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Periodontitis and Preterm Low Birth Weight: Is there any Association?

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Abstract

The aim of this paper is to indicate possible etiopathogenetic associations between destructive periodontitis in pregnant women and preterm low birth-weight deliveries. Strong pro-inflammatory potential of chronic periodontitis may attack the whole organism of the future mothers. The destructive inflammatory character of various forms of periodontitis with its bacterial, cytokinal and proteolytic expressions can raise the pro-inflammatory and proteolytic status in the fetoplacental unit and cause premature rupture of chorioplacental membranes. In our study, there are presented possible associations of both states manifested through bacterial, mediatory, genetic, proteolytic and oxidative mechanisms. The majority of other papers report associations of individual ethiopathogenetic mechanisms, by means of which chronic destructive inflammation of periodontium negatively afflicts the feto-placental structures. In spite of wide research in this field, causal associations have not yet been unanimously proven.

Introduction

There are two major types of periodontal diseases: gingivitis and periodontitis. While gingivitis is inflammation afflicting the gingival part of the periodontium, periodontitis is a bacterial disease manifested with presence of anti-inflammatory response; a reaction to the presence of periodontal pathogens in the periodontium. The anti-inflammatory response of periodontal tissues can have an impact on other tissues and organs due to penetration of the microorganisms from the periodontium into the bloodstream; an inflammatory reaction in individuals with weakened immunity is stimulated. Temporary bacteraemia and penetration of various germs into the bloodstream can occur e.g. during medical examination with a periodontal probe, or during chewing, or simple dental hygiene procedures, such as tooth brushing, flossing, etc. [1-2]. Periodontitis is a serious inflammatory disease connected with osteolysis, destruction of periodontal ligaments and formation of periodontal pockets filled with anaerobic bacteria. For advanced stages and forms, penetration of the most virulent strains and bacteria into the periodontal structures is typical. Prolongation of the chronic process increases the total pro-inflammatory status of the organism and enables dissemination of bacteria, virulent components and other inflammatory mediators by blood. The surrounding tissues are often invaded with periodontal pathogens and bacteraemia is caused with hematogenous spreading of these pathogens into distal tissues and organisms [3]. Nowadays periodontitis is seen as a serious systemic disease. It afflicts pregnant women when the periodontal pathogens with their virulent toxins overcome fetoplacental barriers, attack the fetal membranes and cause a preterm labor [4,5].

Definition and Epidemiology

Preterm low birth weight (PLBW) children, preterm ruptures of membranes (PROM) and Intrauterine Growth Retardation Syndrome (IUGRS) are serious prenatal and perinatal complications that are sometimes hard to distinguish. According to a WHO report the incidence of preterm low birth weight infants varies from 8% in Europe up to 26.2 % in South-Eastern Asia [6]. PLBW children are designated as infants born before the 37th week of gestation with body weight less than 2500 g. Total morbidity in further development of these children is considerably higher and presents serious medical, social, and economic problems. A chronic oral infection is just one of the possible contributors to preterm low birth weight. Other risk factors can be infections of the urogenital tract, mainly bacterial vaginosis, chorioamniotitis, mother's age, race, diabetes, high blood pressure, alcohol abuse, tobacco smoking, low socio-economic status, as well as previous deliveries of PLBW infants [4,5,7,8].

Besides increased mortality in neonatal and perinatal periods, total morbidity in further development of these children is a serious medical and social problem. Preservation of etiological factors, prevention, and introduction of new preventive and therapeutic programs can save society considerable financial resources [8]. It is necessary to mention that PLBW infants can suffer various psychomotor neurological disorders, damage of cognitive functions, congenital anomalies, respiratory diseases and overall retardation of the individual [6,9].

Ethiopathogenesis of PLBW Children

Nowadays etiopathogenic problems of PLBW and PROM are mostly considered to be a matter of infection and immunity, with destructive periodontitis during pregnancy seen as one of the possible ethiopathogenetic factors of its development. Increased numbers of preterm low birth weight children are connected in some epidemiological studies with the severity of destructive changes in the periodontium [10]. In other studies, periodontitis in future mothers is not considered to be a possible risk factor in development of preterm low birth weight infants [11]. During the last trimester of fetal development, the whole fetoplacental unit gets prepared for the coming labor. In fetal membranes, myometrium and amniotic space, competent immune cells and substances of catabolic character start to accumulate to induce uterine contractions and the right timing of rupture of chorioplacental membranes followed by definite expulsion of the fetus from the mother's body. These mechanisms seem to be centrally controlled and timed by hormones and immunity. They

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are needed because the fetus disposes of half of the father's proteins, which behave as antibodies with regard to developing HLA of the fetus. Delivery is the only effective mechanism able to solve this situation [3,7,12]. Immunologically and hormonally controlled proteolysis of the fetal membranes is caused by progressive accumulation of monocytes, fibroblasts and other pro-inflammatory altered imunocytes which increase production of pro-inflammatory mediators in the fetoplacental unit. These destructive and proteolytic substances mainly include the pro-inflammatory lipid mediators PGE2, TNF-alpha, IL-1,-2 -6,-8 and others. Increased concentration of pro-inflammatory cells and substances stimulate formation of metalloproteinases, which catabolize extracellular matrix, collagen, elastin and other protein components of fetal membranes. The physiological proteolysis of fetal membranes, induced by destructive and altered remodeling, pushes these membranes to self-destruction leading to their rupture and subsequent delivery [12,13].

