ORIGINAL ARTICLE: ENDOMETRIOSIS

Higher prevalence of chronic endometritis in women with endometriosis: a possible etiopathogenetic link

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Objective: To evaluate the association between endometriosis end chronic endometritis (CE) diagnosed by hysteroscopy, conventional histology, and immunohistochemistry.
Design: Case-control study.
Setting: University hospital.
Patient(s): Women with and without endometriosis who have undergone hysterectomy.
Intervention(s): Retrospective evaluation of 78 women who have undergone hysterectomy and were affected by endometriosis and 78 women without endometriosis.
Main Outcome Measure(s): CE diagnosed based on conventional histology and immunohistochemistry with anti-syndecan-1 antibodies to identify CD138 cells.
Result(s): The prevalence of CE was statistically significantly higher in the women with endometriosis as compared with the women who did not have endometriosis (33 of 78, 42.3% vs. 12 of 78, 15.4% according to hysteroscopy; and 30 of 78, 38.5% vs. 11 of 78, 14.1% according to histology). The women were divided into two groups, 115 patients without CE and 41 patients with CE. With univariate analysis, parity was associated with a lower risk for CE, and endometriosis was associated with a statistically significantly elevated risk of CE. Using multivariate analysis, parity continued to be associated with a lower incidence of CE, whereas endometriosis was associated with a 2.7 fold higher risk.
Conclusion(s): The diagnosis of CE is more frequent in women with endometriosis. Although no etiologic relationships between CE and endometriosis can be established, this study suggests that CE should be considered and if necessary ruled out in women with endometriosis, particularly if they have abnormal uterine bleeding. Identification and appropriate treatment of CE may avoid unnecessary surgery. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Chronic endometritis, endometriosis, hysteroscopy, immunohistochemistry, infertility

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Chronic endometritis (CE) and endometriosis have many features in common. Both disorders are chronic inflammatory diseases of unclear pathogenesis that may cause abnormal uterine bleeding, pain, and impaired reproduction.

The accumulated data have indicated that the eutopic endometrium is affected in women with endometriosis, and their endometrial receptivity is impaired. Women with endometriosis also have higher rates of spontaneous miscarriages as compared with endometriosis-free controls (1). A recent population-based retrospective cohort study examined 347,185 autologous fresh and frozen assisted reproductive technology (ART) cycles from the Society of Assisted Reproductive Technology (SART) reported that endometriosis is associated with lower implantation and pregnancy rates in ART (2).

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A chronic inflammation of the endometrium, CE remains ignored by most fertility specialists due to the relative paucity of symptoms and difficulty of diagnosis. Indeed, CE may be asymptomatic or may present with mild and nonspecific symptoms such as abnormal uterine bleeding, pelvic pain, dyspareunia, and leukorrhea for extended periods of time. Contributing to the difficulty of diagnosis are the lack of specific clinical signs or findings on uterine ultrasound. Consequently, the diagnosis of CE is frequently missed.

Histologic confirmation of CE relies on identifying plasma cells infiltrates in the endometrial stroma, which remains the gold standard for diagnosis. This procedure is not only cumbersome, as it requires an endometrial biopsy, but also makes accurate diagnosis difficult because of the normal presence of leukocytes in the endometrium (3). We have reviewed how CD138 immunohistochemistry staining for plasma cell identification provides higher diagnostic accuracy and sensitivity, and reduced intraobserver and interobserver variability as compared with simple histology (4). In previous publications we also described how the use of diagnostic hysteroscopy is a promising alternative for diagnosing CE based on identifying characteristic findings such as micropolyps, stromal edema, and focal or diffuse hyperemia (5, 6).

Studies have shown that CE is found in 14% to 60% of patients who present with repeated implantation failures in ART (7–10) and 27% to 60% of women with recurrent pregnancy loss (9–11). Furthermore, we and others have shown that adequate antibiotic treatment significantly improves outcomes in women with CE (6, 8, 9).

