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Periodontal disease of the mother and incidence of preeclampsia

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Introduction

Periodontitis is a chronic inflammatory disease, which is progressing in a slow pace and leads to gingival tissue destruction and alveolar bone resorption. If left untreated, it will lead gradually in tooth loss. It is caused by the simultaneous action of bacterial virulence factors and the response of the immune system[1,2]. In the literature there is growing evidence of a possible link between periodontal disease and systemic health. The relationship between periodontitis and diabetes mellitus[3], atherosclerosis and cardiovascular diseases[4,5,6], renal disease[7,8], cognitive impairment[9,10], cancer[11,12], metabolic syndrome[13] and complications in pregnancy (premature birth[14], low birth weight[15,16] and preeclampsia) has been discussed in the literature. Preeclampsia is an important factor of mother and infant morbidity and mortality and it is affecting 5-7% of pregnancies[17,18]. Preeclampsia is defined as a rise in blood pressure (systolic pressure ≥140mmHg or diastolic pressure ≥90mmHg) combined with proteinuria (≥300mg/24h)[17,18]. The cause of preeclampsia is unknown, however in the literature there are documented several risk factors such as antiphospholipid antibody syndrome, renal disease, prior preeclampsia, systemic lupus erythematosus, nulliparity, chronic hypertension, diabetes mellitus, high altitude, multiple gestations, strong family history of cardiovascular disease, obesity, family history of preeclampsia and advanced maternal age[18]. It has been proposed that in the pathogenesis of preeclampsia, the immune system plays an important role. Given the role of inflammation in the pathogenesis of preeclampsia, it is suggested that the disease might have also an etiology of microbial origin[19]. In fact it has been proposed that the main dysregulations that accompany preeclampsia, which are abnormal trophoblast invasion of the placenta, anti-angiogenic responses, oxidative stress and inflammation, could be explained by an infection caused by microbes that are dormant and as a result difficult to detect[18].

Epidemiologic studies

In the literature there is growing evidence of a link between periodontitis and preeclampsia. Until 2018, ten systematic reviews and meta-analyses have been conducted. Four reported a mild association and six a strong association between periodontitis and preeclampsia[20]. The majority of the scientific papers, which research the association between periodontitis

and preeclampsia, are observational studies (89.6%) and the intervention studies are the minority (10.4%). However, although observational studies indicate an association between the aforementioned multifactorial diseases, intervention studies do not show reduction in the risk of preeclampsia after periodontal therapy during pregnancy[21]. This can be interpreted either as absence of etiologic link between periodontitis and preeclampsia or as if the pathologic mechanisms which link periodontitis and preeclampsia, preceded the time of the intervention or even pregnancy.

Hypothetical pathogenic mechanism

Two are the possible mechanisms, which explain the possible link between periodontitis and preeclampsia. Firstly periodontitis, which is characterized by chronic inflammation of the periodontium, the supportive structure of the tooth, results in incidents of bacteremia and finally dissemination of bacteria to the foetoplacental unit. There they cause an ectopic infection and/or trigger an inflammatory reaction which elevates levels of inflammatory cytokines and mediators, which ultimately result in preeclampsia[22], probably by causing a shift in immune response, that causes failure of human trophoblast invasion and spiral artery remodeling. Secondly, cytokines and mediators produced by the inflamed periodontium enter the bloodstream through which they reach either the foetoplacental unit, where they enhance the accumulation of larger amounts of these mediators or the liver where they cause an inflammatory response with a production of CRP and fibrinogen[22,23,24]. The aforementioned cytokines and mediators eventually enter the foetoplacental unit and cause preeclampsia.

