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Periodontitis as a potential risk factor for premature delivery

Ana Turcu-Duminică[1], Anca Silvia Dumitriu[2], Stana Paunica[2], Corina Gică[1], Radu Botezatu[1,3], Nicolae Gică[1,3*], Gheorghe Peltecu[1,3], Anca Maria Panaitescu[1,3]

[1]*Filantropia Clinical Hospital, Department of Obstetrics and Gynecology, Bucharest, Romania*
[2]*Carol Davila University of Medicine and Pharmacy, Department of Periodontal Disease, Bucharest, Romania*
[3]*Carol Davila University of Medicine and Pharmacy, Department of Obstetrics and Gynecology, Bucharest, Romania*
[#] *All authors have contributed equally as first author*

ABSTRACT

Pregnancy is a particular period of time for a woman, so that it is important to accurately determine the impact of adjacent pathologies on the natural evolution of the nine months of pregnancy. Although there is still much to debate on the association between periodontal disease and pregnancy, the conclusion seems to remain the same: untreated periodontal pathology in pregnancy could have adverse consequences such as premature birth or low birth weight fetuses. Periodontopathies are introduced as risk factors, the novelty of the subject being the association between untreated periodontal pathology and the evolution of pregnancy. The affected periodontal tissue has the potential of releasing microorganisms that could colonize the placenta, ultimately having adverse consequences on the evolution of pregnancy, consequences such as premature birth or inadequate birth weight. The purpose of this review is to assess the association between periodontal disease and the negative consequences on pregnancy. Using databases such as PubMed, more than 1,500 articles were screened, including systematic reviews, case-control studies and prospective cohort studies assessing the association between periodontitis and pregnancy. Only 54 from the above-mentioned papers were included in the final review.

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* **Corresponding author:**

Nicolae Gică,

Filantropia Clinical Hospital, Department of Obstetrics and Gynecology, Bucharest, Romania
E-mail: gica.nicolae@umfcd.ro

Introduction

Preterm birth remains one of the main concerns of public health management with significant psychological and financial connotations, the scientific community never ceasing to explore the possible outcome of infections during pregnancy. Preterm birth is defined as delivery before 37 weeks of gestation, the limit for extreme preterm birth being set by the World Health Organization at 28 weeks of gestation [1]. In December 2016, Liu et al. concluded that the objective to scale down child mortality under five years of age by two thirds was not accomplished. It did not only happen in the United States of America, but throughout the entire world [2,3]. Preterm births count for over 15 million births annually all around the globe, more than half of them taking place in Africa or in South Asia, counting-up to 18% of live births, with high rates in Pakistan, Indonesia, and Mauritania, among others [1]. Corroborated with these results, along with those from 2019, UNICEF reported that the mortality rate in Romania was 7 per 1,000 live births [4].

Up to 30% of the preterm births are associated with indications such as preeclampsia or intrauterine growth restriction, while impromptu labor is described as the main cause of premature birth [5]. There is still a long way to understand the process that stands behind preterm delivery, different pathways acting either on an individual or combined level [6]. An extreme preterm birth infant is prone to develop neurological impairments, including sensory, cognitive or motor disabilities as it has been shown in a review published by Rogers and Hintz [7]. There are risk factors that contribute to preterm delivery, such as the parturient's age, race or mundane habits, among others, as they are presented in Table 1 [8]. Many states around the globe have implemented health policies in order to identify women with associated risk factors and they do not only offer healthy guidance, but also psychological support [9], with the objective of reducing perinatal

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morbidity rates through specific treatments such as tocolysis, corticotherapy or antibiotic therapy, among others [10].

Although more than 25 years have passed since Offenbacher et al. studied the association between parodontitis and pregnancy, it still continues to be a present-day problem factor for risk pregnancies. Moreover, several studies have demonstrated that periodontitis has a systemic echo, not only being associated with injurious pregnancy consequences, but also inducing an inflammatory environment and thus participating in the process of atherosclerosis, cardiovascular disorders, aggravation of diabetes or Alzheimer's disease [11]. The ethnic characteristics were brought into discussion, as it was noted that South Asia has a high prevalence of small for gestational age babies, various factors being involved, such as teenager parturition, dietary deficiency before pregnancy, underweight expectant mothers or constitutionally short women [12].

Preterm birth and growth restriction infants could be the result of preeclampsia, a serious pregnancy disorder, which develops after 20 weeks of pregnancy in previously normal blood pressure women, having the potential of altering all organ systems, especially the liver and the kidneys, as a consequence of maladjusted maternal endothelium, a component of an excessive systemic inflammatory feedback [13].

