Pregnancy gingivitis and periodontitis and its systemic effect

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Abstract

Oral infection, especially gingivitis and periodontitis may affect course and pathogenesis of a number of systemic diseases, such as cardiovascular disease, preeclampsia and low birth weight. The purpose of this essay is to evaluate current status of oral infections, especially periodontitis, as a causal factor for systemic diseases.

GINGIVITIS

It is the inflammation of gingiva which surrounds the tooth and covers the alveolar bone .During pregnancy, the inflammatory response to dental plaque is increased, leading to swollen gingivae which tend to bleed on brushing. The hormonal changes of pregnancy also termed as pregnancy gingivitis,Pregnancy gingivitis do not differ histologically from that in the non pregnant state. Pregnancy gingivitis commonly becomes apparent later in the second month of gestation and worsens as the pregnancy progresses before reaching a peak in the eighth month. In the last month of gestation, gingivitis usually decreases and immediately post-partum the gingival tissues are found to be comparable to those seen during the second month of gestation.

The clinical features of pregnancy gingivitis may be localized or generalized, the changes affecting the anterior teeth are most obvious despite increased amounts of plaque being associated with the posterior teeth.

Although gingivitis is considered to be plaque induced, it is interesting that pregnancy gingivitis is not caused by an increase in dental plaque. This may be due to the effects of pregnancy on the gingival tissues where both estrogen and progesterone receptors are found, although exactly how these hormones increase gingival inflammation. It is not know the pregnancy related gingival changes might be explained by increased vascularity and vascular flow alongside alterations in the immune system and/or changes in connective tissue metabolism.

Management of pregnancy gingivitis involves regular dental visits for professional cleaning and monitoring with education of the woman regarding both the etiology and prevention of the condition. Also elimination of factors that compromise removal of plaque, for example overhanging restoration margins, should be carried out so that plaque levels can be minimized.

PREGNANCY EPULIS (PYOGENIC GRANULOMA OF PREGNANCY)

The pregnancy epulis is a localized, soft hyperplastic lesion developing on the gingiva in up to 5% of pregnancies. This is a red, vascular lesion, which may have small white flecks superficially, usually pedunculated and can measure up to 2 cm in diameter. Although it can arise from any gingival site it mostly occurs on the interdentally papillary gingiva, particularly on the labial aspect and more commonly on the upper jaw than the lower. It is clinically and histologically indistinguishable from the pyogenic granuloma in men and nonpregnant women. During pregnancy, non-surgical management involves elimination, or at least the significant reduction, of dental plaque, particularly around the epulis.

Surgical removal should only be performed during pregnancy if the epulis is traumatized by opposing teeth or restorations resulting in pain and bleeding. However, if surgery cannot be delayed, removal should be done during the second trimester and the woman informed of the risk of recurrence.

EFFECT OF PREGANANCY ON ORAL CAVITY

Bacteria colonize sub gingival sites and ultimately infiltrate the underlying connective tissue, which many aspects of the host response are evaded. It appears that many facets of the

immune response with regard to the periodontium are affected by pregnancy, with the overall effect being one of decreased activity and efficiency. The key developments being decrease in the number of neutrophils, decreased chemotaxis and phagocytosis, and depressed antibody responses and cell-mediated immunity.

Oestrogen and progesterone receptors are found in the periodontal tissues and the progressive increase in levels of these hormones in pregnancy also affects the response of the tissues. The extra cellular matrix, gingival vessels and fibroblasts are all affected. Estrogen regulates of cellular proliferation, differentiation and keratinisation and thus oestrogen seems to stimulate matrix synthesis, along with progesterone, enhances the localized production of inflammatory mediators, especially prostaglandin E_2 (PGE_2), a potent inducer of osteoclastic activity. Progesterone compromises tissue homeostasis by reducing fibroblast proliferation, altering the pattern of collagen production and reducing the level of plasminogen activator inhibitor type 2 (PAI-2), which is an important inhibitor of tissue proteolysis.