Evidence in the literature supporting the proposed mechanistic model

There is growing evidence in the literature, which support the proposed mechanistic model. Periodontitis (but also gingivitis and daily activities such as chewing and tooth brushing, however in less extent) causes episodes of bacteremia[25]. Today we know that bacteria exist in anatomic areas, which were thought to be sterile. Broad-range PCR can detect prokaryotic rDNA in samples, which were negative in culture. Examples are endocarditis, interstitial cystitis, endophthalmitis, meningitis and orthopedic samples[26]. Placenta harbors its own unique microbiome. Placenta microbiome resembles the most the microbiome of the gingival plaque, tongue and tonsils. By contrast, the proximal anatomic sites and potential contaminants during delivery of the placenta (stool and vagina) bore no evidence of similarity. This may be evidence of a hematogenous establishment of the placental microbiome [27]. Four main classes of dysregulation characterize preeclampsia. Abnormal trophoblast invasion of the placenta, anti-angiogenic responses (increase of sFLT1 & sEnd and decrease of PLGF), oxidative stress and inflammation (increase of IL-6, TNFα and decrease of IL-10), all of which may be caused by bacteria infection[19]. In in vitro studies periodontal pathogen microbe Porphyromonas gingivalis induces the apoptosis of human extravillous trophoblast derived HTR8 cells. Extravillous trophoblast cells play an important role in spiral artery remodeling[28,29]. Also periodontal pathogen Aggregatibacter actinomycetemcomitans LPS induce the apoptosis of human placental trophoblast cells[30]. In addition Porphyromonas gingivalis infection increased the placental Th1/Th2 cytokine ratio in mice[31], decreased the numbers of decidua $CD56^{bright}$ dNK and $CD56^{+}$ dNK cells[32] and increased the numbers of Th17 lymphocytes and decreased the numbers of Treg lymphocytes in plasma of human patients with periodontitis[33]. These changes have been observed in preeclampsia[31,32,32]. Periodontal pathogenic bacteria Porphyromonas gingivalis, Fusobacterium nucleatum, Treponema denticola, Prevotella intermedia and Aggregatibacter (Actinobacillus) actinomycetem-

comitans have been found in higher proportion in placenta of women with preeclampsia[34]. Also pregnant women with periodontitis have higher numbers of periodontal pathogenic bacteria in placenta[35].

In patients with periodontitis serum levels of IL-1β, IL-6, TNF-α and CRP are elevated[36,37]. These mediators are also elevated in preeclampsia[38]. It is proposed as mentioned above that these cytokines and mediators produced by the inflamed periodontium enter the bloodstream through which they reach either the foetoplacental unit, where they enhance the accumulation of larger amounts of these mediators or the liver where they cause an inflammatory response with a production of CRP and fibrinogen[22,23,24]. The aforementioned cytokines and mediators eventually enter the foetoplacental unit and cause preeclampsia by raising the topical levels of inflammatory cytokines and mediators and eventually cause an inflammatory reaction.

Genetic factors linking periodontitis to preeclampsia

Periodontitis and preeclampsia are both caused by a hyper inflammatory reaction of the immune system. The possible link between single nucleotide polymorphisms (SNPs) of IL1A, IL1B, IL1RN, IL6, IL10, vitamin D receptor (VDR) and COX-2 genes and periodontitis or preeclampsia manifestation has been researched in the literature. Polymorphisms IL1A-889T, IL1B-3953/4T, IL6-174G, IL10-592C, IL10-819C, IL10-1082G, VDR ApaI A and VDR TAqI T increase the risk for periodontitis. IL1RN+2018C has no association or decreases the risk of periodontitis and for COX-2-765 literature presents conflicting results[39,40,41,42,43,44,45,46,47,48,49,50,51]. In the same time polymorphisms

IL1A-889C, IL10-819C and IL1RN+2018C increase the risk for preeclampsia, polymorphisms IL1B-3953/4T and IL6-174G do not have any effect on the risk for preeclampsia, polymorphisms of COX-2 and VDR have not been studied yet and polymorphisms of IL10-592, IL10-1082 have had inconclusive results [52,53,54,55,56,57,58,59] (Table 1). In conclusion there could be a genetic linking factor between periodontitis and preeclampsia, especially regarding SNPs of IL10-592, IL10-819, IL10-1082 and COX-2 -765 but definitely more scientific data are needed in order to have solid evidence.

Multifactorial nature of preeclampsia and possible microbial etiology

Preeclampsia is believed to develop in two stages. In the first stage there is inadequate remodeling of

Table 1.

	PERIODONTITIS	PREECLAMPSIA
IL1A-889T(IL1A-889C)	↑ (↓)	↓ (↑)
IL1B-3953/4T	↑	X
IL6-174G(IL6-174C)	↑[a,c] / X[c]	↑[e]/X
IL10-592C(IL-10-592A)	↑ (↓)	↑(↓)/↓(↑)
IL10-819C	↑	↑
IL10-1082G(IL10-1082A)	↑(↓)/↓(↑)	X/↓(↑)
VDR ApaI A	↑	No evidence
VDR TaqI T	↑	No evidence
IL1RN+2018C	X/ ↓	No evidence
IL1RN rs315952C	X	↑
COX-2 -765C	X/ ↓/ ↑	↓

