometrial sampling performed with a blind technique (conventional or Novak curettage or Pipelle biopsy) or hysteroscopic-guided endometrial biopsy directly after hysteroscopic evaluation.

The primary outcomes for this meta-analysis were the DTA of hysteroscopic criteria for CE using the following statistics: diagnostic odds ratio (DOR), area under the curve (AUC) of the summary receiver operator curve (SROC) and summary estimates of the sensitivity and specificity. The secondary outcomes were the positive likelihood ratio (PLR) and negative likelihood ratio (NLR). For the outcomes, it was required that the reference test used histopathological analysis of endometrial biopsy specimens acquired from the same patient.

The abstraction forms were created specifically for this DTA meta-analysis. Key characteristics recorded included: patient descriptors, study duration, setting, hysteroscopic criteria used, features of the cohort and endometrium, outcomes evaluated, mean follow-up length, results, and quality elements.

Two authors (G.R., S.G.V.) independently examined, reviewed, and classified all the abstracts. The same 2 authors separately collected significant data regarding the features and outcomes of interest mentioned in the study and carried out a full-text assessment of the eligible studies, reaching a consensus on plausible relevance. After discussing each inconsistency, if needed, a third author (J.P.P.) was consulted. If further unpublished data was required, it was acquired by directly contacting the original study authors whenever the methodology suggested that more outcome data should be submitted.

Assessment of risk of bias

The risk of bias of the included studies was analyzed using the Quality Assessment Tool for Diagnostic Accuracy Studies 2 (QUADAS-2) (University of Bristol, Bristol, United Kingdom), as recommended by the Agency for Healthcare Research and Quality.[23] This tool consists of 4 domains: 1) patient selection, 2) index test, 3) reference standard, and 4) flow and timing. All domains are assessed for risk of bias, and the first 3 domains are assessed for applicability concerns by indicating a low, high, or unclear risk.

The assessment of risk of bias was independently judged by 3 authors (D.L., A.E., and L.C.). Discrepancies and disagreements were resolved by discussion with a fourth author (P.D.F.).

Data extraction and statistical analysis

Statistical parameters—including true positive (TP), true negative (TN), false positive (FP), and false negative (FN)—were directly extracted from the study, and, if not available, they were calculated and arranged in a 2 × 2 table; for these circumstances, we used the following formulas: sensitivity = TP/(TP + FN) and specificity = TN/(FP + TN).

To calculate the overall DTA, we used the bivariate model according to Reitsma et al,[21] which incorporates both sensitivity and specificity while accounting for study-level heterogeneity. We evaluated the DOR through the DerSimonian-Laird random-effects model and the AUC of the SROC. These methods apply weighted averages based on the precision (inverse variance) of individual studies. The SROC curve and its derived AUC have been recommended to represent the performance of a diagnostic test, based on data from a meta-analysis. SROC curve represents the relationship between sensitivity and specificity across involved studies.[22] In practice, AUC values are categorized as for low (0.5≥AUC≤0.7), moderate (0.7≥AUC≤0.9), or high (0.9≥AUC≤1) accuracy. We then obtained paired forest plots, showing the variation in accuracy between studies for sensitivity and specificity. The PLRs and NLRs were calculated through summary estimates of the sensitivity and specificity.

Heterogeneity was assessed using the Higgins I^2 index in which 0% means no heterogeneity and 100% represents the highest degree of heterogeneity. In case of significant heterogeneity, meta-regression analysis on specific subsets of variables was carried out. Publication bias was assessed using the Deeks funnel plot asymmetry test, and a P value <.05 was considered to reflect significant publication bias. For all data analyses, Stata 14.1 (StataCorp LLC, College Station, TX) with *MIDAS* package was used to calculate DOR, AUC, to generate paired forest plots of sensitivity and specificity and to draw SROC curves.

Results

Results of search

We identified and screened 847 initial studies (Figure 1). We excluded 617 articles as duplicates. Therefore, 230 articles underwent title and abstract screening. Of these, 207 were excluded. Therefore, 23 full texts were reviewed. We excluded 3 studies for not providing diagnostic accuracy data, 2 for not reporting the main outcomes of interest, 1 for analyzing the same cohort of patients of a previous included study, 3 for being out of topic, and 1 study for unclear reporting of hysteroscopic criteria. Therefore, 13 studies[24–36] involving 7388 women who underwent consecutive outpatient hysteroscopy and histopathological analysis of endometrial biopsy for suspected CE were considered for inclusion in this meta-analysis (Table 1).

Study characteristics

Table 1 shows the main characteristics of studies qualified for quantitative analysis. Among the 13 studies, 6 out 13 had a prospective design while 7 out 13 were retrospective analyses. All the included studied had a crossover design in which hysteroscopic criteria were the diagnostic test and histopathology with or without immunohistochemistry the reference standard. Four studies were conducted in Italy, 3 in China, and 1 in each of the following countries: Belgium, Canada, Iran, Egypt, Greece, and Spain.

