Volume 56, Number 1
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CME REVIEW ARTICLE 2

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Focus on Primary Care Periodontal Disease: Implications for Women's Health

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A definite relationship is emerging between periodontal infections and systemic conditions. The objective of this review is to address this relationship as it pertains to cardiovascular disease and diabetes mellitus. Furthermore, because recent reports link the presence of periodontal disease to preterm delivery, the possible relationship between the development and progression of periodontal disease and certain hormonal states in women such as puberty, oral contraceptive use, menopause, and pregnancy will also be discussed. Although the current literature suggests a strong association between periodontal disease and a number of the discussed systemic conditions, causality can only be established with prospective studies. Intervention studies are needed to address how treatment effects the incidence and/or severity of periodontal disease-related systemic illness.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to describe what is periodontal disease and the difference between gingivitis and periodontitis, to list the conditions associated with periodontal disease, and to outline the potential risk factors for periodontal disease.

There is emerging evidence from the dental literature that periodontal disease may be a risk factor for systemic disease such as cardiovascular disease and diabetes mellitus. In addition, several investigators report a link between periodontal infections and preterm labor. There is very little, if any, information discussing these new developments in the medical literature, particularly in obstetrics and gynecology. However, at the same time, popular scientific journals as well as women's magazines, which focus on health issues and are read by many of our patients, all have addressed this topic. The purpose of this report is, therefore, to familiarize the reader with hypothesized or scientifically proven pathophysiological pathways that may explain the two-way relationship between periodontal disease and these systemic conditions. Although many reports were published decades ago, they represent "classic" papers and thus are included in this review.

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The authors have disclosed no significant financial or other relationship with any commercial entity.

WHAT IS PERIODONTAL DISEASE?

It is estimated that at least 35% of the adults 30 years of age and older in the U.S. have periodontitis—22% have a mild form and 13% have a moderate or severe form (1). Periodontitis is the most common cause of tooth loss in adults. Bleeding of the gums is often the first sign; with tooth mobility usually being detectable in the more severe stages of disease. In most cases, this disease is painless and asymptom-

atic. Gingival inflammation results from bacterial products invading the gingival epithelium, which eventually may lead to destruction of the supporting tissues. In gingivitis, the inflammatory response is limited predominantly to the gingival tissues and not accompanied by loss of alveolar bone. Periodontitis, on the other hand, is characterized by destruction of periodontal tissues, including bone and bacterial infection 5 mm or more below the surface of the gingiva (Fig. 1). Approximately 90% of the patients undergoing periodontal surgery experience bacteremia during the procedure (2). Also, simple intraoral manipulations such as tooth brushing (3, 4) and even mastication (2) result in a transient bacteremia in a significant proportion of subjects. Subsequent production of inflammatory mediators and proteolytic enzymes by monocytes are major mechanisms involved in the degradation of the periodontal tissues (5). Considerable evidence suggests that there is a genetic predisposition for severe periodontal disease. Certain polymorphisms associated with excessive interleukin-1 production might confer risk for more severe forms of periodontal disease (6). Additional risk factors are depicted in Table 1 (6–11). Clinical management of periodontal disease focuses on the daily removal of all bacterial plaque. Professional care involves removal of accretions, including calculus from the crowns and root surfaces and surgical therapy to regenerate periodontal tissues and reduce plaque-retentive factors. For more information on periodontal disease, the reader is referred to an excellent review article by Williams (12).

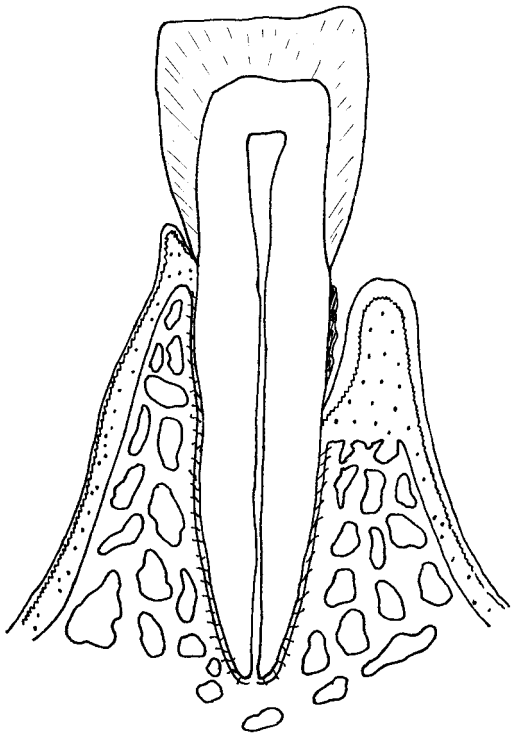

Fig. 1. Healthy gingiva and normal bone height is seen on the *left side* of this tooth. The *right side* shows periodontitis with inflamed and swollen gingival tissue. Pocket formation has occurred in which calculus can be seen; there is active bone resorption.

