INCREASED RISK OF PRETERM BIRTH AMONG NON- SMOKING, NON- ALCOHOL DRINKING WOMEN WITH MATERNAL PERIODONTITIS

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Abstract. The aim of this case-control study was to examine the association between periodontitis and preterm birth among non-smoking, non-alcohol drinking women. The cases were 130 women who delivered a live singleton newborn before 37 weeks gestation. A random sample of 260 women who delivered a normal child on the same day as the cases were selected as controls. Periodontal examinations were performed during 24-hour period postpartum at bedside. Other related information was collected by structured questionnaire and medical records. Multiple logistic regression analysis was performed controlling for age, ethnicity, place of residence, education, occupation, income, pre-pregnancy body mass index (BMI), weight gain, antenatal care (ANC), parity, systematic infections, genitourinary infections, antibiotics used, and history of periodontal treatment. Periodontitis (defined as presence of at least 4 teeth having ≥ 1 site with a probing depth (PD) ≥ 4 mm, clinical attachment loss (CAL) ≥ 3 mm and bleeding on probing (BOP) after 10 seconds at the same site) was diagnosed in 33.9% of cases and 10.4% of controls. Periodontitis was significantly associated with preterm birth (adjusted OR = 4.47, 95%CI= 2.43, 8.20). These findings suggest that periodontitis may increase the risk of preterm delivery even among women who do not smoke or drink.

INTRODUCTION

The high prevalence of preterm birth is an important concern for public health in both developed and developing countries (Haram *et al*, 2003; Janet and William, 2005). Recognized risk factors include age, height, weight, socio-economic status, ethnicity, smoking, alcohol, nutritional status, stress, parity, previous complications, antenatal care, maternal hypertension, cardiovascular disease, diabetes, antibiotics used, cervical incompetence, and genital infections (Hauth *et al*, 1995; Hillier *et al*, 1995; Zeitlin *et al*, 2001; Ehrenberg *et al*, 2003; Jepsen *et al*, 2003; Parazzini *et al*, 2003; Vangen *et al*, 2003; Asghar and Kokab, 2005; Bobak *et al*, 2005; Merry *et al*, 2005; Raatikainen *et al*, 2005). However, these risk factors are not present in 25-50% of cases (Yeo *et al*, 2005). Given the importance of this problem, there is a great effort being mad to identify other risk factors. One interesting hypothesis is the effect of maternal periodontitis. The potential pathogenic mechanisms for periodontitis associated pregnancy complications have been explored (Collins *et al*, 1994a,b; Offenbacher *et al*, 1996, 1998).

Although periodontitis has been studied as a risk factor for preterm birth, the results

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have been inconclusive. A positive association between periodontitis and preterm birth has been studied in the Americas (Offenbacher *et al*, 1996; Lopez *et al*, 2002; Jarjoura *et al*, 2005; Lunardelli and Peres, 2005; Offenbacher *et al*, 2006) but not in Europe (Davenport *et al*, 2002; Moore *et al*, 2004, 2005; Noack *et al*, 2005). The association may vary by population-specific characteristics, such as race, environment, genetics, differential rates of disease, potential exposure or other factors. There is the need to study the association between periodontitis and adverse pregnancy outcomes in Southeast Asia and developing countries. The confirmation of periodontitis as an independent risk factor for preterm birth would be of great public health importance. This hospital-based case-control study was conducted to examine the association between maternal periodontitis and preterm birth in a Vietnamese population.

MATERIALS AND METHODS

Study participants

The study population was women in Thai Nguyen who gave birth at the Thai Nguyen Center General Hospital in Thai Nguyen, Viet nam between July 2006 and December 2006. This public hospital is the biggest in Thai Nguyen, where most pregnant women in the province come to give birth. Subjects were enrolled in the a case-control study within 24 hours postpartum after giving informed written consent. The hospital birth register was examined daily by the study team to identify all cases, defined as women who spontoneously delivered before 37 weeks gestation. Controls were women who delivered at term gestational age. The control group was selected daily from the birth register at the same time as the cases by random sampling (selected according to the number of the hospital code) of up to two control women per case. Women who gave birth to a singleton live infant, had normal mental health and ability to communicate, were willing to participate in the study and had at least 20 teeth were eligible for the study. Exclusion criteria included HIV seropositive women, admission to the ICU for any reason, obstetric abnormalities, chronic hypertension, cardiovascular disease and diabetes mellitus. This study was approved by the Thai Nguyen Medical University and Thai Nguyen Center General Hospital Ethics Committee.