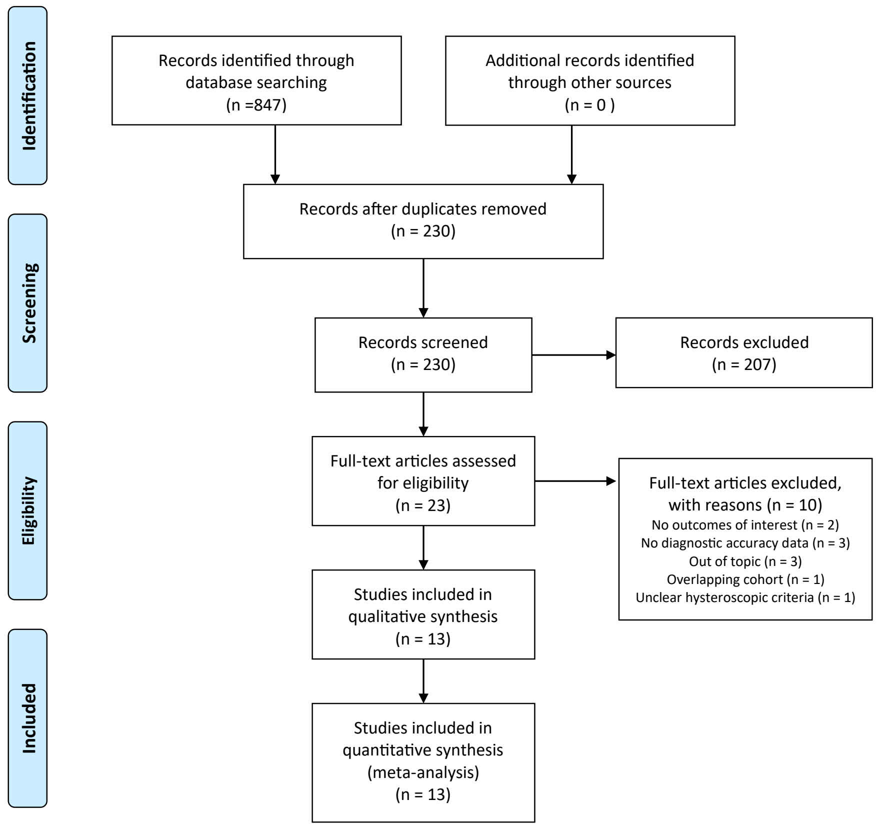
Concerning the hysteroscopic characteristics of the endometrium, micropolyps, stromal edema, and focal or diffuse hyperemia were outlined criteria for visualization in 12 out 13 studies, while one study[25] analyzed the accuracy of micropolyps alone. The strawberry pattern was included among the hysteroscopic criteria in 2 out of 13 papers.[32,33] In all included studies, hysteroscopy was performed in the outpatient setting using a 4 or 5 mm continuous flow hysteroscope.

Inclusion and exclusion criteria are reported in Table 2. While most studies enrolled women with procreative challenges (including RPL, RIF, or primary infertility), 4 out 13 studies evaluated the presence of CE in every woman regardless of reproductive history.[24,25,31,32]

In all the studies, histopathology was the reference test for the final diagnosis of CE. Eight out of 13 studies also employed immunohistochemistry for syndecan-1 (CD138).[26–28,31–35] Additional culture of endometrial tissue to evaluate bacterial growth was carried out in 1 study.[29]

It is notable that only in the study by Perez-Cejuela et al,[36] the endometrial biopsy was performed by means of a 5 Fr hysteroscopic grasping forceps, while in the rest of the studies the endometrium was sampled using blind instrumentation (conventional curette or Novak and/or Pipelle) after completing the diagnostic hysteroscopy.

FIGURE 1
Flow chart of studies identified for diagnostic test accuracy meta-analysis



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Risk of bias

Supplemental Figures 1 and 2 illustrate the methodological evaluation of the included reports based on the QUADAS-2 instrument. For the great majority of the included studies, low risk scores were obtained with regard to bias risk and applicability concerns. The authors deemed only one study to be very susceptible to bias and for which the application of findings was deemed difficult.[25]

To assess publication bias among the qualified studies, the Deeks funnel plot asymmetry test was used. In this meta-analysis, we discovered no discernible publication bias for primary outcome (P=.12) (Supplemental Figure 3).

Synthesis of results

The 13 studies achieved a DOR of 40 (95% confidence interval [CI], 12–133; I^2=99%). Figure 2 shows the SROC curve for hysteroscopy using common criteria for CE, with an AUC of 0.93 (95% CI, 0.90–0.95). The detected AUC suggested high diagnostic accuracy for the hysteroscopic criteria as an index test. For evaluation of the presence or absence of CE, hysteroscopy showed a pooled sensitivity of 84% (95% CI, 0.68–0.93) and specificity of 89% (95% CI, 0.75–0.95) (Figure 3). Therefore, the pooled PLR and NLR were 7.4 (95% CI, 3.2–17.0) and 0.19 (95% CI, 0.09–0.39), respectively.

Meta-regression

In spite of high diagnostic accuracy, the main outcome showed a significant degree of heterogeneity (I^2=99%). To shed light on possible sources for heterogeneity, we performed a subgroup analysis and meta-regression on specific binominal characteristics: population (general population/infertile women), study design (retrospective/prospective), sample size (under/over 500 women), histopathology (presence/absence of specified criteria) immunohistochemistry for CD138 (performed/not performed), ≥5 CD138+ cells at immunohistochemistry (presence/absence), type of biopsy (grasping biopsy/curettage or Pipelle), micropolyps (presence/absence), stromal edema (presence/absence), hyperemia (presence/absence), and strawberry pattern of the endometrium (presence/absence).

TABLE 1

Main characteristics of studies included in diagnostic test accuracy meta-analysis

Author, year	Design	Duration	Location	Primary outcome	Secondary outcomes	Hysteroscopic criteria	Interventional assessment	Reference test	Reference test diagnostic criteria	Sample size
Cicinelli et al, 2005[24]	Retrospective, single center	September 2003—May 2004	Italy	Inflammatory significance of endometrial micropolyps.	NA	Endometrial micropolyps	Outpatient hysteroscopy + Novak curettage	Histopathology	H&E≥1 plasma cell in whole section	820
Perez-Cejuela et al, 2023[36]	Retrospective, single center	January 2021—January 2022	Spain	Agreement rate between hysteroscopy and pathological examination in case of CE.	NA	Focal or diffuse endometrial hyperemia, stromal edema, and micropolyps	Outpatient hysteroscopy + 5 Fr grasping forceps biopsy	Histopathology	H&E (unclear criteria)	115
Cicinelli et al, 2005 (2)[25]	Retrospective, single center	January 2004—January 2005	Italy	Diagnostic criteria for CE	Diagnostic accuracy of hysteroscopy	Hyperemia, stromal edema, and micropolyps	Outpatient hysteroscopy + Novak curettage	Histopathology	H&E≥1 plasma cell in whole section	910
Geysenbergh et al, 2023[26]	Prospective, single center	October 2014—September 2017	Belgium	Prevalence of CE in patients starting ART.	Diagnostic accuracy of hysteroscopy, reproductive outcomes	Micropolyps, focal or diffuse hyperemia, and thickened mucosa	Outpatient hysteroscopy	Histopathology + immunohistochemistry (CD138)	H&E with plasma cell in whole section (number not mentioned); CD138 (unclear criteria) when in doubt	514
Song et al, 2019[27]	Retrospective, single center	September 2016—September 2017	China	Observer variability, sensitivity, specificity, and accuracy of the hysteroscopic features in the diagnosis of CE.	NA	Micropolyps, endometrial hyperemia, and stromal edema	Outpatient hysteroscopy + Pipelle or curettage	Histopathology and immunohistochemistry (CD 138)	H&E (typical nuclear counterstaining for plasma cells); ≥1 CD138+ cells/10 HPFs	1189
Liu et al, 2020[34]	Prospective, single center	February 2017—June 2018.	China	To develop a new hysteroscopic morphologic scoring system to diagnose CE	Improving outcomes of in vitro fertilization pregnancy	Stromal edema, hyperemia, endometrial polyps, micropolyps, endometrial polypoid hyperplasia, and uterine cavity mucus	Outpatient hysteroscopy + curettage	Histopathology + immunohistochemistry (CD138)	H&E (typical nuclear counterstaining for plasma cells) and ≥5 CD138+ cells/unclear HPF	320

