Received: 17 July 2021 | Revised: 29 October 2021 | Accepted: 29 October 2021

DOI: 10.1002/JPER.21-0406

JOURNAL OF Periodontology

ORIGINAL ARTICLE

Mothers' high glycemic levels and the association between periodontitis and low birth weight

Isaac Suzart Gomes-Filho[1] | **Soraya Castro Trindade**[1] | **Simone Seixas da Cruz**[1,2] | **Ana Claudia Morais Godoy Figueiredo**[3] | **Alexandre Marcelo Hintz**[1] | **Luis Fernando Fernandes Adan**[4] | **Eneida de Moraes Marcílio Cerqueira**[1] | **Johelle de Santana Passos-Soares**[5] | **Maria Isabel Pereira Vianna**[5] | **Julita Maria Freitas Coelho**[1] | **Claúdia Maria Coêlho Alves**[6] | **Maurício Lima Barreto**[7] | **Gregory John Seymour**[8] | **Peter Michael Loomer**[9] | **Frank Andrew Scannapieco**[10]

[1] Department of Health, Feira de Santana State University, Feira de Santana, Bahia, Brazil

[2] Health Sciences Center, Federal University of Recôncavo of Bahia, Santo Antônio de Jesus, Bahia, Brazil

[3] Epidemiology Surveillance, Federal District Health State Department, Distrito Federal, Brasília, Brazil

[4] Department of Pediatrics, Federal University of Bahia, Salvador, Bahia, Brazil

[5] Department of Preventive Dentistry, Federal University of Bahia, Salvador, Bahia, Brazil

[6] Graduate Program in Dentistry, Federal University of Maranhão, São Luis, Maranhão, Brazil

[7] Center for Data and Knowledge Integration for Health, CIDACS, Oswaldo Cruz Foundation, FIOCRUZ, Salvador, Bahia, Brazil

[8] School of Dentistry, The University of Queensland, Brisbane, Queensland, Australia

[9] School of Dentistry, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

[10] Department of Oral Biology, University at Buffalo, Buffalo, NY, USA

Correspondence
Isaac Suzart Gomes-Filho, Department of Health, Feira de Santana State University, Avenida Getúlio Vargas, 379, Feira de Santana, Bahia 44025-010, Brazil.
Email: isuzart@gmail.com

Abstract

Background: Maternal hyperglycemia, periodontitis, and adverse gestational outcomes are important health problems. The present study investigated the hypothesis that periodontitis and the glycemic level of mothers may have opposing influences on birth weight (BW). This study evaluated the effect of high glycemic levels, albeit within the normal range, on the association between periodontitis and low birth weight (LBW).

Methods: A total of 732 women took part in this case-control study; 172 were mothers of children with LBW <2,500 g, and 560 were mothers of children with BW ≥2,500 g. The BW of newborns was obtained from medical records, and information on socioeconomic-demographic, lifestyle behavior were obtained through interviews. Glycated hemoglobin (HbA1c) levels were evaluated, and full-mouth periodontal examination was carried out within 7 days postpartum. Hierarchical and logistic regression analysis evaluated the effect of glycemic levels on the association between periodontitis and LBW by subgroups, estimating odds ratios (OR) with 95% confidence intervals (95% CI).

Results: In the group with HbA1c levels <5.6%, a statistically significant relationship existed between periodontitis and LBW. Using the Centre for Disease Control/American Academy of Periodontics criteria, the $OR_{adjusted}$ was 1.55; 95% CI: 1.04 to 2.31; using the Gomes-Filho et al. criteria the $OR_{adjusted}$ was 1.91; 95% CI, 1.06 to 3.45. In the group with higher HbA1c levels but still within the normal range (≥5.6% and <6.5%), the findings showed no association between periodontitis and LBW.

Conclusion: Higher maternal glycemic levels within the normal range, inferior to those indicative of gestational diabetes, diabetes mellitus, or hyperglycemia, and periodontitis have opposing effects on BW, altering the association magnitude.

KEYWORDS
epidemiology, glycated hemoglobin A, low birth weight infant, periodontal medicine, periodontitis, pregnancy

1 | INTRODUCTION

It is now 25 years since the pioneering study of Offenbacher et al.[1] first suggested the association between periodontitis and adverse gestational outcomes. Over the past two and a half decades, numerous studies have investigated this relationship. Many observational epidemiologic studies have verified a positive/moderate association between periodontitis and gestational outcomes.[2] Early intervention studies showed that non-surgical periodontal therapy in pregnant women was safe and might reduce the risk of adverse gestational outcomes.[3] More recent high-quality randomized clinical trials reported that treatment did not affect the prevention of these outcomes.[4,5]

Nevertheless, an improved data analysis procedure has been used[6] and a reanalysis of this previous study[7] demonstrated that periodontal treatment provided to mothers with mild to moderate periodontitis before 21 weeks of gestation prevented premature deliveries.[6]

Further epidemiological and intervention studies are required in which the effective use of confounding and effect modifier covariables are included in the analysis models. The relevance of effect modifiers in the association between periodontitis and adverse gestational outcomes was recently highlighted[8] in a study by Gomes-Filho et al.[9] In this study, women with normal glycated hemoglobin levels (HbA1c) showed a positive association between periodontitis and low birth weight (LBW) newborns. In contrast, in women with a higher level of HbA1c but still within the normal range, the association disappeared, suggesting the possible effect of maternal glycemic level on birth weight (BW).[9]

