Relationship Among Mothers' Glycemic Level, Periodontitis, and Birth Weight

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Background: The aim of this study is to determine the influence of glycemic level on the relationship between periodontitis and low birth weight (LBW).

Methods: A case-control study was conducted with 372 females divided into cases (109 mothers of newborns with birth weight <2,500 g) and controls (263 mothers of newborns with birth weight ≥2,500 g). The birth weight of children was obtained from medical records, whereas information on sociodemographic, lifestyle, and health characteristics of the participants was obtained through an interview. Glycated hemoglobin (HbA1c) levels were measured, and probing depth, clinical attachment levels, and bleeding on probing were used to determine the periodontal status. Results were analyzed using logistic regression.

Results: The likelihood of having children with LBW among the mothers with periodontitis was six times greater than that observed among mothers without periodontitis (adjusted odds ratio [$OR_{adjusted}$] = 6.02, 95% confidence interval [CI] = 2.47 to 15.17), even after adjustment. There was also a strong, statistically significant relationship between periodontitis and LBW in both the normal glycemic–level group (HbA1c levels <5.6%, unadjusted odds ratio [$OR_{unadjusted}$] = 8.30, 95% CI = 3.56 to 19.35) and the high glycemic–level group (HbA1c levels ≥5.6% and <6.5%, $OR_{unadjusted}$ = 5.73, 95% CI = 1.75 to 18.70). After adjustment for confounders, the magnitude of the association continued to be strong in the normal glycemic–level group ($OR_{adjusted}$ = 7.59, 95% CI = 2.7 to 24.28), an increase of 25% when compared to the main association measurement. In those with high glycemic levels ($OR_{adjusted}$ = 4.03, 95% CI = 0.81 to 19.96), the OR decreased almost 50%, and the association lost statistical significance.

Conclusion: Periodontitis and glycemic levels appeared to have opposing influences on birth weight, with periodontitis being associated with LBW and the magnitude of the association being altered depending on maternal blood glucose level. *J Periodontol 2016;87:238-247.*

KEY WORDS

Epidemiology; hemoglobin A, glycosylated; infant, low birth weight; periodontitis; pregnancy.

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Some studies[1-4] have indicated the necessity for a more precise control of glycemic levels during pregnancy to prevent perinatal complications. It is now believed that maternal glycemic levels lower than those considered indicative of diabetes are also associated with an increase in gestational complications.[1,3,4] Moreover, a recent multicenter Japanese study[2] has suggested that the glycated hemoglobin (HbA1c) reference range during pregnancy should be less than that currently accepted for the general population.

Although the HbA1c reference intervals for the general population are well established, reference intervals for healthy pregnant females are not defined clearly. In previous studies, there is no consensus on the reference range of HbA1c in pregnant females, and there is controversy as to the ideal HbA1c level in females at different gestational ages.[1-3]

Favorable blood glucose control is an important factor for ensuring a good perinatal outcome, and poor glucose control may cause miscarriage, congenital malformation, macrosomia, stillbirth, preeclampsia, high perinatal mortality, and morbidity. Thereby, it is worth highlighting the importance of hyperglycemia as a major risk factor for gestational complications. However, other factors, such as obesity, hypertension, other metabolic diseases, infections, and inflammation, including periodontal diseases, may contribute to the gestational outcome.[3-5]

The association between periodontitis and gestational complications, such as low birth weight (LBW), has been investigated widely for almost 2 decades, but there is still no consensus view.[6-12] The justification for this lack of consensus relates to other determinants that affect LBW and hence may camouflage the relationship with periodontitis. Although glycemic level is a well-recognized factor for gestational complications, no studies have, as yet, considered the role of glycemic levels on the relationship between periodontitis and LBW.

