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ENDOMETRIOSIS: ORIGINAL ARTICLE

Chronic Endometritis and Endometriosis: Two Sides of the Same Coin?

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Abstract

Both chronic endometritis and endometriosis are common entities in infertile patients. The association and the co-existence of these two entities are poorly evaluated. The aim of this systematic review and meta-analysis was to examine the association between chronic endometritis and endometriosis and to find the prevalence of chronic endometritis in women with endometriosis. A systematic electronic search was conducted using the MEDLINE, Scopus and Cochrane databases up to May 2022. Observational studies which examined the prevalence of chronic endometritis in women with endometriosis were included. Newcastle–Ottawa Scale was used for the quality assessment. Odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and pooled prevalences with 95% CIs were calculated. 855 studies were identified, of which six studies were included in the systematic review and five in the meta-analysis. The prevalence of chronic endometritis in women with endometriosis was 28%, with higher frequency observed in women with endometriosis rASRM stage III-IV (43%) in comparison to women with endometriosis rASRM stage I-II (25%). The meta-analysis showed a significantly higher chronic endometritis in women with endometriosis in comparison to the control group (five studies, 264 endometriosis vs. 435 control, OR = 2.07; 95% CI 1.11–3.84, I^2 43%, $p = 0.02$). The present meta-analysis showed a significantly higher risk of chronic endometritis in women with endometriosis in comparison to the control group. These findings contribute to a better understanding of the causes and consequences of endometriosis and chronic endometritis and may help in the development of more efficient treatment strategies for women with associated infertility.

Keywords Endometriosis · Chronic endometritis · Plasma cells · CD-138 · Infertility · Implantation failure

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Introduction

Chronic endometritis (CE), the persistent inflammation of the endometrium, is often asymptomatic or has non-specific symptoms such as leukorrhea, pelvic pain, and dysfunctional uterine bleeding [1]. CE is underestimated due to the oligosymptomatic profile of this condition, with a prevalence varying between 0.2% to 46% depending on the patient profile and the biopsy method [2]. The alteration of endometrial microbiome and intrauterine infection by common bacteria such as *Escherichia coli, Enterococcus faecalis, Streptococcus, Staphylococcus, Mycoplasma/Ureaplasma, and Mycobacterium* represent the major causes in the pathogenesis of CE [3]. Histologically CE is characterized by the presence of inflammatory cells in the endometrial stroma, such as plasma cells, lymphocytes, eosinophils and lymphoid follicles. The main method used for the diagnosis of CE is the immunohistochemical analysis to assess the presence of plasma cells in the endometrial biopsy samples. However the number of plasma cells per microscope field which is

needed for the diagnosis of CE is still controversial, as some authors proposed that a small amount of plasma cells could also exist in women without CE [4–7]. A recent meta-analysis examining the correlation between plasma cell count and reproductive outcomes found a significant association between miscarriage rates and plasma cell counts exceeding 5 per high-power field (HPF) (RR = 2.4; $p = 0.007$), while the thresholds of plasma cells which were associated to adverse pregnancy outcomes were higher (10 and 50/HPF) [8]. Focal or diffuse hyperemia, endometrial micro polyps and superficial edema are some of the macroscopic endometrial changes proposed for the diagnosis of CE [9]. The prevalence of CE in women with infertility varies according to studies from 10.4% to 45% [10, 11] and it seems to be higher in women with recurrent pregnancy loss and/or repeated implantation failures after assisted reproductive techniques (ART) [6, 12, 13]. The high prevalence of CE in infertile patients and the significant positive ART outcomes after treatment of CE, suggest the importance of diagnosis and treatment of this condition in infertile women [14].

Endometriosis is an inflammatory condition characterized by the growth of endometrial-like tissue outside the uterine cavity with a prevalence in women of reproductive age of about 10% [15, 16]. The most common symptoms of endometriosis are endometriosis-associated pain and infertility [17]. The prevalence of endometriosis in infertile women varies from 25 to 50%, while 30 to 50% of women with endometriosis have difficulties to become pregnant. These discrepancies could be explained by the heterogeneous subtypes of endometriosis (superficial, ovarian, and deep endometriosis) and the often coexistence of adenomyosis [18]. In addition, women with endometriosis have significantly higher risk of miscarriage (RR 1.97 (95% CI 1.41–2.75)) [19]. The mechanism of endometriosis-related infertility is not clearly understood, however the anatomical alterations, the disrupted ovarian function and the inflammatory environment are supposed to contribute to this condition [20].

Various molecular alterations in the eutopic endometrium of women with endometriosis and adenomyosis have been described; however, it remains unclear how these changes affect the endometrial receptivity [21]. A recent meta-analysis after analyzing the existing studies and data from two databases found a minimal non-significant decrease of live birth rates in women with endometriosis in comparison to control group after oocyte donation in ART cycles [22]. Since the CE is a common finding in infertile patients and a reason for the impaired endometrial receptivity and the coexistence in women with endometriosis is still inadequately evaluated. The objective of our systematic review and meta-analysis is to determine the prevalence of chronic endometritis in women with endometriosis. Additionally, we aim to assess whether women with endometriosis are at a higher risk of having CE compared to those without endometriosis.

Material and Methods

This is a systematic review and meta-analysis of published data. The protocol was submitted for registration in the PROSPERO international database (ID:CRD42022363867) and the reporting of this study was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [23].

MEDLINE, Scopus and Cochrane databases were searched for eligible studies independently by two authors (DRK, NS). Any discrepancies were resolved through consultation with a third investigator, who was not involved in the initial process (PD).

Combinations of the terms "chronic endometritis", " endometrial inflammation", "endometrial plasma cells", "endometriosis", "endometrioma" were used: ((((chronic endometritis) OR (endometrial inflammation)) OR (endometrial plasma cells)) AND ((((endometriosis/) OR ("endometrio*".ab,kw,ti.)) OR ("endometrioma".ab,kw,ti.)) OR ("chocolate cyst*".ab,kw,ti.))). Studies in English published until May 1st, 2022 were included. References of all relevant studies were screened.

Inclusion criteria were: i) studies that examined the prevalence of CE in women with endometriosis or case–control studies which compared the prevalence of CE in women with endometriosis and control group without endometriosis ii) description of the diagnostic criteria of chronic endometritis and the diagnostic tool of endometriosis. Reviews, abstracts, oral presentations and national or local health statistics were excluded.

The main outcome of our study was the association between CE and endometriosis. Secondary outcomes included the pooled prevalence of CE in women with endometriosis as well as in different subgroups of women with endometriosis. Specifically, different subgroups including patients with laparoscopically diagnosed endometriosis, endometriosis stage rASRM I-II, endometriosis stage rASRM III-IV, endometriosis-related infertility and subgroups according to the histological material used for diagnosis of chronic endometritis (hysterectomy, endometrial curettage) were examined.