Periodontal examination

One dentist, blinded to case-control status, carried out all the periodontal examinations. The examinations were performed with the woman supine in the hospital bed. To ensure the examiner was blinded, the infant was taken to another area in advance. Maternal periodontal status was determined by full mouth examination at 6 sites (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, distolingual) for each tooth except the third molars using a periodontal probe (PCP- UNC 15 probe- Hu Friedy, Chicago, USA). Periodontitis was defined as the presence of at least 4 teeth with ≥ 1 site with a probing depth (PD) ≥ 4 mm, clinical attachment loss (CAL) ≥ 3 mm or bleeding on probing (BOP) after 10 seconds at the same site (Canakci *et al*, 2004). The examiner demonstrated good intra-examiner reliability with a Kappa statistic of 88% for measuring the PD and 94% for measuring the distance between the gingival margin (GM) and the cementoenamel junction (CEJ).

Identification of risk factors

After periodontal examination, face to face interviews with the mothers were carried out using a structured questionnaire. Three trained investigators blinded to periodontal status carried them out. The questionnaire included information regarding general characteristics, socioeconomic status, smoking, alcohol and antibiotic use, antenatal care, obstetric history, medical history, and dental his-

tory. Obstetric history and medical history were obtained from the medical records.

Statistical analysis

Differences between cases and controls were compared using descriptive statistics. Multiple logistic regression was used to determine the effect of periodontitis on preterm birth adjusted for potential confounders. Odds ratios (OR) with 95% confident intervals (CI) and p-values were obtained to evaluate the level of the association. We also used multiple linear regression dealing with the term of delivery as gestational age (continuous variable). Confounding effects were determined using the change in estimate method with a cut point of 10% (Greenland, 1989). All statistical tests were 2 sided with a significant level of 5%.

RESULTS

A total of 390 subjects were recruited for the study; 130 cases and 260 controls. Cases were not significantly different from controls in regard to age groups, pre-pregnancy BMI, presence of systematic infection, parity, and history of periodontal treatment. Women with preterm birth were more likely to be in the minority group, live in a rural area, have a lower socioeconomic status, have less weight gain, poorer ANC, the presence of genitourinary infection, or use of antibiotics during pregnancy, than women with normal birth (Table 1).

For all teeth, the case group had a higher proportion of subjects with PD ≥4 mm, CAL ≥3 mm (Figs 1, 2). The case group had a higher percentage of periodontitis (33.9%) than the control group (10.4%) (Table1) (crude OR= 4.42, 95%CI= 2.49, 7.88). After adjusting for age groups, ethnicity, place of residence, education level, occupation, income, pre-pregnancy BMI, amount of weight gain, level of receiving antenatal care, parity, systematic infection, genitourinary infections, antibiotic use, and history of periodontal treatment, women who had periodontitis were 4.47 times more likely to give preterm birth than those who did not (OR_{adj}= 4.47, 95%CI= 2.43, 8.20) (Table 2). Using the changes in estimate method, only amount of weight gain and history of genitourinary infection showed an effect on the association between periodontitis and preterm birth. The results of multiple linear regression reveal that women with priodontitis were significantly more likely to deliver a baby small for gestational age than those without periodontitis when controlling for those variables mentioned above (R^2_{adj}= 0.20, p<0.001) (Table 3).

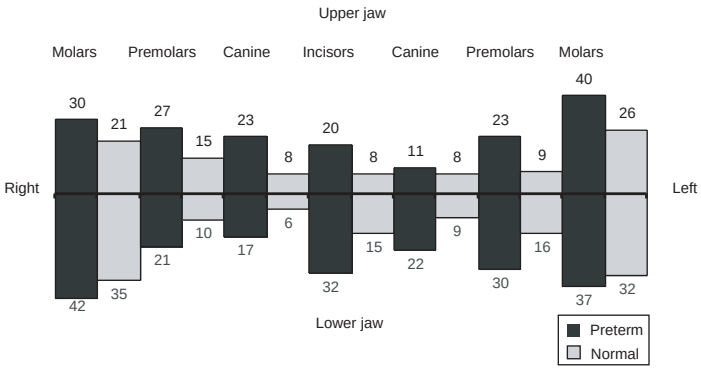

Fig 1–Periodontal status by percentage of subjects with PD ≥ 4 mm by term of delivery.

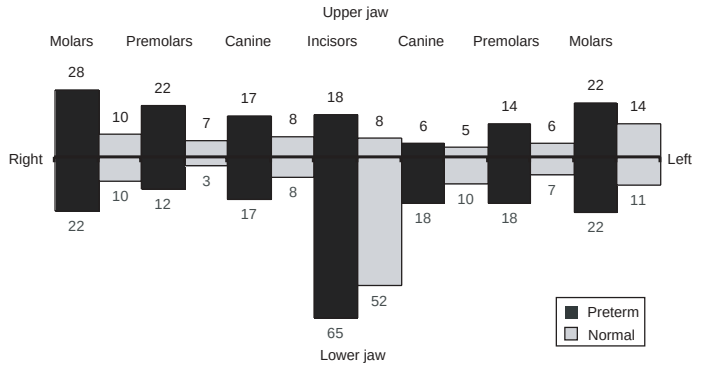

Fig 2–Periodontal status by percentage of subjects with CAL ≥ 3 mm by term of delivery.

