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ORIGINAL ARTICLE

Periodontal disease in gestational and type 1 diabetes mellitus pregnant women

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OBJECTIVE: The present study evaluated the relationship between periodontal disease and its clinical variables in Brazilian non-diabetic pregnant women (C), gestational diabetes mellitus (GDM), or type 1 diabetes mellitus (T1DM).

SUBJECTS AND METHODS: A periodontal exam was performed in one hundred and sixty-one pregnant women (GDM:80; T1DM:31; C:50) by a single-blinded calibrated examiner who recorded plaque index (PI), gingival index (GI), bleeding index (BI), gingival margin location (GM), probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), and tooth mobility index (MI). The medical variables were age, pregestational body mass index (pre-BMI), fasting plasma glucose (FPG), and glycated hemoglobin (HbA_{1c}).

RESULTS: The GI, GM, PD, CAL, BOP, and MI were significantly higher ($P < 0.01$) among GDM and T1DM than for C. The PI was higher in GDM and similar between C and T1DM. The Adjusted Final Model for medical variables to evaluate the effects of groups on periodontal parameters confirmed these results.

CONCLUSIONS: The presence of periodontal disease was significantly higher in Brazilian diabetic pregnancies (GDM and T1DM) when compared to non-diabetic pregnant women (C). The degree of periodontal disease was similar between the GDM and T1DM groups. Age, pregestational BMI, and HbA_{1c} were factors related to CAL development in these two types of diabetes mellitus.
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Keywords: pregnancy; gestational diabetes; type 1 diabetes; periodontal disease

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Introduction

Gestational diabetes mellitus (GDM) is a condition defined as any degree of glucose intolerance that starts or is first recognized during pregnancy, and it is characterized by recent hyperglycemia as a consequence of an association between insulin resistance and inadequate insulin secretion (Buchanan *et al*, 2007). Type 1 diabetes mellitus (T1DM) is characterized by chronic hyperglycemia that is caused by autoimmunity against pancreatic beta cell and insulin deficiency (American Diabetes Association, 2010). Periodontal disease is an infectious disease characterized by the destruction of the periodontal tissues leading to loss of tooth support. It has a multifactor etiology and pathogenesis, resulting from interaction between environmental, acquired, and genetic risk factors (Nishihara and Koseki, 2004).

A few studies have suggested that pregnancy is a modifying factor of periodontal disease (Laine, 2002; Mascarenhas *et al*, 2003). Increased vascularization and gingival inflammation have been reported as a result of an increase in estrogen and progesterone levels during pregnancy (Ojanotko-Harri *et al*, 1991; Raber-Durlacher *et al*, 1994), which also leads to changes in the oral microflora (Kornman and Loesche, 1980; Jensen *et al*, 1981; Gürsoy *et al*, 2010).

The pathogenesis of periodontal disease is complex, because it reflects a combination between the initiation and the maintenance of the chronic inflammatory process, characterized by the presence of a diverse microbial flora and its numerous bacterial products (Nishihara and Koseki, 2004). Subsequently, host response to this infection mediates a complex cascade of tissue-destructive pathways. Additional factors contributing to this multifaceted local disease process in the oral cavity include a number of systemic diseases, especially diabetes, that can amplify the host response to local microbial factors (e.g. endotoxin), resulting in destructive periodontal breakdown (Ryan *et al*, 2003).

Recent studies suggest that subgingival bacteria levels associated with periodontitis (*Actinobacillus actinomycetemcomitants, Porphyromonas gingivalis, Forsythia*

gleaceae, and *Treponema denticola*) do not change in normal pregnancy (Adriaens *et al*, 2009) and that the presence of *T. forsythia* in the vaginal flora is a potential risk factor for GDM (Dasanayake *et al*, 2008). Other studies suggest that diabetes mellitus in and of itself is a risk and modifying factor for periodontal disease (Yalda *et al*, 1994; Verma and Bhat, 2004).