Data from each study were extracted independently by two authors in standardized data extraction form, which included general characteristics of the studies (authors, year, study design, country, method of the diagnosis of endometriosis, method of diagnosis of CE, number of case and control groups, matching factors), clinical characteristics of included women (age, BMI, existence of uterine fibroids or adenomyosis, parity, infertility). Disagreement was solved by consensus. In some cases, the data set was completed through communication with the authors. Specifically, the authors, of three studies were contacted [9,

24, 25]. In order to assess the risk of bias, all studies were examined with the Newcastle–Ottawa Quality Scale [26].

Odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and overall prevalences with 95% CIs were calculated. The I^2 index was used to examine heterogeneity among the outcomes of different studies, with an I^2 value greater than or equal to 50% indicating significant heterogeneity. A random effects model was applied for every outcome. Funnel plots were generated and inspected for asymmetry to identify any biases in the included studies. A p-value of lower than 0.05 was considered statistically significant. Review Manager (RevMan) for Mac (Version 5.3) and the metaprop package in statistical software R were used to conduct the quantitative synthesis.

Results

Our search identified 855 studies. Six studies were included in our systematic review, while five studies were included in the meta-analysis [24, 25, 27–30]. The six studies included a total of 900 women, with 465 endometriosis patients and 435 women without endometriosis (Fig. 1). All of the included studies were retrospective observational studies, consisting of five case–control studies [24, 25, 27, 28, 30] and one single-arm study [29].

CE was diagnosed after detection of plasma cells using CD-138 immunohistochemistry in all included studies. The diagnostic criteria for the diagnosis of CE varied from more than one plasma cell per ten high power fields (HPF) [27, 28] up to more than five plasma cells per HPF [30], and

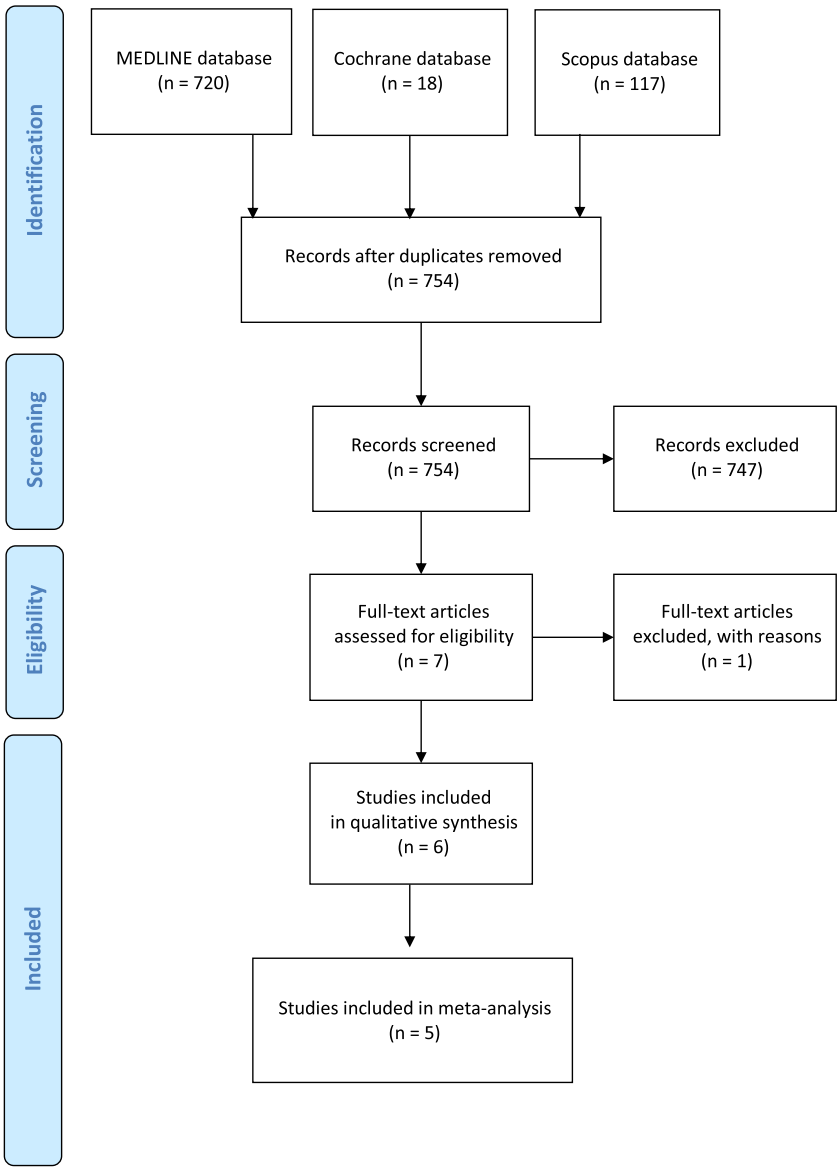


Fig. 1 Study flow chart

the laboratory procedures (clones, dilutions, temperatures, time for incubation and preparation of endometrium) differed between the included studies (Table 1). In most of the included studies, endometriosis was diagnosed via laparoscopic biopsy. The assessed endometrial tissue was received by hysterectomy in three studies [27, 28, 30], while the others used endometrial sampling (curettage [23, 28] and pipelle biopsy [24, 29]). Two of the included studies examined only infertile women [24, 29].

Four of the included studies [24, 27–29] reported that included women were premenopausal, while the remaining two studies did not clearly specify the menopausal status of the patients. Only Khan et al. reported hormonal pretreatment., in which pretreatment with GnRH analogues was comparable between endometriosis and control group [25] and two studies reported the phase of the cycle where the biopsy was performed [27, 29]. The menstrual cycle characteristics (duration of menstrual cycle and duration of bleeding) were reported in Khan and Takebayashi et al., which both studies found comparable durations between endometriosis and control group [25, 27]. The biopsies were conducted in secretory phase in Freitag et al. and in follicular phase in Qiao et al., while in the rest studies the biopsies were conducted in both secretory and follicular phase. A previous history of genital infection, peritonitis, presence of hydrosalpinx or autoimmune disease were not reported in any of the included studies, while two of the included studies explicitly listed clearly severe disease, neoplastic lesions and history of sexual transmitted diseases as exclusion criteria [28, 29].

Regarding the control groups in these studies, three studies included women who underwent hysterectomy for benign gynecological conditions, such as uterine fibroids, prolapse, or endometrial hyperplasia in three studies [27, 28, 30]. One study included fertile women who underwent curettage and laparoscopy for benign ovarian cyst or uterine myomas [31] and another study involved infertile patients without history of endometriosis who underwent curettage [24]. The risk of bias assessment for each study is presented in Table 2.

