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Periodontal manifestations of diseases / conditions related with female sex steroid hormones

Kadın cinsiyet hormonları ile ilişkili hastalıkların / durumların periodontal bulguları

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ABSTRACT

The primary etiological factor for periodontal diseases is microbial dental plaque deposited on tooth surfaces. However, fluctuations in sex steroid hormone levels increase the susceptibility and/or severity of clinical manifestations of periodontal diseases. The aim of this narrative review is to provide current evidence on the clinical findings in women's periodontal tissues regarding changes in female sex steroid hormones. Electronic databases were searched for studies evaluating clinical findings in women with conditions/diseases that cause changes in female sex hormones. Clinical studies published before February 2024 were included in the review. Women show fluctuations in sex steroid hormone levels at various stages of their lives, and these, together with some disease-related changes, lead to characteristic or regular clinical periodontal findings. Close collaboration between dentists and gynecologists can help to ensure early diagnosis and treatment of such conditions.

Keywords: Menopause; menstrual cycle; periodontal disease; pregnancy; polycystic ovary syndrome; puberty

ÖZ

Periodontal hastalıklar için birincil etiyolojik faktör diş yüzeylerinde biriken mikrobiyal dental plaktır. Bununla birlikte, cinsiyet hormon seviyelerindeki dalgalanmalar periodontal hastalıkların klinik belirtilerinin duyarlılığını ve/veya şiddetini artırmaktadır. Bu derlemenin amacı, kadın cinsiyet hormonlarındaki değişikliklerle ilişkili olarak kadınların periodontal dokularındaki klinik bulgular hakkında güncel kanıtlar sunmaktır. Elektronik veri tabanlarında, kadın cinsiyet hormonlarında değişikliklere neden olan durumları/hastalıkları olan kadınlarda klinik bulguları değerlendiren çalışmalar araştırılmıştır. Şubat 2024' den önce yayınlanan klinik çalışmalar derlemeye dahil edilmiştir. Kadınlar yaşamlarının çeşitli evrelerinde seks steroid hormon seviyelerinde dalgalanmalar gösterir ve bunlar hastalıkla ilişkili bazı değişikliklerle birlikte karakteristik veya düzenli klinik periodontal bulgulara yol açar. Diş hekimleri ve jinekologlar arasındaki yakın iş birliği, bu tür durumların erken teşhis ve tedavisinin sağlanmasına yardımcı olabilir.

Anahtar Kelimeler: Menopoz; menstrüel siklus; periodontal hastalıklar; hamilelik; polikistik over sendromu; puberte

INTRODUCTION

Periodontal disease is a chronic inflammatory disease, and its established form is characterized by loss of periodontal attachment and destruction of the surrounding alveolar bone (1). It is considered one of the two major threats to oral health and is the primary cause of tooth loss. Approximately 800 species of bacteria have been identified in the oral cavity and the interaction between bacterial infection and host response is complex (2). Periodontal disease has a high global prevalence. It is estimated that severe periodontitis affects 11% of the World population. Disease progression and severity depend on the balance between subgingival plaque bacteria and the individual host immune response, which is modulated by genetic, epigenetic context and environmental factors such as smoking (3). There are studies in the literature stating that periodontal diseases are more common in men (4,5). The possible explanations are men's neglect of oral care, higher B lymphocyte activation and the level of antibodies produced in women(4). However, a recent study of a large group of Italian people showed that periodontitis affects women more than men, with a ratio of 3 to 2. This ratio was also similar among the younger patients (those under 35 years old) (6). The physiological changes in female sex hormones, the distribution of estrogen and progesterone receptors, and the metabolism of these hormones became a field of

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investigation to uncover the pathogenetic mechanisms underlying periodontal disease in women. Associations between periodontal disease and puberty, menstruation, pregnancy, oral contraceptive use, and menopause have been reported in several studies (7). The aim of this narrative review is to present data on the relationship between sex hormones, systemic diseases in women, and periodontal disease.

A literature search was conducted using PubMed, Web of Science and Scopus search engines. Electronic databases were searched for studies evaluating clinical findings in women with conditions/diseases that cause changes in female sex hormones. Only studies in the Turkish and English language were considered. Clinical studies published before February 2024 were included in the review.

