Original Article

Towards a Common Etiopathogenesis: Periodontal Disease and Endometriosis

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Abstract

Context: Periodontal disease and endometriosis are seen to share a common pathogenesis. There is only one report suggesting the possible association between the two conditions. **Aims:** To study the association between endometriosis and periodontal disease. **Settings and Design:** This was a case–control study. **Subjects and Methods:** Periodontal screening was carried out in 25 women with endometriosis and 25 women without endometriosis. Severity of periodontal disease was classified based on the extent of loss of attachment. **Statistical Analysis Used:** Student's *t*-test, Mann–Whitney U test, and Karl Pearson correlation coefficient tests were used for statistical analysis. **Results:** The proportion of women with severe periodontitis was seen to be higher among women with endometriosis (70%). **Conclusions:** The results of the present study indicate the existence of a relationship between endometriosis and periodontal disease. However, further studies among larger cohorts of endometriosis may provide evidence about the association.

Keywords: *Endometriosis, inflammatory burden, periodontal disease*

Introduction

Endometriosis is a common and important health problem of women. It is estimated to be present in 3%–10% of the women in the reproductive age group and also in 25%–35% of infertile women.[1] Endometriosis is many a times without symptoms. However, when present, they may include abdominal cramps or back pain during menstruation, painful urination or bowel movements especially during menstruation, and/or abnormal or heavy bleeding during menstruation. It is a disorder in which functional endometrium is present in locations other than the uterine inner lining; the cause of it however remains unknown. Retrograde menstruation with transport of endometrial cells, hematogenous or lymphatic spread, or direct transplantation of endometrial cells accounts for the leading theories of endometriosis. Another possible explanation is an alteration in the cellular local and humoral immune response which may affect the body's natural ability to recognize and destroy any misdirected growth of endometrial tissue.[2]

Periodontitis, a chronic inflammatory disease of the supporting structures of tooth, which is seen to occur in >85% of the general population, is also considered to manifest in individuals with altered host immunomodulatory response.[3] This may explain the variation in susceptibility to periodontal disease among individuals despite considerable accumulation of bacterial plaque including the presence of putative pathogens. Periodontal disease is usually painless, with occasional sensitivity to heat and/or cold on exposed root surfaces, localized dull pain radiating deep into the jaw, and/or gingival tenderness or "itchiness" maybe experienced by few patients.

Periodontal disease is linked to a chronic systemic inflammatory burden secondary to the systemic dissemination of periodontal pathogenic bacteria, their products (e.g., lipopolysaccharides), and locally produced inflammatory mediators (i.e., interleukin [IL]-1 β, IL-6, tumor necrosis factor [TNF]-α, prostaglandin E2, and

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thromboxane B2). As is the case for endometriosis, autoimmunity has been implicated in the pathogenesis of periodontal disease.[4]

Commonality with altered levels of immune modulators in patients with endometriosis and periodontal disease prompted us to explore the association between the two.

Subjects and Methods

This was a case–control study carried out among women attending the gynecology care facility of the Department of Obstetrics and Gynaecology at a Government District Hospital affiliated to Medical College. The study was initiated after approval from the Institution Ethics Committee. The sample size for the study was 50, of which 25 were women with endometriosis taken as cases and 25 were those without endometriosis taken as controls. The control were age and socioeconomic status matched.

Women in the age group of 18–45 years willing to participate in the study were recruited, following written informed consent process. Pregnant women, smokers, those who had received systemic antibiotics in the last 3 months, those who had undergone periodontal treatment in the last 6 months, and those who had <20 teeth were not recruited in the study.

The recruitment of cases and controls was made by the gynecology team. The diagnosis of endometriosis was made based on the examination at laparoscopy or laparotomy whenever the patient had undergone the procedure. The patient records during the period of study of those women who had undergone laparoscopy for interval tubal sterilization, tubal evaluation for fertility workup, and those getting operated for ovarian endometrioma were screened. Their clinical and sonographic findings were noted.

