PERIODONTAL DISEASE AND RISK FOR PRE-TERM BIRTH: A CASE-CONTROL STUDY

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PARODONTOPATIJA I RIZIK ZA NASTAJANJE PREVREMENOG POROĐAJA: STUDIJA SLUČAJ-KONTROLA

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ABSTRACT

Maternal periodontal infection has been recognizsed as a risk factor for preterm and low birth weight infants. It is hypothesized that pathogens causing periodontal disease might translocate to the amniotic cavity and contribute to triggering an adverse pregnancy outcome. The growing evidence that an infection remote from the foetal-placental unit might have a role in preterm delivery has led to an increased awareness of the potential role of chronic bacterial infections in the body. The aim of this study was to evaluate whether the presence of chronic periodontitis might influence the incidence of preterm labour and preterm birth.

This study was designed as a hospital-based case-control study. Seventy pregnant women aged 18-40 years, with a single live pregnancy were recruited from the Department of Gynaecology and Obstetrics of a general hospital in Sibenik, Croatia, from March 2013 to March 2014.

The case group included: 30 pregnant women who were hospitalized with signs of preterm labour. The control group included 40 normal pregnancy patients, who were analysed for up to 48 h after the delivery of a term baby having a birth weight of more than 1500 g. A full-mouth periodontal examination was performed on all the patients. Information was collected on the demographics, health behaviours, and obstetric and systemic diseases that might have an influence in preterm delivery.

The presence of chronic periodontitis tended to be higher in women with a preterm delivery (the case group), with 20 cases (66%), than in the women in the, control group, in which chronic periodontitis was found in 14 cases (35%); this difference reached statistical significance ($p \leq 0.01$). The PTB cases had a significantly worse periodontal status than the controls ($p \leq 0.001$). From the PTL group, 18 patients delivered preterm, and chronic periodontitis, found in 15 cases (83%), was more prevalent than in the control group. The risk of women having periodontitis or attachment loss ≥ 4 mm developing PTB showed an OR of 3.7 (95% CI: 1.91 to 4.86; $P < 0.001$).

SAŽETAK

Infekcija parodoncijuma majke se smatra faktorom rizika za prevremeni porođaj i malu telesnu masu novorođenčeta. Pretpostavlja se da patogeni koji uzrokuju parodontopatiju mogu da dospeju u amnionsku šupljinu i da doprinesu pokretanju događaja koji za posledicu imaju naželjeni ishod trudnoće. Sve veći broj dokaza koji ukazuje na činjenicu da infekcije udaljene od feto-placentalne jedinice mogu da imaju ulogu u nastajanju prevremenog porođaja su izazvali povećanje interesovanja za potencijalnu ulogu hroničnih bakterijskih infekcija u organizmu. Cilj ove studije je procena povezanosti hronične parodontopatije i incidencije prevremenog porođaja.

Studija je dizajnirana kao hospitalna slučaj-kontrola studija. 70 trudnica, starosti od 18 do 40 godina, sa prvom uspešnom trudnoćom, su ispitivane između marta 2013. i marta 2015. godine, na Odeljenju ginekologije i akušerstva Opšte bolnice u Šibeniku, Hrvatska.

Grupa „slučajeva": Ovu grupu je činilo 30 trudnica hospitalizovanih sa znacima prevremog porođaja. Kontrolna grupa: Kontrolnu grupu su činile trudnice sa normalnom trudnoćom, koje su ispitivane 48 h nakon porođaja, čije je dete rođeno u terminu i imalo težinu na rođenju iznad 2500 g. Svim pacijentkinjama je izvršen pregled parodoncijuma celih usta, a prikupljeni su i demografski podaci, informacije o zdravstvenim navikama, akušerskim i sistemskim oboljenjima koje mogu da utiču na porođaj.

Hronični parodontitis je bio više zastupljen kod žena koje su imale prevremeni porođaj (grupa „slučajeva") – 66% (20 žena) u poređenju sa ženama koje su se porodile u teminu (kontrolna grupa) – 35% (14 žena), i ova razlika je statistički značajna ($p \leq 0,01$). Žene u PTB grupi su imale značajno gore stanje parodoncijuma u odnosu na kontrole ($p \leq 0,001$). 18 žena iz PTL grupe je rodilo nedonesenu decu, a hroinčni parodontitis je bio češći – 83% (15 žena), u odnosu na kontrolnu grupu. Rizik za nastajanje prveremenog porođaja za žene koje imaju parodontitis ili gubitak vezivnog tkiva ≥4 mm je pokazao OR (odds ratio) od 3,7 (95%CI: 1,91 do 4,86; $p < 0,001$)

The study shows a significant association between periodontal chronic disease and an adverse pregnancy outcome. Periodontal disease represents a strong, independent risk factor for preterm births, and periodontal prevention and therapy should be a part of preventive prenatal care.