Table 1
Univariate analysis of risk factors for preterm birth.

Characteristics	Normal term (n=260) n (%)	Preterm birth (n=130) n (%)	p-value
Maternal age			
18-24 years	75 (28.8)	54 (41.5)	0.089
25-29 years	121 (46.5)	47 (36.2)	
30-35 years	50 (19.2)	23 (17.7)	
≥ 36 years	14 (5.4)	6 (4.6)	
Ethnicity			
Kinh group	200 (76.9)	87 (66.9)	0.024
Minority group	60 (23.1)	43 (33.1)	
Place of residence			
Urban	124 (47.7)	48 (36.9)	0.028
Rural	136 (52.3)	82 (63.1)	
Education			
Primary	26 (10.0)	31 (23.8)	0.001
Secondary	135 (51.9)	65 (50.0)	
High	99 (38.1)	34 (26.2)	
Occupation			
Housewife	71 (27.3)	26 (20.0)	0.005
Farmer	69 (26.5)	58 (44.6)	
Labor	36 (13.8)	14 (10.8)	
Official	84 (32.3)	32 (24.6)	
Income			
Low	14 (5.4)	18 (13.8)	0.008
Medium	134 (51.5)	70 (53.8)	
High	112 (43.1)	42 (32.3)	
Pre-pregnancy BMI			
Underweight	73 (28.1)	35 (26.9)	0.971
Normal	183 (70.4)	93 (71.5)	
Overweight	4 (1.5)	2 (1.5)	
Maternal weight gain			
Low	22 (8.5)	44 (33.9)	<0.001
Normal	143 (55.0)	78 (60.0)	
High	95 (36.5)	8 (6.1)	
Antenatal care			
Poor attendance	25 (9.6)	33 (25.4)	<0.001
Fair attendance	194 (74.6)	77 (59.2)	
Good attendance	41 (15.8)	20 (15.4)	
Parity	89 (34.2)	45 (34.6)	0.630
Systematic infections			
No infection	250 (96.2)	121 (93.1)	0.148
Infected at 1st trimester	5 (1.9)	2 (1.5)	
Infected at 2nd trimester	1 (0.4)	4 (3.1)	
Infected at 3rd trimester	4 (1.5)	3 (2.3)	
Antibiotics used	16 (6.2)	19 (14.6)	0.006
Genitourinary infections			
No infection	218 (83.8)	90 (69.2)	<0.001
Infected at 1st trimester	19 (7.3)	6 (4.6)	
Infected at 2nd trimester	7 (2.7)	3 (2.3)	
Infected at 3rd trimester	16 (6.2)	31 (23.8)	
History of periodontal treatment	18 (6.9)	6 (4.6)	0.256
Periodontitis	27 (10.4)	44 (33.9)	<0.001

Table 2
Multiple logistic regression model for the association between periodontitis and preterm birth[a].

Preterm birth	OR	SE	p-value	95%CI
Periodontal disease	4.47	1.39	<0.001	2.43-8.20
Maternal weight gain				
Low	1.00			
Normal	0.35	0.11	0.001	0.19-0.66
High	0.06	0.03	<0.001	0.02-0.14
Genitourinary infection				
No infection	1.00			
At 1st trimester	1.16	0.67	0.794	0.37-3.62
At 2nd trimester	0.90	0.68	0.887	0.21-3.93
At 3rd trimester	5.66	2.13	<0.001	2.71-11.83

[a]Adjusted for age, ethnicity, place of residence, education level, occupation, income level, pre-pregnancy BMI, maternal weight gain, ANC, parity, history of preterm birth, systematic infections, genitourinary infections, antibiotics used, and history of periodontal treatment.

Table 3
Multiple linear regression model for the association between periodontitis and gestational age[a].

Gestational age (weeks)	β	SE	p-value	95% CI
Periodontal disease	-1.50	0.38	<0.001	-2.25,-0.75
Maternal weight gain				
Normal	1.35	0.39	0.001	0.58, 2.12
High	2.60	0.45	<0.001	1.70, 3.49
ANC				
Fair	1.43	0.40	<0.001	0.64, 2.22
Good	1.75	0.51	0.001	0.74, 2.76
Genitourinary infection				
At 1st trimester	0.00	0.57	0.998	-1.12, 1.12
At 2nd trimester	-0.90	0.88	0.306	-2.62, 0.83
At 3rd trimester	-1.04	0.43	0.015	-1.88, -0.20
Constant	35.42	0.47	<0.001	4.50, 36.34

[a]Adjusted for age, ethnicity, place of residence, education level, occupation, income level, pre-pregnancy BMI, maternal weight gain, ANC, parity, history of preterm birth, systematic infections, genitourinary infections, antibiotics used, and history of periodontal treatment.