PERIODONTAL DISEASE AND SYSTEMIC DISEASE

Cardiovascular Disease

During the past decade, several observational studies—case-control as well as longitudinal and even the popular press— have indicated that there is a relationship between coronary heart disease and periodontal infection (13–15). These studies have adjusted for established cardiovascular risk factors such as age, gender, cholesterol, weight, smoking, diabetes, and hypertension. It seems that the associations between cardiovascular disease and periodontal disease are remarkably consistent across different populations studied and that periodontitis is an antecedent condition. The strength of this association is comparable with that of other cardiovascular risk factors such as smoking or a family history of heart disease. For example, in a cross-sectional study, male subjects less than 50 years of age with periodontitis had a relative risk (RR) of 1.72 (95% confidence interval (CI) = 1.10; 2.68) for developing cardiovascular disease (16). Similarly, in a prospective study of 1372 Pima Indians, periodontal disease conferred a RR of 2.7 (95% CI = 1.3; 5.5) for development of cardiovascular disease (17). Finally, in a 15-year longitudinal study of 1000 men in good health at baseline, those with clinically significant periodontal disease were at significantly elevated risk for subsequent development of cardiovascular disease (RR 1.5, 95% CI = 1.04; 2.14), fatal cardiovascular dis-

TABLE 1 **Risk factors for periodontal disease[6–11]**

Risk Factor	Odds Ratio	95% Confidence Interval
Smoking (<15 packs/year)	2.05	1.47–2.87
Smoking (>30 packs/year)	4.75	3.28–6.91
Genetic factor (IL-1 polymorphism)	6.8	1.01–45.62
Genetic factor and smoking	18.9	1.04–343.1
Diabetes mellitus type 1 and 2	2.32	1.17–4.60
Ages 35–44	1.72	1.18–2.49
Ages 65–74	9.0	5.86–13.89

ease (RR 1.9, 95% CI = 1.10; 3.43) and stroke (RR 2.8, 95% CI = 1.45; 5.48) (18).

In contrast to the above mentioned associations, a recent meta-analysis (19), as well as a large and well-designed prospective cohort study published in the *Journal of the American Medical Association* (20), did not find convincing evidence of a causal association between periodontal disease and cardiovascular disease risk. In this study, 8032 adults with no reported history of cardiovascular disease at baseline were followed for approximately 20 years. Periodontitis was associated with a nonsignificant increased risk for cardiovascular disease event (hazard ratio of 1.14 with a 95% CI of 0.96–1.36).

It seems that the interpretation of previously reported associations is difficult. Whether they are causal or artifactual depends for the most part on study design and the inherent adjusting for possible confounding mechanisms. Incomplete adjustment for socioeconomic status, for instance, may be responsible for the observed associations, particularly as it pertains to coronary heart disease, inasmuch as many risk factors are also responsible for periodontal disease.

There are several proposed mechanisms by which chronic systemic Gram negative/anaerobic dental bacteremia may trigger events leading to thrombus formation, coronary artery occlusion, and, ultimately, myocardial infarction (21). Monocytes from some individuals with a "hyperinflammatory" phenotype respond to a microbial and/or lipopolysaccharide (LPS) challenge with an abnormally high production of proinflammatory mediators to include thromboxane A_2 (TXA_2), prostaglandin-E_2 (PGE_2), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1); each of these can initiate and exacerbate atherogenesis and thromboembolic events (6). In addition, aggregation of platelets and subsequent thrombus formation is induced by the platelet aggregation-associated protein (PAAP) expressed on bacteria present in dental plaque (22). Although these processes may explain the link between periodontal disease and heart disease, insufficient firm evidence exists to support a cause and effect relationship currently. Evidently, still larger and even better-controlled studies will be required to identify a definite association between periodontal disease and coronary heart disease.