The biological mechanisms explaining how maternal glycemic levels influence the association between periodontitis and LBW have not been investigated. However, maternal blood glucose levels during pregnancy and fetal growth and size at birth are well established, with high levels of maternal blood glucose being associated with macrosomia.[10–13] Moreover, the contradictory theory proposes that high maternal glycemic levels can lead to both large newborns for gestational age, and intrauterine growth restriction and, in consequence, decreased BW.[14–16]

Notwithstanding this apparent paradox, maternal glycemic levels may be fundamental in determining the association between periodontitis and adverse gestational outcomes. Therefore, the present study investigated the hypothesis that the glycemic levels of mothers, albeit within the normal range (less than those indicative of gestational diabetes, diabetes mellitus, or hyperglycemia during pregnancy), may modify the relationship between periodontitis and LBW. Although, we have previously published a study on this topic,[9] with the same design and a sample from the same population, the novelty of the present study lies in the period of data collection, the increased sample size, the definitions of periodontitis used to determine the exposure, and the effect of confounders through hierarchical level analysis. With a larger sample size and more statistical power, the effect of maternal glycemic levels was evaluated through stratified analysis: two strata of maternal glycated hemoglobin levels.

2 | MATERIALS AND METHODS

Mothers without diabetes mellitus of live newborns from a public health institution that assists pregnant females in Feira de Santana, BA, Brazil, were recruited to take part in this case-control investigation. The study was

developed and ran from 2012 to 2015. Mothers of newborns with BW <2,500 g composed the case group, whereas the control group comprised mothers of live newborns with BW ≥2,500 g.[17] Mothers of children with BW <2,500 g who were in the institution after delivery were invited to participate in the study. The control group was obtained from the same time and source, comprising mothers of children with BW ≥2,500 g, selected randomly. For each case, three controls were selected at the same time.

The Ethics Committee of Feira de Santana State University approved the study conducted following the Helsinki Declaration of 1975, as revised in 2013. All women signed an informed consent form.

All postpartum women hospitalized in the public health institution, in a period <7 days after the delivery, and who met the eligibility criteria were able to participate in the investigation. The exclusion criteria were: 1) those with a diagnosis of diabetes mellitus (DM); 2) postpartum women who had HbA1c levels ≥6.5%; 3) those with multiple pregnancies; 4) those with bleeding disorders; 5) postpartum women of children with malformation and chromosomal abnormalities; and 6) those who had cardiovascular disease or any other systemic illness that required antibiotic prophylaxis for dental procedures or who had undergone periodontal treatment during pregnancy.

2.1 | Calculation of the sample size

The minimum sample size calculation used the following parameters, a study power of 80%, a confidence level of 95%, and a ratio of controls to cases equal to 3:1. A periodontitis frequency of 19.8% for the case and 10.7% for the control groups were used, based on a previous study of glycemic levels, periodontitis, and birth weight.[9] Based on this analysis the sample size was estimated to be 168 cases and 504 controls.

2.2 | Data collection procedures

Information on socioeconomic-demographic characteristics, gestational history, lifestyle behavior, and all women's general and oral health conditions were collected through interviews. The data on children weight were obtained from the hospital records.

After each interview, an oral assessment was conducted by a trained dentist, who did not know the newborn's weight at the time of the evaluation. The full-mouth examination included periodontal evaluation from all teeth, except the third molars, in six sites per tooth: mesio-vestibular, mid-vestibular, disto-vestibular, mesio-lingual, medium-lingual, disto-lingual. Probing depth,[18] gingival recession,[19] clinical attachment level,[19] and bleeding on probing[20] were collected. The visible plaque was recorded at four sites (mesial, distal, buccal, palatal/lingual) per tooth.[20]

In ≈10% of the sample and utilizing an experienced periodontist as a reference (ISG-F), the reproducibility of the periodontal replicate measurements was estimated. The interexaminer Cohen Kappa index (k index ± 1 mm) for probing depth and gingival recession were 0.75 and 0.85. The k index (± 1 mm) was 0.82 and 0.88 for these clinical parameters in intraexaminer agreement, respectively.

Finally, a health professional collected three milliliters of blood on the same day of the oral clinical assessment to measure mothers' glycemic levels.

2.3 | Exposure factor—periodontitis severity levels

Using the periodontitis diagnostic criteria from the US Center for Disease Control and the American Academy of Periodontology (CDC/AAP),[21,22] the postpartum women were classified according to periodontitis severity: mild, moderate, severe periodontitis, and without periodontitis (see Supplementary Table S1 in online *Journal of Periodontology*). Finally, women were classified as having no periodontitis or periodontitis (mild, moderate, and severe).

To include bleeding on probing, periodontitis was also defined using diagnostic criteria described by Gomes-Filho et al.[23] Women without a diagnosis of periodontitis were classified with gingivitis if they showed at least 25% of periodontal sites with bleeding on probing.[24]

2.4 | Outcome–LBW

Participants were distributed into the case group and control group based on children's BW,[17] obtained from the birth certificate records or the newborn card. The newborns' weight was collected in a standardized way, 1 hour after delivery, using a digital scale to avoid the interference caused by postnatal weight loss.