Endometriosis was considered as present if on laparoscopy/laparotomy if any of the following were present:

- "Powder-burn" or "gunshot" lesions on the serosal surfaces of the peritoneum (black, dark brown, or bluish nodules or small cysts containing old hemorrhage surrounded by a variable degree of fibrosis) or
- "Chocolate cysts" containing a thick, viscous dark brown fluid.

Histopathological confirmation was available for only those who had surgery for endometrioma of larger than 4 cm.

The periodontal screening was carried out by a periodontist soon after recruitment. The periodontal parameters recorded were plaque index, gingival index, probing pocket depth, and loss of attachment (LOA). Periodontal disease was considered to be present if any of the following were present: if plaque index score of 1 or greater, gingival index score of ≥1.1, probing depth ≥4 mm, and LOA >3 mm.[5]

Instruments used for the periodontal screening were mouth mirror, Williams's periodontal probe (Hu-Friedy, Chicago, IL, USA), dry gauze piece or cotton, and torch for illumination.

All surfaces of all the teeth present were examined in the plaque index and gingival index and the mean was recorded.[6,7]

Periodontal pockets were measured as the distance from the gingival margin to the location of the tip of Williams's periodontal probe inserted in to the pocket. Pocket depth was measured on each tooth, on six sites, i.e., mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual, and the mean was obtained.

LOA was measured as the distance from a fixed point, i.e., the cementoenamel junction to the base of the probable pocket using Williams probe. Based on the mean scores of LOA, the severity of periodontal disease was classified.[8]

Student's *t*-test, Mann–Whitney U-test, and Karl Pearson correlation coefficient tests were done to evaluate the association between endometriosis and periodontal disease. For all statistical calculations, the Statistical Package for the Social Sciences (Version 20, SPSS, IBM, USA) was used.

Results

The mean age of women with endometriosis was 29.72 ± 6.11 years and that of women without endometriosis was 29.48 ± 5.87 years.

Scores for plaque index were similar among cases and controls (1.26 ± 0.47 and 1.26 ± 0.3 for cases and controls, respectively; $P = 0.662$). The measures for probing pocket depth (3.73 ± 1.12 and 3.79 ± 0.66 in cases and controls, respectively) and LOA (4.75 ± 1.35 and 4.50 ± 0.63 in cases and controls, respectively) also did not show any statistical difference, irrespective of the presence or absence of endometriosis.

However, the gingival index was seen to be significantly higher in patients with endometriosis (1.55 ± 0.53 and 1.12 ± 0.25 in cases and controls, respectively; $P = 0.001$).

When severity was assessed, proportion of women with moderate-to-severe periodontitis was seen to be higher among women with endometriosis [Table 1].

When the individual parameters were assessed for their inter-influence using Karl Pearson correlation, it was found that a good correlation existed on the effect of gingival index and plaque index on the remaining variables. A linear relationship was found between plaque index [Graph 1], gingival index [Graph 2], probing pocket depth [Graph 3], and LOA [Graph 4] among subjects with endometriosis.

