Preterm birth and oral infections interplay

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Abstract

Preterm delivery associated with low birth weight is one of the adverse outcomes of pregnancy. Oral infections, mainly the periodontal diseases, is claimed to be a risk factor. The Gram-negative anaerobic infection from gingival pockets, which is capable to induce transitory bacteremia, has the potential to pathogenically influence the maternal-fetal membranes and enhance previous inflammation of women's genitourinary tract. The incidence of preterm low birth weight may depend on the progress of periodontal disease. In addition to study design, the right definition of pregnancy outcomes and chronic gingival inflammation seem to be the pivotal issues that govern the assessment of association between preterm birth and periodontal disease, as contributor of adverse effects in pregnancy.

Keywords: *pregnancy, oral infections, preterm birth*

Rezumat

Prematuritatea și greutatea scăzută la naștere sunt unele din complicațiile frecvente ale sarcinilor. Infecțiile orale, în special bolile parodontale, reprezintă un factor de risc. Infecția anaerobă Gram-negativă din spațiile gingivale, care este capabilă să inducă bacteriemie tranzitorie, are potențialul de a influența patogeneza membranelor materno-fetale și de a spori inflamația tractului genitourinar al femeilor. Incidența greutății scăzute la naștere poate depinde de evoluția bolii parodontale. Din rezultatele studiului se poate observa că inflamația gingivală cronică pare a fi o problemă esențială care determină evaluarea asocierii dintre nașterea prematură și boala parodontală, contribuind la efectele adverse în timpul sarcinii.

Cuvinte-cheie: *sarcină, infecții orale, naștere prematură*

Submission date: 27.01.2019
Acceptance date: 15.04.2019

Rolul infecțiilor orale în nașterea prematură

Suggested citation for this article: *Iliescu AA, Perlea P, Earar K, Gheorghiu IM, Iliescu MG, Iliescu A, Mitran M. Preterm birth and oral infections interplay. Ginecologia.ro. 2019;24(2):38-41.*

Introduction

During pregnancy, the women experience a significant impact of steroid hormones. By modulating the periodontal tissue turnover and vascular dynamics based on growth factors signaling pathways, the fluctuant level of estrogen and progesterone facilitates the likelihood of increased local inflammation. The interaction of elevated estradiol, estriol and progesterone secretion with inflammatory mediators worsens the initial gingival inflammation induced by bacterial biofilms and results in pregnancy gingivitis[1].

The decreased keratinization of gingival mucosa simultaneously with the increase of capillary permeability and tissue glycogen suppress the immune response, deteriorating the efficiency of antimicrobial defense. Since the prevalence of pregnancy gingivitis ranges between 35% and 100%, it is not surprising that this local inflammatory condition might be implicated in a bidirectional causal relationship, with adverse pregnancy outcomes[1,2].

The oral infections, mainly marginal periodontal disease, are suspected to be potential risk factors for low birth weight (LBW) of an infant and preterm birth (PTB)[3,4]. Commonly, LBW is defined as an infant weight under 2500 g, and PTB as a birth earlier than 37 weeks of gestation[5,6].

PTB or its more comprehensive alternative set phrase, preterm low birth weight (PTLBW), is considered a major negative pregnancy outcome that results in a serious public health dilemma not only in the third world countries as, despite of various prevention efforts, this challenge is not yet under control[3-5].

It is worthy to note that in the last years the chronic apical periodontitis, though to a lesser extent, is also incriminate as a plausible generating condition of PTLBW[7].

A variety of epidemiological studies give details about the deterioration of periodontal inflammatory status during pregnancy progress and, conversely, the significant relationship between the adverse effects of oral infections both in marginal and apical periodontitis, which influence the pregnancy outcome[8-10]. However, for the time being, due to the heterogeneity and limitations of research methodology, the results on the topic of association between oral infections and adverse pregnancy outcomes are still rather controversial[5].

PTLBW etiology

Nowadays in industrialized countries occurs an overall significant turn down of infant mortality. However, all over the world, the rate of PTLBW newborns is practically unchanged. Actually, in high developed countries, the preterm delivery is responsible for about 10% of births, two-thirds out of them being spontaneous PTB[2,3].

Despite the still high ratio of unknown PTLBW etiology, undoubtedly the infection is gaining an increasing place as contributory factor[2,3,11,12]. It seems that pivotal are genitourinary tract infections, more exactly bacterial vaginosis (BV), which is found in 10% of pregnant women, and chorioamnionitits. Though it is mostly induced by Gram-negative bacteria, basically BV is characterized by initial lactobacillus flora decline simultaneously with proliferation of anaerobes and facultative bacteria species, such as *Gardnerella vaginalis*, *Bacteroides ureolyticus*, *Prevotella bivia* and *Mobiluncus curtsii*[13].