↑: increases risk, ↓: decreases risk, ✠: no association, **a**: aggressive periodontitis, **c**: chronic periodontitis, **e**: early onset preeclampsia

the spiral arteries in early gestation, which results in poor placental development. In the second stage, poor placental development results in ischemia/reperfusion injury and oxidative stress, maternal endothelial cell dysfunction and finally to the clinical manifestations of preeclampsia. However, poor placentation can be present without preeclampsia and preeclampsia can occur in pregnancies with neonates large for dates. It is proposed, that for the development of preeclampsia and instigation of stage two, maternal and placental factors modify the risk either by increasing maternal susceptibility or by increasing placental loading respectively. Maternal factors, which increase maternal susceptibility, are genetic susceptibility, obesity, advanced maternal age, maternal hypertension and pre-pregnancy endothelial damage. Placental factors, which increase placental loading, are increased placental volume, increased placental mass (e.g. twins) and severe uteroplacental insufficiency. In addition infection and/or inflammation can, according to Pennington et al, and Kell and Kenny, serve to lower the threshold for preeclampsia in cases of inadequate placentation.

As stated before, although the scientific research has not concluded yet regarding the etiology of preeclampsia, the dysregulations that accompany preeclampsia could be explained by microbial infection[19]. A systematic review of epidemiological studies in 2008 found that any bacterial or viral infection was associated with a two-fold higher risk of developing preeclampsia compared to women without infection[60]. A meta-analysis of 2008 found that urinary tract infection and periodontal disease during pregnancy were associated with an increased risk of preeclampsia[61]. Recent studies have associated infections with high-risk human papilloma virus, Chlamydia trachomatis, periodontitis, Chlamydia pneumoniae and cytomegalovirus IgG seropositivity with preeclampsia. On the other hand, some studies have not found an association of preeclampsia with infection with cytomegalovirus, Chlamydia pneumonia, Herpes simplex virus 2, or respiratory tract infection. HBsAg carriage has even been found to be associated with a reduced incidence of preeclampsia[62].

Although no association has been found between Toxoplasma gondii and preeclampsia[62], spiramycin, which is an antibiotic prescribed for treating Toxoplasma gondii infection, led to a decrease in preeclampsia incidence

(0, 5% incidence of preeclampsia in the group who were treated with spiramycin and 5, 2% incidence of preeclampsia in the control group; odds ratio =0.092 95% confidence interval 0.021, 0.399; $P < 0.001$)[63].Interestingly, spiramycin is also effective against periodontal pathogens[64].

Pregnancy, inflammation of periodontal tissues, cytokine and hormonal changes during pregnancy

Immune system suppression and high levels of progesterone favor certain microbe growth in periodontium. This results in the well-established pregnancy induced gingivitis in second trimester (13-24 weeks of gestation) and third trimester (25-36 weeks of gestation)[65]. Inflammation and sex hormones result in increased vascular permeability and alter the effectiveness of the epithelial barrier to the oral microbiota[29]. This theoretically could enhance incidence of bacteremia. In mid third trimester (~32 weeks of gestation) although progesterone levels remain high, immune system suppression weakens, because IL-10 and IFN-γ levels rise again[66]. Interestingly, preeclampsia occurs after 20th week of gestation and is more common after 32th week of gestation[67].

Conclusion

There is growing evidence about a possible link between periodontitis and preeclampsia. The evidence which support an association derive from

observational studies, studies in animal models and in vitro studies. Experimental studies and substantial number of studies conducted in developed countries do not support such evidence. The cause of this discrepancy may lie in differences in periodontitis' definition, genetic factors, differences in sample size, and differences in studies' design. On the other hand, the cause may lie in the time microbes react with the host's immune system. Preeclampsia may be caused by periodontal bacteria, independently of the clinical parameters of periodontitis. Periodontal bacteria may also have colonized placenta and foetoplacental unit by bacteremia caused by other pathways than inflammation of periodontal pockets such as gingivitis and pericoronitis. This may explain the number of studies, which do not support an association in developed countries, in which there is optimal access to dental care. In addition, periodontitis can be divided in to two pathologic entities, chronic periodontics and aggressive periodontitis, in which the genetic background differs. Also preeclampsia is divided in early on-set preeclampsia and late on-set preeclampsia. In most of the studies these parameters were not taken into account. In addition in most of the studies third molars are not taken into account in the periodontitis assessment, however the third molar region might host deep pockets, which act a reservoir of anaerobic microbes. In conclusion, more studies with different design are needed in order to cast light in the relationship of periodontitis, periodontal bacteria and preeclampsia.

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