A biological interaction between periodontal disease and hyperglycemia has been reported (Grossi and Genco, 1998; Iacopino, 2001; Taylor, 2001; Katz *et al*, 2010), even though the exact mechanisms involved in the pathogenesis of this condition during diabetes still remain unclear (Mealey and Oates, 2006; Lalla, 2007). It is believed that complex interactions between the following factors may increase the prevalence and severity of periodontal disease in patients with diabetes: genetic predisposition, accumulation of advanced glycation end-products in periodontal tissues, alterations in host immune responses and collagen metabolism, and changes in gingival crevicular fluid and microflora (Solskolne and Klinger, 2001). Periodontal disease serves as a reservoir for Gram-negative anaerobic mediator organisms, lipopolysaccharides, and inflammatory mediators (including PGE_2 and TNFα) and can consequently trigger or increase insulin resistance (Nishimura *et al*, 2005; Engebretson *et al*, 2007).

Periodontal disease is recognized as the sixth complication of diabetes and multiple epidemiologic studies have demonstrated that both T1DM and type 2 diabetes mellitus (T2DM) are predictors of periodontal disease when the systemic condition is poorly controlled (Löe, 1993). Periodontal inflammation during pregnancy may be associated with adverse pregnancy outcomes such as preeclampsia, low birth weight, and preterm birth (Offenbacher *et al*, 1996; Cota *et al*, 2006; Xiong *et al*, 2006a,b; Toygar *et al*, 2007).

A few reports have shown the prevalence of periodontal disease in GDM and in pregnant patients with T1DM (Guthmiller *et al*, 2001; Novak *et al*, 2006; Xiong *et al*, 2006a,b, 2009; Dasanayake *et al*, 2008; Kasaj *et al*, 2008). However, there are no data comparing the factors related to periodontal disease among these two types of diabetes. Likewise, it remains to be determined whether the mechanisms involved are the same in both T1DM and GDM. Therefore, the objective of the current study was to evaluate the presence of periodontal disease and its associated factors within a well-characterized cohort of Brazilian non-diabetic pregnant women, women with GDM, or women with T1DM.

Individuals and methods

Individuals

The study was conducted with two groups tracked by the Diabetes Centre consisting of 80 patients with GDM and 31 pregnant patients with T1DM, compared to a group of 50 non-diabetic pregnant patients (C) tracked by the Obstetric Outpatient Clinic at São Paulo Federal University, São Paulo, SP, Brazil. The study was approved by the University's Ethics Committee, where it was carried out (Protocol Number: CEP/UNIFESP 0547/05). All evaluated patients were randomly selected according to the criteria of variables for including and excluding subjects, and all patients agreed to participate in the study voluntarily by signing an informed consent form. The criteria of variables for including patients were the stage of pregnancy between the second and third trimester, the presence of at least 12 teeth, and a proven diagnosis of GDM, T1DM, or normal glucose tolerance in accordance with the American Diabetes Association (Metzger *et al*, 2007). The criteria for excluding patients were HIV-positive women, smokers, alcohol and drug users, and patients who had used antibiotics or had been undergoing periodontal treatment at any time during the 3 months preceding the study (by patient's medical records; confirmed during dental anamnesis). A periodontal examination was undertaken, followed by instructions regarding dental treatment and promotion of oral health for all participants and their children.

Methods

The periodontal evaluation was performed by a single-blinded, calibrated, and well-trained examiner. The intra-class correlation coefficient at site level ranged between 0.82 and 0.89, and at subject level for mean probing depth (PD) between 0.87 and 0.95. A manual probe (PCPUNC-15; Hu-Friedy, Chicago, IL, USA) was used for periodontal examination. All teeth present, with the exception of the third molars, were examined. Probing was performed on six sites per tooth and the following periodontal parameters were evaluated: gingival margin location (GM), PD, clinical attachment level (CAL), gingival index (GI) (Löe and Silness, 1963), plaque index (PI) (Silness and Löe, 1964), bleeding index (BI), bleeding on probing (BOP), and tooth mobility index (MI) (Newman *et al*, 2007). These parameters were related to the following medical variables: age, stage of gestation (SG), pregestational body mass index (pre-BMI – by medical charts) (kg m^{-2}), fasting plasma glucose (FPG) [mg dl^{-1} (by glucose-oxidase method)], and glycated hemoglobin (HbA_{1c}) [HPLC method; normal values (4.0–6.3%)].

