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Periodontitis and pregnancy complications

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SUMMARY

The paper presents the present state of knowledge regarding the mechanisms associating chronic periodontitis with adverse pregnancy outcomes, with the emphasis on preterm low birth weight.
Key words: periodontitis; pregnancy; preterm birth

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INTRODUCTION

The impact of periodontitis on general health has been a subject of numerous studies. Even though a direct relationship cannot be proven in an unequivocal way, it is very important to consider any type of oral inflammation as a potential hazard for the general health and a risk factor of, for instance, preterm birth (PTB), low birth weight (LBW), and pre-eclampsia. Periodontal diseases belong to the most common inflammatory conditions in humans and, as diabetes, are currently classed as social diseases. Epidemiological studies have revealed that only 1% of Polish adults aged 35–44 do not have any periodontal symptoms, and over 16% of people in this group are diagnosed with advanced periodontitis [1]. The dramatic epidemiological situation deteriorates even more with the population age.

A large majority of periodontal diseases are bacterial inflammatory conditions that initially involve the gingival tissue only. When local and systemic conditions are adequate, the connective tissue barrier is disturbed and biofilm starts migrating to the apex, which is accompanied by destruction of periodontal tissues. This infection causes increased inflammatory response of the organism, during which a non-specific component of the immune response amplifies the connective tissue and bone destruction process. As a result, chronic infection and inflammation develop and may persist for years. The first symptoms are typical of gingivitis and include: periodontal pockets, bleeding, red, swollen and soft gums, and bad breath. The symptoms that follow are specific for periodontitis. They include: periodontal pockets, prolonged clinical tooth crowns, moving and loosened teeth, and finally tooth loss.

Periodontologists have been interested in the impact of periodontitis on the general patient's state for over 20 years. It is estimated that in advanced periodontitis the involved tissue surface ranges from 8 to 20 cm2 [2]. Due to bleeding accompanying each mechanical tissue injury (e.g. when brushing teeth or eating hard

foods), these patients have almost constant bacteremia with elevated circulating levels of immunocompetent factors. Bacteria that participate in periodontal inflammation activate the patient's immune system, which presents mostly as increased levels of inflammatory mediators, such as IL-1, IL-6 and TNF-α, and CRP. The available literature indicates that this activation may play an active role or be a risk factor of atherosclerosis, stroke, cardiovascular diseases, preterm births, low birth weight, cancer, asthma, and diabetes [3].

AIM

The aim of the paper was to present available study results regarding a relationship between periodontal diseases and adverse pregnancy outcomes (APOs), with particular attention paid to the impact of periodontitis treatment and to guidelines for periodontitis management during pregnancy.

PERIODONTAL DISEASES AND ADVERSE PREGNANCY OUTCOMES – A LITERATURE REVIEW

A relationship between periodontitis and pregnancy complications was already investigated in the mid-1990s. The study conducted by professor Steven Offenbacher in a group of 124 pregnant women was a pioneering and breakthrough work. It revealed that the periodontal condition was significantly worse in 93 patients with preterm low birth weight (defined as birth before week 37 of gestation with birth weight below 2,500 grams) compared to women with normal pregnancies. The logistic regression analysis and the inclusion of the remaining risk factors helped estimate the odds ratio of preterm low birth weight (PLBW) in women with periodontitis at 7.9 [4]. This significant conclusion, suggestive of a very strong relationship between the two conditions, has become an incentive for various research projects. A meta-analysis conducted by Vergnes and Sixou has shown that the risk of preterm birth almost triples in women with periodontitis [5]. Similar studies on the outcomes of periodontal treatment that largely reduces periodontal inflammation have also revealed a positive effect on the reduction of the number of preterm births in the studied populations [6,7]. However, not all studies yield such outcomes. In light of discrepancies, it is almost certain that if there is a cause and effect relationship between periodontitis and PLBW, one or several phenomena described below really do take place:

- interaction between the two conditions is negligent;
- the relationship is limited to certain subtypes of the disease entities;
- the relationship between the two conditions is dependent on individual and environmental variables which must also be taken into account.