2.5 | Assessment of the glycemic level

High-performance liquid chromatography was used to determine glycated hemoglobin level (HbA1c). Postpartum women were further classified depending on their HbA1c level.[25,26] Women with HbA1c ≥5.6% and <6.5% were classified with a high glycemic level within the normal range. In comparison, those women with an HbA1c <5.6% were

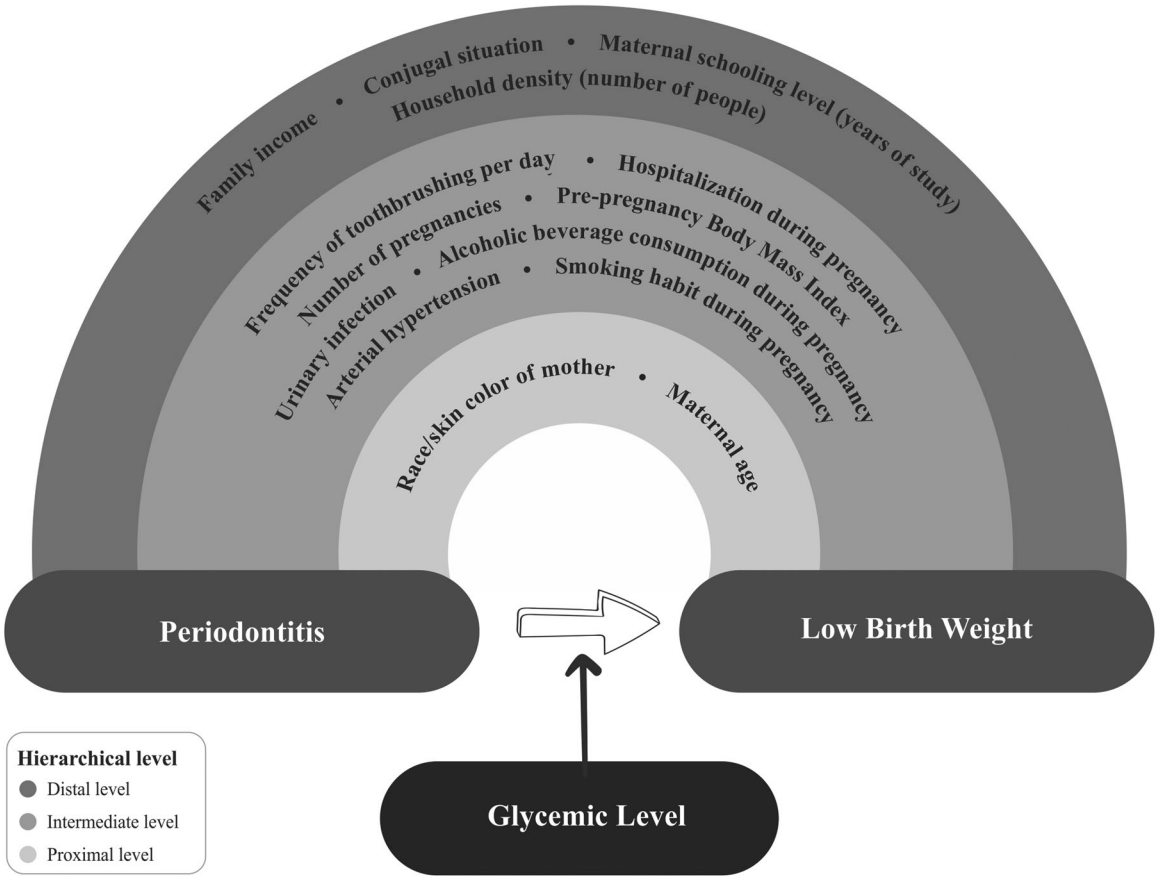

FIGURE 1 Theoretical-conceptual model for the association between maternal periodontitis and low birth weight, using hierarchical level for possible confounders covariables, and the glycemic level as an effect modifier covariable

considered to be within the normal range for the gestational period.

2.6 | Maternal characteristics investigated

Maternal characteristics were investigated based on a hierarchical level. A theoretical model of social determinants of health was built upon the association between maternal periodontitis and LBW, considering possible covariables and their distribution in the sample (Fig. 1). These covariables were evaluated to be chosen as confounders, and the glycemic level as an effect modifier covariable.[8,9] At the distal hierarchical level, the socioeconomic characteristics comprised of family income (in minimum wages), conjugal situation (with or without a companion), maternal schooling level (in years of study), and household density (number of people in the household). At the intermediate level, the covariables were related to lifestyle behavior, to the health condition, including gestational history, and to healthcare information: smoking habit during pregnancy (yes, smoker/ex-smoker, or non-smoker), alcoholic beverage consumption during pregnancy (yes, drink/have drank or not), having the following diseases/conditions (yes or no–self-reported) arterial hypertension, urinary infection, and hospitalization during pregnancy, number of pregnancies (multiparous or primiparous), pre-pregnancy body mass index (BMI <19 kg/m^2 or ≥19 kg/m^2), and frequency of toothbrush per day (number of brushing). At the proximal hierarchical level, demographic information comprised maternal age (in years) and the race/skin color of the mother (non-Black or Black).