Diabetes Mellitus

In patients with diabetes mellitus, the prevalence, progression, and severity of periodontal disease is well recognized (23–26). Some of the most informative studies have involved the Pima Indians native to Arizona. Pima Indians are known to have a very high prevalence of type 2 diabetes (23–25) and these diabetic subjects also have a higher prevalence and severity of periodontal disease compared with nondiabetic subjects in this population. Other findings suggesting a link between diabetes and periodontal disease include the observation that teenagers with type 1 diabetes are more susceptible to destructive periodontitis (26). Similarly, diabetic patients who are poorly controlled have more severe periodontal disease (27–29), and periodontal treatment improves diabetic control by reducing insulin requirements (30, 31). Periodontitis in diabetic subjects also is associated classically with chronic recurrent abscess formation and suppuration (32). The predisposition of diabetic subjects for periodontal disease has been attributed to an impaired host response, increased insulin resistance, and vascular changes that increase susceptibility to infection (32). More specifically, it is suggested that in diabetic gingival tissue, enhanced accumulation of advanced glycation end products and increased oxidant stress are important in the pathogenesis of diabetes-associated periodontitis. In particular, advanced glycation end products can alter cellular phenotype and function by activation of cell-signaling pathways that result in activation, of the inflammatory response (33). For instance, it has been demonstrated that diabetic subjects have both an exaggerated gingival secretion of PGE_2, IL-1β, and possibly TNF-α, as well as an enhanced peripheral blood monocytic response to a LPS challenge (9).

ROLE OF SEX HORMONES IN PERIODONTAL DISEASE

Several pathways exist for estrogens and progestins, as well as androgens to exacerbate gingival inflammation and promote periodontal disease. Human gingiva can function as an estrogen target tissue because it has specific high-affinity estrogen receptors (34). Elevated concentration of these sex steroids is associated with changes in microvascular topography and permeability, resulting in gingival edema and increased gingival crevicular fluid flow (35–37). Moreover, the keratinization of the gingiva is decreased under the influence of sex steroids, and this, together with an increase in epithelial glycogen, impairs the effectiveness of the gingival epithelial barrier. Sex hormones also may alter the host defense mechanisms against bacterial plaque. For example, an increased number of polymorphonuclear leuko-

cytes and increased PGE_2 production in the gingiva enhance the inflammatory response (37, 38). Elevated levels of androgens caused a downregulation of interleukin-6 production by human gingival fibroblasts *in vitro*, thereby reducing the normal resistance to the inflammatory challenges produced by bacteria (39). Lastly, estradiol and progesterone can promote growth of *Bacteroides* subspecies in the gingiva. Thus, these hormones seem to have the potential for altering the subgingival microbial ecology implicated in periodontal disease (40, 41).

Puberty

A 1972 longitudinal study of 127 children between the ages of 11 and 17 first demonstrated a relationship between puberty and the development of gingivitis (42). In a more recent longitudinal study of 24 subjects progressing normally from prepuberty to puberty, there was a significant increase in gingival inflammation as well as in the proportion of specific periodontal pathogens in puberty relative to the baseline value (43). These increases were correlated with an elevation in systemic levels of estrogen and progesterone. These studies indicate a modulating role for sex hormones concerning the development of gingivitis that seemed to be independent from dental hygiene.

Oral Contraceptives

Studies evaluating the effect of oral contraceptive use and the development of periodontal disease are more than 20 years old. Overall, they conclude that gingival inflammation is increased in women taking oral contraceptives and is related to the duration of use (35, 37, 44–47). The greatest gingival response was seen in the first few months after oral contraceptive use, but could continue to worsen in some cases. Unfortunately, these studies evaluated women taking several different hormonal regimens. For currently marketed oral contraceptive pills, no published information is available.

Menopause/Osteoporosis

Periodontal alveolar bone loss is the major cause of tooth morbidity in the aging population. Loss of teeth may occur (47) and, in severe cases, the residual bone ridge may resorb beyond the former location of the root apices. Periodontal alveolar bone loss could be due to systemic osteoporosis, but more so to periodontal disease. Several authors have suggested that mandibular bone density may be indicative of systemic bone density (48, 49). Just recently, Jeffcoat et al. (50) presented preliminary data from the women's health initiative oral ancillary study again demonstrating the same. It has to be recognized, however, that existing studies are preliminary in nature and cross-sectional in design. Few studies have directly evaluated the relationship between periodontal disease and its sequelae in postmenopausal women, particularly assessing the influence of hormonal replacement therapy. Two studies reported no difference in alveolar bone loss with hormone replacement therapy but demonstrated less gingival bleeding (51, 52). Two large cohort studies evaluating women taking estrogen demonstrated a significant reduction in tooth loss, where the duration of hormone replacement therapy is inversely correlated with the proportion of women with edentulism. Unfortunately, these studies may be confounded by selection bias (53, 54). Longitudinal studies could address whether the progression of periodontal disease is augmented for patients with osteoporosis compared with patients with normal bone density. Currently, it is not feasible to address this correlation from only cross-sectional studies.