Our current understanding of the pathophysiology of CE points at immunologic and paracrine alterations of the endometrium. In women with CE, we observed an abnormal pattern of lymphocyte subsets in the endometrium (12). We also found that in women with CE there is an aberrant endometrial microenvironment with altered expression of some genes involved in the inflammatory cascade and cellular replication (up-regulation of IGFBP1, BCL2, and BAX and down-regulation of IL11, CCL4, IGF1, CASP8) (13).

Endometriosis, a disorder that causes pelvic pain and infertility, is characterized by the presence of an inflammatory reaction in the ectopic endometrial tissue and also in the eutopic endometrium (14, 15). The pathophysiology of endometriosis encompasses several factors, including inflammation, angiogenesis, cytokine/chemokine expression, and endocrine alterations affecting steroid and steroid receptor expression. Recent work has added other factors, including genetics and epigenetics (16).

At present, endometriosis is thus considered an inflammatory disease with an abnormal immune response (17, 18). The distribution of immune cells in the pelvic cavity has been reported to differ between endometriosis and nonendometriosis cases (19, 20). Increased activation of macrophages along with increased secretion and synthesis of different proinflammatory mediators has been reported in women with endometriosis (21–25). It is interesting that gene expression and protein secretion are also modified in the eutopic endometrium in women with endometriosis compared to healthy women (25–28). Furthermore, in endometriosis the immune system appears to be greatly modified in both ectopic lesions and in the eutopic endometrium.

Further supporting the view that common factors exist between endometriosis and CE, Takebayashi et al. (29) reported that the prevalence of CE, diagnosed by localized immunostaining for CD138 in the endometrial stroma was statistically significantly higher in women with endometriosis as compared with women without endometriosis (52.94% vs. 27.02%; $P<.05$) (29). The cultures of *Gardnerella*, *α-Streptococcus*, Enterococci, and *Escherichia coli* were statistically significantly higher in the endometrial samples from women with endometriosis as compared with the controls. These findings suggest the existence of subclinical uterine infection with features of CE in women with endometriosis (30).

Both studies relied on a histopathologic diagnosis of CE. However, the reliability of the diagnosis of CE based on plasma cells as well as positive CD138 immunostaining has been questioned. Indeed, $CD138^{+}$ cells are absent in 25% of endometrial biopsies in which plasma cells were identified by conventional histology. In women at low risk for pelvic infection, flow cytometric analyses detected plasma cells in 30% of endometrial biopsy specimens, suggesting that these cells, even when accurately identified, only nonspecifically identify upper genital tract inflammatory processes (31). Plasma cells were also detected in 5% to 10% of women undergoing an endometrial biopsy for irregular vaginal bleeding, suggesting that these cells may nonspecifically identify endometrial inflammation (32, 33).

We undertook the present study to identify any association between endometriosis and CE. In view of the diagnostic difficulties we have described, CE was positively diagnosed only when confirmed by histology, immunohistochemistry, and hysteroscopy. Using this approach, we evaluated the prevalence of CE in women who had undergone hysterectomy with a histologic diagnosis of endometriosis. Women who had a hysterectomy for benign conditions in whom endometriosis was excluded served as the controls.

MATERIALS AND METHODS

Study Design

We conducted a retrospective analysis of a total of 156 patients who underwent hysterectomy in our department from January 2010 to June 2016 for benign gynecologic indications, of whom 78 women had histology-proven endometriosis and 78 women had endometriosis surgically excluded. All patients were of reproductive age, in good general health, and had no history of antibiotic or anti-inflammatory treatment for at least 3 months. Patients with preneoplastic or neoplastic lesions were excluded.

The local ethics committee of the Department of Obstetrics and Gynecology, University of Bari, Italy, approved the study, and all women consented to the anonymous use of their personal data. There were no known conflicts of interest associated with this study, and there was no pertinent financial support for this work.

All women presenting to our institution for abnormal uterine bleeding have a preliminary ultrasound evaluation and hysteroscopy during the follicular phase (cycle day

7–12), and the images are saved. No woman included in the study had emergency surgery. Only patients who had a complete and satisfactory presurgical evaluation were included in the study.