Periodontitis and its Effect on the Organism

Chronic periodontitis has a huge virulent and infectious potential due to periodontal pockets filled with anaerobic bacteria and their toxins. The walls of periodontal pockets are covered with a layer of subgingival biofilms formed by specially organized antibacterial substances. To destroy bacteria in subgingival biofilm, thousand times higher concentrations are needed. Due to these facts application of antibacterial medication requires subgingival mechanical depuration by means of professional dental hygiene [14,15]. It was detected that even during common mastication and oral hygiene, bacteria and their toxins and various pro-inflammatory substances and mediators penetrate into the bloodstream. In advanced and serious periodontitis, release of LPS endotoxins and prostaglandins is a serious and health-threatening issue [1-3,16-18].

The whole timing and destructive activity of several components leading to rupture of placental membranes is determined by the described mechanism. It is obvious that proteolysis of these membranes is strongly influenced by the pro-inflammatory activity of various cells, immunologically active substances arising mainly in the progressively changing fetoplacental unit. This mechanism can be stimulated and accelerated by existing infection [19-21].

Today there is enough evidence that historically understood dental (oral) focal infection presented in a form of transient bacteria has to be supplemented by new scientific knowledge which will confirm penetration of various bacterial products, pro-inflammatory mediators and substances into the bloodstream with their subsequent possible impact on other body structures and organs as well as their stimulation of a pro-inflammatory status of several tissues or even the whole organism. However it is obvious even today that these mechanisms cannot be unified and generalized because they undergo very complicated and individually modulated immunological processes with complicated genetic, epigenetic and environmental interactions. This complicated system is probably a reason why not all studies from this field bring equal results and confirm associations of these diseases in a positive way [22-25].

Periodontitis and its Possible Etiopathogenic Consequences on Preterm Deliveries

On the basis of given facts, the following etiopathogenic mechanisms (caused by oral infection and inducing increased prevalence of preterm born infants with low birth weight) are suggested:

Bacteria and their toxins (LPS-toxins) can penetrate into the fetoplacental unit

Where they form colonies, infect the fetoplacental structures, and induce inflammatory processes followed by a preterm delivery. As for periodontal bacterial pathogens participating in preterm deliveries, the *Porphyromonas gingivalis* are mostly associated. The immune homeostasis of the fetus, its environment and membranes can be altered through different mechanisms. The mentioned microbes were found in amniotic water of mothers in danger of preterm deliveries. The trophoblast infection /HTR-8/ was reported to be able to modulate production of cytokines via *P. gingivalis* and influence on the course of pregnancy [26]. Increased production of pro-inflammatory cytokines and restriction of fetal growth after infection was detected even in animal experiments [27]. Possible associations between preterm deliveries and periodontal pathogens, periodontal status and PGE2 concentration in crevicular fluid have long been reported [12].

The possible decreased expression of growth and development of determining genes and factors caused by *Campylobacter rectus* infection is reported in another study [28]. Other review studies see the results of associations between periodontal infection and preterm deliveries of low birth weight infants to be rather controversial and require further research [29].

Cytokines and other pro-inflammatory mediators

Increased serum concentrations of pro-inflammatory cytokines / IL-1-beta, PGE2/ in future mothers afflicted with periodontitis have been confirmed in several studies [13,14,27,30,31].

In some studies an increased concentration of cytokines in gingival crevicular fluid over a certain level is considered to be a limiting factor of association with these diseases [12]. However no significantly important associations in production of pro-inflammatory mediators and markers have been detected by some other authors [32].

Genetic polymorphisms of immunologically active substances

Some genetic polymorphisms of pro-inflammatory mediators can be associated with preterm low birth weight deliveries. It is supposed that identical or similar polymorphisms can induce periodontitis. These associations can be mainly in polymorph forms of interleukins-1 and their antagonists [33]. In similar correlations other immunological substances and their receptors are also tested. Research in this field is expected to make progress in the near future [34].

Increased oxidation and decreased concentrations of antioxidants in the last trimester

In women in the last trimester of pregnancy, a decreased concentration of antioxidants and higher systemic and crevicular levels of oxidative substances have been detected [35]. Destructive periodontitis is a rich source of strong oxidative substances, as their production is the basic antibacterial mechanism of destruction and elimination of periodontal bacteria. However, if this process is prolonged and is not stopped early by immune mechanisms, oxidants can destroy periodontal tissues and penetrate into the bloodstream and afflict distal organs and tissues [36].

