

Does the relationship between endometriosis and periodontal disease really exist? A systematic review.

Abstract

Background: Endometriosis and periodontal disease are chronic and inflammatory diseases, studies, assumptions and opinions try to elucidate this possible relationship. The aim of the present systematic review was to evaluate the relationship between endometriosis and periodontal condition.

Methodology: The following databases: Medline, Scopus, Embase, Web of Science, Cochrane Library and Goolge Scholar, the descriptors applied were: endometriosis and periodontal disease in English, in the period from 1995 to 2023, and 10 abstracts were located that had the entire article submitted to inclusion analysis. The eligibility criteria were: clinical trials, observational and specific studies on endometriosis with periodontal diagnosis. Case reports, laboratory studies, research without the periodontal condition of the participants were excluded. The abstracts were evaluated by two examiners.

Results: After adopting the eligibility criteria, two studies were included in this review, one cross-sectional and one case-control. The included studies do not allow comparison, have different periodontal diagnostic criteria, and have the development more focused on the biological plausibility of the increase in circulating cytokines in the body than on the observed results.

Conclusion: Nowadays the relationship between endometriosis and periodontal disease does not exist, the studies point to a biological plausibility only, clinical studies with adequate methodological design are necessary to prove such a relationship.

Key words: endometriosis, periodontal disease, periodontitis, women health.

Introduction

Endometriosis is a pathology considered benign and systemic. Endometriosis affects about 10% (190 million) of women and girls of reproductive age worldwide. It is a chronic disease associated with severe, life-impacting pain during menstruation, intercourse, bowel movements and/or urination, chronic pelvic pain, abdominal distention, nausea, fatigue, and sometimes depression, anxiety and infertility. Currently, there is no known cure for endometriosis and treatment generally aims to control symptoms [1]. Endometriosis is a condition that affects not only patients but also their families, jobs, societies and countries [2].

The endometrium grows outside the uterine cavity, forming lesions and physiological changes, however it does not have a precise etiology. It is a chronic condition that results from an abnormal accumulation of endometrial cells outside the uterus, when these cells are usually found inside the uterus. This causes a chronic inflammation detrimental to the female reproductive system, characterized by intense bowel pain [3]. Many immune mediators (both leukocyte subsets and cytokines) have been identified as being different in eutopic endometrium and peritoneal fluid between women without and those with endometriosis, as well as within endometriosis [4]. The cytokines - interleukin (IL)-1, IL-2, IL-6, IL-10, tumor necrosis factor, have been implicated in the pathogenesis of endometriosis [5].

Periodontal disease affects the tissues that surround and support the teeth. The disease is characterized by bleeding or swollen gums (gingivitis), pain and sometimes bad breath. In its most severe form, the gum can become detached from the tooth and supporting bone, causing teeth to loosen and sometimes fall out. Severe periodontal disease is estimated to affect about 19% of the global adult population, accounting for more than 1 billion cases worldwide. The main risk factors for periodontal disease are poor oral hygiene and tobacco use [6].

When cytokines are released in the periodontium, they induce the host's inflammatory and immune response, activate macrophages and lymphocytes to synthesize chemical mediators, such as cytokines, prostaglandins, metalloproteinases, among others, which will activate osteoblasts and osteoclasts, whose imbalance results in bone resorption [7]. These changes are associated with tissue inflammatory response and periodontal attachment loss, and are related to platelet aggregation and adhesion [8]. Currently, the relationship between the progression of periodontal disease and high levels of cytokines is well established, numerous cytokines are involved in this network and participate in the pathophysiology, **but this network is not completely established.(pathophysiology is unknown)** In this context, studies have shown

that the inflammatory mediators most consistently associated with periodontitis are: IL-1 β , IL-6, TNF- α and PGE2 [9].

The association between endometriosis and periodontal disease has been proposed through inflammatory mechanisms, although only two cross-sectional studies could provide such information [10,11]. In particular, women suffering from endometriosis had a 57% increased risk of having diagnosed with periodontal disease[10]. Also, moderate to severe periodontal disease was higher among women with endometriosis[11]. Endometriosis also promotes a subclinical inflammatory state, with increased pro-inflammatory cytokines and markers such as IL-1 beta, IL6, IL-8, IL-10, TNF- α , which may complicate the periodontal disease condition with further periodontal tissue destruction [10,12]. The justification that PD can be a direct cause of intrauterine and chorionic tissues infection through bacterial dissemination tries to be proven [13,14].

The biological plausibility seems to exist, interleukins present in both conditions seem to relate the pathologies, but do we have studies with consistent results that allow extrapolating the findings to a true relationship between the periodontal condition and endometriosis? The aim of this literature review is to try to elucidate the relationship between periodontal disease and endometriosis to assist professionals in both areas in making clinical decisions.