Keywords: *periodontal disease, preterm labour, preterm delivery*

Studija pokazuje značajnu povezanost između hronične parodontopatije i neželjenog ishoda trudnoće. Parodontopatija predstavlja jak, nezavistan faktor rizika za prevremeni porođaj. Usled toga prevencija parodontopatije i terapija bi trebalo da budu deo prvencije prvermenog porođaja.

Ključne reči: *parodontopatija, prevremeni porođaj, prevremeno rođenje*

INTRODUCTION

Oral health is an integral component of the general health and well being of an individual. The knowledge regarding the link between periodontal disease and systemic health is increasing rapidly (1). Recently, many 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, and pulmonary diseases (2, 3). Periodontal disease refers to a group of endogenous polymicrobial infections that cause inflammation and destruction of the supporting structures of teeth. No overt pathogen has been identified; however, its aetiology is strongly associated with anaerobic Gram-negative bacilli (4). In response to these gram-negative bacteria, the human body activates its host immune response, and immune cells secrete inflammatory mediators. Of particular importance in periodontal disease are cytokines, prostaglandins and matrix metalloproteinases. The destruction of periodontal tissues, including the breakdown of the gingival connective tissue and alveolar bone, results mainly from activation of the immune cells (5). The inflammatory mediators that have been discussed in relationship to incidences of preterm birth include cytokines, prostaglandins and matrix metalloproteinases. Several cytokines play an important role in the initiation and progression of periodontal disease. These cytokines include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor (TNF-a). Prostaglandins are responsible for most of the alveolar bone destruction observed in periodontal disease, particularly prostaglandin [E. sub. 2] (PGE 2). Matrix metalloproteinases (MMP) are a family of enzymes that work together to destroy connective tissue. It is istheorized that these inflammatory mediators from subgingival plaque are able to enter the bloodstream and travel to the maternal-foetal interface, thus contributing to preterm labour (6). During pregnancy, PGE 2 plays an important role in regulating the onset of labour, contractions and delivery. (PGE 2) levels rise throughout gestation, and when a critical threshold level is reached, labour is induced (7). These associations explain the basic theories for the link between the presence of maternal periodontal disease and the risk for adverse pregnancy outcomes.

However, accumulating evidence demonstrates that oral bacteria might translocate directly into the uterus in during pregnancy, causing localized inflammation and an adverse pregnancy outcome. Studies in humans and animals have demonstrated that oral bacteria could translocate to the uterus in pregnancy through haematogenous transmission. These recent discoveries shed new light on our understanding of pregnancy complications. (8, 9) Although infections of any type in pregnant women represent a risk for adversities in the developing foetus, periodontal disease might have a significant role in the pathogenesis of adverse pregnancy outcomes.

The term periodontal disease encompasses a variety of diseases ranging from gingivitis to periodontitis. Standard diagnostic tools that are used to determine the presence of periodontal disease include full- mouth periodontal examinations, measurements of the pocket depths (PD), the clinical attachment levels (CAL), gingival recession (GR), visible signs of gingival inflammation (such as bleeding on probing (BOP)) and dental radiographs. No dental radiographs were taken in this study because of the special conditions of the patients.

OBSTRICAL OUTCOMES

Preterm birth (PTB) and low birth weight (LBW) are leading perinatal problems worldwide and have evident public health implications because their incidence does not decrease in spite of the many attempts to prevent perinatal problems. Preterm birth, defined as birth before 37 weeks of gestation, is the leading cause of neonatal mortality, infant morbidity, and long-term sequelae. PTB is a major medical, social, and economic concern. Preterm infants are 75 times more likely to experience early death, and PTB, the leading direct cause of neonatal death, is responsible for 27 per cent of neonatal deaths worldwide, comprising over one million deaths annually (10). The long-term disabilities for surviving preterm infants include pulmonary abnormalities, asthma, cerebral palsy, poor motor skills and neurological or developmental disabilities (11). Human observational studies have identified a number of risk factors for preterm delivery, and some are reversible, whereas others are permanent (12). The risk factors occur in combination, and, therefore, developing effective preventive strategies could be challenging.