Prevalence of Chronic Endometritis in Women with Endometriosis

The pooled prevalence of CE in women with endometriosis in the six included studies was 28% (95% CI 15–45, $I^2 = 86\%$, $n = 465$, six studies) (Fig. 2A). Subgroup analysis of the studies that included women with laparoscopically diagnosed endometriosis found a prevalence of 39% (95% CI 28–51, $I^2 = 84\%$, $n = 378$, four studies) (Fig. 2B). After excluding the low-quality studies, the heterogeneity decreased and the prevalence was 45% (95% CI 37–52, $I^2 = 16\%$, $n = 177$, 3 studies) (Fig. 2C). Prevalence rates were significantly higher ($p = 0.02$) in women with endometriosis rASRM stage III-IV in comparison to endometriosis rASRM I-II (43%, 95% CI 34–52, $I^2 = 57\%$, $n = 103$, two studies vs 25%, 95% CI 20–32, $I^2 = 42\%$, $n = 210$, 2 studies) (Fig. 2D, E). In women with endometriosis and infertility, the prevalence of CE was found to be 19% (95% CI 11–30, $I^2 = 77\%$, $n = 268$, 2 studies) (Fig. 2F). The pooled prevalence of CE varied depending on the sample used for the diagnosis. In women with endometriosis undergoing hysterectomy, the observed prevalence of CE was 29% (95% CI 10–61, I2 = 76%, $n = 132$, three studies) (Fig. 2G), while, when the sample was obtained through curettage, the prevalence of CE was 26% (95% CI 13–45, I2 = 90%, $n = 333$, three studies) (Fig. 2H).

Comparison of Chronic Endometritis Prevalence Between Women with and Without Endometriosis

The meta-analysis of all eligible studies demonstrated a significantly higher prevalence of CE in women with endometriosis compared to the control group (five studies, 264 endometriosis vs. 435 control, OR = 2.07; 95% CI 1.11–3.84, I^2 43%, $p = 0.02$) (Fig. 3A).

Regarding the stage of endometriosis according to rASRM classification, the only study including rASRM I-II patients endometriosis women [27], found no significant difference between the two groups (one study, 9 endometriosis vs. 37 control women, OR = 2.16; 95% CI 0.48–9.70, $p = 0.31$). On the other hand, a subgroup analysis for women with endometriosis stage rASRM III-IV, found a higher CE prevalence in endometriosis group (two studies, 103 endometriosis vs. 115 control women, OR = 2.39; 95% CI 1.53–3.71, $p = 0.0001$) (Fig. 3B).

The only study that included women with endometriosis and a history of infertility showed no significant difference between the two groups (one study, 67 endometriosis vs. 53 control women, OR = 2.26; 95% CI 0.57–8.98, $p = 0.25$) [24].

The subgroup analysis of the studies, where the endometrial tissue was gained by curettage did not show a significant difference between the two groups (two studies, 132 endometriosis vs. 106 control women, OR = 1.45; 95% CI 0.76–2.78, I^2 0%, $p = 0.48$) (Fig. 3C). Similarly, the meta-analysis of the studies, where endometrial tissue was extracted from the hysterectomy did not show a significant difference between endometriosis and control women (three studies, 132 endometriosis vs. 329 control, OR = 2.43; 95% CI 0.94–6.26, I^2 52%, $p = 0.07$) (Fig. 3D).

The meta-analysis of the studies in which endometriosis and control groups were matched for age showed a significantly higher prevalence of CE in women with endometriosis (three studies, 177 endometriosis vs. 168 control women, OR = 2.39; 95% CI 1.18–4.82, I^2 54%, $p = 0.02$) (Fig. 3E). However, the synthesis of the studies that were matched

Table 1 Characteristics of the included studies

Study characteristics			Endometriosis group									Control group							
Study	Study design	Country	n	CE	CE prevalence according to rASRM stage	Age (y)	BMI(kg/m^2)	Leiomyoma	Adenomyosis	Parity	Infertility	n	CE	Age (y)	BMI(kg/m^2)	Leiomyoma	Adenomyosis	Parity	Infertility
Kitaya et al. [30]	retrospective single-arm study	Japan	20	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	214	25	n/a	n/a	n/a	n/a	n/a	n/a
Takebayashi et al. [27]	retrospective case–control study	Japan	34	18	stage I 2/5 stage II 2/4 stage III 7/10 stage IV 7/15	44.15 (3.65)	22.08 (4.83)	23	16	1.38 (1.04)	0%	37	10	44.33 (3.06)	21.94 (3.45)	35	3	1.92 (0.95)	0%
Khan et al. [25]	prospective case–control study	Japan	65	31	n/a	36.5 (7.1)	n/a	n/a	n/a	0.57 (0.8)	n/a	53	22	35.8 (7.9)	n/a	n/a	n/a	0.85 (1.1)	n/a
Cicinelli et al. [28]	retrospective case–control study	Italy	78	30	stage IV 78	44.3 (2.8)	27.3 (4.2)	31	25	1.3 (0.7)	0%	78	11	44 (2.3)	27.2 (4.3)	61	0	1.8 (0.7)	0%
Freitag et al. [24]	retrospective case–control study	Germany	67	8	n/a	n/a	n/a	n/a	n/a	n/a	100%	53	3	n/a	n/a	n/a	n/a	n/a	100%
Qiao et al. [29]	retrospective single-arm study	China	201	49	stage I-II 201	28.61 (3)	20.39 (2.48)	0	0	0.07 (0.26)	100%	-	-	-	-	-	-	-	-

Age, BMI and parity are presented as mean and standard deviation

CE: chronic endometritis, *BMI*: body mass index, *rASRM*: revised American Society of Reproductive Medicine classification for endometriosis

for BMI and the phase of the menstrual cycle did not find a significant difference (two studies, 99 endometriosis vs. 90 control women, OR = 1.85; 95% CI 0.80–4.25, I^2 47%, $p = 0.15$) (Fig. 3F).

A subgroup analysis of studies in which endometriosis was diagnosed via laparoscopy with biopsy, found a significant higher prevalence of CE in women with endometriosis (three studies, 177 endometriosis vs. 168 control, OR = 2.39; 95% CI 1.18–4.82, I^2 54%, $p = 0.02$) (Fig. 3G).

Furthermore, a sensitivity analysis, after excluding the low-quality studies according to the quality assessment performed, confirmed a significantly higher prevalence of CE in the endometriosis group (three studies, 177 endometriosis vs. 168 control, OR = 2.39; 95% CI 1.18–4.82, I^2 54%, $p = 0.02$) (Fig. 3H).