(continued)

TABLE 1

Main characteristics of studies included in diagnostic test accuracy meta-analysis *(continued)*

Author, year	Design	Duration	Location	Primary outcome	Secondary outcomes	Hysteroscopic criteria	Interventional assessment	Reference test	Reference test diagnostic criteria	Sample size
Bouet et al, 2016[33]	Prospective, single center	November 2012—March 2015	Canada	Number of positive endometrial biopsies using the immunohistochemical criteria	Sensitivity and specificity of outpatient hysteroscopy	Micropolyps, stromal edema, hyperemia, and ‘‘strawberry aspect’’	Outpatient hysteroscopy + Pipelle biopsy	Histopathology + immunohistochemistry (CD138)	>5 CD138+ cells/10 HPFs	132
Tsonis et al, 2021[32]	Retrospective, single center	April 1997—September 2020	Greece	To examine proposed hysteroscopic features suggestive of endometritis	To carry out subgroup analyses in specific subgroups	Micropolyposis, stromal edema, focal or diffuse hyperemia, and “strawberry aspect”	Outpatient hysteroscopy + Pipelle biopsy	Histopathology + immunoistochemistry (CD 138)	H&E (unclear criteria); ≥1 CD138+ cells/ 10 HPFs	2675
Zargar et al, 2019[31]	Prospective, single center	October 2016—October 2017	Iran	Prevalence of CE in patients with RIF and RPL	NA	Focal or diffuse endometrial hyperemia, stromal edema, and micropolyps	Outpatient hysteroscopy + curettage	Histopathology + immunoistochemistry (CD 138)	H&E (unclear); ≥5 CD138+ cells/20 HPFs	85
Yang et al, 2014[28]	Retrospective, single center	May 2010—April 2012	China	Consistency between abnormal hysteroscopy finding and histological CE	NA	Hyperemia, mucosal edema, and micropolyps	Outpatient hysteroscopy +.Pipelle biopsy	Histopathology + immunoistochemistry (CD 138)	NA	202
Cicinelli et al, 2015[29]	Retrospective, single center	January 2009—June 2012	Italy	Accuracy of hysteroscopy for diagnosing CE	Reproductive outcomes	Micropolyps, polypoid endometrium, stromal edema, and focal or diffuse hyperemia	Outpatient hysteroscopy + Novak curettage	Microbiology + histopathology	H&E≥1 plasma cell in whole section	106
Viana et al, 2015[30]	Prospective, single center	January 2010—December 2011	Italy	Hysteroscopic accuracy	Bacterial endotoxin measurement	Micropolyps, stromal edema, and focal or diffuse hyperemia	Outpatient hysteroscopy + vacuum aspiration	Histopathology	NA	100
Abdel Moneim et al, 2022[35]	Prospective, single center	July 2018—January 2020	Egypt	Accuracy of hysteroscopy for diagnosing CE	NA	Micropolyps, stromal edema, and focal or diffuse hyperemia	Outpatient hysteroscopy + Novak curettage	Histopathology + immunoistochemistry (CD138)	H&E with plasma cell in whole section (number not mentioned); CD138 (unclear)	220

ART, assisted reproduction technique; *CD138*, syndecan-1; *CE*, chronic endometritis; *H&E*, hematoxylin & eosin; *HPF*, high-power field; *NA*, not available; *RIF*, repeated implantation failure; *RPL*, recurrent pregnancy loss.

TABLE 2
Inclusion and exclusion criteria

Author, year	Inclusion criteria	Exclusion criteria
Cicinelli et al, 2005[24]	NA	Heavy bleeding, severe cardiovascular disease, suspected pregnancy, cases of suspected endometrial malignancy
Perez-Cejuela et al, 2023[36]	Women without uterine malformations at ultrasound and known history of infertility or RPL	Presence of endometrial hyperplasia of any type, any antibiotic treatment for known chronic or infection, and current pregnancy.
Cicinelli et al, 2005 (2)[25]	NA	Heavy bleeding, severe cardiovascular disease, suspected pregnancy, and suspected endometrial malignancy
Geysenbergh et al, 2023[26]	Asymptomatic infertile women (18—45 y) scheduled for diagnostic hysteroscopy before starting ART.	Suspected gynecological infections, known endometritis, menstrual or intermenstrual blood loss at the moment of hysteroscopy, and sonographic signs of intrauterine abnormalities.
Song et al, 2019[27]	NA	Suspected reproductive tract infection, intrauterine contraceptive device, history or presence of endometrial carcinoma, positive pregnancy test, acute uterine bleeding, use of hormone therapy in the previous 3 mo, and previous hysteroscopic surgery within 3 mo
Liu et al, 2020[34]	Patients aged 20—45 y with RPL, no uterine malformation, and no history of malignant tumors.	Uterine anomalies, endometrial atypical hyperplasia, intrauterine adhesions, and severe systemic pathology
Bouet et al, 2016[33]	Patients between 18 and 43 y of age with a history of RIF or RPL.	Positive pregnancy test, unexplained uterine bleeding, history of antibiotic treatment in the month before the biopsy, uterine malformation, submucosal myoma, and endometrial polyp>5 mm.
Tsonis et al, 2021[32]	Women in reproductive age, with infertility issues/IVF screening, history of RPL, menopausal women, women with hysteroscopic AUB or PMB.	History of pregnancy or spontaneous abortion within 6 mo prior to the procedure, confirmation of a female reproductive tract infection, acute uterine bleeding or menstruation during the procedure, and the administration of hormonal treatment within 9 mo prior to the intervention
Zargar et al, 2019[31]	Women with a history of RIF after IVF or RPL, with regular infertility workup.	Smoking habit or alcohol use
Yang et al, 2014[28]	Women with a history of RIF.	Submucous myoma, adhesion of the uterine cavity, endometrial hyperplasia or tuberculosis by histological diagnosis, and uterine abnormalities (ie, Uterine septum, unicornuate uterus).
Cicinelli et al, 2015[29]	Women with a history of RIF or unexplained infertility.	FSH on 3 exceeding 10 mUI/ml, BMI exceeding 30 mUI/ml, a history of clinically significant repeated pregnancy loss, a history of myoma and/or endometriosis surgery, an ultrasound diagnosis of ovarian endometriomas, corticosteroid treatment or other immune-suppressive medical treatments, a known clinical autoimmune disease, antiphospholipid syndrome, thrombophilic condition requiring anticoagulant therapy, the presence of antisperm antibodies.
Viana et al, 2015[30]	Infertile women undergoing IVF.	Secondary infertility, endometriosis stage III—IV, hydrosalpinx, FSH>12 pg/ml, echosonographic suspicion of polyp and myoma, and history of antibiotic use
Abdel Moneim et al, 2022[35]	Infertile women undergoing ICSI.	Chronic general diseases (immunological, cardiac, hepatic, diabetes mellitus), severe vaginal bleeding, previous failed ICSI, PCOS, and endometriosis