Infections and inflammation, maternal or foetal stress, uterine bleeding, and stretching of the uterus are isrecognized as the most common reasons for PTB. Intrauterine infections and maternal bacterial vaginosis are well known risk factors; however, distant infections, even subclinical infections, could induce preterm births. Periodontal disease is associated with infections and inflammation. The presence of periodontal disease and the maternal physical changes that occur during pregnancy enable bacteria to enter the blood stream, leading to "placental seeding" (13, 14). The significance of the relationship of periodontal disease and PTB is evident when the number of affected women and children is considered. At least 20% of the women aged 30 to 50 years have periodontitis. In addition, 12% of all the births worldwide are premature (delivered at less than 37 weeks of gestation); this problem affects many women of child-bearing age in our country, with lasting consequences to their past, present and future children.

The objective of this paper is to examine, from an evidence-based perspective, whether periodontal disease might contribute to the risk for PTB.

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 of General Hospital, Sibenik. Informed and written consent was obtained from all of the subjects for this study.

Material

The study population included the following: a case group of 30 pregnant women from 28 to 36+6 weeks of gestation, with clinical signs of preterm labour, who were hospitalized in our department; and a control group of 40 pregnant women with normal pregnancies, who delivered, at term (37-42 g.w), a baby with a birth weight over 2500 gr.

The inclusion criteria included pregnant women, aged 18-40 years, with a single live pregnancy, who signed written informed consent forms.

The Exclusion criteria included: multiple gestation, polyhydramnios, uterine anomalies, a history of second trimester abortion, a history of cervical surgery, cerclage in the present pregnancy, a previous preterm delivery, substance abuse, smoking, an acute symptomatic vaginal infection, and acute oral infection.

Methods

The gestational age of the subjects was determined with the best obstetrical estimation methods using the definitive menstrual history and ultrasonography performed in the first trimester. The diagnosis of preterm labour is generally based on the clinical criterion of regular painful uterine contractions (4 every 20 minutes or 8 every 60 minutes), accompanied by cervical changes, including cervical effacement of at least 80 per cent or cervical dilatation greater than 2 cm. All the subjects with signs of preterm labour were followed and routinely treated in our department, and they were managed according to the hospital protocol for preterm labour.

One dentist performed a full-mouth periodontal examination on all of the patients at the time of their inclusion in the study (the case group, at the time of hospitalization, and the control group, within 2 days of delivery). The periodontal examination was performed with the patient supine on a hospital bed, using artificial light. The following data were recorded: bleeding on probing (BOP), the probing depth (PD) at the floor site per tooth, gingival recession and the clinical attachment level (CAL) on all of the present teeth. The patients were diagnosed with periodontal disease if they exhibited a PD of 4 mm or greater in four or more teeth and a CAL greater or equal to 3 mm at the same site. The BOP was recorded; however, it was not used to determine a diagnosis of periodontal disease. Demographic, socioeconomic and medical data on known risk factors were obtained from the charts of the patients, and an examiner-administered questionnaire was completed. This questionnaire was designed to gather the demographic details, pregnancy and medical history, health behaviour and dental condition. The aim of the questionnaire was to collect information on as many of the known risk factors for an adverse pregnancy outcome as possible.

Statistical analysis:

The sample size was calculated using a statistical package (SPSS Version 10.0, SPSS, Inc., Chicago, IL, USA). Univariate and bivariate analyses were performed. The chi-square test or Fischer's Exact test were used for analysing the categorical variables. To compare the mean values, we performed the t-test. The Spearman correlation coefficient was used to reveal the correlation between the variables. The unadjusted and adjusted ORs were calculated with 95% confidence intervals. Multivariate logistic regression models were developed and performed stepwise to identify the risk factors for PTB; a p value < 0.05 was considered as the cut-off point for the level of significance.

RESULTS

The main demographic and obstetrical data of all the subjects are summarized in Table 1.