Discussion

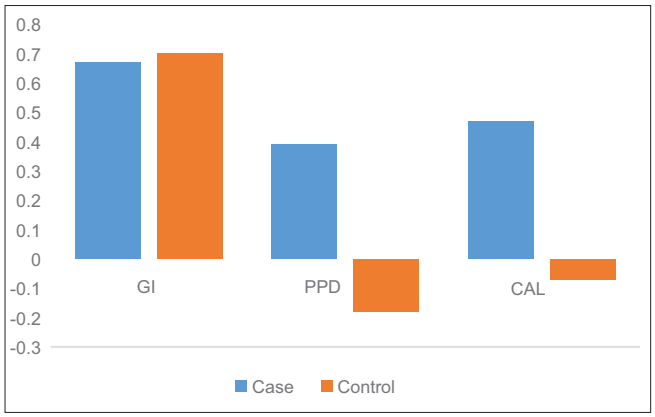
The main finding of this study is that severe periodontal disease was seen to be associated with endometriosis. The question arises if the two be related. Since there are oxidative stress and increased reactive oxygen species (ROS) production even in periodontal disease, can this oxidative stress augment the stress for endometriosis? Similarly, the immune dysregulation seen in periodontal disease can account for the local immune deficiency propagating endometriosis. Endometriosis is an estrogen-dependent inflammatory disease that is defined histologically by the presence of endometrial gland and stroma-like tissue outside the uterus. Many theories, viz., retrograde menstruation, metaplasia, hormones, oxidative stress and inflammation, immune dysfunction, apoptosis suppression, and genetic and stem cells, have been proposed to explain the pathogenesis of endometriosis, and to date, they all remain to be conclusively confirmed.[9] However, of interest are the theories of oxidative stress and immune dysfunction. It is well described that in periodontal diseases, there is oxidative stress and the immune function is altered.

The peritoneal fluid in patients with endometriosis is seen to harbor ROS.[10] These ROS cause lipid peroxidation which leads to deoxyribonucleic acid (DNA) damage in the endometrial cells. Furthermore, the oxidative stress signals generated from ROS cause inflammation which leads to the recruitment of lymphocytes and activated macrophages which produce cytokines and induce oxidation of enzymes that promote endothelial growth.[11] The resultant accumulation of ROS propagates endometriosis. The findings that autoimmune

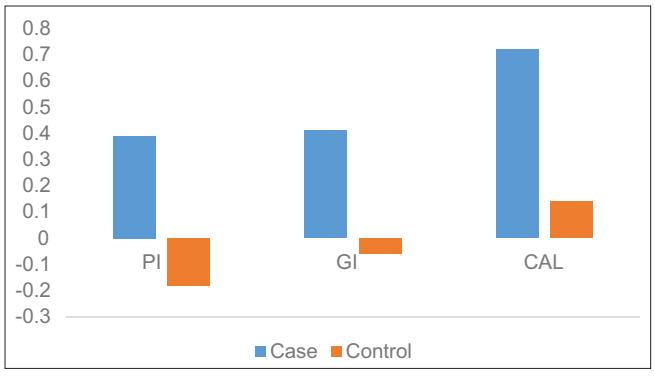
Table 1: Relationship between severity of periodontal disease and endometriosis

Periodontal disease (*n*)	Endometriosis		Significance
	Present, *n* (%)	Absent, *n* (%)	
Mild (3)	2 (66.7)	1 (33.3)	Fisher's exact *P*=0.09
Moderate (34)	14 (41.2)	20 (58.8)	RR: 1.6 (0.95-2.68)
Severe (13)	9 (69.2)	4 (30.8)	OR: 2.9 (0.76-11.33)

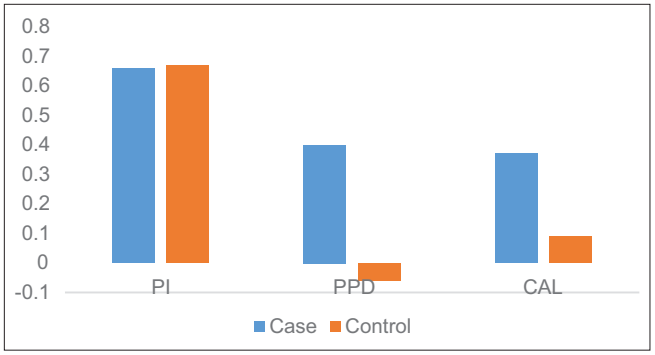
Values are mean (1SD). RR=Relative risk, OR=Odds ratio, SD=Standard deviation