The diabetic and control groups were followed up throughout their gestational period. The GDM group was treated with diet alone or diet plus insulin when their FPG level was above 94 mg dl^{-1} and/or their 2-h postprandial glucose level was above 120 mg dl^{-1}. Insulin management was individualized, but most patients with gestational diabetes required 0.7 units per kg of weight per day. About two-thirds of the basal insulin was administered in the morning and one-third at night. Ultra-rapid-acting insulin was administered with the main meals or when necessary. Diversely, glycemic treatment was optimized for patients presenting T1DM during gestation, with two or three doses of basal insulin administered in parallel with multiple doses of ultra-rapid-acting insulin.

Statistical analysis

For characterization of the study sample, the mean and standard deviation (s.d.) was described. Spearman's

correlation coefficients and the respective P values obtained for the sample were used to evaluate the correlation between the variables of interest. Quantitative variables were compared between groups using generalized linear models, assuming that normal or gamma distribution gives the best fit for clinical and laboratory periodontal trials, and P-value goodness of fit >0.10 for comparison between groups. The linear model was adjusted for age, GA, FPG, pre-BMI, and HbA_{1c} to evaluate the effects of groups on teeth, PI, GI, MI, CAL, PD, GM, and BOP. The differences were considered to be significant when $P < 0.05$.

Results

Table 1 shows the clinical baseline and laboratory characteristics among the 161 participants studied. Patients with GDM were older ($P < 0.01$) and presented higher values of BMI before gestation ($P < 0.01$) compared to the T1DM and C groups. The differences show that FPG ($P < 0.01$) and HbA_{1c} ($P < 0.01$) were higher in the T1DM when compared to the other two groups; moreover, these variables were higher in the GDM ($P < 0.01$), in relation to the C group. The gestational stage (GS) was shorter in T1DM ($P < 0.01$) in relation to GDM and C groups. However, we did not find a significant relationship between GS and CAL in any of these groups studied.

In Table 2, the same initial estimates were presented to evaluate the periodontal parameters and in all cases, the differences among the groups were significant ($P < 0.01$). The GDM group showed less number of teeth ($P < 0.01$) and a higher PI level ($P < 0.01$), when compared to the T1DM and C groups. When comparing GI, GM, PD, CAL, BOP, and MI parameters between GDM and T1DM, no significant differences were observed, but all of them were significantly higher when compared to the control group. The Adjusted Final Model for medical variables (GA, age, FPG, preBMI, and HbA_{1c}) to evaluate the effects of groups on periodontal parameters confirmed that PI, GI, MI, CAL, PD, GM, and BOP showed significant differences among the groups ($P < 0.01$). The number of teeth was the only periodontal parameter to show no difference significant among the tree groups by this analysis ($P = 0.09$).

The prevalence of gingival bleeding was 98.80% in GDM, 93.54% in T1DM, and 84% in C subjects, with a significant ($P < 0.004$) difference between groups.

The distributions of CAL in the groups are illustrated in Figure 1. Considering all the subjects studied as a whole group, the Spearman's correlation coefficients

Table 1 Clinical and laboratorial parameters in the groups studied

	Normal control		*GDM*		*T1DM*		
Variable	*N*	*Mean (s.d.)*	*N*	*Mean (s.d.)*	*N*	*Mean (s.d.)*	P-*value*
Age (years)	50	27.22 (5.38)^{A}	80	32.60 (6.23)^{B}	31	24.61 (5.78)^{C}	<0.01
Pre-BMI (kg m^{-2})	50	22.51 (3.32)^{A}	80	27.05 (3.69)^{B}	31	23.46 (3.42)^{A}	<0.01
FPG (mg dl^{-1})	50	77.22 (9.54)^{A}	80	102.61 (34.54)^{B}	31	166.97 (64.41)^{C}	<0.01
HbA_{1C} (%)	40	5.04 (0.54)^{A}	74	5.58 (0.85)^{B}	31	8.34 (2.41)^{C}	<0.01
TDDM (months)	–	–	80	3.12 (1.76)^{A}	31	126 (67.6)^{B}	<0.01
GA (weeks)	50	20.44 (5.70)^{A}	80	26.85 (7.49)^{B}	31	18.77 (5.23)^{C}	<0.01

s.d., standard deviation; Pre-BMI, pregestational body mass index; FPG, fasting plasma glucose; HbA_{1C}, glycated hemoglobin; TDDM, time of diagnosis of diabetes mellitus; GA, gestational age; GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus. Different letters: significant differences between groups ($P < 0.05$).