Table 1. Preterm delivery risk factors [8]
Extreme parturient's age: low or high
Ethnic group: especially black
Social factors
Mundane habits: - alcohol, - drugs, - eating disorders.
Obstetrical record: - previous pregnancy, - previous preterm delivery.
Hereditary records
Metabolic syndrome

Discussions

According to Zenclussen, during pregnancy, at the maternal-fetal interface, there are minor histocompatibility antigens, while maternal T cells acknowledge paternal elements in the fetal units and shield them [14]. A Th2 immune response characterizes pregnancy, progesterone and prostaglandin E balancing Th1-Th2 permutation, while Th17 and regulatory T-cells (Treg) enact as a decisive part in Th2 cytokine management and diminish decidual natural killer unit's activity [15]. On the other hand, when inflammation at the maternal-fetal level eventuates, the most prevalent model involved is Th1 cytokine archetype [16]. The fertilized egg might be dismissed by the maternal body via a coagulation pathway which results in vasculitis, a Th1 feedback that triggers decidual macrophages to discharge nitric oxide and TNF-α at a high level [16]. There are numerous pathogens that can induce intrauterine infection, leading to adverse pregnancy outcomes, from bacteria such as Group B Streptococcus, Listeria monocytogenes, Chlamydia trachomatis, Neisseria gonorrhea to viruses, such as those involved in TORCH or parasites such as Plasmodium falciparum or vivax, among others [17]. Adams noted that preterm birth is associated with intrauterine infection, with consequences on the fetal lungs and brain as a result of preterm labor [17]. Although there are different pathways that result in intrauterine infections, the ascending pathway from the vagina to the uterus is the most prevalent one, Adams also remarking that gram-negative pathogens such as Escherichia coli or Gardnerella vaginalis, gram-positive such as Group B Streptococcus and anaerobic bacteria such as Mycoplasma hominis are commonly determined in the amniotic fluid or the fetal membranes, corroborated with the results that show that rapid inter-organ passage is endorsed by the carbon particles influx from the vulva into the abdominopelvic cavity in a period of half an hour in the non-gravida [17].

The conjecture of pregnancy and the periodontal disease

Occasionally, the histopathological examination of the preterm infant's placenta disclosed numerous anaerobic pathogenic microorganisms, thus raising a new debate: could these microorganisms have a distinctive source other than the urogenital tract? In 2014, in a study on 320 subjects, Aagaard et al. identified a particular placental microbiome consisting of *Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes,* and *Fusobacteria phyla*, with similarities to the human oral microbiota [18]. It was hypothesized that the fetal-placental unit could be contaminated with the bacteria aggregated in the infected periodontal tissue, thus contributing to low-weight or premature birth [19].

Periodontitis defines the cessation of juxtaposition between the tooth crown and the periodontal tissue, resulting in a persistent damage in the clinical attachment level (CAL) [20]. An enlarged periodontal tissue unveils a significant inflammation; the depth of the periodontal pocket being assessed by the probing depth (PD) [20]. The clinical attachment level and the probing depth values are important factors in assessing periodontitis and they could contribute to injurious pregnancy consequences. On the other hand, defined as a reversible pathology and without contributing to negative pregnancy consequences,

gingivitis during pregnancy represents the inflammation of the gingivae generated by augmented levels of estrogens and paired with microorganism colonization such as Bacteroides intermedius [20]. In a plausible affiliation of causality, as vaginal infections during pregnancy could lead to negative events, such as preterm delivery, it was hypothesized that periodontitis and vaginal infection have a common component: the modification of local flora with anaerobic microorganisms overspread through the hematogenous pathway, as shown in Table 2, the two key events generating the entire process being infection and inflammation [20].