A total of 70 pregnant women were included 40 in the control group and 30 in the preterm labour group (PTL). In the case group (PTL), 18 patients did not respond to therapy and delivered a preterm baby (PTB) in our hospital. The age of the subjects was distributed normally, without statistical significance between the mean values (p= 0.72). Most of the women had secondary levels of education. There was no significant difference in the marital status or in the pre-natal care. None of the obstetrical risk variables displayed a significant association with PTB in this study.

Table1. Demographic and obstetric information in the control and case groups

Demographic and obstetric information	Control group (n=40)	Group with ptl (n= 30)	Subgroup ptb (n= 18)
Mean age ± SD	26.6 ± 6.0	25.9 ± 4.2	25.4 ± 1.6
First pregnancy [n / (%)]	16 (40%)	11(36,7%)	7 (38,8%)
Second pregnancy	18 (45%)	17 (56.6%)	10 (55,6%)
≥3 pregnancies	6 (15%)	2 (6,7%)	1 (5,6%)
Prenatal care			
No pre-natal care	2 (5%)	0	0
< six visits	11(27.5%)	7 (23,3%)	6 (33,4%)
Six + visits	27(67,5%)	23 (76.7%)	12 (66,6%)
Marital status [n / (%)]			
Single	3(7,5%)	2 (6,7%)	0
Married	22(55%)	18(60%)	10(55,5%)
Non-married couple	15(37,5%)	10(33,3%)	8(44,5%)
Education level [n / (%)]			
Elementary school	2(5%)	3(10%)	2(11,1%)
Secondary school	33(82,5%)	24(80%)	14(77,8%)
University	5(12,5%)	3(10%)	2(11,1%)

ptl- preterm labour; ptb -preterm birth

Table 2. Periodontal condition in patients with preterm labour and the control group subjects

Periodontal condition	Control group (n=40)	Case group (n= 30)	P- Value
Healthy	26 (65%)	10 (33,3%)	< 0.01
Chronic periodontitis	14 (35%)	20 (66,7%)	<0.01
Clinical parameters (mean ± SD)			
PD (mm)	3.1±0.06	4.1±0.09	<0.001
CAL (mm)	2.9±0.04	4.0±0.08	<0.001

PD- probing depth, CAL- clinical attachment level

The periodontal condition is presented in Table 2.

Periodontal disease was diagnosed in 66,7% (20 cases) of the patients with preterm labour and in 35% (14 cases) of the patients in the control group, and this difference reached statistical significance (p ≤ 0.01). In the group of 18 patients who delivered preterm, chronic periodontitis was more prevalent in 83% (15 cases) more cases than in the control group (p ≤ 0.001), which is considered to be very statistically significant. The risk for women having periodontitis or an attachment loss ≥ 4 mm to develop a PTB showed an OR of 3.7 (95% CI: 1.91 to 4.86; P< 0.001). Additionally, more CAL was found in the PTB group than in the control group. The only risk factor for preterm delivery that showed statistical significance at 95% CI was periodontal disease.

DISCUSSION

The results of this study support the hypothesis that chronic periodontal infection increases the risk of preterm labour and delivery. The multivariate analysis showed a significant association between PTB and periodontal disease. The main levels of PD and CAL tended to be higher in the preterm labour group (the case group) than in the term delivery group (the control group); the differences were statistically significantly higher in the women with preterm births than in the woman with term deliveries, adjusting for the baseline levels. This study showed a significant risk of preterm delivery in the women with periodontal disease than in the women without. Similar positive associations between periodontal infection and preterm birth were reported by Boggess et al (15). and Sharlene W. J. Afrika (16). This finding suggests that pregnant woman with preterm labour and chronic periodontal infection more often delivered a preterm baby. Gibbs et al (17). 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. The growing evidence that infection remote from the foetal-placental unit might 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 approximately 15 years, maternal periodontal disease has been implicated in a poor pregnancy outcome. In 1996, Offenbacher and his group reported a seven-fold increased risk of a mother with periodontal disease delivering a PTLBW baby (18), and many studies on the subject have been completed, with varying results (19, 20). Lopez et al. confirmed periodontal disease as an independent risk factor and observed that periodontal therapy significantly reduces the incidence of preterm birth with low birth weight in a population of women with periodontal disease (21). A recent meta-analysis confirmed a significant risk of preterm delivery for pregnant women with periodontitis (overall risk ratio: 1.70) and a significant risk for having a low birth weight infant (overall risk ratio: 2.11) (22).

