

CAN ORAL ANAEROBIC BACTERIA CAUSE ADVERSE PREGNANCY OUTCOMES?

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Look to the mouth; diseases enter here
George Herbert (1593–1632)

Abstract

Aim: Maternal periodontal infection has been recognized as a risk factor for premature and low birthweight infants. It is suspected that pathogens causing periodontal disease may translocate to the amniotic cavity and so contribute to triggering an adverse pregnancy outcome. The aim of this study was to evaluate whether the presence of specific periodontal pathogens may influence the incidence of preterm labor and premature birth.

Material and Methods: This study was designed as a hospital-based case-control study. A total of 70 pregnant women, aged 18–40 with single live pregnancy were recruited from the Department of Gynecology and Obstetrics at a General hospital in Šibenik, Croatia, between March 2013 to March 2014. The case group: 30 pregnant women who were hospitalised with signs of premature labor. Control group: 40 patients with normal pregnancy post-delivery up to 48 hrs, who had given birth at term, and the baby had a weight of more than 2500 gr. These women had undergone microbiological examination at the time of recruitment, microbial samples, paper point subgingival swabs were obtained in both groups and processed by anaerobic culturing. Standard procedures were used for culture and identification of bacteria. Information was collected on demographics, health behaviors, and obstetric and systemic diseases that may have influence the premature delivery.

Results: The levels of periodontal pathogens tended to be higher in the premature (case group) labor compared to the term deliveries (control group). Levels of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces actinomycetemcomitans* were statistically significantly higher in premature births as compared to term deliveries, adjusting for baseline levels. The joint effects of red and orange microbial clusters were significantly higher in the premature group compared to the term group.

Conclusions: The study shows a significant association between periodontal anaerobic infection and adverse pregnancy outcome. High levels of periodontal pathogens during pregnancy are associated with an increased risk for preterm delivery. Further studies elucidating the role of the microbial load and maternal immune response as related to pregnancy outcome seem merited.

Key words: oral anaerobic bacteria, preterm labor, preterm delivery.

Oral health is an integral component of general health and well-being of an individual. Knowledge about the link between disturbance of the oral microflora and systemic health is

growing rapidly. The relationship between periodontal bacteria and systemic diseases was investigated extensively during the past two decades [1]. More recently, a wealth of epidemiological, clinical and laboratory studies have provided irrefutable evidence that periodontitis is a risk factor for various systemic diseases such as cardiovascular diseases, atherosclerosis, diabetes mellitus, pulmonary diseases [2, 3]. Periodontal disease has also been implicated as a risk factor for adverse pregnancy outcomes and refers to a group of endogenous polymicrobial infections that cause inflammation and destruction of the supporting structures of the tooth. No overt pathogen has been identified, but its etiology is strongly associated with anaerobic Gram-negative bacilli. This study will focus on the association of the anaerobic Gram-negative bacteria implicated in periodontal disease and examine their potential to cause adverse pregnancy outcomes.

Oral microflora

The mouth harbors a diverse, abundant and complex microbial community. This highly diverse microflora inhabits the various surfaces of the normal mouth [4, 5]. Bacteria accumulate on both the hard and soft oral tissues in biofilms. The relatively aerobic environment of the healthy gingival sulcus tends to preclude the growth of obligate anaerobes and the predominant cultivable flora includes facultative anaerobes, predominantly Gram-positive rods and cocci.

Dental plaque is the material that adheres to the teeth and consists of bacterial cells, Salivary polymers and bacterial extracellular products. If plaque is allowed to accumulate, demonstrable inflammation of the gingiva will occur in 2–4 days due to the production of various noxious metabolites such as endotoxins, lipoteichoic acids, mucopeptides, metabolic end products and proteolytic agents as well as a host of other enzymes such as hyaluronidase and chondroitinase, which may penetrate the gingival tissues causing their destruction by direct injury or by stimulation of inflammatory immune responses which, in turn, results in their further destruction, creating a periodontal pocket [6]. This provides a microbial niche, such that periodontal pockets with depths of 4 mm can harbor on the order of 10^7 to 10^9 bacterial cells [7].

Gram-negative anaerobes frequently implicated in pregnancy periodontal disease include members of the Orange and Red complexes described by Socransky et al. Using cluster analysis, Socransky and his colleagues [8] identified six complexes of bacteria which commonly occur together, and color-coded them as Blue, Green, Yellow and Purple, Orange and Red with the latter two complexes implicated as etiological agents in periodontal disease and therefore as risk factors for adverse pregnancy outcomes. The Orange complex includes species such as *Campylobacter rectus*, *Peptostreptococcus micros*, *Prevotella nigrescence*, *Fusobacterium nucleatum* and *Prevotella intermedia* and provides the lawn for the attachment and colonization of members of the Red complex – *Tannerella forsythia*, *Treponema denticola*, *Porphyromonas gingivalis*. Although clustered within the Green complex, *Aggregatibacter actinomycetemcomitans* have frequently been associated with periodontal disease and with preterm birth and are therefore included in this study.