Puberty

Sex hormones have an effect on the gingival tissue, alveolar bone and formation of subgingival microflora. Hormone levels as well as the frequency of gingival pathologies increase at the age of sexual maturation. Puberty is a temporary physiological state, considered a complex process of sexual maturation, directly linked to increased levels of the sex steroid hormones – oestradiol, progesterone, and testosterone (8,9). The gingival inflammatory response to dental plaque can be affected by both normal and abnormal hormone fluctuations, including alterations in gonadotrophic hormone levels at the onset of puberty. Similarly, alterations in insulin levels in diabetic patients can influence gingival health. In both instances, there is an elevated inflammatory response to dental plaque. However, the gingival condition generally improves with the comprehensive removal of bacterial deposits and enhanced daily oral hygiene practices. The effects of these hormones on gingival inflammation have not been fully studied yet. While it is undisputed that the biofilm plays a key role in the occurrence of a gingival inflammatory response, it is not yet clear whether the sex hormones participate in the aggravation of this response (9).

Menstrual Cycle

Menstruation is regulated by hormones synthesized in the hypothalamus, pituitary gland, and ovaries. The lining of the uterus sheds in an orderly fashion during the menstrual cycle. The menstrual cycle comprises the follicular phase, lasting 14 days, and the luteal phase, which ranges from 10 to 16 days. Cycle length is defined as the number of days between the first day of bleeding and the start of the next period. The typical menstrual cycle lasts 28 days and the average duration of menstruation is 4 to 6 days (10). Alterations in sex steroid hormones, evident during the menstrual cycle in women, may influence periodontal health (11). Khosravisamani et al (12). suggested that changes occurring during the menstrual cycle influence the periodontium and induce inflammatory conditions. The corpus luteum is a hormone-secreting yellow body found in the ovaries of women and secretes higher TNF- α during the late luteal phase compared to the early luteal phase. One study shows that there are marked fluctuations in tumor necrosis factor-alpha (TNF- α) levels in the blood during the menstrual cycle, which is also observed during periodontal disease (13). In one study, 27 female participants received oral hygiene instruction at baseline, and for two months their plaque index scores were taken once a week, along with the gingival index, bleeding on probing (BOP) and probing depths to determine the periodontal status of the participants. The menstrual cycle's duration and regularity were also recorded. Gingival crevicular fluid (GCF) samples were collected to measure the levels of interleukin (IL)-1beta and TNF-α on the first menstruation day (MD), estimated ovulation day (OD), and estimated predominant progesterone secretion day (PgD). It has been shown that gingival inflammation during the menstrual cycle is influenced by changes in sex steroid hormones (14). In the study of Becerik et al. (11), twenty-five patients with gingivitis and twenty-five periodontally healthy individuals with regular menstrual cycles were examined during menstruation (ME) (first to second days), ovulation (OV) (12 to 14 days), and the premenstrual phase (PM) (22 to 24 days). GCF and saliva samples were obtained, and periodontal indicators such as plaque index and bleeding on probing were documented during each menstrual phase. Exact menstrual cycle days were determined by analyzing salivary estrogen and progesterone levels. GCF levels of IL-6, prostaglandin E_2 (PGE_2), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor (PAI)-2 were measured by enzyme-linked immunosorbent assay (ELISA). It was suggested that fluctuations in sex steroid hormones throughout the menstrual cycle may have a slight effect on the inflammatory condition of the gingiva, and that GCF cytokine levels remained unaffected (11). In another study, it was indicated that ovarian hormones have a negligible effect on clinically healthy periodontium. However, these hormones may exaggerate pre-existing inflammation in gingival tissues, but the clinical significance of these changes remains uncertain (7).

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), the most prevalent endocrinopathy in women, predominantly affects the reproductive system but also has significant negative effects on cardiovascular, psychological, and metabolic functions. PCOS is a multifaceted, heterogeneous endocrine condition, distinguished by menstrual irregularities (oligomenorrhea or amenorrhea), chronic anovulation or oligo-ovulation, clinical or biochemical indicators of hyperandrogenism (hirsutism, acne, or androgenic alopecia), and ultrasound findings. It typically impacts women during their reproductive years (15). Akcali et al. (16) conducted the first study to examine the correlation