Discussion

Our study found a significantly higher risk of CE in women with endometriosis compared to control women (five studies, 264 endometriosis vs. 435 control women, OR = 2.07; 95% CI 1.11–3.84, I^2 43%, $p = 0.02$). The pooled prevalence of CE in women with endometriosis was found to be 28%, and it was even more elevated (43%) in women with moderate/severe endometriosis.

There is a high inconsistency in the prevalence of CE in women with endometriosis, ranging from 5% in Kitaya et al. [30] to 52.9% in Takebayashi et al. [27]. These variations can be attributed to differences in the diagnostic criteria of CE, the number of HPFs and amount of tissue examined per patient. For instance, Kitaya et al. required the presence of more than five plasma cells in 10 HPFs for diagnosis, while Takebayashi et al. considered a single plasma cell in 10 HPFs sufficient for diagnosis.

Moreover, the lack of consensus on the histological diagnosis of CE, interobserver variations and the different immunohistochemical staining methods used, further contribute to the differences in prevalence observed between studies [32]. Furthermore, the different types of endometrial samples used for the diagnosis of CE may also contribute to the variation in CE prevalence, as half of the included studies examined the uterus after hysterectomy [27, 28, 30], while the remaining studies only used curettage as endometrial samples [24, 25, 29]. The discrepancies in the phase of menstrual cycle between the included studies could also contribute in the heterogeneity of the results. Takebayashi et al. examined at least two sections from patients, while Kitaya et al. examined one section from patients [27, 30]. However, in other studies, the number of sections examined is not clearly reported [24, 28, 29, 31]. In this meta-analysis, we did not identify any study which used hysteroscopy for the diagnosis of CE. According to previous studies, hysteroscopic findings including presence of local or diffuse hyperemia, edema of the stroma and presence of micropolyps had a correlation about 90% with the histologic findings [33]. A previous study showed that hysteroscopy-guided endometrial biopsy is more accurate than blind aspiration biopsy as it provides homogeneous tissue samples in satisfactory amounts, prevents artifacts such as blood infiltration into the samples, and preserves the integrity of tissue architecture [34].

A common macroscopic finding associated with infertility and recurrent pregnancy loss, observed at a high frequency

Table 2 Diagnostic criteria and quality assessment of the studies included

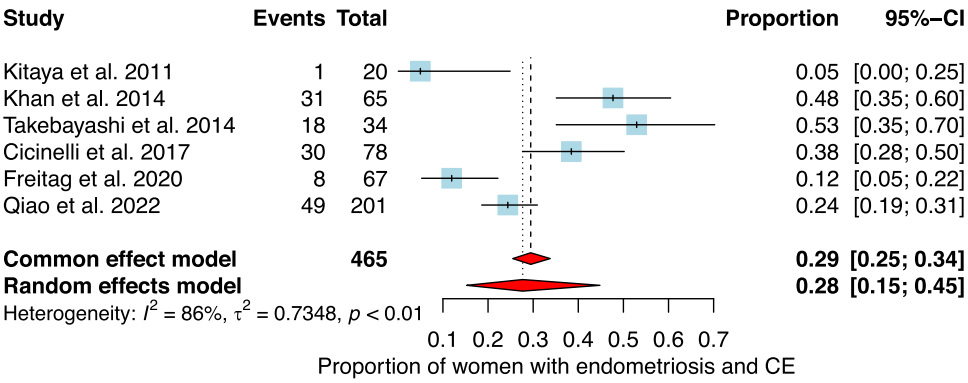
Study characteristics	Diagnostic tools		Quality Assessment
Study	diagnosis of endometriosis	diagnosis of chronic endometritis	
Kitaya et al. [30]	interview	CD138 (hysterctomy) > 5 plasma cells in 10 HPFs (400-fold magnification)	Poor
Takebayashi et al. [27]	laparoscopy	CD138 (hysterectomy) > 1 plasma cell in 10 HPFs (400-fold magnification)	Fair
Khan et al. [25]	laparoscopy	CD138 (curettage) > 1 plasma cell in 15 HPFs (100-fold magnification) or in 3 or more sections	Good
Cicinelli et al. [28]	laparoscopy	CD138 (hysterectomy) > 1 plasma cells in 10 HPFs (100-fold magnification)	Good
Freitag et al. [24]	medical history or laparoscopy	CD56 and/or CD138 (curettage) > 300 uNK cells or > 5 plasma cells per mm2	Poor
Qiao et al. [29]	laparoscopy	Both CD138 and CD38 (curettage) 5 plasma cells per 30 HPFs	n/a

HPF: high power fields

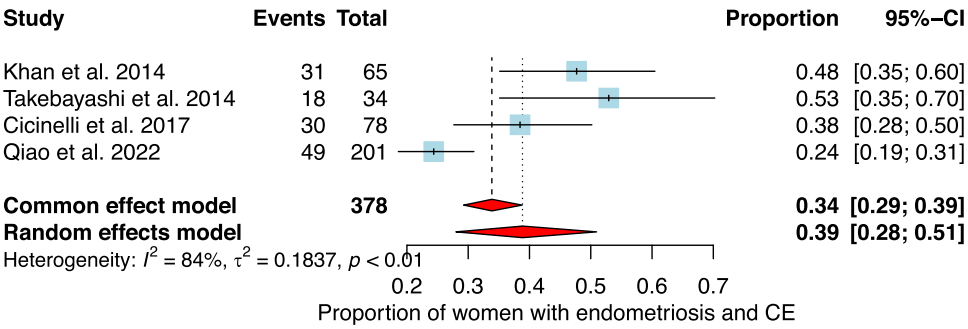
uNK: uterine natural killer cells

Fig. 2 Proportion of women with endometriosis and chronic endometritis

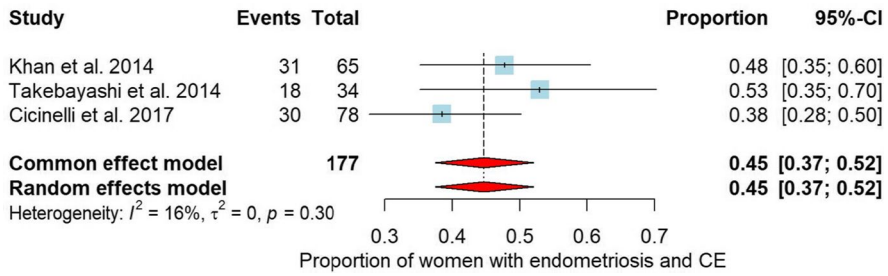
A) Incidence of chronic endometritis in women with endometriosis



B) Subgroup analysis. Incidence of chronic endometritis in women with laparoscopically diagnosed endometriosis