The concept that maternal glycemic levels influence the relationship between periodontitis and LBW is biologically plausible. The association between high glucose levels and macrosomia has been widely documented.[1,13-16] There is evidence that a direct relationship between maternal blood glucose levels during pregnancy and fetal growth and size at birth exists, even when maternal blood glucose levels are within a normal range.[4] In addition, there is the paradoxic hypothesis proposing that elevated maternal glycemic levels may lead to both macrosomia and intrauterine growth restriction and, consequently, decreased birth weight.[17-19] Maintaining blood glucose concentrations within normal parameters during pregnancy may reduce the incidence of an adverse gestational outcome. Thus, there may be an interaction among maternal glucose levels, periodontal infection, and birth weight.

Therefore, in this context, the aim of the present study is to determine the relationship between the mothers' glycemic level, periodontitis, and birth weight. Maternal glycemic levels lower than those indicative of diabetes mellitus, gestational diabetes, or hyperglycemia were considered, in accordance with the current knowledge concerning maternal blood glucose level within acceptable ranges during pregnancy.[1-4] The hypothesis of the present study is that the mothers' glycemic level may have an opposing influence on the birth weight, and this factor may alter the association between periodontitis and the gestational outcome.

MATERIALS AND METHODS

In a public health institution that provides assistance to pregnant females (Inácia Pinto da Silva Hospital in Feira de Santana, Bahia, Brazil), a case-control study was developed from October 2010 to January 2012, with mothers (without diabetes [DM]) of live newborns. The case group (n = 109) comprised mothers of children with birth weight <2,500 g, whereas the control group (n = 263) consisted of mothers of live newborns with birth weight ≥2,500 g.[20] The mean ± SD age of the participants was 23.86 ± 6.6 years, with a median of 23 years, and minimum limit of 12 years and maximum of 45 years.

This study was approved by the Research Ethics Committee of Feira de Santana State University, Bahia, Brazil (number 152/2008), and all the participants signed an informed consent form.

Mothers of newborns with birth weight <2,500 g who were in the institution after delivery, as well as those who were scheduled to return within 1 week of delivery for medical monitoring, were invited to take part in the study. The control group was obtained from the same source and time, comprising mothers of newborns with birth weight ≥2,500 g, selected randomly. For each case, two controls were selected at the same time.

Although all mothers of newborns hospitalized in the Inácia Pinto da Silva Hospital, in a period <7 days after the delivery, were eligible to take part in the study, the following females were excluded: 1) those with bleeding disorders; 2) those with diagnosis of DM; 3) those with multiple pregnancy; 4) 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; and 5) mothers of newborns with malformation and chromosomal abnormalities.

Sample Size

The minimum sample size was calculated†† and estimated to be 103 cases and 206 controls, with a confidence

†† Epi Info program, CDC, Atlanta, GA.

level of 95% and a study power of 80%. Furthermore, because there were no previous studies that had investigated the relationship among glycemic levels, periodontitis, and birth weight, based on Offenbacher et al.,[6] a periodontal disease prevalence of 18% and 4.7% was postulated for the case and control groups, respectively.

Data-Gathering Procedures

The data regarding newborn weight were obtained from the hospital records, as was general information about the participants. All participants, in both the case and control groups, were invited to answer a questionnaire with the following sections: 1) identification; 2) socioeconomic-demographic data; 3) gestational history; 4) life habits; and 5) factors related to oral health.

After each interview, a single, previously trained dentist (ECP) conducted a full-mouth periodontal clinical examination.

Last, a blood sample to measure glycemic levels was obtained by a health professional (MTO) trained in the collection, processing, and preservation of blood samples, on the same day of the oral clinical examination. Females (n = 105) who did not agree to perform the blood collection were still able to participate in the study.

Periodontal Clinical Examination

Probing depth (PD) and clinical attachment level were measured at six sites per tooth for all teeth, except the third molars, using a manual periodontal probe as described by Pihlstrom et al.[21] Bleeding on probing (BOP) was determined within 10 seconds after removal of the probe as described by Lang et al.[22] The presence of visible plaque was evaluated at four sites (mesial, buccal, distal, and lingual) using the same probe.