Hysteroscopies were performed using a 2.7-mm mini-telescope lens with 105° angle vision equipped with a 4.5-mm double-flow operative sheath (Karl Storz). Normal saline was used to distend the uterine cavity at a pressure generated by a simple drip from a bag suspended 1 m above the patient. A 300 W light source with a xenon bulb and high definition digital camera (Karl Storz) were used. During the hysteroscopy, both the anterior and posterior uterine walls were thoroughly examined by passing the hysteroscope parallel to the endometrial surface. Using this approach, any surface irregularity was easily identified.

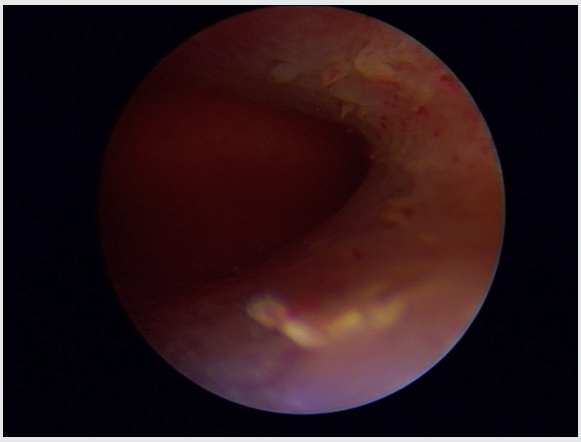
The evaluation of hysteroscopic pictures was performed by two of the authors (E.C., M.Marinaccio), who were unaware of histologic findings; they used the diagnostic criteria previously elsewhere described for the hysteroscopic diagnosis of CE. Briefly, the diagnosis was based on detecting at least one of the following signs, such as focal or generalized periglandular hyperemia, stromal edema, and isolated or diffuse micropolyps (Fig. 1) (34).

Paraffin-embedded endometrial specimens were reanalyzed for our study purposes. The slides were fixed overnight in 4% formaldehyde (in phosphate buffer, pH 7.3; Nacalai Tesque) and embedded in paraffin (Nacalai Tesque). The specimens were examined on a conventional histology preparation and with immunohistochemistry.

Descriptive Pathology

Five microsections were stained with hematoxylin and eosin. The histologic examinations were performed by pathologists (L.R., M.Mar.) who were unaware of the hysteroscopic findings. A positive diagnosis of CE was made in the presence of a stromal infiltrate dominated by lymphocytes and plasma cells and a "spindle cell" change of stromal cells, infiltration compressing adjacent glands, and inflammatory cell clusters inside the glands. Micropolypoid excrescences formed in the endometrium may also be seen as macroscopic evidence of an inflammation-related process and are useful markers for the presence of CE.

FIGURE 1



Hysteroscopic appearance of chronic endometritis. On the endometrial surface many micropolyps, which are little outgrowths floating in the distention medium, are easily detectable. Focal hyperemia and whitish surface due to stromal edema are also evident.

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Immunohistochemistry

The histologic diagnosis of CE was performed by two separate blinded investigators (L.R., M.M.). In all cases the presence of plasma cells was confirmed by immunohistochemistry with incubation with anti-syndecan-1 antibodies (CD138) as previously described elsewhere (35). All cases of CE diagnosis based on classic hematoxylin and eosin slides were found to be positive at immunohistochemical staining. The inflammatory status of the CE was graded as reported in a previous study (34):

Mild (grade 1): mild and superficial inflammatory infiltration, edema, and venular angiectasias.

Moderate (grade 2): diffuse inflammatory infiltration and glandular emperipolesis.

Severe (grade 3): massive diffuse and endoglandular infiltration.