Maternal periodontal infection could directly and/or indirectly influence the health of the foetal-maternal unit (23, 24, 25). In a study evaluating the relationship between foetal inflammatory and immune responses to oral pathogens and the risk for PTB, umbilical cord blood specimens were examined for the presence of foetal immunoglobulin M (IgM) antibody against oral pathogens and levels of C-reactive protein, IL-1, IL-6, TNF-alfa and PGE2. The results showed that the presence of IgM antibodies to oral pathogens and increased levels of TNF-alfa were associated with increased rates of PTB and that the combined effects of foetal IgM, C-reactive protein, TNF-alfa and PGE2 resulted in a significantly increased risk for PTB (26). Hill demonstrated that *Fusobacterium*

nucleatum could be isolated from amniotic fluid cultures of women with preterm labour and intact membranes, suggesting that the transient bacteraemia had originated from the mouth via haematogenous spread and infection of the amniotic fluid through the placenta (27). More recently, Han et al. reported, by association, a term stillbirth case caused by F. *nucleatum*, and she had previously demonstrated that *F. nucleatum* induced premature and term stillbirths in pregnant mice (28, 29). The majority of these species has been associated with pregnancy complications in humans, although their sources of infection were not previously known. The oral cavity might be a significant yet previously overlooked source of infection inside the womb.

Two meta-analyses of case-control studies reported that periodontal diseases in pregnancy significantly increase the risk of a subsequent preterm birth or LBW, and the estimated OR was 1.78 (CI 95%: 1.58, 2.01) for preterm births, 1.82 (CI 95%: 1.51, 1.20) for low birth weight infants and 3.00 (CI 95%: 1.93, 4.68) for preterm low-birth weight infants (30, 31). Studies on the effect of periodontal disease treatment on the pregnancy outcome showed varying results. A study reported that there was a lack of association of periodontitis and preterm birth in a multivariate analysis, which supports the report of a meta-analysis showing a lack of effect of periodontal disease treatment on the preterm birth rate (32). Conflicting results were reported from India showing a significant association of periodontal disease treatment with preterm delivery (33).

Future studies should investigate these mechanisms to understand the host susceptibility to oral-uterine transmission. Only when a thorough understanding of the mechanism is achieved could meaningful intervention studies be designed to utilize effective therapies, target the appropriate populations, and measure the relevant outcomes.

CONCLUSION

It is urgent to determine the extent to which chronic periodontitis affects pregnancy outcomes. 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 that might be deleterious to the pregnant mother and foetus. Future research should focus on the reasons why some women develop adverse pregnancy outcomes because of an oral inflammatory burden whereas others do not. In the future, we hope to identify the women at risk for developing oral bacteria-associated pregnancy complications so that preventive measurements could be taken to manage each case individually. An in-depth knowledge of the disease mechanism is the basis of ispersonalized medicine. Only if there was a clear understanding of the causes would it be possible to develop therapeutic and preventive measures to identify the women at risk as well as to improve the birth outcome, and, ultimately, the quality of lives.

REFERENCES

1. Cullinan MP, Ford PJ, Seymour G. Periodontal disease and systemic health: curent status. Australian Dental Jurnal, 2009; 54(1):62-69
2. Wu T, Trevisan M, Genco RJ, Dorn JP, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition survey and its follow- up study. Arch. Intern. Med. 2000;160:2749-2755
3. Willershausen B, Kasaj A, Willershausen I, Zahorka D, Briseño B, Blettner M, Genth-Zotz S, Münzel T. Association between chronic dental infection and acute myocardial infarction. J Endod. 2009 May; 35(5):626-30.
4. Spratt D. 4.1 Dental plaquae and bacterial colonization. In: Medical biofilms. Jass J, Surman S, Walker J,editors, John Wiley and Sons Ltd, 2003: 175-98.
5. Lee W, Aitken S, Sodek J, McCulloch CA. Evidence of a direct relationship between neutrophil collagenase activity and periodontal tissue destruction in vivo: role of active enzyme in human periodontitis. J Periodontal Res. 1995;30:23–33.
6. Klebanoff M, Searle K. The role of inflammation in preterm birth – focus on periodontitis. BJOG. 2006 Dec;113 Suppl 3:43-5.
7. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N. Engl. J. Med. 2000;342(20), 1500–1507
8. Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. J Nutr.2003; 133:1592S1596S.
9. Pretorius C, Jagatt A, Lamont RF. The relationship between periodontal disease, bacterial vaginosis, and preterm birth. J Perinat Med. 2007;35(2):93-9
10. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012; 379:2162.
11. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379:445.
12. Romero R, Espinoza J, Goncalves LF, Kusanovic JP, Friel LA, Nien JK. 2006. Inflammation in preterm and term labour and delivery. Semin Fetal Neonatal Med 11:317-326.
13. Marakoglu I, Gursoy UK, Marakoglu K, Cakmak H, Ataoglu T. Periodontitis as a risk factor for preterm low birth weight. Yonsei Med J.2008; 49:200-203.
14. Offenbacher S, Jared HL, O'Reilly PG, Wells SR, Salvi GE, Lawrence HP. Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontol 1998; 3:233.
15. Boggess KA, Moss K, Murtha A, Offenbacher S, Beck JD. Antepartum vaginal bleeding, fetal exposure to oral pathogens, and risk for preterm birth at <35 weeks of gestation. Am J Obstet Gynecol 2006; 194:954.
16. Africa CW. Oral colonisation of gram negative anaerobes as a risk factor for preterm birth, Virulence 2011;2(6): 498-508;

