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Interleukin-1 receptor antagonist gene polymorphism, adverse pregnancy outcome and periodontitis in Turkish women

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ABSTRACT

Objective: The aim of this study was to determine associations between interleukin (*IL*)-*1A* (*+4845*), *IL-1B* (*+3954*), and *IL-1* receptor antagonist (RN) variable number tandem repeat polymorphisms and adverse pregnancy outcomes and periodontitis in a Turkish women.
Design: A total of 156 patients, including 64 women with normal birth outcome (NB) and 92 women with preterm/low birth weight outcome (PLBW) were included in this case-control study. Within 24 h after labor, maternal demographic characteristics and clinical periodontal parameters were recorded. The distribution and genotype frequencies of *IL-1* were analyzed with polymerase chain reaction-restriction fragment length polymorphism assay. Statistical analyses were carried out for clinical periodontal parameters, genotype frequencies, and to identify explanatory variables for PLBW.
Results: PLBW was associated with maternal age ($p < 0.05$), irregular prenatal care ($p < 0.001$), previous PLBW ($p < 0.05$), and antibiotic use during pregnancy ($p < 0.05$). Measurements of probing depth and clinical attachment level (CAL) were significantly higher in the PLBW group than in the NB group ($p < 0.001$). PLBW was associated with *IL-1RN* allele 2 ($p < 0.001$). Moreover, stepwise logistic regression analysis showed that CAL (OR 1.39, 95% CI: 1.04–1.85) and *IL-1RN* polymorphism (OR 7.92, 95% CI: 2.76–22.79), previous PLBW (OR 5.01, 95% CI: 1.08–23.17), age (OR 1.22, 95% CI: 1.04–1.44) were predictors found to increase the risk of PLBW ($p < 0.05$). There was a negative association between PLBW and regular prenatal care, total number of births, use an antibiotic during pregnancy period ($p < 0.05$).
Conclusion: Our study showed that, *IL-1RN* allele 2, periodontal disease characterized with clinical attachment loss, previous PLBW and age could be an important risk factors for PLBW.

1. Introduction

Preterm birth (PB) (any live birth before 37 weeks of gestation) and/or low birth weight (LBW) (less than 2500 g) are the primary causes of neonatal morbidity and mortality (Saigal & Doyle, 2008). Many risk factors have been known to influence the pregnancy outcome, including alcohol, smoking, high or low maternal age, low socioeconomic status, inadequate prenatal care, low maternal body mass index, hypertension, generalized infections, genitourinary tract infections, and diabetes (David & Collins, 1997; Offenbacher et al., 1996). Previous cohort studies (Boggess, Beck, Murtha, Moss, & Offenbacher, 2006; Offenbacher et al., 2001; Santos-Pereira et al., 2007) and case-control studies (Konopka, Rutkowska, Hirnle, Kopec, & Karolewska, 2003; Radnai et al., 2006) have shown potential associations between chronic periodontitis and reduced fetal weight. On the other hand, conflicting results have been observed in the literature in this regard (Buduneli et al., 2005; Davenport et al., 2002). The exact etiology of preterm low birth weight (PLBW) is still under discussion.

Interleukin-1 (IL-1) is the most extensively investigated proinflammatory cytokine, and it is well known to play a central role in the pathogenesis of periodontitis and adverse pregnancy outcomes (Konopka et al., 2003; Michalowicz et al., 2009; Noack, Klingenberg, Weigelt, & Hoffmann, 2005). There is evidence that susceptibility to inflammation is influenced by genetic variation in cytokine genes (Attur et al., 2010; Dewberry, Holden, Crossman, & Francis, 2000). The *IL-1* gene cluster encodes the production of cytokines that affect many inflammatory processes, including degradation of the extracellular matrix (Graves & Cochran, 2003;

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Page, 1991). The IL-1 receptor antagonist (ra) is an anti-inflammatory cytokine, which prevents receptor binding of the proinflammatory family members IL-1α and IL-1β. The *IL-1* gene cluster on the long arm of chromosome 2 (2q13) encodes cytokines of the IL-1 family, including IL-1α, IL-1β, and IL-1ra (Kornman et al., 1997). The *IL-1A* and *IL-1B* genes encode the agonist proteins IL-1α and IL-1β, respectively, while the *IL-1RN* gene encodes IL-1ra. In effect, monocytes from subjects carrying the T allele of the *IL-1B* (*+3954*) gene produced a greater amount of IL-1β than individuals lacking this allele (Pociot, Mølvig, Wogensen, Worsaae, & Nerup, 1992). The *IL-1A* (*–889*) T allele has been associated with an almost four-fold increase in IL-1α levels in gingival crevicular fluid (Shirodaria, Smith, McKay, Kennett, & Hughes, 2000) whereas allele 2 of the *IL-1RN* gene has been reported to be associated with enhanced IL-1β secretion in vitro (Pociot et al., 1992).

In 1997, Kornman et al. (1997) found that allele 2 of the *IL-1A* (*–889*) (or the concordant +4845) and *IL-1B* (*+3954*) (formerly designated +3953) genes among the white North American population was associated with severe chronic periodontitis in non-smokers. Of interested, Pociot et al. (1992) reported that the presence of the +3953 polymorphism of the *IL-1β* gene is correlated with monocyte function. The *IL-1* gene cluster, particularly the T allele at both *IL-1A* (*–889*) and *IL-1B* (*+3954*) described by Kornman et al. (1997) has been extensively studied and is associated with periodontitis in different populations (Galbraith, Hendley, Sanders, Palesch, & Pandey, 1999; Konig, Ruhling, Plagmann, Meisel, & Kocher, 2005; Kornman et al., 1997; Lopez, Jara, & Valenzuela, 2005; Shirodaria et a l., 2000). Although some studies have suggested a complex allele-dependent regulating effect of this gene on IL-1 secretion (Santtila, Savinainen, & Hurme, 1998; Vamvakopoulos, Green, & Metcalfe, 2002) few studies have investigated the relationship between periodontitis and allele 2 of the *IL-1RN* gene, which encodes IL-1ra, in detail.