Table 2. *Vaginal infection and periodontitis characteristics* [20]

	Vaginal infection	**Periodontitis**
Area	Vagina	Periodontal cavity
Natural microorganisms	Lactobacills spp	-
Pathogenic microorganisms	Gardnerella vaginalis (facultative anaerobic) Mycoplasma hominis (without Gram stain)	Porphyromonas gingivalis (anaerobic) Fusobacterium nucleatum
Ethnic group	Especially black	-

Pathogens that colonize supra- and subgingival tissue lead to inflammation, causing periodontitis, various forms being described: chronic, when the loss of periodontal tissue is gradual and unceasing; aggressive, when the periodontal ligament and the alveolar bone are affected in an accelerated and peremptory mode; generalized, when it alters nearly all the teeth; and localized, when it is assigned to a faction of them [21 - 24]. The pathognomonic signs of periodontitis are periodontal pockets, correlated with gingival bleeding or retraction, tooth mobility, halitosis, abscess, bone loss or spontaneous tooth loss. According to Tonneti, periodontitis is the result of either excessive virulent species found in the oral cavity or the consequence of their action in a vulnerable host [25]. The microbial ecosystem associated with the subgingival plaque was investigated by Socransky on 185 subjects with or without periodontitis, identifying Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia as key factors in chronic periodontitis [26], while Faveri associated the aggressive generalized or localized form either with P. gingivalis, T.denticola, T. Forsythia or with the facultative Gram negative Aggregatibacter actinomycetemcomitans, particularly serotype b or c [27]. In an explorative cross-sectional study conducted by Cairo et al., inflammatory substances released in the serum were alike in different patterns of periodontitis, while in terms of cytokines, the aggressive periodontitis displayed protein-1-a (MIP-1a), IFN-g-induced protein 10 (IP-10) and its receptors CCR5 and CXCR and chronic periodontitis expressed monocyte chemotactic protein 1 (MCP-1) and its receptor CCR4 [28, 29]. Pro-inflammatory cytokine IL-17 which promotes prostaglandin E2 (PGE2) and bone loss is prevalent in gingival crevicular fluid (GCF) of aggressive periodontitis, while IL-11, an anti-inflammatory substance which promotes osteoblastic differentiation and bone formation is frequently found in gingival crevicular fluid (GCF) of chronic periodontitis [30 - 32].

During pregnancy, there is an increased gingival inflammation, prevailing in 36–100% of pregnant women, high levels of progesterone having the potential of inducing P. Gingivalis development [33]. Preterm birth was associated with periodontal microorganisms and inadequate maternal IgG antibody feedback to periodontal microorganisms throughout parturiency [34]. Also, during pregnancy, there is an impressive alteration in the visceral ecosystem, better observed in the third trimester, with an enhancement of Proteobacteria and Actinobacteria [35].

Oral microorganisms and their feasible extra-oral effect

Developed in the first weeks of pregnancy, the placenta represents an immune and endocrine unit that protects the fetus throughout pregnancy, any variation in the placental tissue having the potential of altering the pregnancy outcome [36]. Numerous clinical studies and review papers addressed the association between periodontitis and pregnancy. In a study conducted by Blanc et al. on 57 pregnant women, with or without periodontitis and using Nested-PCR, the placentas were assessed: 63% resulted from preterm births and 37% from term births [37]. The results showed that periodontal circumstances influence placental colonization with oral microorganisms and in the periodontitis group with preterm or low weigh births Fusobacterium nucleatum was more prevalent ($P = 0.033$), while Porphyromonas gingivalis, Treponema denticola or Prevotella intermedia were not discovered [37]. Additionally, a prospective study that evaluated the relationship between oral health and small-for-gestational-age infants in a group of 1,017 pregnant women concluded that moderate or severe periodontal condition is related to small-for-gestational-age infant births [38]. This axiom is corroborated with findings that show that several microorganisms were commonly discovered in neonatal gastric aspirates and in maternal gastrointestinal or oral cavity [39]. Among the above-mentioned microorganisms, Porphyromonas gingivalis antigens were detected in placental tissues: placental syncytiotrophoblasts, chorionic

trophoblasts, decidual cells, amniotic epithelial cells and vascular cells, having the potential to induce preterm birth as noted by Katz [40] and Fusobacterium nucleatum which has been identified in placental and fetal tissues, including amniotic fluid, cord blood, fetal membranes and neonatal gastric aspirates, whose origin corresponds to the maternal or paternal subgingival tissues, which could lead to preterm birth, stillbirth, neonatal sepsis or hypertensive affliction in parturiency [41].