ART, assisted reproduction technique; *AUB*, abnormal uterine bleeding; *BMI*, body-mass index; *FSH*, follicle-stimulating hormone; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization; *NA*, not available; *PMB*, postmenstrual bleeding; *RIF*, repeated implantation failure; *RPL*, recurrent pregnancy loss.

The results of the meta-regression analysis are shown in Figure 4. Among the covariates, none were found to be a significant source of heterogeneity (P>.05), and therefore would not statistically affect the diagnostic accuracy of the hysteroscopic evaluation (Figure 4).

Detailed sensitivity and specificity for covariate subgroup analysis are depicted in Table 3.

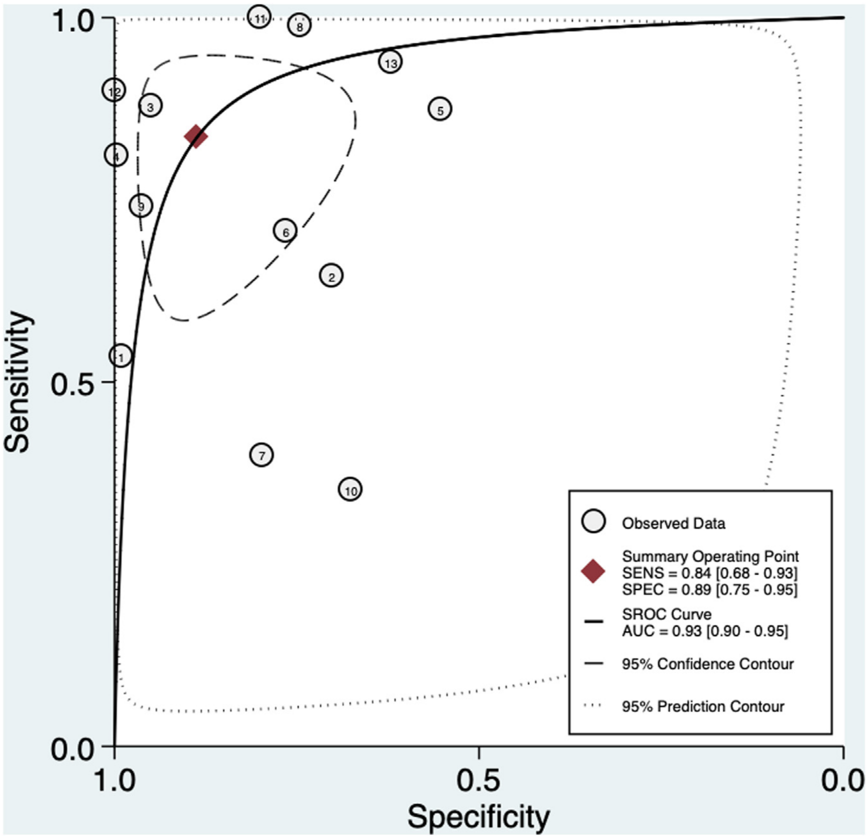
Comment

Principal findings

This systematic review and DTA meta-analysis shows that the use of currently available hysteroscopic features for diagnosing CE has high accuracy. Data could be computed from all 13 papers that were part of the systematic review. Hysteroscopy has results comparable to the gold standard of histopathology, as seen by the area under the SROC curve, which indicates high accuracy for the index test. A high PLR (>5.0) and low NLR (<0.2) are additional requirements for a diagnostic test to be deemed effective. The PLR score of 8.3 in our meta-analysis indicates that women meeting at least one hysteroscopic criterion are nearly 9 times more likely to test positive for endometritis at histopathology. Moreover, in women without hysteroscopic suggestive findings, the NLR value of 0.20 represents a 5-fold reduction in the likelihood of having CE. CIs for the evaluated outcomes overlapped, suggesting good quality evidence.

FIGURE 2

SROC curve for hysteroscopic criteria for detecting chronic endometritis



AUC, area under the curve; *SENS*, sensitivity; *SPEC*, specificity; *SROC*, summary receiver operator curve.