Statistical Analysis

The statistical analysis was performed using Prism 6.0 (GraphPad Software). Data were analyzed using Student's *t*-test or the nonparametric Mann-Whitney *U* test when appropriate. The prevalence of CE in the endometriosis and nonendometriosis groups and the intensity of inflammation were examined using Fisher's exact test. Univariate and multivariate analyses and logistic regression analysis using age, body mass index (BMI), gravidity, parity, and presence of myomas or endometriosis were performed to examine any independent effect of each variable on the risk of CE.

RESULTS

All patients in the endometriosis group had stage IV endometriosis according to the Revised American Society for Reproductive Medicine classification (36). For the nonendometriosis group, the indications for surgery and concomitant findings are described in Table 1. The clinical characteristics of the women in the endometriosis and nonendometriosis groups are also displayed in Table 1. No differences were observed between the endometriosis and nonendometriosis groups regarding age and BMI. Parity was slightly but statistically significantly higher ($P<.05$) in the nonendometriosis compared with the endometriosis group.

A diagnosis of CE was statistically significantly more frequent in the endometriosis group than in the nonendometriosis group (33 of 78, 42.3% vs. 12 of 78, 15.4% at hysteroscopy; and 30 of 78, 38.5% vs. 11 of 78, 14.1% at histology;

TABLE 1

Clinical data of women enrolled in the study: women diagnosed with endometriosis at surgery and histology and women without endometriosis.

	Endometriosis		
Parameter	**Yes**	**No**	***P* value**
No. of patients	78	78	
Age (y)	44.3 ± 2.8	44.0 ± 2.3	NS
BMI (kg/m^2)	27.3 ± 4.2	27.2 ± 4.3	NS
Parity (n)	1.3 ± 0.7	1.8 ± 0.7	< .05
Indications/concomitant pathologies (n)			
Endometriosis	78	0	
Myoma	31	61	
Adenomyosis	25	0	
Prolapse	0	10	
Nonatypical hyperplasia	2	7	

Note: BMI = body mass index; NS = not statistically significant.

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both $P<.001$) (Table 2). In both groups of patients, the diagnosis of CE based on hysteroscopy and histology was highly concordant (33 of 30 and 12 of 11, hysteroscopy vs. histology plus immunohistochemistry).

At hysteroscopy, the number of women showing intermediate/severe signs of CE (generalized hyperemia and/or diffuse micropolyps) as previously described elsewhere (34) was statistically significantly higher in the endometriosis group than the nonendometriosis group (24 vs. 1, respectively; $P<.001$), whereas mild cases (focal hyperemia and isolated micropolyps) were found in 9 and 11 cases, respectively. The distribution of mild and intermediate/severe cases of CE on histology in both groups is illustrated in Supplemental Figure 1 (available online). It is interesting that the number of intermediate/severe cases was statistically significantly higher in the women with endometriosis than in those without endometriosis (25 vs. 1, respectively; $P<.001$). In the latter group, most positive cases were graded of mild intensity.

The 156 patients with or without endometriosis were divided into two groups: 115 patients without CE (non-CE group) and 41 patients with CE (CE group). The women with endometriosis again had a greater incidence of CE ($P<.001$).

In our univariate analysis, age and BMI were not risk factors for CE. Parity was associated with a lower risk for CE, and endometriosis statistically significantly increased the risk of CE (odds ratio [OR] 3.8). In our multivariate analysis, parity continued to be associated with a lower risk, but no relationship was found for age and BMI. Notably, the variable "endometriosis" was a highly statistically significant risk factor for CE (OR 4.9).

Myomas were found in 39.7% of women with endometriosis and in 78.2% of women from the nonendometriosis group (see Table 1). Regarding the association between myomas and CE, we diagnosed CE in 23 out 92 (25%) women with myomas, with no statistical significance in both univariate or multivariate analyses (Table 3).

Regarding adenomyosis—which were sought and thus identified only in the endometriosis group—7 out 25 women were diagnosed with CE (28.0%). However, there was no statistically significant association with CE on univariate analysis, and a nonsignificant trend on multivariate analysis.

TABLE 2

Cases diagnosed with chronic endometritis (CE) in women with and without endometriosis.