All clinical periodontal measurements were performed by a single examiner (ECP) who, at the time of the examination, did not know the weight of the newborn. Reproducibility was determined by periodontal replicated measurements using an experienced periodontist (ISG-F) as a reference in ≈10% of the sample. The κ interexaminer for PD and recession measurements was, respectively, 0.78 and 0.88. In intraexaminer agreement, the κ index was 0.80 and 0.87 for these measurements, respectively.

Diagnosis of Periodontitis

Periodontitis was defined as at least four teeth with at least one site with PD ≥4 mm, attachment loss ≥3 mm, and BOP at the same site.[23]

Evaluation of the Glycemic Level

High-performance liquid chromatography was used to determine HbA1c. Three milliliters of blood were collected in a tube containing EDTA and stored at 2°C until processing.

Participants were further classified depending on their HbA1c as described by Hiramatsu et al.[2] and adapted to this Brazilian sample as described by Nielsen et al.[24] Those with HbA1c ≥5.6% and <6.5% were considered to have a high glycemic level, but less than that defining gestational diabetes, whereas those with an HbA1c <5.6% were considered to be within normal range for the gestational period.[2,24] Females who had levels ≥6.5% were excluded from these defined groups.

Evaluation of Birth Weight

Birth weight was obtained from the birth certificate records or the newborn card. A nurse or nursing assistant took the newborns' weight in a standardized way, 1 hour after delivery, using a digital scale to avoid the interference caused by loss of postnatal weight.

Statistical Analyses

First, descriptive analyzes were conducted for all variables considered in the study in relation to birth weight. Each variable was categorized according to normal birth weight or LBW. The following covariables were considered in the analyzes: 1) age; 2) education level; 3) family income; 4) maternal occupation; 5) hospitalization during pregnancy; 6) type of delivery; 7) primiparity; 8) history of newborn with LBW; 9) household density; 10) conjugal situation; 11) place of residence; 12) smoking habit; 13) alcoholic beverage consumption; 14) race/color; 15) prenatal consultation; 16) urinary infection; 17) hypertension; 18) DM; 19) pregestational weight; 20) height; 21) prenatal educational activity; 22) periodontitis; 23) frequency of brushing teeth; 24) use of dental floss; 25) visits to dentist; and 26) professional advice about oral hygiene. The categorization of continuous variables, when required, was made based on their distribution or according to cutoff points identified in the literature. The simple frequencies and measurements of central tendency were obtained, and statistical differences between case and control groups were evaluated using the χ^2 test for categorical variables and Student *t* test for continuous variables, with a significance level of 5%.

The estimation of the influence of the glycemic level on the relationship between periodontitis and birth weight was performed with two groups: 1) normal glycemic level; and 2) high glycemic level. This association was obtained by odds ratio (OR) and respective 95% confidence intervals (CIs). In univariate analysis, the candidates for confounding factors were selected for modeling. Potential confounding variables were selected, taking into consideration the influence of the covariables on both the exposure and the outcome. Also, the empirical base was used considering a relative difference as ≥20% between the measurements set by the Mantel-Haenszel method for each covariable and the crude association measurement.

Table 1.

Glycemic Level and General Characteristics Comparing Case (mothers of newborns with LBW) and Control (mothers of newborns of normal weight) Groups (n = 372 and 264, respectively)