Table 2 Periodontal parameters in the groups studied

	Normal control		*GDM*		*T1DM*			
Parameters	*N*	*Mean (s.d.)*	*N*	*Mean (s.d.)*	*N*	*Mean (s.d.)*	P-*value*	P-*value**
Teeth	50	26.30 (2.55)	80	22.85 (4.34)	31	25.61 (3.44)	<0.01	0.09
PI	50	1.48 (0.72)^{A}	80	1.99 (0.66)^{B}	31	1.65 (0.69)^{A}	<0.01	<0.01
GI	50	0.84 (0.47)^{A}	80	1.52 (0.51)^{B}	31	1.26 (0.61)^{B}	<0.01	<0.01
GM (mm)	50	−0.10 (0.47)^{A}	80	0.26 (0.48)^{B}	31	0.22 (0.59)^{B}	<0.01	<0.01
PD (mm)	50	2.46 (0.49)^{A}	80	3.12 (0.72)^{B}	31	3.03 (1.03)^{B}	<0.01	<0.01
CAL (mm)	50	2.36 (0.43)^{A}	80	3.39 (0.79)^{B}	31	3.25 (1.46)^{B}	<0.01	<0.01
BOP (%)	79	14.17 (13.90)^{A}	29	29.92 (28.52)^{B}	42	26.93 (23.88)^{B}	<0.01	<0.01
MI	50	0.02 (0.07)^{A}	80	0.45 (0.67)^{B}	31	0.14 (0.53)^{C}	<0.01	<0.01

s.d., standard deviation; Teeth, number of teeth; PI, plaque index; GI, gingival index; GM, gingival margin; PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing; MI, mobility index; GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus. *Adjusted Final Model for medical variables (gestational age, age, fasting plasma glucose, and glycated hemoglobin). Different letters: significant differences between groups for adjusted final model ($P < 0.05$).

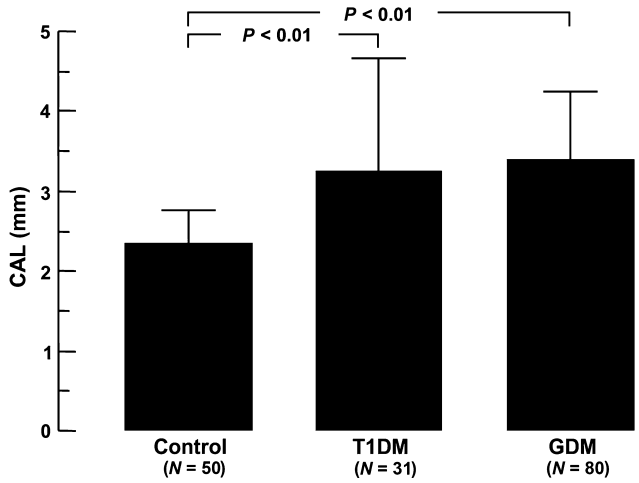

Figure 1 Distribution of clinical attachment level in the groups studied. Brazilian pregnant women ($n = 161$). C: non-diabetic pregnant women, GDM: gestational diabetes mellitus and T1DM: type 1 diabetes mellitus

Table 3 CAL and clinical variables: initial and final adjusted

	CAL	*CAL*
Medical variable	*Initial model:* P-*value*	*Final model: p-adjusted*
Age	< 0.01	< 0.01
Pre-BMI	0.01	0.01
FPG	< 0.01	< 0.01
HbA_{1C}	< 0.01	0.03

CAL, clinical attachment level; Pre-BMI, pregestational body mass index; FPG, fasting plasma glucose; HbA_{1C}, glycated hemoglobin. Initial model: *P*-value by Spearman's correlation coefficients and final model: adjusted *P*-value by linear gamma model.