The vaginal microbiota, periodontal disease and preterm labor

Throughout lifetime, the vaginal microbiota has the potential to change, being influenced by the hormonal variation during the menstrual cycle or menopause or between different ethnic groups. In healthy women, in a proportion of nearly 70%, the vaginal microbiota, which exerts a protective local action, primarily consists of Lactobacillus species with the determining role of inhibiting the expansion of repellent external pathogens [42]. Throughout pregnancy, the vaginal microbiota might experience an increase in microorganisms such as Lactobacillus, Clostridiales, Bacterodies or Actinomycetales, without leading to adverse pregnancy outcomes [43]. There are three approaches in relation with preterm birth and periodontal disease: microorganism dissemination, release of inflammatory mediators and fetal-maternal immune feedback to dental microorganism invasion [44]. Microorganism dissemination could originate in the lower genital tract or in the oral cavity via a hematogenous pathway, contaminating the amniotic fluid and leading to chorioamnionitis [45]. In extreme cases, a considerable exchange area of 15 to 20 cm2 forms between microorganisms and the bloodstream, releasing considerable amounts of bacteria and hence leading to cytokine and metalloproteases production, the activation of neutrophils and triggering preterm birth [46]. As a result of periodontitis, inflammatory mediators such as PGE-2, TNF-α, IL-6 or IL-1β are released, Dörtbudak noting that parturients with high amniotic fluid levels of PGE2, IL-6 and IL-8 in the 15–20 weeks of gestation and diagnosed with periodontitis are prone to premature birth [47]. Furthermore, several studies have evaluated the fetal-maternal immune feedback to the invasion of dental microorganisms. Boggess concluded that conceptus interaction with oral microorganisms confirmed by an IgM feedback is correlated with preterm birth, 35.2% produced IgM in response to one oral bacterium, while 26.6% were IgM positive in response to more than one oral bacterium [48]. Current observations state that preterm labor could be a consequence of placental ischemia, hemorrhage or fetal stress apart from inflammation and infection, various markers being described in women diagnosed with periodontitis and experiencing preterm labor: phospholipase A2 which elaborates prostaglandines, cytokines as a result of infection leading to preterm labor or spontaneous abortion, endotoxins which induce uterine contractions and fetal adrenal glands which produce high levels of cortisone, all of the above-mentioned inducing uterine contractions, membrane rupture, alterations in the cervical structure and eventually, preterm delivery [49].

Periodontal treatment and the result on preterm birth incidence

The already existing data indicate the adverse outcomes on pregnancy such as premature delivery and low birth weight, which could be associated with periodontitis. Auxiliary studies were carried out in order to determine whether the periodontal treatment could reduce the incidence of negative pregnancy events, unluckily with inconsistent results in connection with the diversity of the considered subjects and various risk factors such as racial features, tobacco use, socioeconomic status or periodontal disease description [50]. Furthermore, periodontal post-therapeutic effects could be altered contingent upon the nature of periodontal care, without neglecting drawback factors such as thin therapeutic window or acute periodontitis with rapid progression [50]. A pilot study conducted by Kaur assessed the effect of non-surgical treatment, health education and counseling of the pregnant women diagnosed with gingivitis, the results showing that the clinical signs of gingival inflammation and the levels of TNF-α and IL-1β in gingival crevicular fluid diminished, but being a vulnerable pilot study, results are prone to circumspect analysis [51]. A systematic review and meta-analysis of randomized controlled trials concluded that scaling and root planning managed to reduce the risk of preterm delivery only in the high-risk preterm delivery group [52]. A study conducted on 400 pregnant women in Chile concluded that the non-surgical treatment of periodontitis reduced low-weight births and premature delivery from 10.11% in the control subjects (19/188) (odds ratio [OR] 5.49, 95% confidence interval [CI] 1.65 to 18.22, P= 0.001) to 1.84% (3/163) in the test women, with the mention that the experimental subjects were treated before 28 weeks of gestation, while the control subjects were treated after delivery [53]. Another factor worth mentioning is the opportune week of gestation in which periodontal treatment should be performed in order to influence pregnancy outcomes. Offenbacher reported that the risk of preterm delivery was reduced by 3.8 times if periodontal treatment was given during the second trimester of pregnancy [54], but it remains still effortful to evaluate all the variables involved.

Conclusions

Subsequent pathologies have the potential of influencing the natural evolution of a pregnancy, especially in the last trimester, with preterm birth or low weigh birth infants as possible negative consequences on the

pregnancy. The latest studies continue to debate the possible association between periodontitis and the adverse pregnancy outcomes, but indubitably with incomplete data due to other variables involved. The implementation of health care programs is crucial for the identification of women with associated risk factors in order to detect periodontitis early and to properly treat it. Understanding the mechanisms involved in periodontitis is essential in providing the means for future guidelines. Furthermore, health care providers, both obstetricians and periodontists should collaborate for the benefit of the future mother and the fetus, with additionally scientific evidence needed to be taken into account.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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