C) Sensitivity analysis, excluding poor quality studies. Incidence of chronic endometritis in women with endometriosis



D) Subgroup analysis. Incidence of chronic endometritis in women with endometriosis rASRM I-II

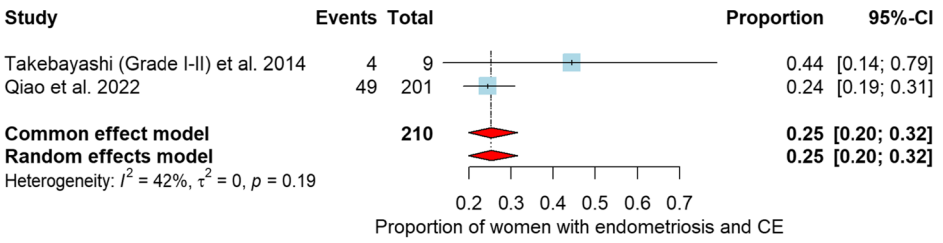
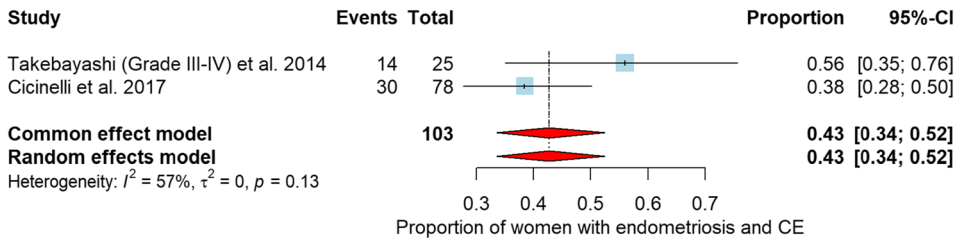
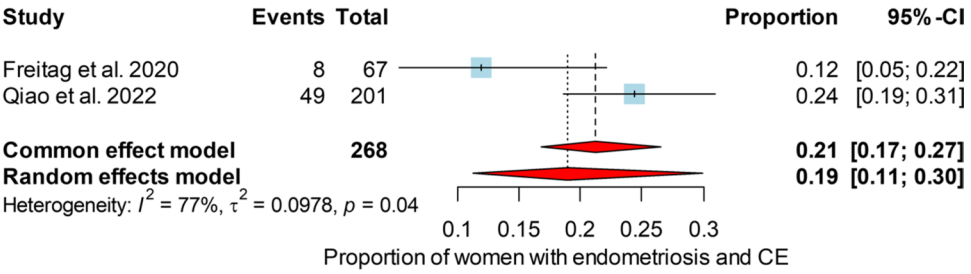


Fig. 2 (continued)

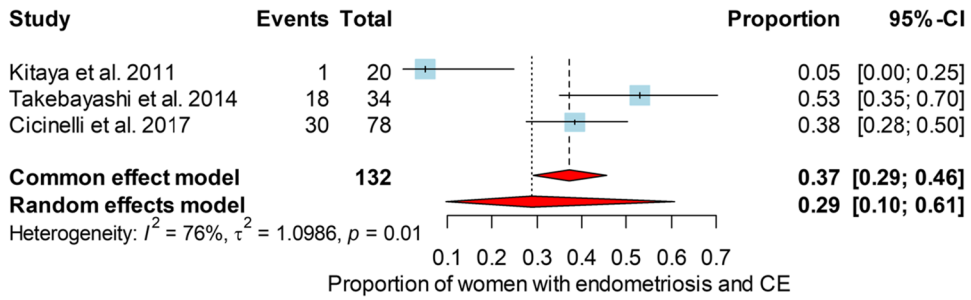
E) Subgroup analysis. Incidence of chronic endometritis in women with endometriosis rASRM III-IV



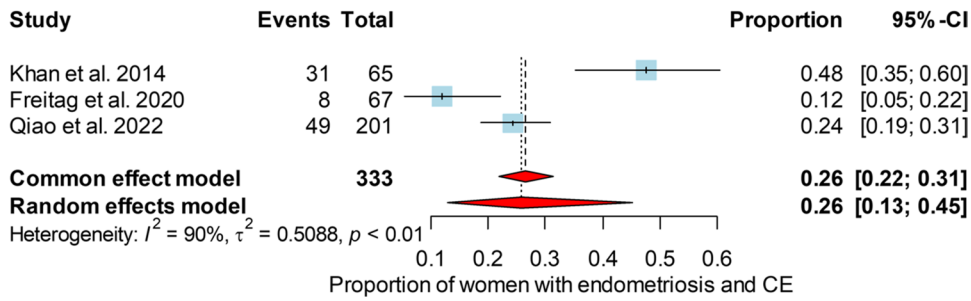
F) Subgroup analysis. Incidence of chronic endometritis in women with endometriosis and infertility



G) Subgroup analysis. Incidence of chronic endometritis diagnosed after hysterectomy in women with endometriosis



H) Subgroup analysis. Incidence of chronic endometritis diagnosed after endometrial curettage in women with endometriosis



in both patients with endometriosis and those with CE, is the presence of endometrial polyps. The prevalence of endometrial polyps was reported to be approximately 50% in women with endometriosis [35] and up to 50% in women with CE, as reported in a recent meta-analysis [36]. It has been suggested that chronic inflammation and altered endometrial

gene expression, particularly those related to inflammation, cell proliferation, and apoptosis, may contribute to the development of endometrial polyps [12].

According to our results, the prevalence of CE is significantly higher in women with endometriosis rASRM stage III/IV versus rASRM stage I/II. These results need to be interpreted with caution, as only three studies [27–29] reported the prevalence of CE according to the rASRM stage of endometriosis.

The different diagnostic criteria and the different way of sample collection complicate the comparability of the study results.

The coexistence of adenomyosis in women with endometriosis should also be considered, as it is associated with a high prevalence of CE (approximately 60%), as reported by Khan et al. [31]. Only two of the studies included in this meta-analysis reported the diagnosis of adenomyosis in the endometriosis group (Cicinelli et al. 32% [28] and Takebayashi et al. 47% [27]), but a much higher association could be assumed. The diagnosis of adenomyosis has been improved only a few years ago with the technical progress of ultrasound scans. Thus, overall, it can be assumed that the prevalence of adenomyosis may also be higher in patients with CE.

Proper treatment of CE in women with infertility appears to have a positive effect on ART outcomes, as shown by Cicinelli et al. [28]. After antibiotic treatment of CE they reported significantly higher clinical pregnancy and live birth rates in women with cured versus persistent CE. The first line treatment for CE is doxycycline 100mg twice a day for 10 to 14 days [2].