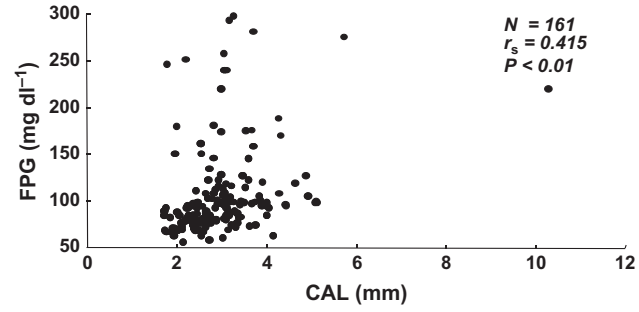

Figure 2 Correlation between fasting plasma glucose and clinical attachment level considering all the individuals studied as a whole group

showed that the CAL (Table 3) was correlated with the clinical variables: age (rS = 0.35; $P < 0.01$), pregestational BMI (rS = 0.25; $P = 0.01$), FPG (rS = 0.41; $P < 0.01$), Figure 2), and HbA_{1c} (rS = 0.27; $P < 0.01$, Figure 3). The effect of the medical variables, as a whole, in the CAL was evaluated by gamma linear model, which demonstrated in the final model a significant effect of age ($P < 0.01$), preBMI ($P = 0.01$), FPG

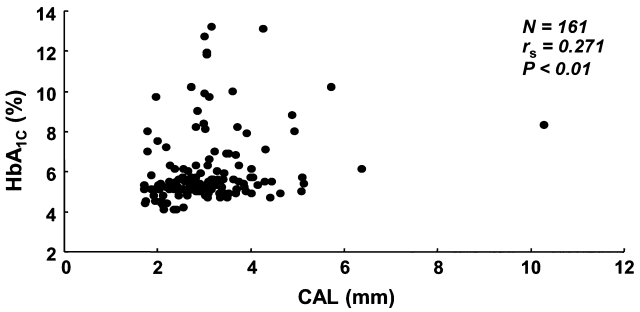

Figure 3 Correlation between glycemic control (HbA1C) and clinical attachment level considering all the individuals studied as a whole group

($P < 0.01$), and HbA_{1c} ($P = 0.03$) in the CAL. According to the results of Adjusted Final Model for medical variables, the CAL differences among the C and diabetic pregnancies (GDM and T1DM) groups still were statistically significant (GDM/C: $P < 0.01$; T1DM/C: $P = 0.01$; GDM/T1DM: $P = 0.29$).

Discussion

The analyses of this study showed that periodontal inflammation and destruction were significantly higher in diabetic pregnancies (GDM and T1DM) when compared to non-diabetic pregnant women (C), although no significant difference was revealed between the GDM and T1DM groups. It is important to clarify that GDM does not exclude the possibility that unrecognized glucose intolerance may be present prior to pregnancy (Metzger *et al*, 2007). Therefore, a probable undiagnosed case of hyperglycemia could be responsible for the increased level of periodontal disease in our GDM group.

The analysis of the demographic data (medical variables) of the three groups showed difference between the parameters, and it may interfere in the interpretation of the periodontal data. However, even after the final adjustments, the difference among those groups is expected, because they were pregnant women patients with different physical and behavioral profile (GDM, T1DM, and C).

Both gingival bleeding and BOP showed high values in all pregnant patients and confirmed that gingival inflammation is more evident in diabetic groups when compared to the C group. According to the literature, gingivitis is frequently associated with pregnancy (Löe and Silness, 1963; Silness and Löe, 1964; Miyazaki *et al*, 1991). Furthermore, diabetes affects the host defense systems, acting as a risk and a modifying factor for developing periodontal disease (Yalda *et al*, 1994; Verma and Bhat, 2004). The literature points to the importance of identifying women with a history of GDM, as this condition might increase the possibility of developing periodontal disease during pregnancy (Friedlander *et al*, 2007).

Plaque index values were significantly higher in GDM when compared to the other groups. A possible

explanation for this finding could be that a recent diagnosis of diabetes may have an effect upon oral health care behavior. Supporting this possibility, Anttila *et al* (2006) showed that symptoms of anxiety and depression are associated with a low frequency of tooth brushing. It reinforces the importance of oral health education in the prenatal care of patients presenting with GDM. However, no significant difference in PI was found between the T1DM and C groups; this supports the hypothesis that there are other etiological factors, apart from the PI, associated with periodontal inflammation and destruction in patients with diabetes. Sustaining this finding, Cianciola *et al* (1982) suggested that gingival inflammation is significantly increased in patients with diabetes when compared to normal control subjects, even after adjusting for oral hygiene levels.