17. Gibbs RS. The relationship between infections and adverse pregnancy outcomes: an overview.Ann Periodontol. 2001 Dec;6(1):153-63.

18. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996; 67:1103.

19. Offenbacher S, Lieff S, Boggess KA, Murtha AP, Madianos PN, Champagne CM. Maternal periodontitis and prematurity. Part I: Obstetric outcome of prematurity and growth restriction. Ann Periodontol 2001; 6:164.

20. Madianos P. N., Lieff S., Murtha A. P., Boggess K. A., Auten R. L., Beck J. D., Maternal periodontitis and prematurity. Part II: maternal infection and fetal exposure. Ann. Periodontol.2013;6 :175–182.

21. Lopez Nj, Da Silva i, Ipinza J, Gutierrez J. Periodontal therapy reduces the rate of preterm low birth weight in women with periodontal disease. J Periodontol. 2005;76:2144-53

22. Chambrone L, Guglielmetti MR, Pannuti CM, Chambrone LA. Evidence grade associating periodontitis to preterm birth and/or low birth weight: I. A systematic review of prospective cohort studies. J Clin Periodontol. 2011;38:795-808

23. Han YW. Can oral bacteria cause pregnancy complications? Womens Health (Lond Engl) 2011; 7:401.

24. Goepfert AR, Jeffcoat MK, Andrews WW, Faye-Petersen O. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol 2004; 104:77

25. Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. Infect. Immun.2010; 78(4), 1789–1796

26. Boggess KA, Moss K, Madianos P, Murtha AP, Beck J, Offenbacher S. Fetal immune response to oral pathogens and risk of preterm birth. Am J Obstet Gynecol 2005; 193:1121.

27. Hill GB. Investigating the source of amniotic fluid isolates of fusobacteria. Clin. Infect. Dis.1993;16(Suppl. 4), S423–S424 .

28. Han YW, Fardini Y, Chen C, Iacampo KJ, Peraino VA, Shamonki JM. Term stillbirth caused by oral Fusobacterium nucleatum. Obstet.Gynecol.2010;115, 442–445

29. Han YW, Redline RW, Li M, Yin L, Hill GB. Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. Infect. Immun. 2004;72(4), 2272–2279

30. Khader YS, Taani Q. Periodontal disease and the risk of preterm birth and low birth weight: A meta-analysis. J Periodontol 2005; 76:161-65

31. Corbella S, Taschieri S, Francetti L, De Siena F, Del Fabbro M. Periodontal disease as a risk factor for adverse pregnancy outcomes: A systematic review and meta-analysis of case-control studies. Odontology2011; (doi:10.1007/S10266-011-0036-z)

32. Polyzos NP, Polyzos IP, Zavos A, Valadis A, Mauri D, Papanikolaou G.E, Tzioras S, Weber D. Obstetric outcomes after treatment of periodontal disease during pregnancy: Systematic review and meta-analysis. BMJ2010; 341:c7017

33. Tarannum F, Faizuddin M. Effect of periodontal therapy on pregnancy outcome in woman affected by periodontitis. J Periodontol 2007; 78:2095-2103