Passing through the cervix, these bacteria elicit a maternal-fetal membranes inflammation, namely chorioamnionitis. Gradually, the infection comes up to amniotic fluid and placental tissues. Lastly, the inflammation/infection of uterus and maternal-fetal membranes results in preterm delivery of infant[2].

Similar to BV, the periodontal disease has also the potential to pathogenically influence the maternal-fetal membranes since it is a Gram-negative anaerobic infection capable to induce transitory bacteremia. Any dental infection, either marginal periodontal disease or chronic apical periodontitis, might induce Gram-negative bacteremia, and results in enhancing previous inflammation of women's genitourinary tract[2].

Maternal immunity and periodontal pathogens

Genetically, half of fetus cells are of paternal inheritance and it is expected that the pregnant woman has to develop special mechanisms aiming to avoid a plausible immunologically-based reject of fetus. These mechanisms consist in complex and extremely subtle changes of her both innate and adaptive immune system[8].

The major components of maternal innate immunity are monocytes, neutrophils, natural killer cells (NK), complement, and acute-phase reactants. Neutrophils chemotaxis is intensified by progesterone and diminished by estradiol. A double stimulation *in vitro* of monocytes with endotoxin and sex hormones enhanced the gingival inflammation *via* increased PGE2 secretion[8].

Particularly during the last six months of gestation, neutrophils weaken their inhibitory effects by gradually slowing down of myeloperoxidase and superoxide anion generation, synchronized with the decrease of phagocytosis. Similar decrease of cytotoxic effect and IFN-γ synthesis were observed in NK cells. A marked neutrophils deactivation was obvious chiefly at the maternal-fetal interface[8].

In pregnancy, the complement is participating by increased levels of C3, C4, C1q fractions and regulatory proteins CD46, CD55 and CD59. Fibrinogen and ceruloplasmin, as acute-phase reactants, are also raising their values[8].

The expected fine-tuning of adaptive immune system is illustrated by a mild suppression of Th-1 lymphocytes in contrast with stimulation of Th-2 lymphocytes, resulting in the increase of B-cells activity. It follows an up-regulating of IL-4, IL-5 and IL-10, produced in Th-2 cells, and TGF-β, secreted in Th-3 cells, as opposed to down-regulating of Th-1 cells synthesis of IFN-γ, TNF-β and IL-2[8].

While the maternal immune mechanisms are well prepared to avoid the fetus reject in oral healthy pregnant women, in case of pregnancy coexistence with dental infections the balance might slip in a wrong direction. Thus, in an experimental animal model of pregnant hamster, it was demonstrated that inoculated *Escherichia coli* lipopolysaccharide (LPS) endotoxin provoked spontaneous abortion and low fetal weight[14].

Other studies in pregnant animals using *Porphyromonas gingivalis* have shown the same unfavorable outcomes of pregnancy and, at more elevated levels of microbial LPS, highlighted the intraamniotic increase of TNFα and PGE2[14].

Considering birth weight bellow 2,500 g and gestation less than 37 weeks, a clinical survey in humans found out that in PTLBW women the periodontal disease was significantly more advanced than in controls (normal birth weight). The risk factor with adjusted odds ratio of 7.9 proved the association of adverse pregnancy outcomes with periodontal disease in pregnant women[3].

Moreover, assessing other known PTLBW risk factors, the maternal periodontal disease has to be regarded as an independent risk factor, since it increases in direct relationship with the condition's severity[15]. Of paramount importance is also the finding that an independent worsening of periodontal inflammation may aggravate the PTB risk of ongoing gestation[2].

The pathogenic reservoir of Gram-negative anaerobic bacteria, bacterial endotoxins, and proinflammatory mediators (TNFα, IL-1β, PGE2) residing in dental foci of infection represents a permanent potential threat for fetus. It is noteworthy that in fetal cord blood samples were found specific immunoglobulin IgM for periodontal pathogens *Prevotella gingivalis* and *Tannerella forsythia*, suggesting that is capable of independent immune response[2].

Periodontal status in pregnancy

The physiological and immunological changes in pregnancy, even in cases while its course is normal, open a window of the increased risk to maternal infections. One of them is usually the gingival inflammation that involves 100% of pregnant women[8]. However, it is already well documented the reverse process born in inflamed marginal periodontium and conducting to adverse pregnancy outcomes[8].