Comparison with existing literature

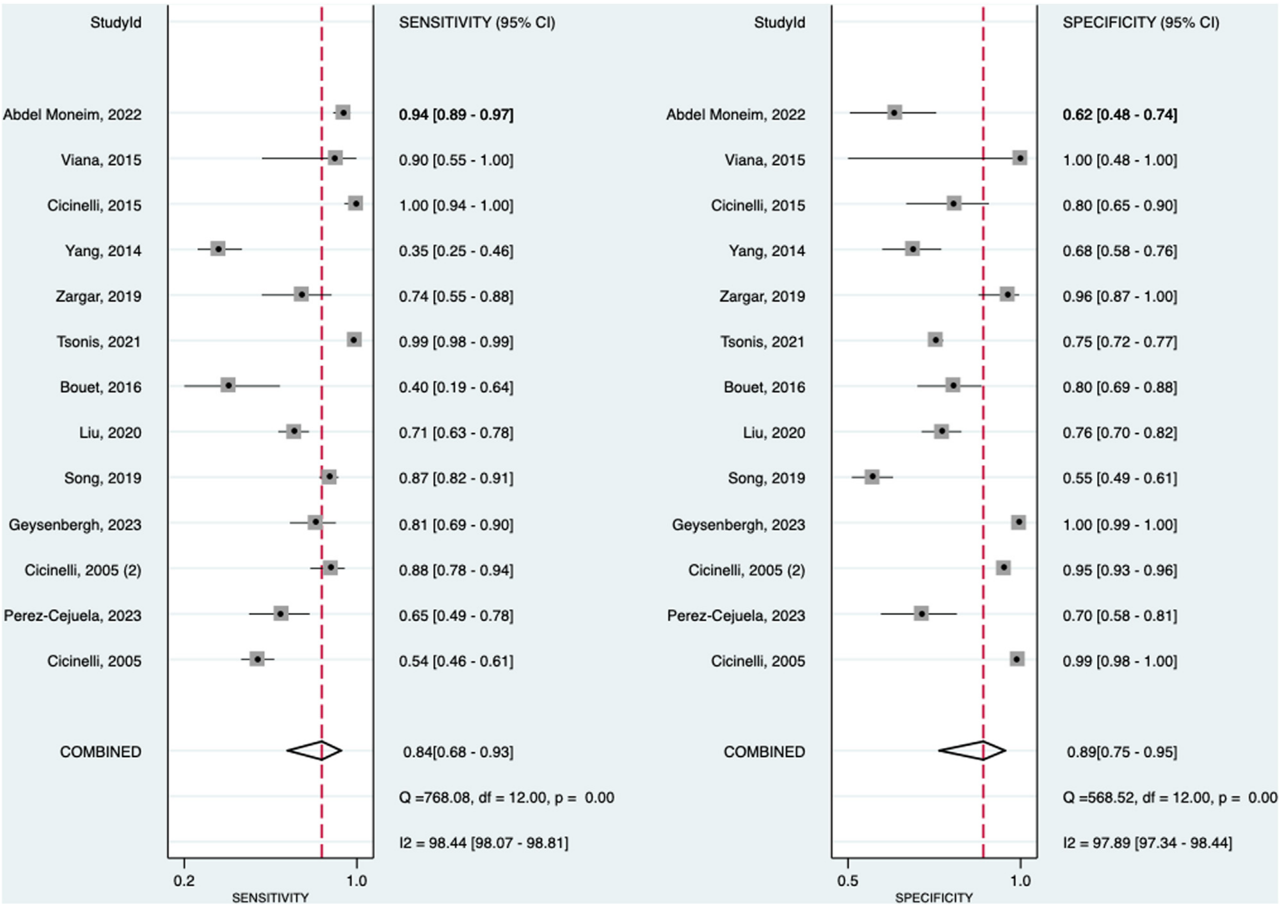
In a recent Delphi consensus, the International Working Group for the standardization of CE diagnosis made an initial effort to suggest a set of diagnostic standards for CE at hysteroscopy.[37] They discovered that, despite gynecologists' increased focus on CE, particularly for those in the field of reproductive medicine, very few studies examine the clinical-pathological relationship between hysteroscopic and histologic signs of the condition.[37] Similarly, given the volume of original articles on CE that have been published in the last years, the persistence of this issue was a surprisingly shared concern.

Most of the evidence used in the Delphi poll to reach consensus on the diagnostic criteria was derived from published research. Micropolyps, focal hyperemia, and stromal edema were linked to CE as early as 2005, and other researchers subsequently confirmed this association. Other authors describe the endometrial strawberry aspect as, "large areas of hyperemic endometrium flushed with white central points." One more criterion that their group agreed upon was the appearance of "endometrial hemorrhagic spots.".[36] Patients with CE frequently have focal red areas of the endometrium with sharp, uneven borders, either by themselves or in conjunction with other endometrial abnormalities like focal hyperemia. However, only a few studies included the "strawberry pattern" among the analyzed criteria and even fewer incorporated hemorrhagic spots. In addition, meta-regression analysis did not show a pivotal role of the strawberry pattern in increasing (or decreasing) the accuracy of the hysteroscopy in the diagnosis of CE.

The presence of endometrial stromal plasma cells serves as the primary diagnostic marker for the traditional diagnosis of CE, which is based on endometrial biopsy and histopathologic analysis.[38] However, endometrial stromal fibroblasts, monocytes, and plasma cells may not be readily distinguishable, making the microscopic identification of plasma cells challenging at times when using conventional staining techniques (eg, hematoxylin and eosin).[39] It was recently discovered that the inclusion of CD138 immunohistochemical staining, also referred to as syndecan-1, a transmembrane heparin sulfate proteoglycan that is a specific plasma cell marker, improved the precision of microscopic examination and decreased the likelihood of misdiagnosis.[40]

However, the histopathologic diagnosis of CE remains subjective and can

FIGURE 3
Pooled sensitivity and specificity plots



Red dashed line indicates summary pooled estimate. *Gray squares* indicate weighted estimates of sensitivity or specificity for each individual study. *Diamond shaped symbol* indicates pooled summary estimate of sensitivity or specificity. *Black dots* indicate individual study estimates.