The cohort study by Mitter et al. [6, 12, 13] showed that diagnosis of CE and antibiotic administration resulted in pregnancy and live birth more rapidly within 18 months. Additionally, a meta-analysis found that women with recurrent pregnancy loss and CE showed higher pregnancy rates (OR = 4.02), live birth rates (OR = 6.81), and implantation rates (OR = 3.24) after successful treatment compared to those with persistent CE [14].

Liu et al. compared the prevalence of CE in fertile to infertile women, without referring the diagnosis of endometriosis, using different diagnostic methods [10]. According to the method with the lowest observer variability, the cell count per section, they found no statistical difference between the two groups. Their study showed a prevalence of CE 10.4% in women with infertility and 5% in the control group. According to ESHRE guidelines for Recurrent Pregnancy Loss, the prevalence of CE in women with recurrent pregnancy loss varies between 7 and 58%, however systematic screening for CE, due to the lack of evidence, is currently not recommended [37].

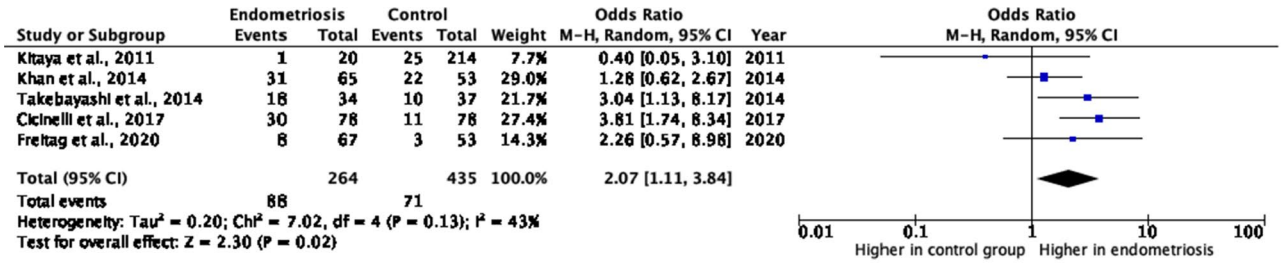
In our study the pooled prevalence of CE in women with both, infertility and endometriosis, was 19% (95% CI 11–30, two studies, $n = 268$ women with endometriosis).

Regarding the link between CE and endometriosis, various hypotheses suggest a bidirectional interaction between these two conditions (Fig. 4). Plasma cells produce anti-endometrial antibodies such as anti-SLP2, anti-TMOD3, anti-TPM3, and anti-PDIK1L, that can be found in the endometriotic lesions, peritoneal fluid, and serum, leading to an auto-immune endometritis [38–40]. It has also been suggested that these anti-endometrial autoantibodies may play a crucial role in infertility associated with endometriosis, by interfering with implantation and affecting early embryonic development [41]. Additionally, inflammatory mediators such as cytokines, growth factors and prostaglandins may be transported from endometriotic lesions through peritoneal fluid and the fallopian tubes into the uterine cavity, contributing to the development of CE [27, 29] and thereby affecting embryo implantation.

Several studies have observed significant differences in the genital tract microbiome between patients with and without endometriosis. Notably, there is an increase of *Proteobacteria, Enterobacteriaceae, Streptococcus, Escherichia coli and Gardnerella* in endometriosis patients [42]. The dysbiosis may potentially result in chronic inflammation, linked to compromised immune tolerance arising from diminished function and quantity of regulatory T cells. [43]. In addition, the microbiome may influence estrogen metabolism by increasing active isoforms of estrogens that may support the development of endometriosis [44]. Dysbiosis is also proposed to be a major factor contributing to CE. As demonstrated by Cicinelli et al., where adjusted antibiotic treatment based on the identified pathogen (Ciprofloxacin for Gram-negative infections, Amoxicillin and Clavulanate for Gram-positive infections, Josamycin, Minocycline, or Doxycycline for Mycoplasma and Ureaplasma urealyticum, and Ceftriaxone, Doxycycline, and Metronidazole for women with negative cultures) improved endometritis-associated infertility [28]. Studies have demonstrated an overgrowth of bacteria, such as *Escherichia coli, Streptococcus, Staphylococcus, Chlamydia, Mycoplasma and Ureaplasm*a, in cases of endometritis [45]. Therefore, endometriosis may lead to CE through a dysfunctional microbiome. In particular, lipopolysaccharides expressed on the surface of *Escherichia coli* have been shown to selectively induce extravasation of plasma cells into the stroma of the endometrial functional layer in CE [46].

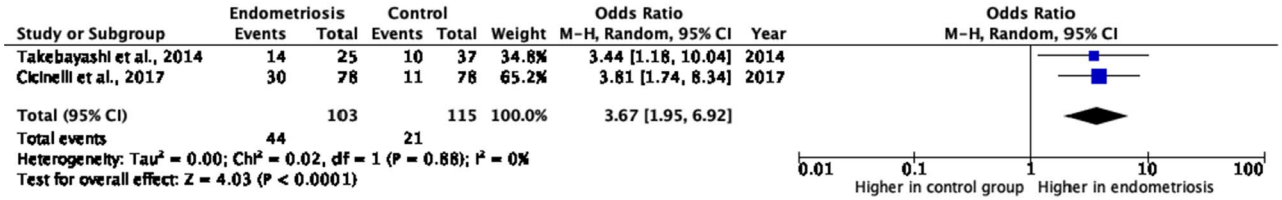
Previous studies demonstrated that CE can induce a transformation of the eutopic endometrium during secretory phase, leading to alterations of the BCL2 and BAX-associated apoptotic pathways [47, 48]. In normal endometrium anti-apoptotic BCL2 levels are high during the proliferative phase and decrease rapidly in the secretory phase, while the pro-apoptotic BAX is expressed during the mid-luteal phase and menstruation [49]. In contrast to non-pathological endometrium, in CE BCL2 remains on a high level [47]. A decrease of BCL2/BAX ratio normally activates