Material and Methods

A systematic review was conducted until July 20, 2023, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [15]. Medline, Scopus, Embase, Web of Science, Cochrane Library, and Goolge Scholar databases were use for articles research. Search formulas included: For PubMed: (endometriosis [MeSH Terms]) AND (periodontal disease [MeSH Terms]); For Scopus, Embase: TITLE-ABS-KEY INDEXTERMS (endometriosis AND "periodontal disease"); For Web of Science, Goolge Scholar: TS = (endometriosis AND periodontal disease).

Results were not filtered by date of publication; the entire time period was included in the search. Records were screened by title, abstract and full text by two independent investigators. The studies included in this review met all predefined criteria according to PICOS ("Population", "Intervention", "Comparison", "Outcomes" and "Study design"). A detailed research flow diagram is presented in the Results section. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42023439694.

Two people independently screened records for inclusion (CVGRT and ME). Researchers were blinded to each other's decisions. Information on study design and methodology, participant demographics and baseline characteristics and numbers of events were extracted from the documents. In an Excel spreadsheet the data were pooled.

As initial eligibility criteria clinical trials and observational studies evaluating patients with endometriosis and their periodontal condition would be included and excluded were: case reports, laboratory studies, studies without the periodontal condition of the participants.

The following were considered to assess the risk of bias: randomization methods, treatment allocation, blinding. Divergences between reviewers' judgments did not exist during the process. Patients' periodontal status data such as probing depth, clinical attachment level, plaque index and bleeding index should be related to the diagnosis of endometriosis. A minimum of 2 observational studies should be included to extract complete periodontal condition data with endometriosis diagnosis. Statistical program R will be used for pooling and synthesis of data.

Only studies where the periodontal and endometriosis diagnosis is clearly identified should be included. Periodontal variables should be detailed, mean, standard deviation, classification of periodontal disease adopted. Studies that do not have the diagnosis of endometriosis made by physicians will not be included. The groups analyzed should be: women with periodontal disease with endometriosis and women without periodontal disease with endometriosis. The secondary variables that make up the periodontal diagnosis should be analyzed individually and also related to the diagnosis of endometriosis.

Results

The results after thorough search in Medline, Scopus, Embase, Web of Science and Google Scholar databases found only two studies on endometriosis and periodontal disease. Two observational studies, one case-control [11] and one cross-sectional study [10].

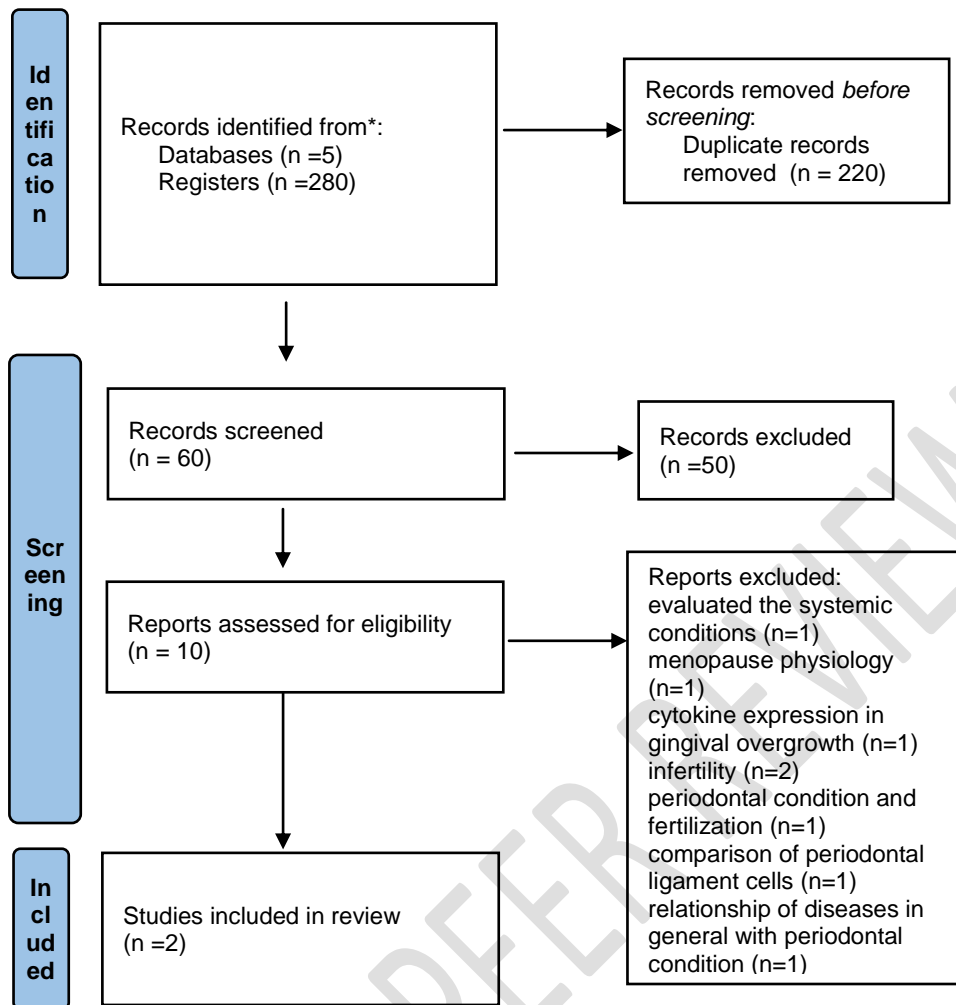


Fig. 1. PRISMA diagram of study identification and screening

The others found are literature reviews on biological plausibility, menopause, male infertility, cytokine expression in gingival growth, pain management in endometriosis, etc.

