Journal of Advances in Medicine and Medical Research

Volume 35, Issue 19, Page 346-351, 2023; Article no.JAMMR.104377
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Does the Relationship between Endometriosis and Periodontal Disease Really Exist? A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i195168

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/104377

Systematic Review Article

Received: 26/07/2023
Accepted: 06/08/2023
Published: 14/08/2023

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ABSTRACT

Background: Endometriosis and periodontitis are chronic and inflammatory diseases. Studies, assumptions and opinions try to shed light on this possible relationship. The aim of this systematic review was to investigate the association between endometriosis and periodontal disease.
Methods: The following databases: Medline, Scopus, Embase, Web of Science, Cochrane Library, and Goolge Scholar, the descriptors used were: Endometriosis and Periodontal Disease in English, during the period from 1995 to 2023. 10 abstracts were found that had submitted the entire article for inclusion analysis. The eligibility criteria were: clinical trials, observational studies, and specific studies of endometriosis with periodontal diagnosis. Case reports, laboratory studies, and studies without periodontal disease in participants were excluded. Abstracts were evaluated by two investigators.
Results: After accepting the eligibility criteria, two studies were included in this review, a cross-sectional study and a case-control study. The included studies do not allow for comparison, have different periodontal diagnostic criteria, and focus more on the biological plausibility of the increase in circulating cytokines in the body than on the observed outcomes.
Conclusion: Nowadays there is no association between endometriosis and periodontal diseases, the studies only indicate a biological plausibility, clinical studies with adequate methodological design are necessary to prove such an association.

Keywords: Endometriosis; periodontal disease; periodontitis; women's health.

1. INTRODUCTION

Endometriosis is a pathology considered benign and systemic. Worldwide, endometriosis affects approximately 10% (190 million) of women and girls of childbearing age. It is a chronic disease associated with severe, life-threatening pain during menstruation, intercourse, bowel movements and/or urination, chronic pelvic pain, abdominal pain, nausea, fatigue and sometimes depression, anxiety and infertility. Currently, there is no known cure for endometriosis, and treatment is generally aimed at controlling symptoms [1]. Endometriosis is a disease that affects not only patients, but also their families, workplaces, societies, and countries [2].

Endometriosis is a chronic disease that results from an abnormal accumulation of endometrial cells outside the uterus, although these cells are normally located inside the uterus. This leads to chronic inflammation that affects the female reproductive system and is characterized by severe pain in the bowel [3]. Many immune mediators (both leukocyte subsets and cytokines) have been identified as different in the eutopic endometrium and peritoneal fluid of women without and with endometriosis, and 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 surrounding and supporting the teeth. The disease is characterized by bleeding or swollen gums (gingivitis), pain, and sometimes bad breath. In its most severe form, the gums can separate from the tooth and supporting bone, causing the teeth to loosen and sometimes fall out. It is estimated that severe periodontal disease affects about 19% of the world's adult population, representing 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 trigger a host inflammatory and immune response and activate macrophages and lymphocytes to synthesize chemical mediators such as cytokines, prostaglandins, metalloproteinases, and others, which in turn activate osteoblasts and osteoclasts, the imbalance of which leads to bone resorption [7]. These changes are associated with an inflammatory response of the tissue and loss of periodontal attachment and are related to platelet aggregation and adhesion [8]. Currently, the association between periodontal disease progression and high cytokine levels is well established. Numerous cytokines are involved in this network and participate in the pathophysiology, but this network has not been fully elucidated. In this context, studies have shown that the inflammatory mediators most consistently associated with periodontitis are: IL -1β, IL -6, TNF-α, and PGE2 [9].

The association between endometriosis and periodontal disease has been suggested to be due to inflammatory mechanisms, although only two cross-sectional studies could provide such information [10,11]. Specifically, women who had endometriosis had a 57% increased risk of being diagnosed with periodontal disease [10]. Moderate to severe periodontal disease was also more common in women with endometriosis [11]. Endometriosis also promotes a subclinical inflammatory state with elevated proinflammatory cytokines and markers such as IL -1 beta, IL6, IL -8, IL -10, TNF-α, which can complicate the periodontal disease state with further destruction of periodontal tissues [10,12]. The rationale that PD may be a direct cause of infection of intrauterine and chorionic tissues by bacterial dissemination attempts to prove [13,14].

The biological plausibility seems to be given, because the interleukins present in both diseases seem to be related to the pathologies, but are there studies with consistent results that allow extrapolation of the results to a real relationship between periodontitis and endometriosis? The goal of this literature review is to shed light on the relationship between periodontal disease and endometriosis to help professionals in both fields make clinical decisions.