In our data, CAL was statistically significant higher in GDM and T1DM than in the C group. These data are in accordance with those of Guthmiller *et al* (2001) who showed that in the T1DM pregnant group, CAL was four times higher than in normal pregnancies. Data from Third National Health and Nutrition Examination Survey (NHANES III, USA) analyzed a large sample of women that defined periodontitis as having at least one site with CAL or PD ≥4 mm, and showed that periodontitis is more frequent in pregnant patients presenting with GDM, T1DM, T2DM, and in women with previous history of GDM than in a normal control group (Novak *et al*, 2006; Xiong *et al*, 2006a,b). GDM has been considered a great risk for developing more severe periodontal disease (Dasanayake *et al*, 2008; Kasaj *et al*, 2008; Xiong *et al*, 2009).

Considering all the patients studied as a total group, the CAL was positively correlated to age, pregestational BMI, FPG, and HbA_{1c}.

Age is an acknowledged periodontal disease risk factor (Kaye *et al*, 2010) as it is a modulation factor of apoptotic cascade, which may contribute to damage of the gingival tissues, particularly in periodontal disease after 50 years of age (Das *et al*, 2009), and it could be a reason for our result pattern. However, all of our patients were in the young adult age range, and the difference in the periodontal parameters observed among the C and diabetic (GDM and T1DM) groups were still statistically significant when adjusted for age (medical variable).

The literature shows that obesity is a predisposing factor to GDM (Chatzi *et al*, 2009) and that adipose cells have the potential to produce pro-inflammatory cytokines (Metzger *et al*, 2007). In our study, the incidence of pregestational obesity was higher in the GDM group and a positive correlation between BMI and CAL was observed in the analysis, when all patients were considered as a whole group. These findings, even though preliminary, are consistent with the current understanding that obesity is associated with the development of a systemic inflammatory state and that reports suggest a significant correlation between periodontitis and BMI in adult women (Saito *et al*, 2005).

Descriptive analysis and multiple comparisons among our findings revealed that inflammatory process and periodontal destruction were significantly higher in patients with GDM and T1DM when compared to the C group. Within this context, dental clinicians must be alert to diagnose and manage periodontal disease in pregnant patients presenting with GDM and T1DM. The reduction or elimination of periodontal infection during pregnancy will decrease maternal and fetal risks for developing systemic problems (Offenbacher *et al*, 1996; Cota *et al*, 2006; Toygar *et al*, 2007).

The multiple comparisons revealed no significant difference in inflammatory process and periodontal destruction between the GDM and T1DM groups, even though the average time for periodontal destruction after receiving a diabetes diagnosis was 10 years (126 months) for the T1DM group and 0.25 years (3 months) for the GDM group. It is known that a diagnosis of GDM may disclose previously undiagnosed T2DM, which can remain asymptomatic for an uncertain period.

The T1DM group of the present study was younger and had a glycemic control that could be considered fair (HbA_{1c} = 8.3%). Tervonen and Oliver (1993) showed that the glycemic control level is more important than type or duration of diabetes, regarding increasing the prevalence, severity, and extent of periodontitis in patients with T1DM.

The importance of diabetes as a risk factor for developing periodontal disease was demonstrated by this study. However, it was not possible to demonstrate any difference in the periodontal parameters studied between the two levels of glycemic control (HbA_{1c} 8.3% *vs* 5.5%), duration of hyperglycemia (10 *vs* 0.25 years), and type of diabetes (T1DM *vs* GDM). These findings highlight the complexity of the mechanisms by which diabetes adversely affects the periodontium through various combinations of metabolic, hormonal, and physiological alterations. All of these factors constitute the degree of diabetes exposure. As a consequence of this scenario, diverse functional and morphologic alterations develop and lead to chronic diabetic complications affecting the eyes, the kidneys, and the heart, as well as the periodontium. Further studies that include a larger number of diabetic pregnant groups will shed more light on these associations, other factors involved, and the nature of the development of periodontal changes in diabetes.

In conclusion, we observed that Brazilian pregnant patients with diabetes, independent of etiology, presented with a worse periodontal condition than non-diabetic pregnant women. As periodontal diseases are largely preventable and the destructive process can be best arrested when identified at its early stages, screening for periodontal changes and implementing prevention and treatment programs could be considered as standard care for pregnant patients with all types of diabetes.

Author contributions

DR Ruiz performed research, analyzed data, wrote the paper; GA Romito contributed with analytic tools and analyzed the

data; SA Dib designed research, contributed to analyzed data and to write the paper.

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