Both periodontal disease and PLBW are conditions with various risk factors involved. Table 1 compares these factors and indicates which of them are common for the two entities. As data from the table show, a number of environmental factors are common for both entities (Tab. 1). This might be the cause of the discrepancies in epidemiological studies as the coexistence of two diseases not necessarily attests to the existence of a cause and effect relationship between them. Moreover, studies aiming to demonstrate such a relationship must take into account the influence of these factors during the recruitment stage, which makes this process much more difficult. It must be noted, however, that the order of the factors listed in the table is conventional. Smoking is believed to be the most relevant risk factor of periodontal disease [8], while the most important element affecting preterm birth is, according to gynecologists, a history of PLBW [9].

Scientific workshops organized in 2012 in Segovia, Spain, for two largest periodontal organizations in the world, namely the European Federation of Periodontology and American Academy of Periodontology, were entirely devoted to periodontal medicine. One of the task forces prepared a report on the relationship of the periodontium with adverse pregnancy outcomes [10]. One of the conclusions was the identification of two possible mechanisms by which periodontal disease may contribute to adverse pregnancy outcomes. One of them was direct, in which periodontal pathogens reach the placenta, and the other was indirect, involving inflammatory mediators [10].

In the direct pathway, bacteria penetrate the periodontal tissues either by damaging the internal or the junctional epithelium, from where they reach the fetal–placental unit. A pioneering study addressing these issues was conducted in 1994 by professor Offenbacher's team. It has become the premise for the above mentioned report. In a series of studies in pregnant

female hamsters, the authors have shown a dose-dependent fetal deformity or resorption after intravenous administration of *Escherichia coli* and *Porphyromonas gingivalis* lipopolysaccharide on the 8th day of gestation [11]. In another study, the authors have administered live or killed *Porphyromonas gingivalis* subcutaneously into a previously prepared site. Apart from fetal viability, they have also evaluated the level of reactive inflammatory mediators, such as prostaglandin E2 (PGE2) and tumor necrosis factor alpha (TNF-α), and their relationship with adverse pregnancy outcomes. They have observed a significantly increased level of the studied cytokines and a correlation of their circulating level with fetal survival and birth weight [12]. Han et al. have injected *Fusobacterium nucleatum* intravenously to pregnant mice, and noted bacterial infiltration on the vascular endothelium and greater frequency of preterm births and miscarriages [13]. Another study has shown that chronic exposure of pregnant rabbits to *Porphyromonas ginigvalis* results in bacterial penetration into the placenta and in fetal exposure [14].

The first studies on the potential presence of periodontal bacteria in the human placenta were carried out in 1998 by Hill. He found that *Fusobacterium nucleatum,* which belongs to the orange bacterial complex in the dental biofilm, was the most frequently isolated bacterium in women with preterm birth. Species and subspecies of *Fusobacteriaceae* isolated from the amniotic fluid were the closest to those indigenous to the oral cavity [15]. Han et al. have reached similar conclusions from their study on the amniotic fluid of women with a PLBW episode, using polymerase chain reaction. In one of the patients, *Bergeyella* clone isolated from the amniotic fluid was identical to that present in her subgingival biofilm. Interestingly, this bacterium was not isolated from the patient's genitourinary tract. This suggested the oral origin of the microorganism and its transmission, probably hematogenous, to the fetal–placental unit [16]. In 2011, French authors performed a study among pregnant patients with preterm premature rupture of membranes. Samples of saliva and subgingival biofilm were collected from three volunteers with *Fusobacterium nucleatum* detected in the amniotic fluid and from their partners. In one of the patients and in her partners, bacterial strains isolated from the placenta and oral cavity were identical [17]. Gonzales-Marin et al. have evaluated a fragment of *Fusobacterium nucleatum* genome, and demonstrated that the neonatal gastric aspirate and maternal oral cavity contained the same bacterial cell lines. They also confirmed the fact that these bacteria were not from the vaginal origin, which was supported by sample evaluation [18].

In the second pathway mentioned above, PLBW is potentially caused by circulating immunocompetent substances produced in response to periodontal inflammation. The level of acute-phase proteins has been documented to increase in periodontitis [19]. A team of professor Konopka have investigated the levels of interleukin 1 and PGE2 in 84 women with a PLBW episode and in 44 controls with uncomplicated pregnancy. Primiparous women with preterm birth (39% of the studied group) had increased circulating PGE2 levels. More-

Tab. 1. A comparison of risk factors of periodontal disease and preterm low birth weight (PLBW)

Chronic periodontitis	PLBW
Smoking	
Diabetes	
Genetic factor	
Race	
Age	
Stress	
Obesity	
Socioeconomic status	
Pocket microbiological composition	History of PLBW
Immunocompromising diseases	Pre-eclampsia
Gender	Genital tract infection
Osteoporosis	Alcoholism

over, in primiparous women older than 28 years, the risk of PLBW increased 4-fold depending on periodontitis [20]. Pozo et al. have evaluated 42 pregnant women with periodontitis and observed significantly higher placental levels of cyclooxygenase-2 and endothelial growth factor receptor. Elevated cyclooxygenase-2 levels were correlated with a history of PLBW [21].