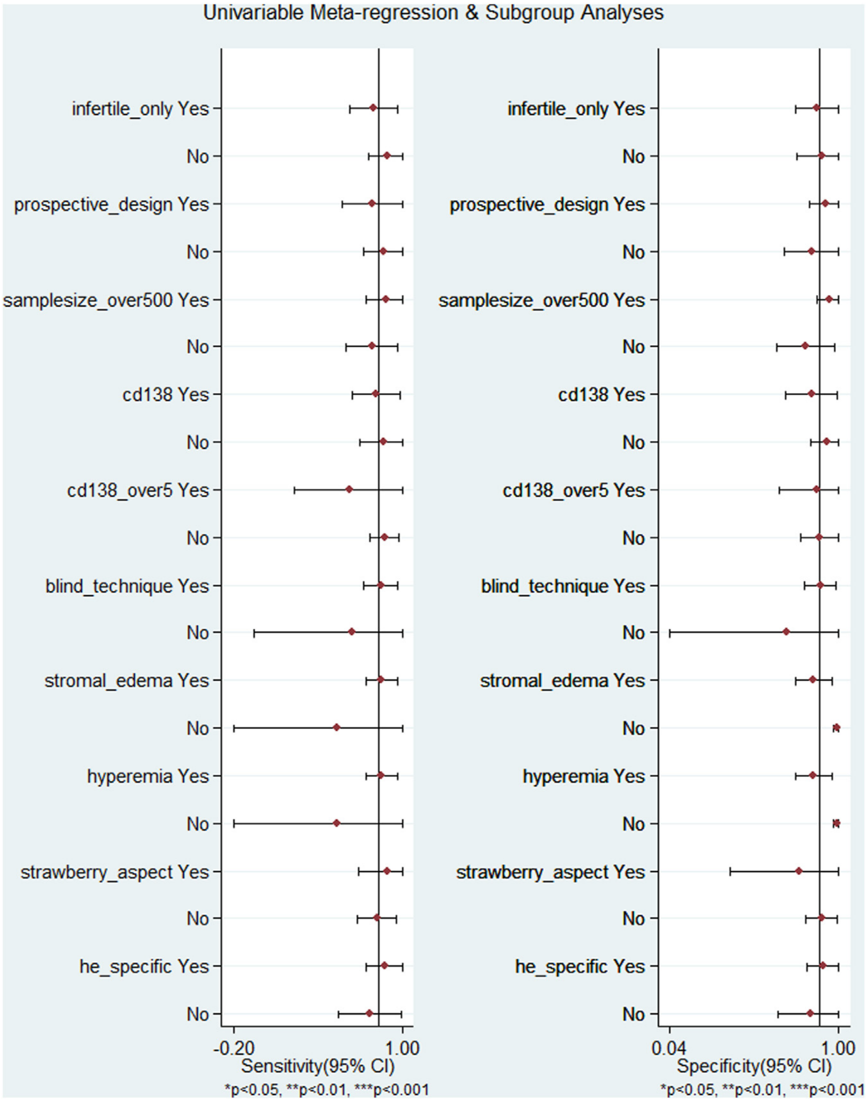
CI, confidence interval.

differ between centers due to the absence of standard criteria for CE classification (ie, there is no agreement on the minimum number of plasma cells used to diagnose CE).[40] In fact, the primary concern for CD138 immunohistochemical staining is that some endometrial glandular/surface epithelial cells can constitutively express proteoglycans that respond to antihuman CD138 antibodies, reducing specificity from just stromal plasma cells. This could result in FP diagnoses of CE.[41]

Hysteroscopic criteria for CE are clinically important due to their ability to provide a real-time assessment of the endometrial cavity, thereby allowing the visualization of macroscopic features that could indicate the presence of active inflammation while maintaining both affordability and accessibility, especially in resource-limited settings.[42] Despite its advantages, some characteristics (eg, stromal edema and hyperemia) overlap with benign or temporary alterations and may result in overdiagnosis. Nonetheless, its real-time usefulness and the possibility of performing targeted biopsies support its clinical relevance. Histopathology, typically considered a reference test for CE, is relatively inexpensive, widely available and provides context to the endometrium's inflammatory state. However, it has some limitations as well since the subjective identification of plasma cells might produce inconsistent results. Conversely, real-time polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) offer more objective and reproducible alternatives, allowing for the detection of both culturable and nonculturable pathogens and addressing the limitations of conventional approaches. Moreno et al[18] reported a 91.67% concordance between NGS and RT-PCR, compared to a much lower 41.54% concordance between RT-PCR and histopathology combined with hysteroscopy. While promising in research settings, their implementation in clinical practice is still limited by the lack of standardization, cost, and difficulty in correlating molecular findings with clinical symptoms since the presence of microbial DNA or RNA does not confirm an active infection and shows low negative predictive value, requiring further validation through large-scale multicenter studies.[18] Integrating RT-PCR alongside hysteroscopy could improve diagnostic precision, particularly in ambiguous cases, ensuring a more comprehensive and accurate evaluation while maintaining the practicality of hysteroscopy. However, while NGS and RT-PCR are not yet standardized as routine methods, histopathology remains the gold standard.

To date, there is no clear data regarding cost comparisons for hysteroscopy with endometrial biopsy and endometrial biopsy alone for CE.[37] However, the macroscopic signs of CE are often focal, potentially leading to an inaccurate histopathological diagnosis when based on a blindly collected sample.[37] Hysteroscopy-directed biopsy is more effective than blind curettage or Pipelle biopsy for detecting endometrial lesions, with better sample adequacy rates. Unlike blind methods that sample only a small portion of the endometrium, hysteroscopy is advantageous in identifying focal pathology or lesions with limited distribution.[42,43]

FIGURE 4
Univariable meta-regression and subgroup analysis for sensitivity and specificity



CI, confidence interval.

Strengths and limitations

This DTA meta-analysis has some limitations. First, it was not possible to evaluate the diagnostic accuracy and its relative SROC curve of each hysteroscopic criteria separately. This relates to the design of included studies where, except for one publication, sub-stratification of diagnostic criteria was not available.