	Endometriosis				No endometriosis			
	CE (+)		CE (−)		CE (+)		CE (−)	
Parameter	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hysteroscopy	33	42.3	45	57.7	12	15.4	66	84.6
Histology	30	38.5	48	61.5	11	14.1	67	85.9
CD138 IHC	30	38.5	48	61.5	11	14.1	67	85.9

Note: Diagnosis was performed with hysteroscopy, histology (descriptive evaluation), and immunohistochemistry (IHC) for plasma cells (CD138).

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DISCUSSION

Our study results provide strong evidence for a higher prevalence of CE in women with severe endometriosis as compared with controls (38.5% vs. 14.1%). Specifically, in women with endometriosis, a diagnosis of CE was 2.7 times more frequent than in women without endometriosis (30 vs. 11 cases, respectively). These findings strongly suggest the existence of an association between endometriosis and CE. Based on our results, however, we cannot establish that there is a cause-effect relationship between CE and endometriosis. Alternatively, because of the similar paracrine and immunologic alterations encountered in these two pathologies, there could be a common predisposing factor for both pathologies.

In recent years, a link between chronic inflammation and endometriosis has been repeatedly proposed by several authors. Kobayashi et al. (37) formulated the hypothesis that there are at least two distinct phases in endometriosis development. First, intrauterine microbes may be critical for the initiation of endometriosis; the initial activation of pathogen recognition receptors by microbial stimuli is followed by activation of proinflammatory pathways. In addition to the response to various exogenous pathogen-associated molecular patterns, Toll-like receptors also recognize a wide range of endogenous danger-associated molecular patterns. Second, the increased expression of danger-associated molecular patterns may be involved in the subsequent process of nuclear transcription factor-κB–dependent sterile inflammation. Therefore, the initial wave of Toll-like receptor activation in modulating innate immune responses would be followed by the second large wave of sterile inflammation (37).

In previous publications we demonstrated that an endometrial infection is found in most women diagnosed with CE based on the histologic and hysteroscopic alterations characteristic of CE. Specifically, we found that in women with CE the endometrial cultures are positive in approximately 60% of cases. In about 70% of positive cases, common bacteria

TABLE 3

Univariate, multivariate, and logistic regression analyses for some risk factors (age, BMI, parity, endometriosis, and myoma) and chronic endometritis.

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age (y), per 1 y increase	0.959 (0.834–1.102)	.554	0.921 (0.779–1.090)	.340
BMI (kg/m^2)	1.067 (0.980–1.161)	.133	1.065 (0.958–1.183)	.244
Parity, per 1 child increase	0.208 (0.114–0.376)	<.0001	0.201 (0.106–0.380)	<.0001
Presence of endometriosis	3.807 (1.783–8.338)	.001	4.904 (1.854–12.971)	.001
Presence of myoma	0.852 (0.414–1.752)	.663	0.844 (0.336–2.123)	.719
Presence of adenomyosis	1.109 (0.426–2.887)	.831	0.355 (0.104–1.213)	.099

Note: BMI = body mass index; CI = confidence interval; OR = odds ratio.

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(*E. coli*, Streptococci, Staphylococci, *Enterococcus faecalis*, *Klebsiella pneumoniae*), mycoplasma, and *Ureaplasma urealyticum* have been detected. It is interesting that *Chlamydia* was found in no more than 8% of cases (9, 34). In the remaining 40% of women positive for CE at hysteroscopy and histology, the endometrial cultures were negative. A possible explanation is that only the microorganisms capable of growing under conventional microbiology conditions can be recovered, while other microorganisms (anaerobic bacteria, viruses, etc.) are missed if no special techniques like polymerase chain reaction are used (4).

Despite our limited number of cases, our study provides further insight into the prevalence of CE in the general population. Indeed, the data on the actual prevalence of CE are still uncertain. The results of our study show that the histology was positive for CE in 11 cases out 78 of nonendometriotic women, resulting in a prevalence of 14.1%. Accordingly, Kitaya (38) immunostained 234 specimens obtained by hysterectomy for benign gynecologic disease and reported that CE was identified in 11.1% of the endometrial specimens.