2. MATERIALS AND METHODS

A systematic review was conducted through July 20, 2023, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Medline, Scopus, Embase, Web of Science, Cochrane Library, and Goolge Scholar databases were used to search the articles. 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.

3. RESULTS

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

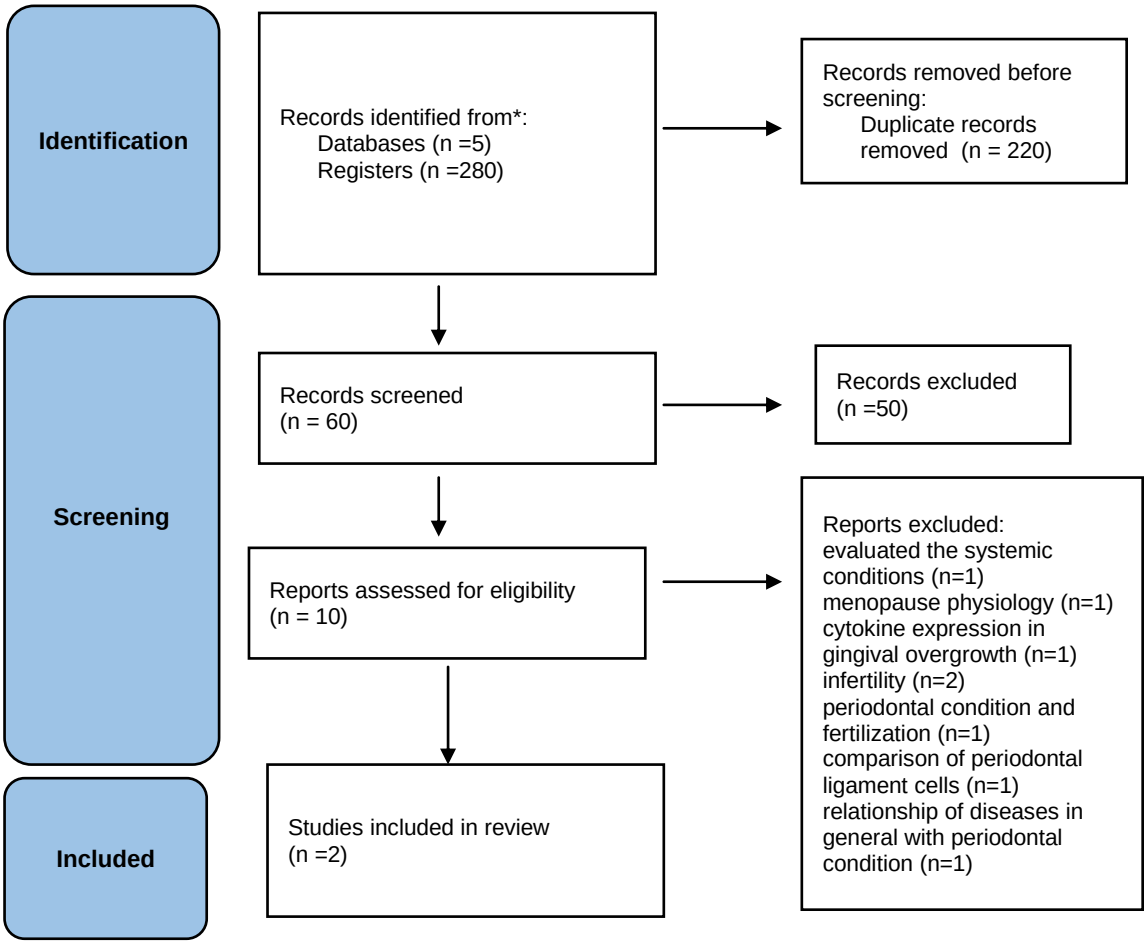

Fig. 1. PRISMA diagram of study identification and screening

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.

4. 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)-1beta, IL-6, IL-8, tumor necrosis factor-alpha, 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-1β, IL-6, TNF-α, prostaglandin E2 and thromboxane B2) [10].

Interleukin-6, along with IL-8 and TNF-a, was higher in the peritoneal fluid of women with endometriosis. 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 a 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 are 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 certain at this time. 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, and even without studies that prove the relationship between endometriosis and periodontal disease, we cannot totally rule out the hypothesis. Randomized clinical trials, with a follow-up of 4-6 years, a 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, and endometriosis; but what we have are observational studies and that do not allow testing 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.

5. CONCLUSIONS

No relationship was found between endometriosis and periodontal disease; the number of studies is limited and the methodology does not allow proving such a relationship.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/104377