A) Endometriosis vs Control

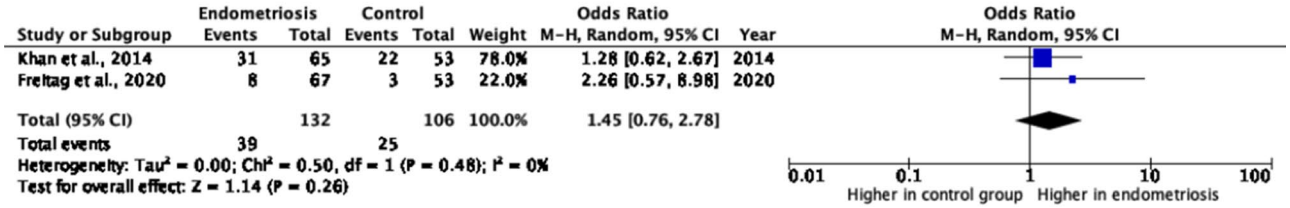


Subgroup Analysis

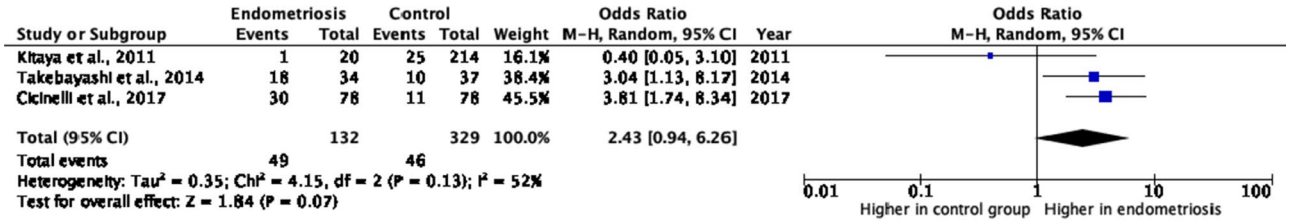
B) Endometriosis rASRM stage III-IV vs Control



C) Endometriosis vs Control (Curettage)



D) Endometriosis vs Control (Hysterectomy)



E) Endometriosis vs Control matched for age

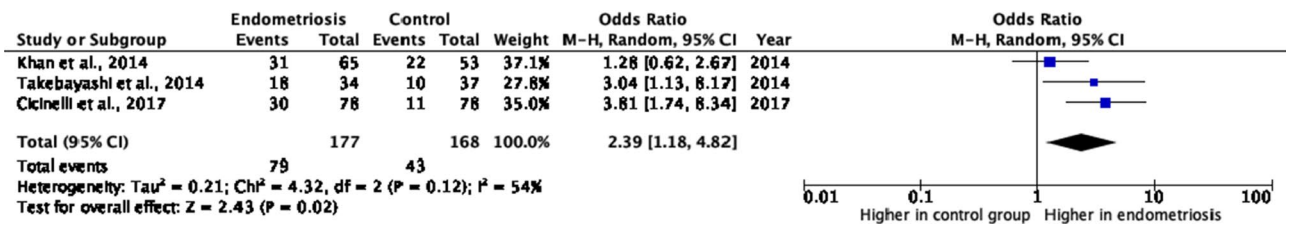
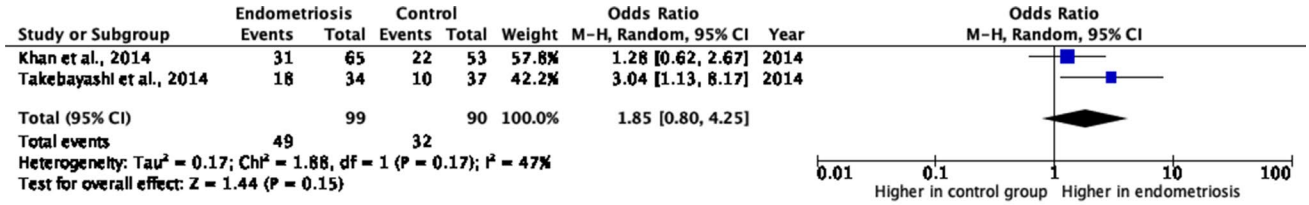
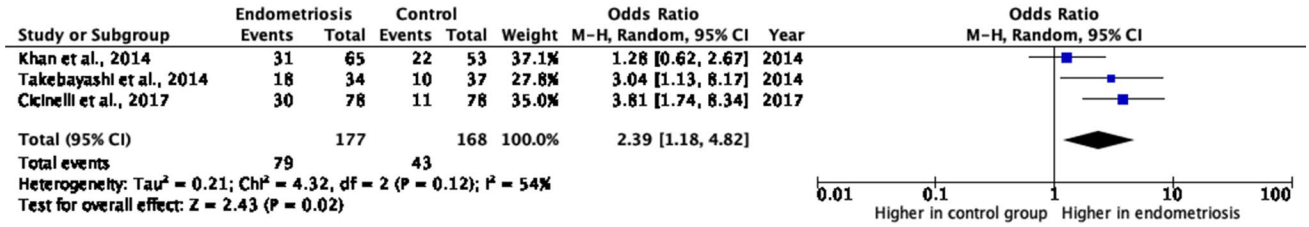


Fig. 3 Chronic endometritis between women with and without endometriosis. **A**) crude rates, **B**)-**G**) subgroup analysis, **H**) sensitivity analysis

F) Endometriosis vs Control matched for BMI and menstrual cycle phase



G) Endometriosis vs Control (endometriosis diagnosed with laparoscopy)



Sensitivity analysis

H) Endometriosis vs Control (Fair/Good quality studies)

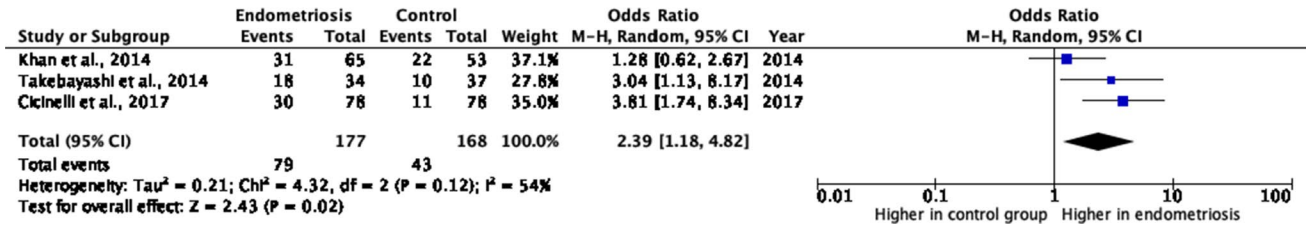


Fig. 3 (continued)

cell-apoptosis during menstruation and endometrial remodeling during embryonal implantation [50]. In addition, in CE a defective decidualization was observed with cell proliferation even during the secretory phase, which could lead to formation of micro polyps and endometriosis [47, 48].

Furthermore, CE leads to a dysregulation of estrogen and progesterone hormone receptors in the endometrium of premenopausal patients [48], a common finding also in eutopic endometrium of patients affected by endometriosis and adenomyosis as well [51, 52]. An up-regulation of estrogen receptor beta, which mediates an estrogen-driven inflammatory process, prostaglandin synthesis and cell proliferation was observed both, in CE and endometriosis [53].

