Pregnancy and periodontal tissues

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REVIEW

Abstract

Periodontitis is today considered to be a serious disease of periodontal tissues, one caused in most cases by bacterial infection which stimulates proteolysis and osteolysis of the tissues. Typical for the disease is formation of periodontal pockets and a chronic destructive inflammation which impacts on the whole organism. Periodontopathic bacteria colonized in a subgingival biofilm cannot be removed by common oral hygiene. Overproduction of bacteria and other pro-inflammatory mediators can increase the total pro-inflammatory state of the organism in pregnant women. Increased levels of some pro-inflammatory cytokines (PGE2) and cells in fetoplacental space can lead to premature rupture of membranes and subsequent delivery of immature babies. An increasing number of studies in this field provide evidence that good professional care and personal oral hygiene can bring benefits through a decreased prevalence of preterm low birth weight infants (PLBWI) in women suffering periodontitis, although definitive conclusions have not yet been reached. Future mothers with periodontitis can run not only an increased risk of PLWBI but often also suffer pre-eclampsia – a state called acute atherosis – which can be ethiopathogenetically associated with high concentrations of various pro-inflammatory mediators. An increased production of female hormones during pregnancy contributes to the development of gingivitis and periodontitis because vascular permeability and possible tissue edema are both increased.

INTRODUCTION

One of the basic characteristics of the connective tissue, which plays a part in the formation of numerous anatomical structures including the tissues of periodontium during pregnancy, is its continuous and purposeful remodeling. A well-balanced remodeling is the principle of growth subsequent labor. Equilibrium between the degradation and production of connective tissue and the extracellular matrix is the basis for adequate and well-timed functioning of these tissues. A single inflammatory reaction disturbs remodeling mechanisms and shifts them to the site of proteolysis, which can lead to their damage or complete destruction (Page-McCaw *et al.* 2007; Offenbacher *et al.* 1996; Ahmad *et al.* 2007). Infections of the fetus and fetal membranes can lead to premature rupture and a preterm delivery of babies with low birth weight (Evaldson *et al.* 1980; Gibs *et al.* 1992; Leon *et al.* 2007). Local infections are accompanied by an overall increase in pro-inflammatory mediators characterized by increased concentrations of pro-inflammatory cytokines, lipid mediators of inflammation, CRP and other cellular and humoral elements of inherited and acquired

immunity in blood circulation (Hasegava *et al.* 2003; Heimonen *et al.* 2009; Lin *et al.* 2003).

Gingivitis and periodontitis are infectious diseases with a great impact on individually modulated or altered inflammatory reactions. A more serious situation is when periodontitis is connected with osteolysis, the destruction of periodontal ligaments and formation of periodontal pockets that are reservoirs of periodontopathic anaerobic bacteria. In advanced stages of the disease, the periodontal pathogens often invade the surrounding tissues and cause backteremia and their dissemination into other tissues and structures of the organism. Nowadays periodontitis is understood as an overall affliction of the organism, which can be proved by its total proinflammatory status, with all consequences including increased concentrations of proinflammatory bio-molecules and oral cavity-induced backteremia. At this point several questions arise which we will try to answer in this article.

I. *How do gingivitis and periodontitis in pregnant women affect the fetus and fetal membranes and preterm births of low weight infants?*

II. *Can periodontal therapy influence the prevalence of preterm low birth weight infants or diminish the level of affliction in these children?*

III. *Is there any association between maternal periodontitis and preeclampsia?*

IV. *What role do female hormones play in these processes during pregnancy?*

I. The influence of periodontitis on preterm low birth weight children

Preterm low birth weight (PLBW) children and preterm ruptures of membranes (PROM) represent one of the most serious complications and causes of an increased prenatal and perinatal mortality and morbidity rate, which ranges from 4 to 15 per cent. Low birth weight can be related to Intrauterine Growth Retardation Syndrome (IUGRS) conditioned by genetic and developmental anomalies. PLBW children are designated as infants born before the 37th week of gestation with body weight less than 2 500 g (Tough *et al.* 2002; Siquera *et al.* 2007). Morbidity in further development of PLBW children considerably varies and affects above all cognitive, sensory and motor functions, which then lead to significant medical, social and economic problems (Borel *et al.* 2006; Xiong *et al.* 2006; Mozurkewich *et al.* 2000). A chronic oral infection is one of the possible contributors to PLBW. Other risk factors can be infections of the urogenital system, age, race, diabetes, high blood pressure, alcohol abuse, tobacco smoking, and previous deliveries of PLBW infants (Goldenberg *et al.* 2000). A chronic oral infections such as periodontitis can leads to intracellular infections of organs and deterioration and disturbances of mitochondria (Nishihara 2009a; b).