2.7 | Statistical analysis

The data analysis used the statistical program STATA.[*] Analyses were based on non-missing data. Descriptive analysis, comparing the case and control groups, was performed. Simple and relative frequencies for all categorical covariables were made. For continuous covariables, measurements of central tendency and dispersion were performed. The degree of comparability between the groups

[*] Data Analysis and Statistical Software–version 15.

was performed through bivariate analysis. Pearson Chi-square test was used based on the normality distribution of covariables, with a significance level of 5%.

The hierarchical analysis of the association between periodontitis and LBW was performed. The covariables selected through bivariate analysis had a significance level ≤20%. The collinearity between the covariables was assessed using the variance matrix, using Pearson correlation coefficient. Moreover, the selection of covariables was performed considering their epidemiological importance after elaborating a theoretical-conceptual model on the topic.

Initially, in the distal hierarchical level, the socioeconomic covariables were assessed in the model with those selected had a $P \leq 0.20$, comprising block I. Then, in the intermediate hierarchical level, the covariables related to lifestyle behavior, health condition, and healthcare information were tested. Those covariables that had a $P \leq 0.20$ were also selected, consisting of block II. Finally, in the proximal hierarchical level, the demographic covariables were tested, and those with a $P \leq 0.05$ value were selected for the final model, comprehending block III. At all levels, the epidemiological importance of the covariable in the association under study was a criterion of choice.

In addition, the association between periodontitis and LBW was evaluated using stratified analysis and logistic regression modeling, obtaining the unadjusted and adjusted odds ratios (ORs), 95% confidence intervals (95% CI), with a significance level of 0.05.

The selection of confounding and effect modifier covariables was performed. Firstly, considering a theoretical model of causality between periodontitis and LBW and the hierarchical level analysis. Then, the maximum likelihood ratio test ($P < 0.05$) was used to analyze the effect modifier covariable. After that, the presence of confounding covariables was verified using the backward strategy, considering the one that produced a change in the association measurement of at least 10%. Thus, the glycemic level was selected as an effect modifier covariable and the following ones, as confounders: maternal schooling level, smoking habit during pregnancy, arterial hypertension, pre-pregnancy BMI, maternal age, and race/skin color of the mother.

Maternal age, smoking habit during pregnancy, arterial hypertension, pre-pregnancy BMI, and race/skin color of mother[9,27] are factors that influence the association between periodontitis and LBW. It is interesting to note that these factors also affect maternal glycemic level.[3–5] In addition, maternal schooling level also influences both periodontitis and glycemic level, with the lower the number of years of study, the greater the occurrence of adverse health events.[27]

For the objectives mentioned above, hierarchical and logistic regression analysis, the statistical models, unadjusted and adjusted, between periodontitis and LBW were used as follows: periodontitis (criteria[21,22]) versus LBW, periodontitis (criteria[23]) versus LBW, periodontitis (criteria[21,22]) versus LBW–in a subgroup analysis of women with normal glycemic level, periodontitis (criteria[23]) versus LBW–in a subgroup analysis of women with normal glycemic level, periodontitis (criteria[21,22]) versus LBW–in a subgroup analysis of women with high glycemic level, and periodontitis (criteria[23]) versus LBW–in a subgroup analysis of women with high glycemic level.

The Hosmer-Lemeshow test was used to evaluate the quality of the fit of all analysis models.

3 | RESULTS

The initial sample included 748 women invited and accepted to participate in the investigation; however, during the examination period, 16 of them withdrew from participation (15 in the case group and one belonging to the control group) constituting a loss rate 2.1%. The final sample included 732 women (172 cases and 560 controls), aged 13 to 52 years, mean ± SD of 24.64 ± 6.65 years (median age of 24 years–interquartile ranges of 19 and 29 years).

The occurrence of periodontitis varied considerably depending on the definition criteria used. However, it was statistically significantly higher among the cases than among controls ($P < 0.05$), irrespective of the definition used. The occurrence was 46.51% in the case group, ≈three times greater when using the CDC/AAP criteria compared with 14.53% obtained using the Gomes-Filho et al., criteria. In the control group, the periodontitis frequency was 37.14%, and ≈4 times higher using CDC/AAP criteria than 9.29% using the Gomes-Filho et al., criteria.

The control group had a statistically significantly higher occurrence of participants with an HbA1c ≥5.6% to <6.5% compared with the case group (28.93% versus 14.53%). There was a statistically significantly higher frequency of women among the cases, compared with controls, in the age ranges of <18 and >35 years (33.14% versus 19.11%), with a diagnosis of moderate periodontitis (43.31% versus 34.61%), and with diagnosis of severe periodontitis (11.00% versus 5.52%). Both groups were homogeneous for the other characteristics (Table 1).