Some epidemiological studies support the idea that periodontal disease in pregnant women is also linked with pre-eclampsia, characterized by hypertension and proteinuria [22,23]. A consensus reached by the European Federation of Periodontology (EFP) and American Academy of Periodontology (AAP) states that pre-eclampsia is associated with the susceptibility of women to periodontal disease [10]. Other pregnancy complications and related neonatal hospitalizations at neonatal intensive care units have been found to be associated with fetal exposure to maternal periodontal pathogens [24].

A subgroup of 411 children aged 24–28 months born by mothers undergoing gynecological and periodontal treatment has been assessed in randomized clinical trials. The study has revealed that non-surgical treatment of periodontal disease during pregnancy is not associated with future cognitive, motor and language development. However, children of mothers with a significant improvement of periodontal disease performed much better in cognitive tests [25]. In the same year, another study was performed among 99 pregnant women with concomitant periodontal disease in Northern Ireland. Each included patient had at least 4 pockets deeper than 4 mm and 4 sites with lost connective tissue junction greater than 2 mm. The group was divided into 2 subgroups. Women from the first group had SRP performed, received proper instructions and had the clinical tooth crowns polished. Women from the second group received instructions and had supragingival plaque removed, while further treatment was conducted after delivery (controls). All treatments were completed before week 24 of gestation. The study showed that despite statistically significant differences and improvement of the periodontal condition, there were no significant differences between the groups in terms of the effect of treatment on preterm birth and low birth weight in both the tested and control groups [26].

The available studies do not provide unambiguous evidence for an influence of non-surgical periodontal disease therapy on adverse pregnancy outcomes, such as pre-eclampsia, preterm birth, and low birth weight. Positive effects of this therapy have been noted only in high-risk women. Discrepancies in the results concerning non-surgical treatment may result from different methodology and assumed criteria, such as degree of disease advancement, timing of the therapy (the later the therapy is performed, the higher the risk of bacterial penetration to the blood and then to the placenta and fetus), and a standard of performed therapy. Moreover, it is potentially possible that other risk factors, such as smoking, low socioeconomic status, obesity or diabetes, may disturb the effects of periodontal therapy on preterm birth or low birth weight. The ongoing debate in this area does not change the attitude of the authors of the present study that treatment of pregnant patients with concomitant periodontal disease is necessary, as supported by clinical trials, and that concerns of both doctors and patients are not well-grounded.

Data of the European Federation of Periodontology (EEP) unambiguously suggest that periodontal disease should ideally be treated in the 2nd trimester of gestation. Procedures such as SRP and other treatments requiring local anesthesia, with avoidance of vasoconstrictors (noradrenaline), can be safely performed, particularly in patients with pre-eclampsia or chronic hypertension. If necessary, diagnostic RVG can be conducted after prior patient protection. If antibiotic therapy is required, metronidazole and amoxicillin (but no tetracycline) can be administered, and when analgesics are needed, paracetamol should be prescribed.

CONCLUSION

The literature analysis clearly suggests that there is no direct evidence that periodontal therapy has an effect on adverse pregnancy outcomes. It is necessary to perform further clinical trials with proper methodology and generally accepted threshold values as well as inclusion and exclusion criteria, in which other risk factors that could bias the study results would be taken into account. These studies should be based on microbiological and serological tests so that their outcomes could be comparable.

When evaluating effects of periodontal treatment on pregnancy outcomes, its timing should be considered to guarantee the positive effect on the course of pregnancy. It seems

sensible to conduct additional randomized clinical trials in which periodontal therapy would be implemented prior to a planned pregnancy. Treatment of periodontal inflammation and a decrease in the counts of bacteria would reduce the risk of adverse pregnancy outcomes. Women in the pre-conception period would be more eager to accept treatment without concerns about the course of pregnancy, and the following maintenance therapy during pregnancy would be a natural continuation of the previous therapy.

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