Characteristics	Total Cases (N = 109)	Total Sample Controls (N = 263)	*P**	Final Cases (n = 70)	Final Sample Controls (n = 194)	*P**
Glycemic level/HbA1c						
<5.6%	53 (75.71%)	127 (65.46%)	0.11	53 (75.71%)	127 (65.46%)	
≥5.6% to <6.5%	17 (24.29%)	67 (34.54%)		17 (24.29%)	67 (34.54%)	0.11
≥6.5% to 7.0%	1	2				
Data not reported	38	67				
Age (years)						
12 to 17 and ≥36	43 (39.45%)	55 (20.91%)		37 (52.86%)	55 (28.35%)	
18 to 35	66 (60.55%)	208 (79.09%)	<0.001	33 (47.14%)	139 (71.65%)	<0.001
Maternal education level† (years of study)						
>4 years	92 (84.40%)	230 (88.46%)		57 (81.43%)	168 (87.5%)	
0 to 4 years	17 (15.60%)	30 (11.54%)	0.28	13 (18.57%)	24 (12.5%)	0.21
Family income (minimum monthly salaries)†						
>1 minimum monthly salary	35 (32.71%)	84 (32.68%)		19 (27.54%)	64 (33.68%)	
≤1 minimum monthly salary	72 (67.29%)	173 (67.32%)	0.99	50 (72.46%)	126 (66.32%)	0.35
Maternal occupation during pregnancy†						
Paid	42 (38.53%)	125 (47.71%)		27 (39.71%)	88 (47.57%)	
Housewife/student/unemployed	64 (58.72%)	132 (50.38%)	0.25	41 (60.29%)	97 (52.43%)	0.27
Not informed	3 (2.75%)	5 (1.91%)				
Hospitalization during pregnancy†						
No	93 (85.32%)	233 (88.93%)		60 (85.71%)	171 (88.6%)	
Yes	16 (14.68%)	29 (11.07%)	0.33	10 (14.29%)	22 (11.4%)	0.53
Primiparity†						
Yes	65 (59.63%)	124 (47.69%)		42 (60%)	97 (50.79%)	
No	44 (40.37%)	136 (52.31%)	0.03	28 (40%)	94 (49.21%)	0.19
History of newborn with LBW†						
Yes	12 (26.09%)	15 (11.11%)		7 (24.14%)	13 (13.98%)	
No	34 (73.91%)	120 (88.89%)	0.01	22 (75.86%)	80 (86.02%)	0.20
Not applicable	63	128				
Conjugal situation†						
Married/stable union	85 (78.71%)	211 (80.53%)		57 (82.61%)	153 (79.27%)	
Single/widowed/divorced	23 (34.1%)	51 (19.47%)	0.41	12 (17.39%)	40 (20.73%)	0.55

Table 1. (continued)

Glycemic Level and General Characteristics Comparing Case (mothers of newborns with LBW) and Control (mothers of newborns of normal weight) Groups (n = 372 and 264, respectively)

Characteristics	Total Cases (N = 109)	Total Sample Controls (N = 263)	*P**	Final Cases (n = 70)	Final Sample Controls (n = 194)	*P**
Household density† (number of people)						
≥4	53 (50.96%)	158 (61.48%)		43 (63.24%)	124 (65.26%)	
<4	51 (49.04%)	99 (38.52%)	0.06	25 (36.76%)	66 (34.74%)	0.76
Place of residence						
Feira de Santana	61 (55.96%)	144 (54.75%)		38 (54.29%)	103 (53.09%)	
Other city	48 (44.04%)	119 (45.25%)	0.83	32 (45.71%)	91 (46.92%)	0.86
Smoking habit during pregnancy†						
Yes	3 (2.75%)	9 (3.44%)		2 (2.86%)	5 (2.59%)	
No	106 (97.25%)	253 (96.56%)	0.73	68 (97.14%)	188 (97.41%)	0.91
Alcoholic beverage consumption during pregnancy†						
Yes	10 (9.17%)	32 (12.21%)		5 (7.14%)	24 (12.44%)	
No	99 (90.83%)	230 (87.79%)	0.40	65 (92.86%)	169 (87.56%)	0.23
Race/color of mother†						
White	16 (14.81%)	24 (9.27%)		12 (17.4%)	20 (10.47%)	
Non-white	92 (85.19%)	235 (90.73%)	0.12	57 (82.6%)	171 (89.53%)	0.13
Prenatal consultation†						
Yes	106 (98.15%)	260 (98.86%)		69 (98.57%)	193 (99.48%)	
No	2 (1.85%)	3 (1.14%)	0.58	1 (1.43%)	1 (0.52%)	0.45
Number of prenatal consultations†						
>6	16 (16.67%)	88 (35.34%)		22 (35.48%)	95 (51.35%)	
≤6	80 (83.33%)	161 (64.66%)	<0.001	40 (64.52%)	90 (48.65%)	0.03
Data not reported	13	14				
Urinary infection†						
Yes	30 (27.78%)	94 (35.88%)		18 (26.09%)	63 (32.64%)	
No	78 (72.22%)	168 (64.12%)	0.13	51 (73.91%)	130 (67.36%)	0.31
Hypertension†						
Yes	22 (20.37%)	33 (12.60%)		10 (14.49%)	21 (10.88%)	
No	86 (79.63%)	229 (87.40%)	0.05	59 (85.51%)	172 (89.12%)	0.43