The association between periodontitis (CDC/AAP criteria) and LBW, evaluated through hierarchical analysis, remained positive and statistically significant at all levels (Table 2). Regarding the distal hierarchical level, the covariables family income and maternal schooling level were selected as confounding. The association measurement estimated that the likelihood of women with periodontitis having newborns with LBW was 1.46 times

TABLE 1 Number and percentage of the glycemic level and women's main characteristics comparing cases (mothers of newborns with LBW) and controls (mothers of newborns of normal weight), based on the distal, intermediate, and proximal hierarchical levels

Characteristics	Cases (n = 172)	Controls (n = 560)	*P*[*]
Glycemic level			
HbA1c	n (%)	n (%)	
<5.6%	147 (85.47)	398 (71.07)	<0.01
≥5.6% to <6.5%	25 (14.53)	162 (28.93)	
Distal hierarchical level			
Family income[a]			
>1 minimum wage	49 (28.49)	175 (31.25)	0.50
≤1 minimum wage	123 (71.51)	385 (68.75)	
Conjugal situation			
With companion	138 (80.23)	449 (80.18)	0.99
Without companion	34 (19.77)	111 (19.82)	
Maternal schooling level (years of study)			
>4 years	142 (82.56)	486 (86.79)	0.17
≤4 years	30 (17.44)	74 (13.21)	
Household density (number of people)			
<4	56 (32.56)	176 (31.43)	0.78
≥4	116 (67.44)	384 (68.57)	
Intermediate hierarchical level			
Smoking habit during pregnancy			
No	152 (88.37)	498 (88.93)	0.84
Yes	20 (11.63)	62 (11.07)	
Alcoholic beverage consumption during pregnancy			
No	97 (56.40)	279 (49.82)	0.13
Yes	75 (43.60)	281 (50.18)	
Arterial hypertension			
No	143 (83.14)	492 (87.86)	0.11
Yes	29 (16.86)	68 (12.14)	
Urinary infection			
No	121 (70.35)	372 (66.43)	0.34
Yes	51 (29.65)	188 (33.57)	
Pre-pregnancy body mass index			
<19 kg/m^2	107 (62.21)	383 (68.39)	0.13
≥19 kg/m^2	65 (37.79)	177 (31.61)	
No. of pregnancies			
Multiparous	80 (46.51)	295 (52.68)	0.16
Primiparous	92 (53.49)	265 (47.32)	
Hospitalization during pregnancy			
No	144 (83.72)	480 (85.71)	0.52
Yes	28 (16.28)	80 (14.29)	
Frequency of toothbrushing per day			
≥1	150 (87.21)	498 (88.93)	0.54
0	22 (12.79)	62 (11.07)	
Proximal hierarchical level			
Maternal age (years)			
18 to 35	115 (66.86)	453 (80.89)	<0.01

(Continues)

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TABLE 1 (Continued)

Characteristics	Cases (n = 172)	Controls (n = 560)	*P*[*]
<18/ >35	57 (33.14)	107 (19.11)	
Race/skin color of mother			
Non-Black	26 (15.12)	60 (10.71)	0.12
Black	146 (84.88)	500 (89.29)	
Periodontal status			
Diagnosis periodontitis (CDC/AAP criteria)			
No	92 (53.49)	352 (62.86)	0.03
Yes	80 (46.51)	208 (37.14)	
Diagnosis of mild periodontitis (CDC/AAP criteria)			
No	89 (98.89)	342 (97.99)	0.57
Yes	1 (1.11)	7 (2.01)	
Diagnosis of moderate periodontitis (CDC/AAP criteria)			
No	89 (56.69)	342 (65.39)	0.05
Yes	68 (43.31)	181 (34.61)	
Diagnosis of severe periodontitis (CDC/AAP criteria)			
No	89 (89.00)	342 (94.48)	0.05
Yes	11 (11.00)	20 (5.52)	
Diagnosis of gingivitis (CDC/AAP criteria)			
No	89 (96.74)	342 (97.16)	0.83
Yes	3 (3.26)	10 (2.84)	
Periodontitis severity levels (CDC/AAP criteria)			
Non-periodontitis	89 (51.74)	342 (61.07)	0.14
Gingivitis	3 (1.74)	10 (1.79)	
Mild periodontitis	1 (0.58)	7 (1.25)	
Moderate periodontitis	68 (39.54)	181 (32.32)	
Severe periodontitis	11 (6.40)	20 (3.57)	

[*]*P* value: significance level ≤0.05.

[a]Minimum monthly wage at the time of data collection: **R$ 678,00 to R$ 788,00** (US$ 340.70 to US$ 299.17).

greater than those without periodontitis: $OR_{adjusted} = 1.46$; 95% CI, 1.03 to 2.07. In the intermediate hierarchical level, the maternal schooling level covariable was incorporated with those of this block, such as smoking habit during pregnancy, alcoholic beverage consumption during pregnancy, arterial hypertension, pre-pregnancy BMI, and the number of pregnancies. In this adjusted model, the chance of women with periodontitis having children with LBW was 1.53 times higher than those without periodontitis: $OR_{adjusted} = 1.53$; 95% CI, 1.07 to 2.18. In the proximal hierarchical level, the covariables maternal age and race/skin color were incorporated in those of the previous model. In this final model, the likelihood of having children with LBW among mothers with periodontitis was the same, 1.53 times greater than those without periodontitis: $OR_{adjusted} = 1.53$; 95% CI, 1.07 to 2.20.