In literature, the old debate suggesting the relationship between the number of births and that of teeth lost by multiparous women with periodontal disease is still unsolved. However, while pregnancy is progressing, it was described at the periodical control an obvious time-depending worsening process of periodontal inflammation associated with implicit increase of

gingival pockets probing depth, even though no significant differences were noticed concerning dental plaque scores[8].

The impact of periodontal disease in negative pregnancy outcomes relies rather on the specific genetic and environmental variations in patients than on pathogenic relationship between the inflammatory status of maternal periodontal tissue and potential gestation complications[8,16,17].

Commonly, the preterm birth is facilitated by infections of upper genital tract, such as chorioamnionitis or choriodecidual infection. The microorganisms frequently involved might be *Mycoplasma hominis*, *Peptostreptococcus*, *Bacteriodes*, and *Gardnerella vaginalis*. Moreover, the prevalence of PTB is higher in women affected by BV (43%) than in controls (14%), illustrating a significant correlation with infections of lower genital tract too[6].

In order to act as a delivery trigger, the periodontal disease has to play the role of an oral microbial and cytokines reservoir capable to send its proinflammatory messages to uterus cervix by blood circulation[8]. In periodontal disease, BV and intrauterine infections were found similar microorganisms such as *Fusobacterium nucleatum* and *Capnocytophaga species*, suggesting that placenta might be seeded by bacteremia originating from periodontal pockets[6].

Involvement of periodontal pathogens in preterm birth

The positive correlation between either periodontal disease or its increasing severity and PTLBW is positioning the dental infectious pathology as risk factor for adverse pregnancy outcomes[18-21].

The incidence of PTLBW records increasing levels depending on the progress of periodontal disease. There are involved various complementary mechanisms, such as periodontal pathogens and proinflammatory mediators that spread to the amniotic liquid and feto-maternal immune response as well, finally resulting in chorioamnionitis[19,22-24].

It is common that non-pregnant women may develop some mild oscillations of estrogens and progesterone related to menstrual cycle without obvious clinical gingival inflammation. Nevertheless, in pregnancy, the same sexual hormones stimulate the multiplication of Gram-negative periodontal pathogens such as *Prevotella intermedia*, *Campylobacter rectus* and *Bacteriodes* species, joining to other previous Gram-negative colonizing bacteria of gingival pockets like *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella nigrescens*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Treponema denticola*, *Fusobacterium nucleatum*, *Enterococcus faecalis*, *Selenomonas noxia*, *Eikenella corrodens*, and *Pseudomonas aeruginosa*[8].

Since in the bacterial etiology of periodontal disease it is involved a complex consortium of microorganisms, usually there may be also found putative Gram-positive species such as *Actinomyces odontoliticum*, *Parvimonas micra*, *Streptococcus intermedius*, *Staphylococcus aureus* and *Peptostreptococcus micros*[8].

Pregnancy and periodontal disease – status of the art

Though the majority of papers regard as PTLBW those newborn delivered at less than 37 weeks of gestation and the weight less than 2,500 g, the size of infants may show a wide discrepancy among populations all over the world[25-28].

To avoid an insignificant association with PTLBW, the main concern should be directed toward a strict definition of periodontal disease, though this objective may result in a reduced sample of pregnant women. An additional sensitivity analysis might be also useful due to the differences in the condition's definition[29].

Of equal importance should also be the chosen moment for oral examination in order to avoid the immediate postpartum period, as the gingival hygiene is obviously impaired[12].

According to the present opinion, the case definition for periodontal disease should rely mainly on two parameters, probing depth and clinical attachment loss, though some studies used either community periodontal index of treatment needs (CPITN)[12], or gingival bleeding index[30]. The rationale consists in the possible underassessment of periodontal pockets and bleeding in case of CPITN and different percent of gingival bleeding at probing in case of gingival bleeding index[12,30].

In turn, the case definition for PTLBW encompasses as compulsory parameters three main components: thinking about birth weight and delivery period as a continuous variable, considering all potential risk factors, and taking into account the least prevalent of them while choosing the sample size of pregnant women[31].

Reviewing the literature, it has to be highlighted that the definition of pregnancy outcomes, the definition of chronic gingival inflammation, and study design seem to be the main issues that influence in clinical survey the assessment of association between PTLBW and periodontal disease, as contributor of adverse effects in pregnancy.

Conclusions

An increased number of cross-sectional, case-control, longitudinal, and experimental studies in pregnant women support the role of periodontal disease in the occurrence of preterm birth. The positive correlation between chronic gingival inflammation and its increasing severity with preterm low birth weight claims the dental infectious pathology to be one of the risk factor for adverse pregnancy outcomes. ■

Acknowledgements: *All authors have an equal contribution to the first author.*

Conflict of interests: The authors declare no conflict of interests.

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