Table 1. (continued)

Glycemic Level and General Characteristics Comparing Case (mothers of newborns with LBW) and Control (mothers of newborns of normal weight) Groups (n = 372 and 264, respectively)

Characteristics	Total Cases (N = 109)	Total Sample Controls (N = 263)	*P**	Final Cases (n = 70)	Final Sample Controls (n = 194)	*P**
DM†						
Yes	1 (0.93%)	0 (0%)	0.11	1 (1.47%)	0 (0%)	0.09
No	106 (99.07%)	262 (100%)		67 (98.53%)	193 (100%)	
Prepregnancy BMI†						
>18.5	63 (77.78%)	177 (93.16%)	<0.001	36 (78.26%)	130 (90.28%)	<0.001
≤18.5	18 (22.22%)	13 (6.84%)		10 (21.74%)	14 (9.72%)	
Data not reported	28	73				
Prenatal educational activity during pregnancy†						
Yes	30 (28.30%)	83 (32.30%)	0.45	17 (24.29%)	66 (34.55%)	0.12
No	76 (71.70%)	174 (67.70%)		53 (75.71%)	125 (65.45%)	

Minimum monthly salary at the time of data collection: R$ 622,00 (US$ 155.50).
* *P* ≤0.05.
† Categories with losses or information not declared.

In logistic regression analysis, the role of the confounding variables was evaluated using the backward strategy in the non-conditional logistic regression analysis, assuming that the covariable would produce a change of at least 20% in the association measurement. In accordance with the knowledge of the influence of the covariables in both the exposure and the outcome, classic confounders were also retained in the model. The data were analyzed using a statistical program.‡‡

RESULTS

A total of 372 females took part in the study: 109 in the case group and 263 in the control group. Of them, 267 agreed to submit a blood sample. After measurement of HbA1c levels, 180 females had levels ≥5.6% and <6.5%, whereas 84 had levels <5.6%. Three females had levels ≥6.5% and <7.0% and were excluded from these defined groups (Table 1). Thus, a total of 264 females took part in the final sample of the study: 70 in the case group and 194 in the control group. It is worth noting that the decrease in the sample number did not influence the statistical significance of the covariables distribution, as seen in Tables 1 and 2.

Table 1 also shows the general characteristics of participants. The comparison between the cases and controls of the final sample showed that they were similar for the majority of the characteristics, except age (*P* <0.001), number of prenatal consultations (*P*= 0.03), and pregestational body mass index (BMI) (*P* <0.001).

There was a higher frequency of mothers in the case group, when compared to mothers from the control group, in the age ranges of 12 to 17 years and ≥36 years (52.86% versus 28.35%), the number of prenatal consultations ≤6 (64.52% versus 48.65%), and pregestational BMI ≤18.5 (21.74% versus 9.72%).

