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