In several studies, maternal destructive periodontitis is shown to be a possible and important ethiopathogenetic factor in PLBW and PROM. Some long-term statistical and epidemiological research associates the degree of periodontium affliction to an increased prevalence of PLBW where other ethiopathogenetic risk factors (such as bacterial vaginosis, smoking, chorioamniotitis, previous PLBW deliveries) were also taken into consideration (Heimonen *et al.* 2009; Siquera *et al.* 2007; Anath & Vintizileos 2006). Other studies do not unanimously confirm chronic periodontitis as a risk factor in development of a PLBW syndrome (Michalowicz *et al.* 2006).

Nowadays we know several mechanisms that take place in birth timing. Besides indirect evidence of the existence of unknown mechanic receptors activating different types of cells, there are also signals coming from the hypothalamus of the fetus. It is highly probable that birth timing is influenced both hormonally and immunologically. As for the problems of PLBW, we are interested in the immunological aspect of these processes. Half of the father's genes are supposed to be able to determine foreign fetal proteins including the fetal HLA and interrupt the immune response of the mother to the presence of differentiating fetal proteins acting as antigens. These mechanisms are determined first of all from hormonal and immunological sides; premature rupture of membranes can be caused by proteolytic enzymes from a group of metalloproteinases, the activity of which is regulated mainly by proinflammatory mediators PGE2, Interleukin-1-beta and alpha, TNF-alpha, IL-6, IL-8. The inflammatory cytokines are produced in larger amounts by various immunity-inducing cells in a fetoplacental unit from the second trimester of pregnancy. Proinflammatory and proteolytic activation fibrinoblasts, monocytes, and other immunocytes increase as the pregnancy advances and lead to destruction of a relatively closed chorioamniotic space. Increased concentrations of proinflammatory mediators activate metalloproteinases which degrade collagen and the extracellular matrix of fetal membranes, and the remodeling of connective tissues is thus shifted to proteolytic mechanisms (Chan *et al.* 2010; Maymon *et al.* 1999; Offenbacher *et al.* 2006a) Reduced or local concentrations of antioxidants and increased formation of reactive oxygen radicals (which is commonly increased in the last trimester) in gingival crevicular fluid (GCF) in pregnant women suffering periodontitis can contribute to the unwanted destruction of the fetoplacental unit (Akalin *et al.* 2009). It is obvious that inflammatory diseases of the urinogenital tract cause increased concentrations of pro-inflammatory mediators and intensify activity of metalloproteinases in the fetoplacental space, as well as increase the risk of preterm low birth weight.

Here arises the question of whether similar destructive mechanisms can be activated by inflammation

in other parts of the organism. Chronic, destructive periodontitis connected with formation of periodontal pockets represents a large reservoir of predominantly gram-negative anaerobic microflora arranged into a specific microbial film inaccessible through common oral hygiene. In literature it is stated that in 1 mg of dental plaque, there can be from 10^8 up to 10^9 bacteria (Loeshe 1994). It was found out that bacteria, LPS-endotoxin, PGE2, IL-1-beta and other pro-inflammatory mediators can enter the bloodstream during mastication, oral hygiene and various types of dental therapy (Limeback 1988; Medianos *et al.* 2001; Scannapieco *et al.* 2003). It is obvious that the historical perception of dental focal infection caused by transient bacteria has to be updated and new evidence confirming penetration of different bacterial products and pro-inflammatory agents into the bloodstream (that cause subsequent inflammatory reactions in tissues, organs or the whole organism) respected. The penetration of bacteria and their toxins first causes ulceration of periodontal pockets and invades periodontal tissues in the intermediate stages of periodontitis (Jarroura *et al.* 2005; Bearfield *et al.* 2002; Costernon et al 1999). For these reasons periodontitis in pregnant women is considered a new and very important risk factor in development of premature low birth weight. Patients with diagnosed periodontitis should have sophisticated home care, they should be instructed properly and their biofilms should be removed through adequate cleaning and therapeutical techniques. All possible risk factors (maternal diabetes, hypertension) should be detected (Offenbacher *et al.* 2006a; Offenbacher *et al.* 2008).

II. The influence of periodontal therapy on development of preterm low birth weight

Present scientific knowledge confirms that periodontal anaerobic infection during pregnancy is a possible risk factor in the preterm delivery of infants with low birth weight. Chronic periodontitis is closely connected with increased levels of pro-inflammatory mediators in periodontal pockets and tissues of periodontium itself (Hasegava *et al.* 2003; Lamster 1992). Reduction of periodontal pathogens through depuration of subgingival space or antibacterial therapy is logically supposed to result in a local as well as total decrease of concentrations of pro-inflammatory mediators. This has been confirmed in pilot studies (Lopez *et al.* 2002; Jeffcoat e al., 2003). Other clinical studies describe a 3.8-fold reduction of preterm deliveries, decreased amounts of periodontal bacteria, IL-1-beta concentration and IL-6 in serum in a group of treated patients (Offenbacher et al 2006a). The effects of maternal periodontitis have not unanimously confirmed an impact on some values connected with preterm low birth weight, results varying considerably (Romero *et al.* 2002).