Moreover, the results of this meta-analysis should also be interpreted with the inherent limitations of each of the included studies, as they all had a crossover design by nature and due to the presence of both prospective and retrospective studies. However, even if such methodological diversity may limit the conclusions of the study, sharing the same crossover design and comparable inclusion criteria and reference standard allow such findings to be noteworthy. There could be diagnostic bias resulting in a greater number of FPs since the pathologist could be influenced by the hysteroscopist's suggested diagnosis. Similarly, variations in histopathology (use of specific criteria in whole hematoxylin/eosin section) and immunohistochemistry (number of CD138+ cells/high-power field [HPF]) criteria may alter sensitivity and specificity. However, meta-regression analysis showed no significant impact on reported findings. The examination of sensitivity and specificity for hysteroscopy has another drawback, as the assessed CI's for both parameters had intermediate amplitudes. This limitation should be associated with the low incidence of CE in all included studies, the various ethnicities involved in the studies, the existence of interobserver variability (since multiple operators oversaw the hysteroscopic examinations in some studies), and the technological advancements in endometrial sampling and hysteroscopic imaging over the course of more than 20 years of scientific progress, which have been improving hysteroscopy's diagnostic accuracy over time. Furthermore, there were only 2 studies

TABLE 3
Meta-regression and subgroup analysis

Parameter	Category	No. of studies	Sensitivity (95% CI)	*P* value	Specificity (95% CI)	*P* value
Infertile-only women	Yes	9	0.82 [0.69—0.95]	.95	0.89 [0.77—1.00]	.99
	No	4	0.76 [0.53—0.99]		0.90 [0.75—1.00]	
Prospective design	Yes	6	0.88 [0.76—0.99]	.54	0.94 [0.85—1.00]	.32
	No	7	0.72 [0.54—0.90]		0.85 [0.69—1.00]	
Sample size>500	Yes	5	0.84 [0.69—0.99]	.99	0.95 [0.88—1.00]	.23
	No	8	0.75 [0.53—0.97]		0.83 [0.67—0.99]	
CD138 immunohistochemistry (at least 1 cell/10HPF)	Yes	8	0.77 [0.61—0.93]	.36	0.85 [0.70—1.00]	.26
	No	5	0.84 [0.68—1.00]		0.95 [0.87—1.00]	
CD138 immunohistochemistry (at least 5 cells/10HPF)	Yes	3	0.71 [0.41—1.00]	.37	0.88 [0.67—1.00]	.90
	No	10	0.82 [0.70—0.94]		0.90 [0.80—1.00]	
Blind endometrial sampling	Yes	12	0.81 [0.70—0.93]	.27	0.91 [0.82—0.99]	.08
	No	1	0.61 [0.03—1.00]		0.70 [0.01—1.00]	
Stromal edema	Yes	12	0.78 [0.65—0.90]	.36	0.87 [0.77—0.97]	.27
	No	1	0.94 [0.81—1.00]		0.99 [0.97—1.00]	
Hyperemia	Yes	12	0.78 [0.65—0.90]	.36	0.87 [0.77—0.97]	.27
	No	1	0.94 [0.81—1.00]		0.99 [0.97—1.00]	
Additional strawberry aspect	Yes	2	0.56 [0.15—0.96]	.14	0.77 [0.35—1.00]	.58
	No	11	0.83 [0.72—0.94]		0.91 [0.83—1.00]	
Micropolyps	Yes	13	NA	-	NA	-
	No	0	NA		NA	
H&E and specific criteria	Yes	7	0.85 [0.73—0.86]	.70	0.92 [082—1.00]	.59
	No	6	0.71 [0.51—0.92]		0.87 [0.70—1.00]	

CD138, syndecan-1; *CI*, confidence interval; *H&E*, hematoxylin & eosin; *HPF*, high-power field; *NA*, not available.

conducted in a low-income setting[31,35], which limited the generalizability of the results. Moreover, since all included women, except for one study,[24] had either RPL, RIF, or primary infertility with a suspected CE, the diagnostic sensitivity and specificity might be overestimated by the clinical suspicion, reflecting lower accuracy in an unselected population. Additionally, since the authors of original studies have inherently higher experience on diagnosing CE, which is operator-dependent, a less experienced operator may report lower accuracy standards. Such limitations may reduce the generalizability of the findings.

Moreover, it should be remarked that only one study[36] used the hysteroscopic grasping biopsy as endometrial sampling method. Meta-regression analysis did not show a significant impact on sensitivity and specificity through the use of a visual vs blind endometrial sampling due to the paucity of available evidence. However, if endometritis is asymmetrically distributed, blind biopsy can bias towards the null, both through missing the affected area and diluting a sample where most of what is obtained is taken from an unaffected region. Given the ease of directed hysteroscopic sampling for endometrial regions with increased suspicion of CE, this could enhance histopathological evaluation through precise and optimal sampling for pathologic analysis.[44,45] It is expected that additional studies, alongside with the spreading of such technique, will help in more subtle cases in which the hysteroscopic criteria for CE are noticeable.

Another limitation is that, to date, there is no agreement regarding the histopathological and immunohistochemistry gold standard technique for a confirmatory diagnosis of CE. Although we tried to address this issue in the meta-regression and subgroup analysis by categorizing studies according to number of CD138+ plasma cells/HPF ($\geq$1 or $\geq$5), the paucity of studies accurately describing their diagnostic criteria reduces the power of such analysis. Moreover, except for one study, data regarding the number of examined slides and sampling methods were not available. These 2 factors might have contributed to increase the heterogeneity level of the DTA analysis and necessitate further consideration in upcoming studies.

In addition, there are some points of strength to report. Firstly, according to the Deeks funnel plot, there was no publication bias in our review. Inherently, all the included studies were considered of high quality, with an overall low risk of bias, increasing the robustness of the synthetized evidence. Another recent systematic review by Tsonis et al[46] also summarized hysteroscopic features suggestive for CE. However, it did not quantitatively evaluate the diagnostic performance of hysteroscopy and neither examined heterogeneity among studies.[46] Conversely, the quantification of overall sensitivity, specificity, PPV, and NPV in our study using a DTA approach of the hysteroscopic criteria for CE in current literature among different clinical settings, emphasized the significant variability in sensitivity and specificity across the available literature and underscored the need for standardized diagnostic approaches, including the plausible role of molecular diagnostics (eg, RT-PCR and NGS) in future studies, to address the limitations of current diagnostic standards and offer a comprehensive approach to CE diagnosis.