Obstetrics outcomes

Preterm birth (PTB) and low birth weight (LBW) are a major cause of infant mortality and morbidity that poses considerable medical and economic burden on the society [9]. PTB remains a significant public health issue and it is the leading direct cause of neonatal death, it is responsible for 27 percent of neonatal deaths worldwide, comprising over one million deaths annually. Those premature or LBW babies who survive suffer health problems including neurological, asthma, cerebral palsy, poor motor skills and functional disability, some of which are long-term [10]. Hence, the need to fully understand which of the risk factors associated with preterm and low birthweight infants are key, and being able to target aspects of poor pregnancy outcome to reduce the chances of such events occurring. There are many risk factors for preterm labor and delivery, some are reversible, others are permanent [12]. Its occur in combination and therefore, developing preventive strategies can be challenging to be effective.

Intrauterine infection is a major cause of adverse pregnancy outcomes such as preterm birth [11]. The most consistent of these observations come from placental pathologists who

have described histological evidence of chorioamnionitis in the placentas of 50 to 75% of PTBs and positive membrane cultures in 40 to 60% of such patients. Accurate diagnosis of the infectious organisms, identification of the source of infection are key to patient management. In addition, the current paradigm indicates that the infectious microorganisms originate from the vaginal tract. Accumulating evidence demonstrates that oral bacteria play a significant yet previously unrecognized role in intrauterine infections. Studies in both humans and animals have demonstrated that oral bacteria can translocate to the pregnant uterus through hematogenous transmission. These recent discoveries shed new light on our understanding of pregnancy complications [13, 14].

Pregnancy causes many changes to a woman's body. One of them is the change of her gingival conditions. Pregnancy-associated gingivitis is highly prevalent, affecting 50–75% of the pregnant population, which goes away after delivery. The bleeding gum provides an entry point for the bacteria in the mouth to enter the blood circulation, a transient bacteremia. Under normal healthy conditions, our body can readily fend off such transient bacteremia. However, if the mother has other underlying conditions that compromise her immune system, the bacteria in the blood may escape her immune defense and invade into her womb.

The growing evidence that infection remote from the fetal-placental unit may have a role in the preterm delivery of LBW infants has led to an increased awareness of the potential role of chronic bacterial infections in the body. For the last 15 years or so, maternal periodontal disease has been implicated in poor pregnancy outcome. Offenbacher and his group in 1996 reported a sevenfold increased risk of a mother with periodontal disease delivering a PTLBW baby [15]. This observation was difficult to ignore and since then many studies have been completed but with varying results [16, 17].

It has been demonstrated by several groups that oral bacteria 'translocate' to the fetal placental unit and induce a maternal or fetal response that can result in the premature birth of an infant [18]. The systemic dissemination via the haematogenous route of inflammatory mediators and prostaglandins such as IL-6, IL-8, and TNF- α , PGE2 originating from the peri-

odontal inflammatory process are not dissimilar to those associated with the onset of labor [19]. Therefore, is the onset of labor a single or cumulative effect of the increased levels of inflammatory process originating from the infected periodontium that acts as a reservoir for microbial products and inflammatory mediators.

Romero characterise the event of preterm labour as when the intrauterine or maternal environment becomes hostile and threatens the well-being of the host and, hence, expulsion of the foetus [20].

Material and methods

A case control study was conducted in the Department of Obstetrics and Gynaecology at General Hospital Sibenik, R. Croatia, from March 2013 to March 2014. The study was approved by the Institutional Ethics Committee, General Hospital, Sibenik. Informed and written consent of all subjects was taken for the study.

Material

The study population included-I group-case group: 30 consecutive pregnant women from 28 to 36 + 6 weeks with clinical signs of preterm labor, hospitalised in our department. Subgroup: Women from this group, who delivered preterm.

II group- control group: 40 pregnant women with normal pregnancy who delivered at term a baby with weight more than 2500 gr, analysed to 48h after delivery.

Inclusion criteria: pregnant women, aged 18–40 years with single live pregnancy, signed written informed consent.