between oral microbiota in saliva and serum antibody responses, as well as gingival inflammation in PCOS. They observed discrepancies in microbiological parameters between PCOS patients and control group with periodontal disease. Patients with PCOS and gingivitis exhibited elevated levels of *P. gingivalis* and *F. nucleatum* in saliva samples, along with antibodies for *P. intermedia, P. gingivalis,* and *S. oralis* in the serum. According to a recent review, the composition of the oral microbiota may be quantitatively impacted by PCOS, which could explain the increased systemic response to specific members of this microbial community (16). The periodontal disease caused by dental plaque might be exacerbated worse by PCOS through a number of pathophysiological pathways, including low-grade systemic inflammation, oxidative stress, insulin resistance, advanced glycation end products (AGEs), and systemic hormone levels (17). Evidence indicates that periodontal disease induces persistent subclinical inflammation, resulting in insulin resistance and subsequently facilitating the onset of type 2 diabetes, a significant characteristic of PCOS. Therefore, we could assume that a bidirectional association exists between PCOS and periodontal disease (17). Another recently published review also indicated a correlation between periodontal disease and PCOS, as periodontal parameters were considerably altered in PCOS patients compared to healthy young women, particularly in the presence of gingivitis and periodontitis. This response may be first influenced by a local and systemic proinflammatory environment that promotes a pro-oxidant condition, resulting in oxidative stress and ultimately causing irreversible damage to periodontal tissue. Nonetheless, the interaction between PCOS and periodontal diseases in exacerbating the burden on cellular pathways remains ambiguous (18).

Pregnancy

Pregnancy is associated with a high prevalence of periodontal disease, particularly gingivitis. This is mainly due to significant changes in the levels of female sex hormones during pregnancy. At the end of the third trimester, plasma concentrations of progesterone and estrogen are 10 and 30 times higher, respectively, than during the menstrual cycle. Increases of these sex hormones during pregnancy have been associated with an increase in the prevalence, and severity of gingivitis (19). Moreover, receptors for these hormones have been identified in various subsets of periodontal cells, making periodontal tissue a potential target. In addition, periodontal disease may trigger local and systemic inflammation and increase levels of reactive oxygen species (ROS). This systemic disorder can jeopardize pregnancy outcomes for expectant mothers. In a case-control study, 187 women (pregnant and non-pregnant) were included, and oxidative stress markers were analyzed in saliva samples of the participants. The results of the study showed that there are changes in the oxidant/antioxidant balance in saliva during pregnancy and after delivery, which may be influenced by the periodontal condition. It has been suggested that early detection of ROS markers in saliva may have clinical value in the periodontal management of pregnant women (20).

Pregnancy Gingivitis

"Pregnancy gingivitis" is a common finding among pregnant women. Although the amount of plaque is low in this disease, clinical signs of gingivitis are prominent. Its pathogenesis is very similar to that of plaque-induced gingivitis. Clinical attachment loss is very uncommon, even with this exacerbated inflammatory response and associated increase in gingival sulcus depth, GCF flow, and bleeding on probing (19).

Epulis Gravidarum

Epulis gravidarum is a benign vascular mucosal lesion observed in pregnant women. It may manifest as a localized inflammatory lesion (i.e., pregnancy granuloma) in 0.2-9.6% of pregnant women. Commonly referred to as lobular capillary hemangioma, it is a benign vascular neoplasm of the skin and mucous membranes observed in children, young adults, and pregnant women. The lesion presents as an exophytic, fragile, red to yellow nodule that may increase in size, hemorrhage, or undergo ulceration. It is usually solitary but can also be seen as multiple satellite lesions. It has been reported that tumor size can vary from a few millimeters to a few centimeters (21). The lesion histologically comprises loose granulation tissue characterized by the proliferation of capillaries and endothelial cells organized in lobules. These lesions are caused by hormonal changes during pregnancy. Even though decreased hormone levels after pregnancy may allow these lesions to resolve, excision is often necessary after delivery (22).