The association between periodontitis (Gomes-Filho et al., criteria) and LBW was also evaluated through hierarchical analysis, showing similar findings in Supplementary Table S2 in the online *Journal of Periodontology*. For most of the regression models, the Hosmer-Lemeshow statistical test indicated good quality.

The associations between periodontitis and LBW for both periodontal diagnosis criteria were then tested through logistic regression (Table 3). Unadjusted association measurements showed positive associations. The adjusted model demonstrated that the likelihood of women with periodontitis, as determined by the CDC/AAP criteria, having a newborn with LBW was 1.50 times higher than among those without periodontitis: $OR_{adjusted} = 1.50$; 95% CI, 1.05 to 2.13. This association was not statistically significant ($OR_{adjusted} = 1.66$; 95% CI, 0.98 to 2.81) for postpartum women with periodontitis as determined by the Gomes-Filho et al., criteria.

The effect of glycemic level in the association between periodontitis and LBW was investigated for both periodontal diagnostic criteria using subgroups analysis based on the HbA1c levels (Table 4). In the normal glycemic level group (HbA1c levels <5.6%), there was a statistically significant association between periodontitis and LBW for unad-

TABLE 2 Hierarchical analysis of the association between periodontitis (CDC/AAP criteria) and low birth weight

Characteristics according to the hierarchical level	Distal level		Intermediate level		Proximal level	
	Odds ratio (95% confidence interval)	*P**	Odds ratio (95% confidence interval)	*P**	Odds ratio (95% confidence interval)	*P**
Block I	1.46 (1.03–2.07)	0.03	—		—	
Family income: up to 1 minimum wage	1.09 (0.84–2.16)	0.65	—		—	
Maternal schooling level: up to 4 years of study	1.35 (0.75–1.60)	0.21	—		—	
Goodness-of-fit test		0.01				
Block II	—		1.53 (1.07–2.18)	0.02	—	
Smoking habit during pregnancy: yes			1.06 (0.60–1.86)	0.85		
Alcoholic beverage consumption during pregnancy: yes	—		0.78 (0.55–1.11)	0.17	—	
Arterial hypertension: yes	—		1.46 (0.90–2.37)	0.12	—	
Pre-pregnancy body mass index: <19 kg/m^2	—		1.29 (0.90–1.84)	0.17	—	
No. of pregnancies: primiparous			1.42 (1.00–2.03)	0.06		
Maternal schooling level: up to 4 years of study	1.42 (0.88–2.29)	0.15				
Goodness-of-fit test				0.51		
Block III					1.53 (1.07–2.20)	0.02
Maternal age: <18 and >35 years	—		—		1.96 (1.31–2.94)	<0.01
Race/skin color of mother: Black	—		—		0.66 (0.40–1.10)	0.11
Maternal schooling level: up to 4 years of study	1.29 (0.79–2.10)	0.31	—		—	
Smoking habit during pregnancy: yes	—		1.00 (0.56–1.78)	1.00	—	
Alcoholic beverage consumption during pregnancy: yes	—		0.78 (0.55–1.13)	0.20	—	
Arterial hypertension: yes	—		1.51 (0.93–2.45)	0.10	—	
Pre-pregnancy body mass index: <19 kg/m^2	—		1.21 (0.84–1.74)	0.32	—	
No. of pregnancies: primiparous			1.25 (0.86–1.81)	0.25		
Goodness-of-fit test						0.15

**P* value: significance level ≤0.05.

justed and adjusted models of both periodontal diagnosis criteria. In comparison with the main general model, the magnitude of the association measurement between periodontitis (CDC/AAP criteria) and LBW showed a slight increase: $OR_{adjusted} = 1.55$; 95% CI, 1.04 to 2.31, whereas in the other model, periodontitis (Gomes-Filho et al., criteria) and LBW, the increase was around 15%: $OR_{adjusted} = 1.91$; 95% CI, 1.06 to 3.45.

When the influence of glycemic level in the association between periodontitis and LBW was investigated in the high glycemic level group (HbA1c levels ≥5.6% and <6.5%), the findings showed no statistically significant association between periodontitis and LBW for unadjusted and adjusted models for both periodontal diagnostic criteria. In both analyses, the Hosmer-Lemeshow statistical test indicated the good quality of the regression models used.

TABLE 3 Unadjusted and adjusted association measurements, odds ratio (OR), 95% confidence interval (95% CI), between periodontitis and low birth weight (N = 732)

Diagnosis of periodontitis	Cases[a]	Controls[b]	Unadjusted model OR (95% CI)	*P**	Adjusted model[c] OR (95% CI)	*P**	Goodness-of-fit test
CDC/AAP criteria							
No	92 (53.49)	352 (62.86)	1.47	0.03	1.50	0.03	0.43
Yes	80 (46.51)	208 (37.14)	(95% CI, 1.04–2.08)		(95% CI, 1.05–2.13)		
Gomes-Filho et al. criteria							
No	147 (85.47)	508 (90.71)	1.66	0.05	1.66	0.06	0.43
Yes	25 (14.53)	52 (9.29)	(95% CI, 1.01–2.77)		(95% CI, 0.98–2.81)		

[a]Cases: mothers of newborns with low birth weight.
[b]Controls: mothers of newborns of normal weight.
[c]Adjusted for maternal schooling level, smoking habit during pregnancy, arterial hypertension, pre-pregnancy BMI, maternal age, and race/skin color of mother.
**P* value: significance level ≤ 0.05.