Exclusion criteria: multiple gestation, polyhydramnios, uterine anomaly, history of second trimester abortion, history of cervical surgery, cerclage in present pregnancy, previous preterm delivery, substance abuse, smoking, acute symptomatic vaginal infection, acute oral infection, 3 months prior to oral swabs without antibiotic therapy.

Methods: Women were sure of dates and the gestational age of the subjects was determined with the best obstetric estimates using definite menstrual history and ultrasonography done in the first trimester. The diagnosis of preterm labor is generally based upon clinical

criteria of regular painful uterine contractions (4 every 20 minutes or 8 every 60 minutes) accompanied by cervical change: cervical effacement of at least 80 percent or cervical dilatation greater than 2 cm. All subjects with signs of preterm labor were followed and treated in our department in a routine manner and managed according to hospital protocol for preterm labor.

One dentist obtained the oral paper points swabs from subgingival sulcus of all patients at the time of inclusion in the study. The samples were collected with complete aseptic precautions, the site of sample collection was isolated with cotton rolls and air-dried. For singled sites, patients with evident periodontal pocket, two sterile paper points were inserted to the bottom of the pocket a 20 s period, and for pooled samples, patient without periodontal pocket, one paper point (from first molar) per site from up to four sites was collected. The swabs were transported in anaerobic transport medium, within 1 hour, to the Department of Microbiology, Public health institute, Sibenik, and analysed by one microbiologist. The samples were cultivated routinely in anaerobic conditions on Schaedler agar for 48 hours. Bacterial identification was based on the colony morphology and pigmentation, staining and biochemical reactions,

Table 1

Spectrum of anaerobes in patients with preterm labor and control group subjects

Gram-negative organisms	Control group	Group with ptl	Subgroup with ptb
<i>Porphyromonas gingivalis</i>	1	5	5
<i>Prevotella intermedia</i>	1	3	2
<i>Fusobacterium nucleatum</i>	2	4	4
<i>Bacteroides sp.</i>	1	2	1
<i>Veillonella sp.</i>	3	1	/
Gram-positive organisms			
<i>Peptostreptococcus micros</i>	3	2	2
<i>Streptococcus intermedius</i>	1	2	/
<i>Actinomyces actinomycetecomitans</i>	1	5	4
<i>Eubacterium lentum</i>	2	1	/

ptl – preterm labor; ptb – preterm birth

Discussion

The results of this study support the hypothesis that chronic periodontal infection increases the risk of developing preterm labor and delivery. The levels of periodontal pathogens tended to be higher in the preterm labor (case group) compared to the term deliveries (control group). The

and after that the same bacteria were taken into the Vitek 2 ANC ID Card and Vitek NH ID Card panels in order to perform identification tests, whilst the identification procedures were followed, according to the methods that were suggested by manufacturer.

Statistical analysis

Chi-square test or the Fischer's Exact test were used for determining the differences in frequencies of various periodontal anaerobes in patients with preterm labor and in control group. **p-value** < 0,05 was considered as cut-off point for level of significance.

Results

Anaerobes were isolated in 83,3% (25 cases) of patients with preterm labor and 37,5% (15 cases) in control group. From the first group 18 patients didn't respond on therapy and delivered preterm. Oral anaerobes were isolated in all of them. The oral anaerobes who are specific for periodontal disease and adverse pregnancy outcome were isolated in 30 patients from all cases 42,8%, and from patients in case group in 70% (21 patients).

present study shows a sevenfold higher risk of development of preterm delivery in women with periodontal anaerobes in subgingival plaque than women without. Levels of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces actinomycetecomitans* were statistically significantly higher in preterm births compared to

term deliveries, adjusting for baseline levels. Similar positive associations between periodontal infection and preterm birth were reported by Boggess et al. [21] and Sharlene W. J. Afrika [22]. The joint effects of red and orange microbial clusters were significantly higher in the preterm group compared to the term group. This finding suggests that the pregnant woman with preterm labor and positive culture of red and orange cluster, more often delivered preterm baby. Gibbs et al. [23] provided an excellent outline of the possible association between infections and adverse pregnancy outcomes in their review article. In their hypothesis, microorganisms and their products enter the uterine cavity during pregnancy by an ascending route from the lower genital tract, or by a blood-borne nongenital route, causing preterm birth. Maternal periodontal infection directly and/or indirectly have potential to influence the health of the foetal-maternal unit [24, 25]. Two major pathways have been identified, one direct, in which oral microorganisms and/or their components reach the foetal-placental unit via haematogenous route and one indirect, in which inflammatory mediators circulate and impact the foetal-placental unit [26]. In a study of evaluating the relationship between fetal inflammatory and immune responses to oral pathogens and risk for PTB, umbilical cord blood specimens were examined for presence of fetal immunoglobulin M (IgM) antibody against oral pathogens and levels of C-reactive protein, IL-1, IL-6, TNF- α and PGE2. The results showed that the presence of IgM antibodies to oral pathogens and increased levels of TNF- α were associated with increased rates of PTB, and that the combined effects of fetal IgM, C-reactive protein, TNF- α and PGE2 resulted in a significantly increased risk for PTB [27]. Hill demonstrated that *Fusobacterium nucleatum* can be isolated from amniotic fluid cultures of women with preterm labour and intact membranes suggesting the transient bacteraemia had originated from the mouth via haematogenous spread and infection of the amniotic fluid through the placenta [28]. More recently, Han and colleagues have reported a term stillbirth case by association was caused by *Fusobacterium nucleatum*, she had previously demonstrated that *Fusobacterium nucleatum* induced premature and term stillbirths in pregnant mice [29, 30].