With regards to periodontal disease, Gram-negative anaerobic bacteria are the main culprits. They include: Prevotella intermedia (P. intermedia), Tannerella forsythensis, Porphyromonas gingivalis (P. gingivalis), Treponema denticola and Actinobacillus actinomycetemcomitans. Although the causal role of specific bacteria in pregnancy associated gingivitis has been not yet established, gingival bleeding and inflammation appears to be associated with a rise in the numbers of Gram-negative rods present. However, an increase in the selective growth of P.intermedia, P. gingivalis and Tannerella species (formerly Bacteroides) has been demonstrated in sub gingival plaque during the onset of pregnancy gingivitis. This is likely to be a result of these species being able to use the pregnancy hormones, particularly progesterone, as a source of nutrition.

This increase in selective growth may also be favored by the changes that occur in the immune system during pregnancy alongside those that develop locally in the gingival crevice, such as blood from bleeding gingivae providing further nutrients and increased pocket depths creating a more favorable environment for anaerobes.

EFFECT OF PREGANANCY ON PERIODONTAL TISSUE

Given the considerable effect of pregnancy on oral health and the impact of periodontal disease on pregnancy outcome has now under scrutiny. The idea that it may contribute to pregnancy outcome was presented in 1931 when Galloway stated that periodontal disease may provide 'sufficient infectious microbial challenge' to have 'potentially harmful effects on the pregnant mother and developing fetus'. Infection, especially symptomatic infection of the genitourinary tract, is considered an important risk factor for preterm birth and/or low birth weight.

Essentially, bacterial infection results in the activation of cell-mediated immunity and the subsequent production of cytokines such as interleukins (IL-1, IL-6), tumor necrosis factor alpha (TNF-α) and prostaglandins, especially PGE_2.Recently proposed mechanism of labour suggests that the intra-amniotic levels of these mediators rise steadily throughout pregnancy until a threshold is reached at which labour is induced. Thus it raises the possibility the presence of infection results in an abnormally elevated production of these normal physiological mediators of parturition, which may trigger preterm birth, also resulting in low birth weight.

More recently, it has been suggested that sub clinical infections such as periodontitis may also pose a challenge to the developing fetus. It is hypothesized that sub clinical infections such as periodontal disease contribute to premature delivery and low birth weight as a result of pathogenic micro-organisms, or indeed their microbial products, such as lipopolysaccharide (LPS), reaching the uterus via the bloodstream, inducing cytokine release in the decidua or the membranes, resulting in increased prostaglandin production or, indeed, uterine muscle contraction. Inflammatory mediators such as cytokines and prostaglandins, when produced in the periodontal tissues or in other systemic organs in response to LPS stimulation, may also pose a real threat to the fetoplacental unit and increase the risk of preterm delivery and low birth weight.

SOME IMPORTANT STUDIES

The results of a case controlled study by Offenbacher et al suggested that periodontitis was a statistically significant risk factor for premature delivery and low birth weight and, indeed, that mothers with periodontal disease were potentially seven times more likely to have a preterm or low birth weight baby. Subsequent research by Jeffcoat et al. supported this suggestion. They found a four-fold increase in the odds of preterm birth before 37 weeks of gestation, rising to a seven-fold increase before 32 weeks of gestation in women with generalized or severe periodontal disease in weeks 21–24 of pregnancy. The work of Madianos et al

added weight to this argument by reporting that preterm delivery and low birth weight were 11 times more likely to occur in women whose periodontal disease worsened during pregnancy compared with those who had good periodontal health. Recently, Offenbacher et al reported that periodontal disease progression in pregnancy might be predictive of birth occurring at less than 32 weeks of gestation. On the other hand, Davenport et al found that the risk actually decreased with increasing pocket depth. Moore et al found no association between periodontal disease and preterm delivery and low birth weight, although, interestingly, this work did suggest a link between indicators of poor periodontal health and late miscarriage. A recent systematic review by Xiong et al concluded that, although periodontal disease may be adversely associated with pregnancy outcome.

CORRELATION BETWEEN ORAL INFECTION AND PREMATURITY

Chronic oral infection like periodontal disease may contribute to preeclampsia, preterm birth, fetal growth restriction, and fetal loss.

Periodontitis an oral gram- negative anaerobic infection is common in women of childbearing age and it presents as infection and inflammation of the gingivae and local support structures of the teeth, resulting in the destruction of the structures supporting the tooth. Fluid that bathes the tooth at the gingival margin, known as gingival crevicular fluid, often contains inflammatory mediators and the oral pathogens associated with periodontitis. The mechanisms underlying this destructive process involves both direct tissue damage resulting from plaque bacterial products, and indirect damage through bacterial induction of the host inflammatory and immune responses. Periodontitis affects up to 50% of the population, including a relatively high proportion of pregnant women. Advancing age, smoking, and diabetes are some risk factors for the development of periodontitis. Periodontitis has recently been recognized as a risk factor for the development of atherosclerosis and rheumatoid arthritis.