Gestational Diabetes

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders during pregnancy, and its current increase in prevalence has been linked to the rising incidence of maternal obesity over recent decades. The etiology of GDM is complex, involving both genetic and environmental factors, as suggested by epidemiological studies (23). Multiple studies have demonstrated an association between periodontitis and GDM (24-26), with current evidence suggesting that pregnant women with severe periodontitis have a higher risk of developing GDM (27). A study based on the National Health and Nutrition Examination Survey (NHANES III) showed the prevalence of periodontitis to be 44.8% in women with GDM and 13.2% in normoglycemic pregnant women (OR = 9.11, $p<0.05$) (28). Additionally, women with a previous history of GDM (with or without existing diabetes mellitus at the time of examination) were more likely to have periodontitis than women without a history of GDM (29). In a cross-sectional study, clinical periodontal parameters, along with the levels of tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), and interleukin-33 (IL-

33) in the gingival crevicular fluid (GCF) and serum, were compared between women with GDM and those without the condition. The results showed that the GDM group had higher plaque index and bleeding on probing (BOP) scores, as well as higher levels of GCF IL-10, which are thought to result from increased inflammation (30). However, to date, there are no prospective longitudinal studies evaluating the possible bidirectional relationship between periodontitis and GDM. It has been suggested that sustained hyperglycemia, a standard feature of diabetes, may have an impact on the severity of periodontitis during pregnancy (31).

Pre-term Birth and Low-Birthweight

Low birth weight is defined as birth weight less than 2500 grams. Today, it continues to be an important public health problem in both developed and developing countries. This situation is usually a direct consequence of preterm birth and is referred to as preterm birth of low-birth-weight infants (PLBW). Although efforts have been made to reduce the impact of risk factors through preventive methods, the incidence of PLBW births has not decreased significantly over the past decade, and the risk factors for PLBW are not fully understood. Identified risk factors for PLBW include old (> 34 years) and young (<17 years) maternal age, African American origin, low socioeconomic status, inadequate prenatal care, drug, alcohol and tobacco abuse, hypertension, genitourinary infections, diabetes and multiple pregnancies. Smoking during pregnancy is associated with 20-30% of low birth-weight births and 10% of fetal and infant deaths (32).

Infection is now recognized as one of the main causes of PLBW births and is responsible for 30% to 50% of all cases. Bacteremia is defined as the passage, intermittent or continuous presence of bacteria into the bloodstream. In periodontitis, the pathogenic subgingival microbiota is in close contact with the ulcerated epithelium of periodontal pockets, resulting in the passage of pathogenic bacteria into the bloodstream. Chronic low-level bacteremia has been proposed as a direct mechanism to explain the link between adverse pregnancy outcomes and periodontitis. The theory that infections at distant sites may cause PLBW has been supported by several studies using the pregnant golden hamster model (33-35). Pregnancy outcomes were evaluated in these animals after inducing experimental periodontitis, (34) creating a localized subcutaneous infection with *P. gingivalis* that did not spread (33) or administering intravenous injections of lipopolysaccharide from *P. gingivalis* (35). Fetal weights were notably reduced in the experimental groups, and the extent of the adverse effects on the fetus correlated directly with the levels of PGE_2 and TNF-α.

Bacterial culture results are negative in many cases of PLBW with histological evidence of chorioamnionitis, indicating that local infection is not a requirement for triggering inflammatory mediators of preterm labour. LPS stimulates prostaglandin production by the placenta and chorioamnion, and high LPS concentrations in amniotic fluid have been measured in PLBW cases. Gram-negative anaerobic bacteria responsible for progressive periodontitis provide a chronic reservoir of LPS that may contribute to PLBW (36).

The pro-inflammatory cytokines, IL-1, IL-6 and TNF-α, stimulate PGE2 synthesis by the human placenta and chorioamnion, and amniotic fluid levels of these cytokines are often elevated in women in preterm labor. These cytokines can cross human fetal membranes and it is conceivable that high concentrations of these cytokines, produced at sites of chronic periodontitis and measured at higher levels in the plasma of patients with periodontitis, may affect the fetoplacental unit and cause PLBW (37). In summary, it can be said that chronic periodontal infection, serving as a reservoir for bacterial products (such as LPS) and/or various inflammatory mediators, may play an important role in the development of PLBW.