Oral health behavioral characteristics are shown in Table 2. Both groups were homogeneous for the majority of parameters. The occurrence of periodontitis among the mothers from the case group was ≈4.5 greater than that found in the mothers from the control group (43.48% versus 9.79%, *P* <0.001).

Overall, the likelihood of having children with LBW among the mothers with periodontitis was 4.5 times greater than that observed among mothers without periodontitis ($OR_{unadjusted}$ = 4.51, 95% CI = 2.63 to 7.74), and this difference was statistically significant. After adjustment of the measurement for the covariables of age, family income, pregestational BMI, number of prenatal consultations, and primiparity, there was an increase in the OR ($OR_{adjusted}$ = 6.02, 95% CI = 2.47 to 15.17), showing a strong association that was also statistically significant.

‡‡ StataCorp v.9.0, StatCorp, College Station, TX.

Table 2.
Characteristics Related to Oral Health Behavior Comparing Case (mothers of newborns with LBW) and Control (mothers of newborns with normal birth weight) Groups (n = 372 and 264, respectively)

Characteristics	Total Cases (N = 109)	Total Sample Controls (N = 263)	P*	Final Cases (n = 70)	Final Sample Controls (n = 194)	P*
Periodontitis†						
No	68 (62.39%)	232 (88.21%)	<0.001	39 (56.52%)	175 (90.21%)	<0.001
Yes	41 (37.61%)	31 (11.79%)		30 (43.48%)	19 (9.79%)	
Frequency of toothbrushing per day†						
Once	12 (11.01)	32 (12.17)	0.75	9 (13.04%)	19 (9.95%)	0.48
Twice or more	97 (88.99)	231 (87.83)		60 (86.96%)	172 (90.05%)	
Use of dental floss†						
No	76 (69.72%)	171 (65.02%)	0.38	45 (64.29%)	121 (62.69%)	0.81
Yes	33 (30.28%)	92 (35.98%)		25 (35.71%)	72 (37.31%)	
Periodic visits to dentist†						
No	82 (75.23%)	187 (71.10%)	0.41	54 (77.14%)	134 (69.43%)	0.22
Yes	27 (24.77%)	76 (28.90%)		16 (22.86%)	59 (30.57%)	
Professional advice about oral hygiene†						
No	91 (83.49%)	214 (81.37%)	0.62	58 (82.86%)	153 (79.27%)	0.52
Yes	18 (16.51%)	49 (18.63%)		12 (17.14%)	40 (20.73%)	

* $P \leq 0.05$.
† Categories with losses or information not declared.

There was a statistically significant relationship between periodontitis and LBW in both the normal glycemic–level group (HbA1c levels <5.6%, $OR_{unadjusted}$ = 8.30, 95% CI = 3.56 to 19.35) and in the high glycemic–level group (HbA1c levels ≥5.6% and <6.5%, $OR_{unadjusted}$ = 5.73, 95% CI = 1.75 to 18.70). In the normal glycemic–level group, the increase in the association measurement was >30% when compared to the main association measurement ($OR_{adjusted}$ = 6.02). Conversely, in the high glycemic–level group, there was a decrease of ≈5% (Table 3).

After adjustment for age, family income, pregestational BMI, number of prenatal consultations, and primiparity, the magnitude of the association showed a slight reduction in the normal glycemic–level group ($OR_{adjusted}$ = 7.59, 95% CI = 2.7 to 24.28), maintaining a strong association with statistical significance. In this group, the increase in the adjusted association measurement was >25% when compared to the main association measurement ($OR_{adjusted}$ = 6.02).

In those with high glycemic levels ($OR_{adjusted}$ = 4.03, 95% CI = 0.81 to 19.96), the OR was decreased almost 50% in relation to the main adjusted association measurement ($OR_{adjusted}$ = 6.02), so the association lost statistical significance (P >0.05).