CARIOVASCULAR EFFECT OF PREGNANCY PERIODONTITIS

A parallel correlation exists between pathophysiology sequele of preeclampsia and atherosclerotic disease. Atherosclerosis, like preeclampsia, is associated with endothelial dysfunction, which may be caused by oxidative stress and subsequent lipid per oxidation, hyperlipidemia, or hyperhomocysteinemia. Molecular variants in the angiotensinogen gene have been associated with both atherosclerosis and preeclampsia, and several epidemiological factors predispose to the development of both atherosclerosis and preeclampsia: obesity, black race, and preexisting hypertension. However, despite the similarities between atherosclerosis and preeclampsia, little is known about potential common putative factors.

Atherosclerosis has been identified that may contribute to the development of adverse pregnancy outcomes. Periodontal disease, a chronic oral gram-negative infection, has been associated with atherosclerosis, thromboembolic events, and hypercholesterolemia. In addition, oral pathogens have been detected in atherosclerotic plaques, where they can play a role in the development and progression of atherosclerosis leading to coronary vascular disease. Periodontal disease may provide a chronic burden of endotoxin and inflammatory cytokines, which serve to initiate and exacerbate atherogenesis and thrombogenesis. Also the placenta may be similarly burdened in pregnant women who develop preeclampsia.

Periodontal disease is characterized by periods of exacerbation interspersed with periods of remission and presents a local microbial burden that initiates local inflammation and local tissue destruction. Women with active periodontal disease during pregnancy may have transient translocation of oral organisms to the uteroplacental unit, inciting placental inflammation or oxidative stress early in pregnancy, which ultimately produces placental damage and the clinical manifestation of preeclampsia. A subset of a cohort of women and had umbilical cord serum assessed for the presence of fetal immunoglobulin M to oral pathogens, demonstrated 16% case fetal immunoglobulin M to the oral pathogen Porphyromonas gingivalis documenting a fetal humoral response to organisms distant from the intrauterine environment and suggesting that translocation of oral pathogens to the uteroplacental unit may occur maternal periodontal disease may also represent a surrogate for another maternal factor that predisposes to the development of preeclampsia.

CARDIOVASCULAR DISEASE AND PERIDONTITIS

Cardiovascular diseases such as atherosclerosis and myocardial infarction occur as a result of a complex set of genetic and environmental factors The genetic factors

include age, lipid metabolism, obesity, hypertension, diabetes, increased fibrinogen levels, and platelet-specific antigen Zwb (P1^{A2}) polymorphism. Environmental risk factors include socioeconomic status, exercise stress, diet, no steroidal anti-inflammatory drugs, smoking, and chronic infection. The classical risk factors of cardiovascular disease such as hypertension, hypercholesterolemia, and cigarette smoking can only account for one-half to two-thirds of the variation in the incidence of cardiovascular disease.

Periodontal disease is capable of predisposing individuals to cardiovascular disease, given the abundance of gram-negative species involved, the readily detectable levels of proinflammatory cytokines, the heavy immune and inflammatory infiltrates involved, the association of high peripheral fibrinogen, and the white blood cell (WBC) counts. Periodontal disease may trigger pathways leading to cardiovascular disease through direct and indirect effects of oral bacteria.

Oral bacteria such as Streptococcus sanguis and Porphyromonas gingivalis induce platelet aggregation, which leads to thrombus formation. These organisms have a collagen-like molecule, the platelet aggregation-associated protein, on their surface. When S. sanguis is injected intravenously into rabbits, a heart attack-like series of events occur. Antibodies reactive to periodontal organisms localize in the heart and trigger complement activation, a series of events leading to sensitized T cells and heart disease. Furthermore, one or more periodontal pathogens have been found in 42% of the atheromas studied in patients with severe periodontal disease. P. Gingivalis can actively adhere to and invade fetal bovine heart endothelial cells, bovine aortic endothelial cells, and human umbilical vein endothelial cells. Invasion efficiencies of 0.1, 0.2, and 0.3% were obtained with bovine aortic endothelial cells, human umbilical vein endothelial cells, and fetal bovine heart endothelial cells, respectively. Proteolytic enzymes referred to as gingipains R, which are released in large quantities from P. gingivalis. After entering the circulation, gingipains R can activate factor X, prothrombin, and protein C, promoting a thrombotic tendency through the ultimate release of thrombin, subsequent platelet aggregation, conversion of fibrinogen to fibrin, and intravascular clot formation.