Interestingly, the majority of these species have been associated with pregnancy complications in humans, although their sources of infection were not previously known. Thus, the oral cavity may be a significant yet previously overlooked source of infection inside the womb.

Conclusion

One urgent question to address now is: to what extent do oral bacteria impact the pregnancy outcome? It is reasonable to suggest that infection of the gingiva and periodontium by Gram-negative anaerobic bacteria provide a reservoir for microbial products and sufficiently challenge the host to produce responses which may be deleterious to both the pregnant mother and the fetus. However, the way has been paved for future research to focus on establishing why some women develop adverse pregnancy outcomes due to an oral inflammatory burden while others do not. The more detailed and sound conclusions need research that will cover the detection of increased inflammatory mediators and prostaglandins. It is our hope that in the future we can identify women at risk for developing oral bacteria-associated pregnancy complications so that preventive measurements can be taken to manage each individual case. An indepth knowledge of the disease mechanism is the basis of personalized medicine. Only when we have a clear understanding of the causes, can we then develop therapeutic and preventive measures to identify women at risk and to improve the birth outcome and ultimately the quality of people's lives.

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Резиме

ДАЛИ ОРАЛНИТЕ АНАЕРОБНИ БАКТЕРИИ МОЖАТ ДА ДОВЕДАТ ДО ЛОШИ ОПСТЕТРИЧКИ ИСХОДИ?

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Вовед: Нарушената орална хомеостаза во полза на анаеробите сè почесто се истражува во опстетрицијата, обвинувајќи ја за лош опстетрички исход: предвремено породување и новороденчиња со ниска родилна тежина за гестациската возраст. Предвременото породување и ниската родилна тежина е главна причина за морталитет и морбидитет, што претставува значаен медицински и економски товар врз општеството. Патогените што ги предизвикуваат

периодонталните болести се смета дека можат да се транслоцираат во амнионот и да влијаат на бременоста – директно преку хематогена дисеминација и индиректно преку системска дисеминација на инфламаторните медијатори и простагландини.

Целта на оваа студија е да утврди дали присуството на специфични периодонтални патогени кај бремените жени го зголемува ризикот од предвремено породување.

Материјал и метод: Студија случаи-контрола

I група – 30 трудници од 28 до 36 + 6. гестациска недела со знаци за претечко предвремено породување (ППП), подгрупа од I група трудници кои и покрај имплементираната терапија за можност од предвремено породување, предвремено родиле.

II група – контролна 40 трудници со уредна бременост, кои се породиле во термин и родиле дете со поголема тежина од 2500 г, евалуирани во период до 48 часа по породувањето. Кај пациентките со можност од предвремено породување се зема микробиолошки субгингивален брис веднаш по хоспитализацијата, а кај пациентките кои служат за контрола до 48 часа по раѓањето. Ќе

се анализираат и останатите веќе докажани ризик-фактори за претечко PPP добиени од прашалник (подготвен за студијата) и болничката историја.

Резултати: Присуството на периодонталните патогени е почесто кај пациентките со PPP, споредено со трудниците кои се породиле во термин. *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces actinomycetecomitans* се изолирани почесто кај пациентките кои родиле предвремено, што е статистички значајно, во споредба со контролната група кога ќе се анализираат и останатите кофактори.

Заклучок: Присуството на оралните периодонтални инфекции кај мајката се поврзани со зголемен ризик од предвремено породување. Откривањето на причините за лош опстетрички исход, посебно пред бременост, ќе отвори ново поглавје во современото акушерство, давајќи време за нивна корекција и дејствување пред или на самиот почеток на бременоста.

Клучни зборови: орални анаеробни бактерии, претечко предвремено породување (ППП).