TABLE 4 Odd ratio (OR) and 95% confidence interval for influence of glycemic level, measured by HbA1c level, on relationship between periodontitis and low birth weight (N = 732)

Main association			**Glycemic level subgroup analysis**				
Periodontitis and low birth weight			**Normal • HbA1c <5.6% • (n = 545)**				
Diagnosis of periodontitis							
CDC/AAP criteria	Cases[a]	Controls[b]	Model	OR	95% confidence interval	*P**	Goodness-of-fit test
No	80 (54.42)	258 (64.82)	Unadjusted	1.54	1.05-2.27	0.03	–
Yes	67 (45.58)	140 (35.18)	Adjusted[c]	1.55	1.04-2.31	0.03	0.78
Gomes-Filho et al. criteria	Cases[a]	Controls[b]	Model	OR	95% confidence interval	*P**	Goodness-of-fit test
No	125 (85.03)	364 (91.46)	Unadjusted	1.88	1.06-3.34	0.03	–
Yes	22 (14.97)	34 (8.54)	Adjusted[c]	1.91	1.06-3.45	0.03	0.56
Periodontitis and low birth weight			**High • HbA1c ≥5.6% and <6.5% • (N = 187)**				
Diagnosis of periodontitis							
CDC/AAP criteria	Cases[a]	Controls[b]	Model	OR	95% confidence interval	*P**	Goodness-of-fit test
No	12 (48.00)	94 (58.02)	Unadjusted	1.50	0.64-3.48	0.35	–
Yes	13 (52.00)	68 (41.98)	Adjusted[c]	1.57	0.65-3.80	0.31	0.51
Gomes-Filho et al. criteria	Cases[a]	Controls[b]	Model	OR	95% confidence interval	*P**	Goodness-of-fit test
No	22 (88.00)	144 (88.89)	Unadjusted	1.09	0.30-4.01	0.90	–
Yes	3 (12.00)	18 (11.11)	Adjusted[c]	1.13	0.30-4.32	0.86	0.73

[a]Cases: mothers of newborns with low birth weight.
[b]Controls: mothers of newborns of normal weight.
[c]Adjusted for maternal schooling level, smoking habit during pregnancy, arterial hypertension, pre-pregnancy BMI, maternal age, and race/skin color of mother.
**P* value: significance level ≤0.05.

4 | DISCUSSION

The findings of this study showed that high maternal glycemic levels, albeit within the normal range, but less than those indicative of gestational diabetes, diabetes mellitus, or hyperglycemia, influence BW and hence modify the association between periodontitis and pregnancy outcome (see Supplementary Figure S1 in online *Journal of Periodontology*). This effect was initially suggested by Gomes-Filho et al.,[9] and highlighted by Beck et al.[8] However, in this previous investigation, the association measurements had low precision due to small sample size, resulting in wide 95% CIs.

To the best of our knowledge, this study is the first to show the effect of maternal glycemic level on the association between periodontitis and LBW with a larger sample size and more statistical power. While the biological mechanism underpinning this effect is unknown, it is well known that higher HbA1c levels at gestation are a recognized risk factor for macrosomia in pregnant women with HbA1c <6.5%.[28–32] Macrosomia is generally defined as the newborn's weight >4,000 g. Many fetuses in pregnancies display accelerated intrauterine growth, especially complicated by diabetes, so their BW exceeds the normal range.

It is known that maternal glycemic levels inferior to those considered indicative of diabetes are also associated with an increase in several gestational complications[10,28–31] and that the HbA1c reference range during pregnancy should be lower than that currently accepted for the general population. In addition, the ideal glycated hemoglobin reference intervals for healthy pregnant females may vary at different gestational ages.[10,25,28,33–35] It is likely, due to physiological alterarions, such as erythrocyte half-life decrease, red blood cell turnover increase, and elevated risk of anemia seen during pregnancy to be lower than that seen in non-pregnant women.[36,37]

Regardless of all this, maintaining blood glucose concentrations within normal parameters during pregnancy may decrease the incidence of adverse gestational outcomes such as macrosomia, congenital malformation, stillbirth, miscarriage, pre-eclampsia, high perinatal morbidity, and mortality. It is worth highlighting the importance of hyperglycemia as the main risk factor for pregnancy complications. However, other factors, such as hypertension, obesity, other metabolic diseases, inflammation, and, infections including periodontitis, can contribute to the pregnancy outcome.[33,34,38]

Based on these principles, the present study sought to reinforce its internal validity in assessing the effect of maternal glycemic level on the association between periodontitis and LBW. Thereby, the estimated association measurements were adjusted by important confounder covariables, such as maternal age, maternal schooling level, pre-pregnancy BMI, smoking habit during pregnancy, race/skin color of mother, and arterial hypertension, to neutralize the influence of these confounders. The selection of these confounders was based on statistical tests, utilizing hierarchical level analysis, and constructing a theoretical-conceptual model for the topic, making the association measurement increasingly precise, represented by their narrow 95% CIs.[39,40]

Urinary tract infection is recognized as a relevant risk factor for adverse pregnancy outcomes.[41] In the present study, this factor had no impact on the association of periodontitis with LBW, as it did not present a statistically significant difference between the case and control groups, and also had a higher occurrence in pregnant women who had children of normal weight.