Hormonal influences

An increased formation of progesterone and estrogens stimulates formation of prostaglandins, mainly PGE2, which have significant pro-inflammatory effects on periodontal tissues. The permeability

and dilatation of vessels and their subsequent exudation is increased by these hormones. One result of hormonal changes is pregnancy gingivitis with prevalence from 37 to 100 per cent [37,38]. If the mentioned changes stimulated by hormones occur in pregnant women with incipient or already developed periodontitis, further deterioration of the disease is highly probable. No changes of bacterial profiles of periodontal bacterial pathogens in the last trimester of pregnancy have been confirmed [38,39].

Intracellular granulocyte infection

Interesting facts about intracellular granulatocyte infection induced by M-cells in Payer's patches have been presented by Nishihara. According to him intracellular granulocytes can be contaminated with an intestinal non-pathogenic infection leading to functional damage of mitochondria and other specialized compartments. These immunological diseases can be diagnosed and listed under diseases of the autoimmune system. According to Nishihra, infection is spread to other tissues and organs with contaminated leukocytes. Production of CRP, anti-nuclear antigen and IgE is stimulated. An intracellular infection can be caused by eating food cooler than 37 degrees Celsius, or by mouth breathing. Such studies have to be further examined and verified [40,41].

Results and Comparisons of Epidemiologic Studies

At the beginning it should be noted that results of epidemiological studies dealing with associations between periodontitis in pregnant women and preterm low birth weight deliveries are not unanimous and neither positive nor negative associations have definitely been confirmed, although the number of positive studies is much higher. Positive studies state that future mothers suffering periodontitis run a statistically significantly higher risk of preterm low birth delivery. In some studies these states are divided into preterm deliveries, low birth weight deliveries and deliveries of infants with retarded growth [4,14,42].

However association between periodontitis in pregnant women and an increased prevalence of preterm deliveries is not unanimously confirmed in all studies. Some studies deny etiopathogenetic associations and require further long-term and sophisticated research [43-45].

Impact of Periodontal Therapy on Development of Preterm Deliveries of Infants

At present periodontal anaerobic infection during pregnancy is considered a possible risk factor in preterm deliveries of low birth weight infants. Chronic and destructive periodontitis is associated with increased levels of serum and local pro-inflammatory mediators as well as transient bacteraemias. Anaerobic infection and its toxins in periodontal pockets or already invaded bacteria and increased amounts of pro-inflammatory cytokines can penetrate into the bloodstream through damaged endothelium, ulcerated mucosa or during mastication and invade distal tissues of the organism [13,23,46].

In spite of dozens of various studies, it is still an open question to what extent periodontological therapy can influence the development and course of preterm deliveries with low birth weight infants. The protective effects of periodontal scaling on the prevalence of preterm deliveries are referred to in some studies [47-49]. A 3.8-fold reduction of preterm deliveries, a decreased amount of periodontal bacteria and a local decrease of IL-1-beta as well as decreased serum IL-6 concentrations are reported in another study [50]. Conventional periodontal scaling reduced preterm deliveries before the 37th week of gestation in 5 %; in a group of women treated with metronidazole, the reduction was only 3.3 % [47].

However not all studies have confirmed a beneficial effect of periodontal therapy on the development and course of preterm deliveries of low birth weight infants and values connected with them. There is high variability among the results. These associations are denied by other authors [51-53]. Similarly, from a statistical viewpoint some studies have not confirmed periodontitis as an important risk factor in the development of preterm low birth weight infants in pregnant women [54]. Nor has research of periodontitis progress unanimously confirmed an association between progress of periodontitis and an increased risk of preterm delivery of low birth weight, although other authors refer to this association as a positive one [21].

Heterogeneous results of studies can also be conditioned by the existence of several risk factors which have to be taken into consideration in their evaluation and which cannot always be eliminated. Among the most serious risk factors is infection of the lower part of the urogenital tract, mainly bacterial vaginosis, which can cause chorioamniotitis and subsequent rupture of amniotic membranes. Other possible factors contributing to increased prevalence of preterm low birth weight infants which have to be mentioned and in future studies taken into consideration is the age of mothers, previous preterm deliveries, as well as education.

Conclusion

In this review study possible etiopathogenetic associations between chronic periodontitis in pregnant women and preterm deliveries of low birth weight infants were outlined. It is obvious that destructive periodontitis is a serious inflammatory disease with impact on the whole organism. In spite of the fact that several etiopathogenetic associations between both examined diseases were confirmed, the exact cause has not definitely been proven. For evaluation of results stated in the studies it is necessary to establish unified diagnostic criteria of periodontitis as well as the grades and severity of periodontal diseases. These factors as well as adequate periodontological therapy have to be taken into consideration in the evaluation of individual studies and their results. The importance of appropriate research into this field with the application of multivariable statistic methods cannot be overlooked.

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