Conclusions and implications

This systematic review and DTA meta-analysis on both infertile and non-infertile women show that the current hysteroscopic criteria for diagnosing CE demonstrate accuracy prior to histopathological confirmation. Accordingly, the absence of hysteroscopic findings suggestive of the presence of CE would not need histologic confirmation and would make supplemental biopsy of more limited yield. However, the limitations of this study and reviewed evidence do not allow us to draw strict conclusions. In fact, when clinical suspicion is high, hysteroscopic results are unclear, or patient anxiety or history warrants additional confirmation, histopathologic confirmation is recommended. Hysteroscopic biopsy and/or second look confirmation may also be extremely important for assessing the therapeutic response to antibiotic regimens and for identifying CE instances that have resistant features and necessitate additional histopathological assessment. Moreover, integrating RT-PCR could increase diagnostic precision, especially in uncertain cases. Additional studies are required to propose the integration of molecular diagnostics as a complementary standard and to clarify the role of hysteroscopic-targeted endometrial biopsy, relative to blind techniques, in obtaining optimal samples for subsequent histopathological analysis in patients with suspected CE. ■

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Appendix 1. Search queries for each electronic database

MEDLINE (accessed through PubMed):

("hysteroscopy"[MeSH Terms] OR "hysteroscopy"[All Fields] OR "hysteroscopies"[All Fields]) AND ("chronic"[All Fields] OR "chronical" [All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics" [All Fields]) AND ("endometritis" [MeSH Terms] OR "endometritis"[All Fields])

EMBASE:

('hysteroscopy'/exp OR hysteroscopy) AND ('chronic endometritis'/exp OR 'chronic endometritis' OR (chronic AND ('endometritis'/exp OR endometritis)))

SCOPUS:

TITLE-ABS-KEY (hysteroscopy AND chronic AND endometritis)

SciELO:

Hysteroscopy AND chronic endometritis

LILACS:

Hysteroscopy AND chronic endometritis

COCHRANE at CENTRAL:

Hysteroscopy AND (chronic endometritis):ti,ab,kw.

CINAHL/PsycINFO/AMED/PsycExtra (accessed through EBSCO — IDEM for Italian Universities)

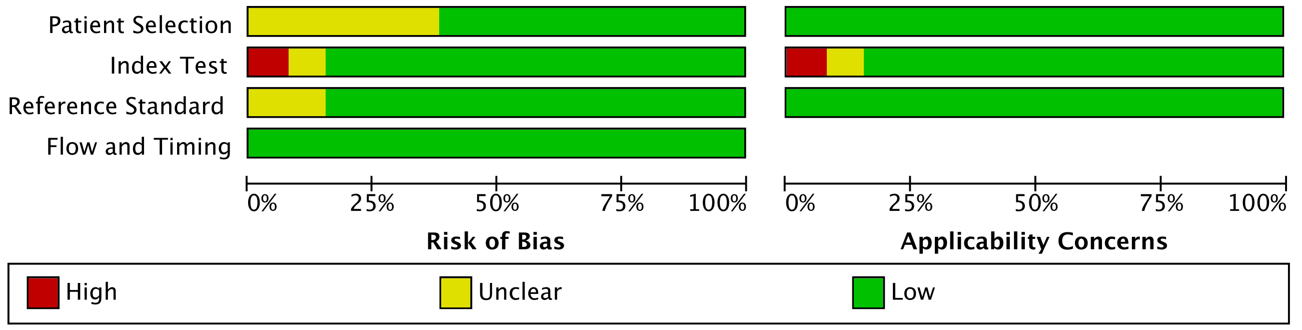
Hysteroscopy AND (chronic endometritis)

Clinicaltrials.gov/ICTRP (accessed through CENTRAL)

Hysteroscopy AND (chronic endometritis):ti,ab,kw.

SUPPLEMENTAL FIGURE 1

Summary of risk of bias and applicability concerns according to Quality Assessment Tool for Diagnostic Accuracy Studies 2 score



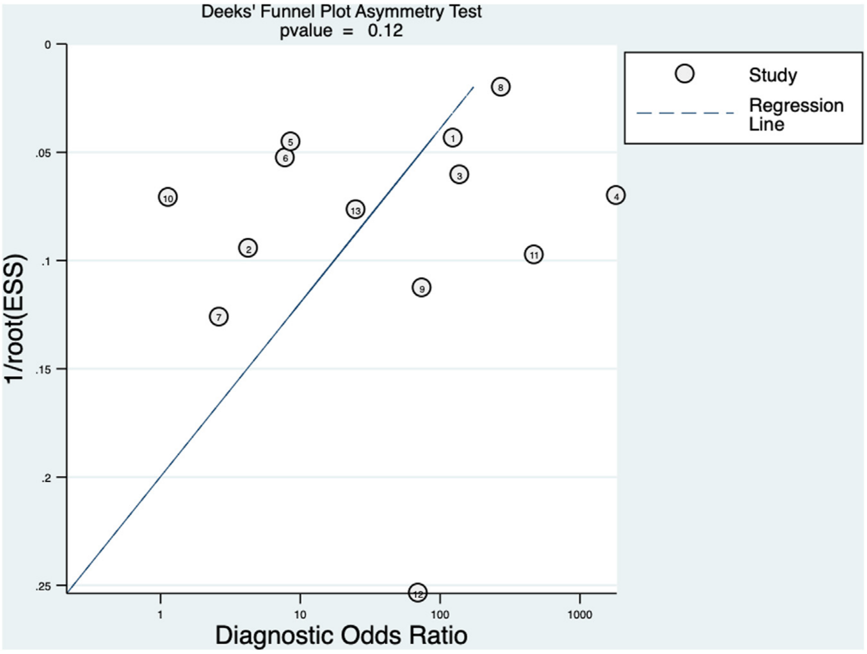
SUPPLEMENTAL FIGURE 2

Detailed risk of bias and applicability concerns for each included study according to Quality Assessment Tool for Diagnostic Accuracy Studies 2 score

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Bouet 2016	+	+	+	+	+	+	+
Cicinelli 2005	?	–	+	+	+	–	+
Cicinelli 2005 (2)	?	+	+	+	+	+	+
Cicinelli 2015	+	+	+	+	+	+	+
Geysenbergh 2023	+	+	+	+	+	+	+
Liu 2020	+	+	+	+	+	+	+
Moneim 2022	+	+	?	+	+	+	+
Peerez-Cejuela 2023	+	+	+	+	+	+	+
Song 2019	+	+	+	+	+	+	+
Tsonis 2021	?	+	+	+	+	+	+
Viana 2015	?	?	?	+	+	?	+
Yang 2014	?	+	+	+	+	+	+
Zargar 2019	+	+	+	+	+	+	+

– High ? Unclear + Low

SUPPLEMENTAL FIGURE 3
Deeks funnel plot for the primary outcome



ESS, effect sizes.