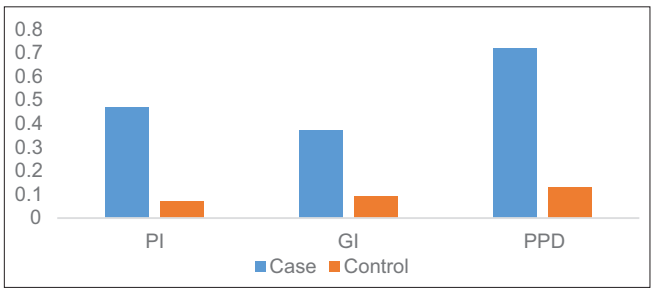
Graph 1: Association of plaque index on endometriosis. GI = Gingival index, PPD = Probing pocket depth, CAL = Clinical attachment level



Graph 3: Association of probing pocket depth on endometriosis. PI = Plaque index, GI = Gingival index, CAL = Clinical attachment level



Graph 2: Association of gingival index on endometriosis. PI = Plaque index, PPD = Probing pocket depth, CAL = Clinical attachment level



Graph 4: Association of clinical attachment level on endometriosis. PI = Plaque index, GI = Gingival index, PPD = Probing pocket depth

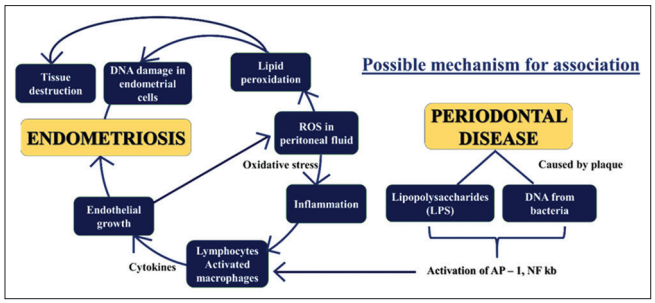


Figure 1: Possible mechanism linking periodontal disease and endometriosis

diseases are common in women with endometriosis suggest the involvement of a defective immune response in these patients.[12] A higher concentration of activated macrophages, decreased cellular immunity, and repressed natural killer cell function is seen in women with endometriosis.[13,14] The growth of endometrial cells in ectopic sites could be due to an inflammatory response that is triggered during the regurgitation of endometrial cells.[15] It could also be due to the secretion of cytokines and growth factors by the immune and endometrial cells, which induce cell proliferation and promote implantation and growth of ectopic lesions.[16]

Periodontal disease is a chronic inflammatory condition, where neutrophils are the predominant inflammatory cells. These neutrophils are implicated in the disease pathogenesis because of oxidative stress during phagocytosis. Moreover, this interaction leads to increased cytokine expression and immunological activity in the gingival tissues.[17] In addition, plaque being the main etiologic factor for periodontal disease, lipopolysaccharides, and DNA from these bacteria caused the activation of activating protein-1 (AP-1) and nuclear factor-kB (NF-kB) and the production of inflammatory cytokines. This causes the recruitment of hyperresponsive neutrophils, which increase the production of ROS. Activation of AP-1 and NF-kB causes activation of osteoclasts and matrix metalloproteinases which cause tissue damage. Tissue destruction further activates macrophages neutrophils and fibroblasts to generate more ROS. Thus, a vicious circle is formed with the presence of periodontal pathogens, ROS, and tissue destruction.[18]

Periodontal disease is very much remote from the area of endometriosis and trying to relate them may appear hypothetical. However, since they share similar pathogenesis, the association as manifested by higher proportion of severe periodontal disease in patients of endometriosis cannot be ignored. It can be hypothesized that the oxidative stress elsewhere, in this case, the periodontal disease, may augment the stress for endometriosis. Similarly, the immune dysregulation seen in periodontal disease can account for the local immune deficiency propagating endometriosis [Figure 1].

Conclusion

The number patients studied were less and hence to compare and relate severity of endometriosis based on its stage and association with periodontal disease could not be carried out. Probably, a study designed to evaluate behavior of periodontal disease among larger cohorts of endometriosis at different stages may provide epidemiological evidence about the association.

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Conflicts of interest

There are no conflicts of interest.

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