Menopause

Menopause is associated with significant systemic and oral manifestations. During menopause, the gingival epithelium becomes thinner and more prone to atrophic and inflammatory changes. Furthermore, various oral conditions develop with the reduction in the salivary flow rate and changes in its composition. The sudden and sharp decrease in estrogen production that occurs at menopause is considered as the main cause of primary osteoporosis, which also affects the jawbones. It has been suggested that this reduction in bone mineral density may contribute to the progression of periodontal disease. Besides its effects on alveolar bone, estrogen also interfere with other periodontal tissues (gingiva and periodontal ligament) and influence the host's immune-inflammatory responses (38). Several studies have associated menopause with various periodontal conditions, although different methods for identifying and evaluating osteoporosis, alveolar bone loss, and periodontitis make it difficult to compare results (39).

Osteoporosis

The majority of published studies have emphasized the relationship between osteoporosis and periodontal disease, suggesting that treatment of one disease will be beneficial in the treatment of the other (40). To better understand the relationship between these two diseases, it is necessary to look at the potential mechanisms. While osteoporosis is a systemic disease that occurs primarily in the cancellous bone, periodontal disease is a localized infection of the periodontium that initially affects the cortical bone and causes a dimensional change in the alveolar bone. Areas of decreased bone density in the jaw bones due to osteoporosis may create a potential for rapid progression of gingival disease. Furthermore, it has been

suggested that the incidence of microfractures increases in the presence of osteoporosis in situations of increased occlusal forces and bone fatigue (41).

Numerous studies have investigated the possible relationship between periodontal disease and osteoporosis. In a study conducted by Tezal et al. (42), in a population of 70 postmenopausal women aged 51-78 years, bone mineral density, clinical attachment level and interproximal alveolar bone loss were measured using dual energy X-ray absorptiometry. The results of the study showed that mean alveolar bone loss and clinical attachment levels were significantly associated with systemic bone mineral density (42). In another study, clinical periodontal measurements were recorded in 100 postmenopausal women (50 osteoporotic, 50 healthy) aged 50-65 years. The results of the study showed that probing depth, clinical attachment level, interproximal alveolar bone loss and the number of teeth lost were significantly higher in the women with osteoporosis compared to those without osteoporosis (43). A systematic review and meta-analysis examining the association between osteoporosis and periodontal disease suggests that postmenopausal women with osteoporosis or osteopenia may have higher clinical attachment loss compared to women with normal bone mineral density (44).

Several hormones play an important role in the regulation of bone homeostasis, including estrogen, testosterone, cortisol, parathyroid and thyroid hormones. Imbalance of these hormones affects calcium/phosphate metabolism, bone homeostasis and inflammatory mechanisms. Decreased estrogen levels in postmenopausal women are an important risk factor for osteoporosis. This deficiency has been found to decrease calcium absorption and increase calcium excretion, and it has been reported that decreased estrogen levels induce osteocyte apoptosis, which disrupts bone homeostasis. It can be speculated that estrogen has both pro-inflammatory and anti-inflammatory functions in inflammation, with low estrogen levels stimulating IL-1 mRNA expression and high estrogen levels reducing oxidative stress. In experimental animal studies, estrogen deficiency has been observed to increase the severity of periodontitis (45). In humans, hormone replacement therapy has been found to improve mandibular bone density and reduce gingival bleeding, and the number of teeth lost to periodontitis (46). These results suggest a potential role for estrogen deficiency in periodontal disease.

Another important hormone for bone homeostasis is the parathyroid hormone, which increases bone resorption to provide adequate calcium in the blood. Intermittent administration of parathyroid hormone has been shown to increase periodontal healing and support bone regeneration at extraction sites (47). These findings suggest that there may be a mechanism linking the interaction of hormones associated with bone remodeling and inflammation, where high levels of systemic pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α have been found in patients with osteoporosis. All these identified cytokines are thought to induce bone resorption. These inflammatory cytokines and other circulating factors not only affect systemic bone remodeling, but also act locally to influence the tissue response to periodontal disease (TNF-α also induces collagenase activity) (48). Similarly, in local infection of the periodontium, these inflammatory cytokines are released into the circulation and have a significant impact on periodontal disease. It is likely that one of the mechanisms underlying both diseases is related to these inflammatory pathways.

CONCLUSION

It is known that women experience various hormonal changes throughout their lives, starting from puberty. The link between hormonal changes, inflammatory pathways and periodontal tissues and diseases should not be neglected. It is important that both physicians and dentists are aware of the possible effects of hormonal changes on the pathogenesis of periodontal disease in women and refer the patient to an appropriate evaluation, prevention and treatment program.

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