A strength of this investigation is the sample size. There is sufficient power to estimate the effect of the glycemic level in the association between periodontitis and LBW. It was performed through the subgroup analysis of women with high glycemic levels within the normal range (HbA1c ≥5.6% and <6.5%) and those considered to be within the normal range for the gestational period (HbA1c <5.6%). Although there was a decrease in the association measurement from 1.66 regardless of the presence of HbA1C to 1.13 among women with "high" HbA1C level ≥5.6% and <6.5%, when using the Gomes-Filho et al., criteria, both were not statistically significant. It should be noted that the influence of the HbA1C level occurred on the association for the stratum considered normal: HbA1c <5.6%.

Another strength is the full examination of the periodontal condition, avoiding underestimating the presence of periodontitis.[22] Although a new classification for the diagnosis of periodontal diseases exists,[42] it cannot be used in this study because the data collection was performed before the publication of the new definition. Nevertheless, the CDC/AAP criteria used to define periodontitis are recognized worldwide and have been previously used to investigate the relationship between periodontitis and LBW.[21,22] In addition, due to the necessity to consider the bleeding on probing, a truly relevant clinical parameter to evaluate periodontal inflammation in pregnant women, a second diagnostic criterion was used, thus reinforcing the main findings.[23]

In this study, the use of HbA1c considered previous researches in the topic,[25,26] who proposed that the normal reference values for the third trimester are 4.4% to 5.6%. Moreover, glycated hemoglobin levels reflect alterations in glycemic control during 2 to 4 months before the exam.[10,25,28,33–35] In the present study, HbA1c levels reflected changes in maternal glycemic control in the 2 to 4 months leading up to delivery. On the other hand, the selection of glycated hemoglobin as a marker of glycemic levels has its limitations since it is influenced by other factors such as folic acid, the amount of bleeding during labor, vitamins B6 and B12 levels, and ferritin.[25]

Although the design of this study is case-control and thus cannot address causality, the temporality between periodontitis exposure and LBW was preserved as well as the maternal glycemic level. Both exposures existed before the delivery, as demonstrated by the methods used to measure both events.

Another limitation is the residual confounding that may have been introduced by other factors so far not considered, such as genetic factors.[43] Finally, the study's external validity applies to pregnant women having general

conditions similar to the population that the present study sample represents.

Pregnancy is a complex event. Many factors need to be considered while evaluating the relationship between periodontitis and gestational outcomes, both in observational and interventional studies. Failure to take glycemic levels into account may contribute to the lack of consensus among the studies, as maternal glycemic levels may be camouflaging the relationship with periodontitis. The present study has shown that there appears to be an interaction between maternal glucose levels, periodontitis, and BW. It is suggested that in all future study designs, this important factor be considered.

5 | CONCLUSIONS

The present study demonstrates a positive association between periodontitis and LBW in the postpartum women considered to be within normal glycemic range for the gestational period, irrespective of the criteria used to define periodontitis. Further, it has demonstrated that this association disappears in women with high glycemic levels, albeit within the normal range, thus supporting the hypothesis that maternal glycemic levels affect the relationship between periodontitis and LBW.

ACKNOWLEDGMENTS

Financial support for this research was provided by the Research Support Foundation of the State of Bahia (FAPESB), Salvador, Bahia, Brazil; The National Council for Scientific and Technological Development (CNPq), Brasilia, Brazil; and Feira de Santana State University, Bahia, Brazil. The authors report no conflicts of interest related to this study.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

ORCID

Isaac Suzart Gomes-Filho https://orcid.org/0000-0002-4270-8491
Soraya Castro Trindade https://orcid.org/0000-0001-7125-9114
Simone Seixas da Cruz https://orcid.org/0000-0002-9410-5676
Ana Claudia Morais Godoy Figueiredo https://orcid.org/0000-0003-2842-9848
Alexandre Marcelo Hintz https://orcid.org/0000-0002-6868-8599
Luis Fernando Fernandes Adan https://orcid.org/0000-0003-4549-2582
Eneida de Moraes Marcílio Cerqueira https://orcid.org/0000-0003-1047-4931
Johelle de Santana Passos-Soares https://orcid.org/0000-0002-4541-1730
Maria Isabel Pereira Vianna https://orcid.org/0000-0003-4478-6941
Julita Maria Freitas Coelho https://orcid.org/0000-0002-9520-5177
Claúdia Maria Coêlho Alves https://orcid.org/0000-0003-4705-4914
Maurício Lima Barreto https://orcid.org/0000-0002-0215-4930
Gregory John Seymour https://orcid.org/0000-0001-7595-5651
Peter Michael Loomer https://orcid.org/0000-0002-4676-0895
Frank Andrew Scannapieco https://orcid.org/0000-0002-8804-6593

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gomes-Filho IS, Trindade SC, Cruz SS, et al. Mothers' high glycemic levels and the association between periodontitis and low birth weight. *J Periodontol*. 2022;1-12. https://doi.org/10.1002/JPER.21-0406