The second factor in this process could be an exaggerated host response to a given microbial or LPS challenge, as reflected in the release of high levels of proinflammatory mediators such as PGE$_2$, TNF-, and IL-1. These mediators have been related to interindividual differences in the T-cell repertoire and the secretory capacity of monocytic cells. Typically, peripheral blood monocytes from these individuals with the hyper inflammatory monocyte phenotype secrete 3- to 10-fold-greater amounts of these mediators in response to LPS than those from normal monocyte phenotype individuals. Genes that regulating the T-cell monocyte response and the host-microbe environment can directly trigger and modulate the inflammatory response. Patients with certain forms of periodontal disease, such as early-onset periodontitis and refractory periodontitis, possess a hyper inflammatory monocyte phenotype.

A third mechanism possibly involves the relationship between bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS from periodontal organisms being transferred to the serum as a result of bacteremias or bacterial invasion may have a direct effect on endothelia so that atherosclerosis is promoted. LPS may also elicit recruitment of inflammatory cells into major blood vessels and stimulate proliferation of vascular smooth muscle, vascular fatty degeneration, intravascular coagulation, and blood platelet function. These changes are the result of the action of various biologic mediators, such as PGs, ILs, and TNF- on vascular endothelium and smooth muscle. Fibrinogen and WBC count increases noted in periodontitis patients may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis.

Periodontitis as an infection may stimulate the liver to produce C-reactive protein (CRP) (a marker of inflammation), which in turn will form deposits on injured blood vessels. CRP binds to cells that are damaged and fixes complement, which activates phagocytes, including neutrophils. These cells release nitric oxide, thereby contributing to atheroma formation. Patients with periodontitis had significantly higher CRP levels than mild-periodontitis patients, and both have been reported to have significantly higher levels. A specific heat shock protein, Hsp65, has been reported to link cardiovascular risks and host responses. Heat shock proteins are important for the maintenance of normal cellular function and may have additional roles as virulence factors for many bacterial species. A significant association exists between serum antibody levels to Hsp65 and the presence of cardiovascular disease. The bacterial infection stimulates the host response to Hsp65, which is a major immunodominant antigen of many bacterial species. The interaction between expressed

Hsp65 and the immune response induced by bacterial infection is hypothesized to be responsible for the initiation of the early atherosclerotic lesion. It has been suggested that chronic oral infection stimulates high levels of Hsp65 in subjects with high cardiovascular risk. Antibodies directed towards bacterial heat shock proteins cross-react with heat shock proteins expressed in the host tissue, especially those found in the lining of blood vessels indicating a link between oral infection and cardiovascular disease.

Edentulous persons with and without dentures and dentate individuals with missing teeth change their eating habits. They may thereby avoid certain nutritious foods because of difficulty in chewing and select high-calorie, high-fat food. When the foods cannot be well pulverized, this has an adverse effect on the internal absorption of nutrients. Such dietary preferences would predispose such individuals to the type of high-fat foods that are recognized as risk factors for cardiovascular disease. In dentate individuals with many missing teeth, the diet-induced elevation of serum low-density lipoprotein has been shown to up regulate monocytic responses to LPS. These subjects have both the diet-induced sensitization of monocytes and the plaque-laden teeth that could provide the LPS challenge to these cells. Instead of having hyper responsive monocytes reacting to any LPS introduced from the plaque, there would be elevated secretion of inflammatory cytokines by monocytes stimulated by elevated low-density lipoprotein levels. This interaction between LPS and monocytes may explain the severity of gram-negative infections in certain diabetic patients, but it could also be operating in individuals who change to a high-fat diet because of missing teeth.

Thus, all the mechanisms by which poor oral hygiene and periodontal disease may contribute to cardiovascular disease described above could also come into play as a result of certain dietary changes secondary to missing teeth.

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