DISCUSSION

The results of the present study show the adjusted OR for the association between periodontitis and preterm birth was 4.47. This association is in line with other studies from the Americas (Offenbacher *et al*, 1996; Jarjoura *et al*, 2005; Lunardelli and Peres, 2005) with an OR varying between 2.6 and 7.9. On the other hand, a different conclusion was reported for some European studies, such as in England (Davenport *et al*, 2002; Moore *et al*, 2005), Germany (Noack *et al*, 2005) and Spain (Moreu *et al*, 2005), which found no significant association between maternal periodontitis and preterm delivery. Limitation in

sample size (Moore *et al*, 2005; Moreu *et al*, 2005; Noack *et al*, 2005; Skuldbol *et al*, 2006), differences in definitions of periodontitis (Davenport *et al*, 2002; Mokeem *et al*, 2004; Moore *et al*, 2005; Skuldbol *et al*, 2006), inappropriate case definitions (Mokeem *et al*, 2004), and insufficient control for confounding variables (Buduneli, 2005; Dortbudak *et al*, 2005; Moore *et al*, 2005; Moreu *et al*, 2005) may explain the discrepancies in the results among the published studies. Some studies defined periodontal disease in terms of Community Periodontal Index for Treatment Needs (CPITN) (Davenport *et al*, 2002; Mokeem *et al*, 2004) which has limited sensitivity for disease detection. Periodontal disease may occur at each site for each tooth, however, in some studies, the researchers examined only part of the tooth (only 2-4 sites per tooth) (Dortbudak *et al*, 2005; Rajapakse *et al*, 2005). This may result in an underestimation of periodontal disease, leading to a reduced risk estimate (OR, RR). In our study, six sites for each teeth were examined. Evaluating the PD at 4 mm, CAL at 3 mm and BOP for each site is more appropriate to assess the periodontal status.

In this study we used a case-control study rather than a cohort study due to the advantage of recruiting all women with a preterm birth during a given time. Moore *et al* (2005) conducted two studies at the same hospital and compared some characteristics of case-control subjects with those in a prospective study. These data highlighted differences in the populations between the two studies and therefore the potential for selection bias in studies which recruited women early in pregnancy (Moore *et al*, 2004, 2005).

The study subjects were homogeneous in that all the women were married and treated at the same hospital in Thai Nguyen city. Although smoking and alcohol drinking were not exclusion criteria, none of the participants smoked or drank during pregnancy giving us an opportunity to study the association between periodontitis and preterm birth in a non-smoking, non-drinking population.

Periodontitis shares many risk factors with preterm birth, such as age, smoking, socioeconomic status, systematic health status, infections, antibiotics used, excessive body mass index, and maternal disorders. We took into account important factors then used both restricted eligability criteria and the change in estimate method to control for confounding effects. To reduce errors, we determined the gestational age by last menstrual period and ultrasound. Interviewers were blinded to periodontal status to control information bias. Oral examination was done after delivery but within 24 hours, to minimize the periodontal status changed. In this study periodontitis was defined as having a PD ≥ 4 mm, CAL ≥ 3 mm, or BOP at the same site, so the results could reliably conclude that periodontitis occurred during pregnancy. In this study, the limitations included information bias that may have occurred with some variables, such as weight before pregnancy, medical history, and dental history.

An explanation of the biological mechanism associated between periodontitis and preterm birth begins with endotoxins from gram-negative, anaerobic, and microaerophilic bacteria that colonize the subgingival area in periodontal disease. Periodontal destruction is associated with activation of cell-mediated immunity, leading to production of cytokines, an increase in interleukins IL-1 and IL-6, tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP) and the ensuing synthesis and release of prostaglandins (especially prostaglandin E2) (Collins *et al*, 1994a,b; Offenbacher *et al*, 1998; Pitiphat *et al*, 2005, 2006). These molecules produced in the periodontium can reach the blood circulation, cross the placental membrane into the amniotic fluid. During normal pregnancy, the intra-amniotic levels of these mediators rise physiologically until a threshold level is reached, at that point labor,

cervical dilatation and delivery are induced. Abnormal production of these mediators in the setting of periodontal infection increases, uterine contractions and premature rupture membranes, triggering preterm labor.

A greater integration of medicine and dentistry may require that dentists take more responsibility for their patients' systemic health and physicians assume a more active role in their patients' oral health. Our findings suggest that periodontitis may increase the risk of preterm birth even among women who do not smoke or drink. Further intervention studies should be performed in this population to provide guidance for program planning and implementation of maternal and child care services.

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