Some studies, however, have not confirmed statistically significant differences in the duration of pregnancy and birth weight in groups of treated and untreated pregnant women (Gazola *et al.* 2007). These heterogeneous results of studies can be conditioned by several factors which have to be taken into consideration during evaluation, factors which cannot always be eliminated. The following factors can affect the prevalence of preterm births: maternal age, PLBW in previous pregnancies, and education. The stage and severity of periodontal disease are very important for the evaluation of results of studies. Some studies have confirmed the fact that the frequency of PLBW rises with advancing destruction of the periodontium (Offenbacher *et al.* 2006b). These facts and adequate periodontal therapy have to be included in evaluation of individual studies and their results. It is necessary to continue with appropriate and sophisticated research in this field.

III. The association between periodontitis and preeclampsia

At present pre-eclampsia is one of the most serious gynecological and neonatal problems. It has become one of the causes of gestational and fetal morbidity and mortality. Its prevalence ranges from 3 to 5 percent of the total number of pregnancies (Paternoster *et al.* 2004). It appears after the 20^{th} week of gestation and is characterized by hypertension and proteinuria of different stages. Further complications of the disease are disorders of coagulation, vascular thrombotisation, damage of liver and kidney functions and placenta abruption (Contreras *et al.* 2006). The most serious risk factors in pre-eclampsia are hypertension, obesity, diabetes mellitus, and family history. Its prevalence is higher in nulliparas and primaparas (Siquera *et al.* 2008). Pre-eclampsia, which is often called acute atherosis, is in its ethiopathogenic and clinical manifestations often similar to atherosclerotic plaques in vessels. Dysfunction of endothelium, thrombotisation of vessels and formation of atherosclerotic lipoprotein lesions are associated with high serum levels of pro-inflammatory mediators and markers /PGE2, TNF-alpha, IL-1-beta, IL-6/ that correlate with the incidence and course of maternal periodontitis (Kelly 2006; Pitiphat *et al.* 2006; Borzychowski *et al.* 2006).

Several studies have confirmed a correlation between pregnant women suffering periodontitis and the prevalence of pre-eclampsia (Contreras *et al.* 2006; Siquera *et al.* 2008; Canakci *et al.* 2004).

IV. The influence of female hormones on periodontal tissues in pregnancy

Increased production of estrogen and progesterone during pregnancy brings higher vascular permeability of gingival tissues, which is the main cause of gingivitis in pregnant women. Its prevalence ranges from 35 to 100 per cent. By applying appropriate hygiene, however, this can vanish (Zachariasen 1989; Adriaens *et al.* 2009).

Increased hormone levels in gingival tissues can induce growth and variability of periodontal pathogens in the second trimester of pregnancy and become a pos-

sible ethiopathogenetic factor in gestational gingivitis and periodontitis (Vittek *et al.* 1982; Person *et al.* 2008). However other studies have not confirmed changes in subgingival concentrations of bacteria directly associated with periodontitis (Adriaens *et al.* 2009).

Using of oral hormonal contraceptives, by many authors, is associated with increasing of gingival inflammation and periodontitis with higher prevalence of some periodontal pathogens /Porphyromonas gingivalis, Prevotela intermedia, Aggregatibacter actinomycetemcomitans/ (Mullally *et al.* 2007; Brusca *et al.* 2010).

CONCLUSIONS

Pregnancy and pregnancy-associated changes exacerbate the state of different periodontal indices and markers. This is evident in clinical practice through the occurrence of gestational gingivitis and the aggravated clinical picture of diagnosed periodontitis and the overall progression of the disease (Lieff *et al.* 2004). Increased inflammatory reaction and destruction of periodontal structures in the subgingival microenvironment encourages the growth of anaerobic periodontal pathogens that produce large amounts of LPS-toxins and other virulent agents forcing related immune cells to produce active immunological biomolecules. Increased local and systemic concentrations of active anti-inflammatory substances can directly act and stimulate the immune system in the fetoplacental unit and activate in this way proteolytic and biological mechanisms leading to preterm rupture of fetal membranes and uterine contractions resulting in development of PLBW and PROM. A positive association between severe forms of periodontitis and PLBW is confirmed in many studies in this medical field. Significant bacteriological differences between pregnant and non-pregnant women were not confirmed in most of the studies however, although some of them provide interesting conclusions (Ebersol *et al.* 2009).

The benefit of periodontal therapy lies in a reduction of amounts of periodontal pathogens and a decrease in concentrations of pro-inflammatory cytokines in local and systemic distributions. Some studies have confirmed a statistically important decrease in the number of preterm low birth weight infants while others have not. That is why it is necessary to continue with further sophisticated research. Similarly a positive correlation between periodontitis in pregnant women and the prevalence of pre-eclampsia has also been confirmed, though this fact is not stated in all research papers. Vascular permeability caused by overproduction of estrogen and progesterone in pregnant women contributes to a higher incidence and prevalence of inflammation of the periodontium. For exact and complete answers to the above-mentioned questions, further research based on numerous studies and analyses is essential.

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