Only two of the included studies reported the phase of the menstrual cycle during which the biopsies were performed. Previous research has shown that biopsies taken during the follicular phase were nearly three times more likely to contain plasma cells than those taken during the luteal phase in patients with infertility and recurrent pregnancy loss (59.3% vs. 19.7%) [54]. Additionally, hormonal pretreatment was not addressed in the majority of the included studies. Prior studies have demonstrated a positive effect on the treatment of CE of dydrogesterone [55, 56] and a higher prevalence of CE in women who were treated with GnRHa [25]. The timing of biopsy collection within the menstrual cycle and the role of hormonal pretreatment should be addressed in future studies.

Moreover, it has been shown that patients with CE present impaired uterine contractility as video-assessed by ultrasound [57]. This may increase the retrograde menstruation and the formation of endometriosis. In addition, hypercontractility may lead to myometrial tissue-injury and repair (TIAR), which is proposed as a key element in the pathogenesis of adenomyosis [58].

Proinflammatory cytokines (interleukin-6, interleukin-1β, tumor necrosis factor α) and plasma cells are increased in

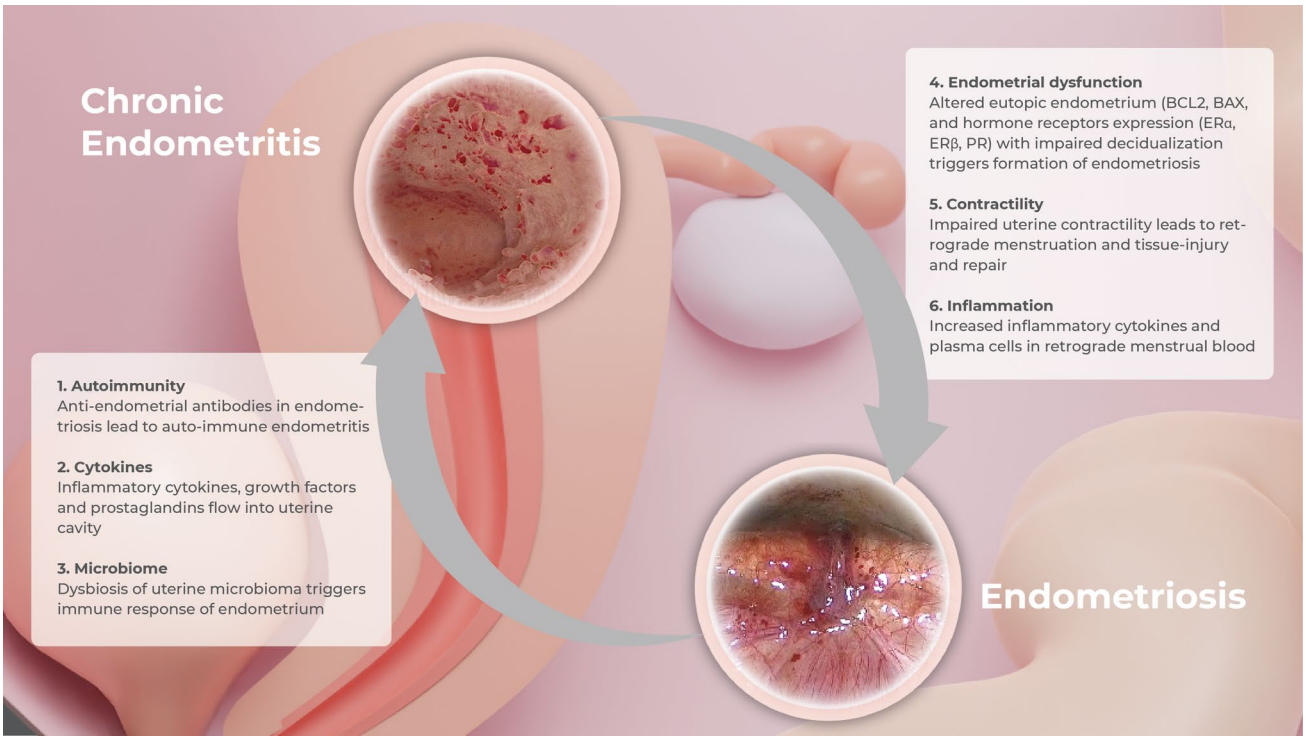


Fig. 4 Proposed common mechanisms between endometriosis and chronic endometritis

the functional endometrial layer and the menstrual blood of CE [46, 59]. Retrograde reflux of these factors may therefore enforce endometriosis-associated inflammatory in the abdominal cavity [27].

To the best of our knowledge, this is the first meta-analysis providing evidence on the association between CE and endometriosis. However, it is important to recognize that this study has certain limitations, with the major limitation the number of included studies, as only six studies fulfilled the inclusion criteria. There were discrepancies between the diagnostic criteria used for CE and different samples were used for its diagnosis. Furthermore, the fact that the study included a heterogeneous population, ranging from women with infertility to women who underwent hysterectomy for various indications such as uterine fibroids, adenomyosis, atypical endometrial hyperplasia, prolapse and carcinoma in situ, potentially limits the generalizability of the findings. In addition, the diagnostic tool of endometriosis differs between the studies (laparoscopy, interview). Therefore, these limitations should be considered when interpreting the study's findings, and in planning future research.

Given that the immune system seems to be significantly modified in both the endometriotic site and the eutopic endometrium of women with endometriosis, while CE represents a persistent inflammation of the endometrium, one could assume that these two conditions may be interrelated. The mechanism of action (if any) is unknown. However, a crucial question is whether patients with endometriosis should be tested for CE and whether CE should be then treated. The debate is still on, as no high-quality studies have yet been performed [60] and several questions regarding the definition of CE, treatment options and finally impact on reproductive outcomes remain unsolved [61]. Currently, the diagnosis of CE is based on reproductive history and recommended in women with repeated miscarriages or implantation failure after transfer of several good blastocysts. The results presented here might form the basis for establishing the specific diagnosis of CE in women with endometriosis who wish to have children.

Conclusion

Although, because of heterogeneity in available studies, conclusions have to be drawn with caution, the present meta-analysis showed a significantly higher risk of CE in women with endometriosis in comparison to control women. These findings contribute to a better understanding of the causes and consequences of endometriosis and CE and may help in the development of better treatment strategies for women with endometriosis-associated infertility.

Author Contribution DRK and NS were involved in the conception and design of the study. UC, PD and GS were involved in the acquisition of

data, analysis and interpretation of data, and drafting of the article. BL, AKS, DRK, NS, PD and UC were involved in revising the manuscript critically for important intellectual content. DRK was responsible for final approval of the version to be submitted.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflicts of Interest DRK has nothing to disclose related to this study, UC has nothing to disclose related to this study, AKS has nothing to disclose related to this study, GS has nothing to disclose related to this study, BL has nothing to disclose related to this study, PD has nothing to disclose related to this study, NS has nothing to disclose related to this study.

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