The data observed in the included studies do not allow comparisons, quality analysis, pooling and synthesis of data.

Discussion

Endometriosis has significant social, public health and economic implications. It can decrease quality of life due to severe pain, fatigue, depression, anxiety and

infertility. Some people with endometriosis experience debilitating pain that prevents them from going to work or school. Addressing endometriosis will empower people affected by it, supporting their human right to the highest standard of sexual and reproductive health, quality of life and general well-being [1,4,11].

Endometriosis and periodontal disease have been shown to be associated with altered levels of immune modulators. Specifically, the presence of endometriotic lesions has been associated with increased levels of cytokines and factors such as IL (interleukin)-1 β , IL-6, IL-8, tumor necrosis factor- α , vascular endothelial growth factor, RANTES (regulated upon activation, normal T cells expressed and secreted) and monocyte chemoattractant protein-1 have been demonstrated in the endometrium, expressed and secreted normal T cells) and monocyte chemoattractant protein-1 were demonstrated in the fluid peritoneum of women with endometriosis [5,16]. Chronic periodontitis is linked to a chronic systemic inflammatory burden secondary to the systemic spread of periodontal pathogenic bacteria, their products (e.g. lipopolysaccharides) and locally produced inflammatory mediators (i.e. IL-1 β , IL-6, TNF- α , prostaglandin E2 and thromboxane B2) [10].

Interleukin-6, along with IL-8 and TNF- α , was higher in the peritoneal fluid of women with endometriosis. [10,30] It is a pleiotropic cytokine that is produced by a variety of cell types, and mediates numerous physiological and pathological processes.[5]. In a recent study the concentration of IL-10 in follicular fluid was different between patients with endometriosis and controls [12].

Periodontal disease has as its etiological factor microorganisms that promote the increase of local cytokines during their colonization and permanence next to the gingival tissues and the removal of the etiological factor allows the return to the state of health. There are some cytokines related to this whole process of health - disease and the increase is real in cases of inflammation / infection. The repercussion of this increase in other areas of the body is possible and proven but we have no real proof for endometriosis. It has been hypothesized that oxidative stress elsewhere, in this case periodontal disease, may increase stress for endometriosis [11]. The biological plausibility between cytokines involved in the two mechanisms seems to exist, but even this relationship is not possible to be certain in this day. The inflammatory response is an important site for further research and should focus, where possible, on a systems biology approach rather than individual components of the inflammatory pathway [4].

Maintaining and being in good oral health is important for general health, even without studies that prove the relationship between endometriosis and periodontal disease we cannot totally rule out the hypothesis. Randomized clinical trials, with follow-up of 4-6 years, with adequate number of participants and evaluating the effect of periodontal treatment may elucidate this

relationship. Endometriosis still has no fully clarified etiologic factor, patients often cannot be diagnosed or even control pain even with strong analgesics.

Access to early diagnosis and effective treatment of endometriosis is important but is limited in many settings, including low- and middle-income countries [1]. Research funding for endometriosis is limited, with funding from bodies such as the National Institutes of Health (NIH) making up just 0.038% of the 2022 health budget - for a condition that affects 6.5 million women in the US alone and more than 190 million worldwide. An important issue is that the diagnosis of endometriosis is often delayed because surgery is required to histologically confirm the diagnosis [2]. The total economic burden of endometriosis in the US is estimated to be as high as \$78-119 billion annually. Endometriosis costs the UK economy £8.2 billion per year in treatment, work loss and healthcare costs [17]. In Australia, the annual cost of endometriosis has been estimated at \$16,970-20,898 per woman, per year, with 75-84% of the total due to productivity losses [2].

Endometriosis research is underfunded relative to other diseases with high health burdens. This may be due to the practical difficulties of developing competitive research proposals on a complex and poorly understood disease that affects only women [4]. And the same applies to periodontal disease, several relationships could be properly investigated and proven as for example: dementia, lung diseases, endometriosis; but what we have are observational studies and that do not allow to test hypotheses and have the conclusions presented and disseminated in an inadequate way. It is important for the medical profession to be careful when disseminating conclusions from studies that do not have the methodological design to do so. Observational studies should be limited to suggesting a hypothesis, but what we see today are these studies being publicized in the media as studies that prove relationships.

Conclusions

No relationship was found between endometriosis and periodontal disease, the number of studies is limited and with methodology that does not allow to prove such a relationship.

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