Pregnancy

Several classic papers describe the gingival condition of pregnant women. The hormonal changes seen in pregnancy are related to increased incidence and severity of gingivitis and periodontitis (38, 55–57). Symptoms of gingivitis may first appear in the second month of gestation and reach maximum severity 1 month before delivery (40, 55). It then declines and regresses after parturition (36). The greatest increase in gingivitis is usually seen in the anterior regions of the mouth but can be more generalized. A transient increase in tooth mobility has been reported (36, 57). During pregnancy, there are alterations in the subgingival microbial flora to include an increased ratio of anaerobes to aerobes and increased proportions of *Prevotella intermedia* and other black-pigmented species (40, 58). For instance, the relative proportions of *Bacteroides* species increased 55-fold in pregnancy (59). In women with marked pregnancy gingivitis, up to 10^7 neutrophils per minute are found in oral rinses, a 100-fold increase over the number found in subjects with healthy gingiva (Dennison, unpublished results). Immune changes associated with hormonal alterations in pregnancy include decreased neutrophil chemotaxis and phagocytosis, altered lymphocyte response, and depressed antibody

production (35, 60–62). The effect of these gestational changes on the periodontal tissues is two-fold: increased gingival swelling, redness, and bleeding occur more easily and increased gingival inflammatory response to bacterial plaque (58). Septicemia due to oral pathogens also has been reported during pregnancy (63), which eventually can result in fetal death (64).

Preterm Labor

It has been demonstrated in two case-control studies, one from the United States and one from Thailand, that women who experience a preterm delivery have more severe periodontal disease (odds ratio 7.9, 95% CI = 1.95; 28.8) compared with those delivered at term (65, 66). Just recently—and not yet unpublished—preliminary results of a prospective study revealed by researchers in Alabama demonstrated similar findings irrespective of any of the well-known risk factors for preterm delivery (67). The risk for prematurity increased with periodontal disease severity. The same researchers have also begun a pilot intervention study to evaluate whether the prematurity attributable to periodontal disease can be reduced by treatment. One or several plausible biologic pathogenic mechanisms are suggested to contribute to preterm labor and low birth weight in the presence of periodontal disease. One biochemical mechanism for preterm labor is infection mediated via prostaglandins and cytokines (68). In this scenario, bacterial endotoxin stimulates macrophages to produce cytokines (69–71), which in turn stimulate prostaglandin production by decidual and chorionic cells (72–75). Indeed, gingival crevicular fluid, PGE_2, and IL-1 levels have been found to be higher in women with preterm delivery and periodontal disease (76). These same women also exhibited higher gingival crevicular fluid concentrations of four specific organisms that are associated with periodontitis, as well as with systemic bacterial products such as LPS. For example, *Fusobacterium nucleatum* and its specific gingival subspecies, common oral organisms, are the most frequently isolated species from amniotic fluid cultures among women with preterm labor and intact membranes (77). Therefore, Gram negative anaerobic periodontal infections may serve as a chronic reservoir for hematogenous spread of bacteria and bacterial products to the fetoplacental unit. The role of the inflammatory host response seems to be a major factor of susceptibility and resultant severity of the condition (76–78). The patient with an altered inflammatory trait may be at risk for both periodontal disease and preterm birth.

CONCLUSION

In the past few decades, major advances have been made in the elucidation of the etiology, pathogenesis, and treatment of periodontal disease. Basic scientific data continue to be collected to enhance our knowledge of the host response. Although the findings currently available suggest a strong association among a number of systemic diseases, certain hormonal states, and periodontal disease, further rigorous randomized, controlled clinical trials are needed to establish causality and benefits of treatment. These developments will be of importance to the obstetrician and gynecologist as periodontal disease may become a potential modifiable risk factor for several systemic conditions, including pregnancy complications encountered in daily practice.

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