Several studies have evaluated gene polymorphisms in women with PB in certain countries. In the African-American population, it was reported that fetal *IL-1B* (*+3953*) polymorphism is associated with PB. Fetuses of Hispanic descent carrying allele 2 of the *IL-1RN* gene were found to be at increased risk for PB (Genç, Gerber, Nesin, & Witkin, 2002). Sata et al. (2009) found that the risk of PB significantly increased in women carrying the *IL-1A* polymorphism. However, studies (Edwards, Ferguson, & Duff, 2006; Engel et al., 2005) found no evidence for the association between maternal *IL-1A* or *IL-1B* polymorphisms and PLBW. Therefore, a shared genetic predisposition might explain the association between periodontitis and PLBW.

Although several studies have investigated the possible association between *IL-1* gene polymorphism, PLBW (Chaves, Babayan, Bezerra Cde, Linhares, & Witkin, 2008; Kalinka & Bitner, 2009; Sata et al., 2009; Schmid et al., 2012; Yılmaz et al., 2012) and periodontitis (Baradaran-Rahimi, Radvar, Arab, Tavakol-Afshari, & Ebadian, 2010; Berdeli, Emingil, Gürkan, Atilla, & Köse, 2006; Guzeldemir, Gunhan, Ozcelik, & Tastan, 2008), no data exists regarding the association between the *IL-1 A*, *IL-1B,* and *IL-1RN* variable number tandem repeat (VNRT) polymorphisms and adverse pregnancy outcomes and periodontitis in the Turkish women. We hypothesized that the *IL-1A* (*+4845*), *IL-1B* (*+3954*), and *IL-1RN* gene polymorphisms may be correlated with PLBW. Smoking has been well documented by numerous studies as a major environmental risk factor for periodontitis and adverse pregnancy outcomes (Kornman et al., 1997; Laine et al., 2001). Therefore, we only selected non-smoking individuals in this study as the smoking-related risk could obscure the polymorphism-related increase in risk for periodontitis and adverse pregnancy outcomes. This study aimed to determine the association between *IL-1A* (*+4845*), *IL-1B* (*+3954*), and *IL-1RN* polymorphisms with adverse pregnancy outcomes and periodontitis in a non-smoking Turkish women.

2. Materials and methods

2.1. Study groups

This unmatched case-control study was conducted between January 2004 and June 2004 at Dr. Faruk Sükan Maternity and Childbirth Hospital, Konya, Turkey. The hospital was visited twice a week regularly. In our study, 321 women were examined, and 165 women (101 women with NB and 64 women with PLBW) refused to participative the study or did not meet the inclusion criteria. The women selected for this study were those who were present and able to be examined and interviewed in their hospital beds. A total of 156 mothers who invited and volunteered to participate in this study selected within 24 h of delivery according to accessibility and availability during the postpartum period. The participants signed an informed consent form after they were informed about the objective and methods of the study. This study was approved by the Local Ethics Committee of the Selcuk University Faculty of Dentistry (project number: 04/01).

Pregnant women between 18 and 35 years of age with single gestation and with ≥20 on-crowded teeth excluding third molars were included in this study. Subjects were divided into normal birth (NB) and PLBW groups on the basis of their pregnancy outcome. Women who delivered an infant with a birth weight of more than 2500 g after 37 weeks of gestation were placed in the NB group. Women who delivered infants whose birth weight was below 2500 g or before 37 weeks of gestation were placed in the PLBW group (Saigal & Doyle, 2008). Current/past tobacco user, alcohol abuse, history of high-risk gestation, hypertension, gestational diabetes, any systemic disease and placenta previa were the exclusion criteria for this study. Maternal, obstetric, and demographic factors such as maternal age, maternal education, regular prenatal care, genitourinary tract infections during pregnancy, total number of births, previous PLBW, and antibiotic use during the pregnancy period were also recorded.

2.2. Clinical periodontal examination

Periodontal examination was performed with the participants in the supine position on a hospital bed. The same calibrated investigator (NAK) carried full mouth periodontal examination of all the participants. The probing depth (PD) and clinical attachment level (CAL) were measured at six sites for teeth using a Williams periodontal probe.[1] The PD was recorded at each location as the distance from the gingival margin to the most apical extent of probe penetration. The CAL was determined using the cemento-enamel junction as a reference point. The PD and CAL measurements were measured using a periodontal probe and rounded to the higher millimeter. The plaque index (PI) (Löe, 1967) and papillary bleeding index (PBI) (Mühlemann, 1977) were also recorded.

The subjects were categorized as follows (Offenbacher et al., 2001): a patient was considered to have moderate to severe periodontitis if there were at least four sites with PD ≥ 5 mm and CAL ≥ 2 mm. Periodontal heath was defined as the absence of any PD > 3 mm and no sites AL > 2 mm. The mild periodontitis was assigned to the women who had less disease than moderate to severe group and had more disease than the healthy group and are referred to as mild periodontitis. Although we measured the bleeding scores, we did not consider for this analysis. These groups

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