An etiopathogenetic link between CE and endometriosis may rely on altered uterine contractility. In women with CE, we demonstrated a characteristic uterine contractile pattern significantly different from that observed in women without CE during the different phases of the menstrual cycle (39). We found notably a decrease in the anterograde subendometrial contractions present during menses, which contribute to the forward emptying of menstrual blood, which thus facilitates retrograde reflux of menstrual bleeding through the fallopian tubes. This leads us to speculate that, according to Sampson's theory (40), CE may represent a facilitating factor for the development of endometriosis.

Higher bacterial contamination of menstrual blood and an increased endotoxin level in menstrual and peritoneal fluids have been found in women with endometriosis as compared with control women (41). A higher risk of increasing intermediate flora (total score 4–6; $P=.05$) was observed in women with endometriosis versus untreated women. The number of colony-forming units (CFU/mL) of *Gardnerella*, *α-Streptococcus*, Enterococci, and *E. coli* was statistically significantly higher in endometrial samples obtained from women with endometriosis than in controls ($P<.05$ for each bacteria). Women treated with gonadotropin-releasing hormone-agonist also showed statistically significantly higher colony formation for some of these bacteria in endometrial samples compared with untreated women (*Gardnerella* and *E. coli* for controls; *Gardnerella*, Enterococci, and *E. coli* for women with endometriosis; $P<.05$ for all).

Our results agree with a recent study by Lin et al. (42) who, based on the Taiwan National Health Insurance database, conducted a population-based cohort study on a total of 79,512 patients with genital tract infection and an equal number of control individuals. The incidence of endometriosis (hazard ratio 2.01; 95% confidence interval, 1.91–2.12; $P<.001$) was higher in patients with genital tract infection than in controls. Cox proportional hazards models showed that irrespective of comorbidities, genital tract infection was an independent risk factor for endometriosis. The investigators concluded that women with infections of the lower genital tract have a substantially higher risk for developing endometriosis (42). Moreover, the frequent finding of endometrial polyps in cases of endometriosis (43) prompts the question of whether polyps could be linked to endometrial inflammation. Accordingly, we demonstrated that high concentrations of interferon-γ were detected in infertile patients with endometrial polyps. Based on these findings, we proposed a possible role for an inflammatory factor in this proliferative pathology, representing a novel view on the genesis of endometrial polyps and its relationship with infertility (44).

In conclusion, although endometriosis is a multifactorial disease in which inflammation, immunology, endocrinology, genetics, and epigenetics play different etiopathogenetic roles, our study demonstrates that CE coexists in roughly 40% cases of endometriosis. We cannot establish a causal relationship between endometriosis and CE, but we can speculate that in women who have endometriosis, common symptoms such as pain or abnormal uterine bleeding may actually stem at least in part from CE. Based on the high prevalence of CE in women with endometriosis—roughly 40%—the presence of CE should be ruled out in symptomatic women who have

endometriosis. Although randomized, controlled trials on antibiotic or other therapies for CE in women with endometriosis are lacking, we may speculate that appropriate treatment might improve symptoms in these women, thus avoiding unnecessary surgery.

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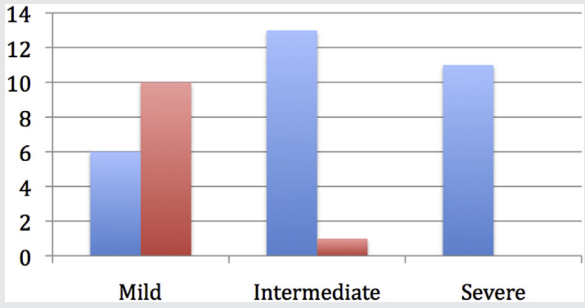
SUPPLEMENTAL FIGURE 1



Distribution of different grading of chronic endometritis (CE) according to previously described criteria (Resta et al. [35]) in women with endometriosis (blue bars) and with no endometriosis (red bars).

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