DISCUSSION

The results of the present study confirm the relationship between periodontitis and LBW in this Brazilian population. This relationship was persistent and appeared to be strengthened after adjusting for age, family income, pregestational BMI, number of prenatal consultations, and primiparity. Moreover, the relationship between periodontitis and LBW was overshadowed/camouflaged because periodontitis and glycemic levels appear to have opposing influences on birth weight, and thus the magnitude of the association was altered depending on maternal blood glucose level.

The association was seen in the mothers in the defined normal glycemic–level group, which also remained strong with an increase of 25%, after adjusting for the above covariables. Conversely, in the high glycemic–level group, the crude association decreased ≈5% when compared to the

Table 3.

OR and 95% CI for Influence of Glycemic Level, Measured by HbA1c Level, on Relationship Between Periodontitis and LBW (n = 264)

	Glycemic Level					
	Normal* (n = 180)			High† (n = 84)		
	OR	95% CI	P‡	OR	95% CI	P‡
Unadjusted	8.30	3.56 to 19.35	<0.001	5.73	1.75 to 18.70	<0.001
Adjusted§	7.59	2.7 to 24.28	<0.001	4.03	0.81 to 19.96	0.08

* Group with normal glycemic level: HbA1c <5.6%
† Group with high glycemic level: HbA1c ≥5.6% and <6.5%.
‡ $P \leq 0.05$.
§ Adjusted for age, family income, pregestational BMI, number of prenatal consultations, and primiparity.

main adjusted association measurement. After adjustment, the decrease was ≈50%, showing the influence of the high glycemic level on birth weight. Nonetheless, in this high glycemic–level group, the association was lost after adjustment, which may be attributable to the fact that the study power of this group was too low to detect this association.

It is well established that high blood glucose levels during pregnancy may lead to an increase in birth weight.[1,14,15,18,25] There is evidence that there is a direct relationship between maternal blood glucose levels during pregnancy and fetal growth and size at birth, even when maternal blood glucose levels are within a normal range.[4] In this context, the results of the present study suggest that a normal glycemic level (<5.6%) in pregnancy does not interfere in the association between periodontitis and LBW. Conversely, a high glycemic level (≥5.6% and <6.5%) in pregnancy may overshadow the influence of periodontitis on the subsequent birth weight of the baby.

The relationship between periodontitis and LBW has been debated in many previous studies.[26] Various studies have described a positive association,[7,10,12,27-29] whereas others have refuted this possible association.[9,30-33] The lack of consensus could be attributable to methodologic strategies that ignored the participation of previously unidentified determinants, for example, the maternal glycemic level, which could influence the relationship between the periodontal infection and the gestational complication.

However, a limitation of the present study is the level of HbA1c used to establish normal levels in pregnancy. In previous studies,[1-3] there is no consensus on the reference range of HbA1c in healthy pregnant females, although the HbA1c reference intervals for the general population are well established, and there is even controversy on the HbA1c range for females at different gestational ages.

Conversely, HbA1c has its advantages. It can reflect the mean blood glucose level for the previous 8 to 10 weeks; it does not depend on accurate glucose detection, the acute change in blood glucose, or the interval between previous meal and HbA1c detection. Additionally, HbA1c detection has good repeatability and is stable and not influenced by the time of blood collection, fasting status, or use of insulin. HbA1c detection is recommended as a gold standard for evaluating the glucose control.[3]

The decision to use HbA1c in the present study is based on Hiramatsu et al.,[2] the most recent multicenter study with Japanese females concerning glycemic levels during pregnancy, which suggested an HbA1c reference range from 4.5% to 5.7%, and adapted to this Brazilian sample as described by Nielsen et al.,[24] who proposed that the normal reference values for the third trimester are 4.4% to 5.6%. Another limitation is the choice of HbA1c as a marker of glycemic levels. Again, however, this is mitigated by the fact that current multicenter studies for control and prevention of gestational diabetes also use the level of HbA1c as a test of choice.[1-4] Despite being recognized that a consensus on the use of this marker does not exist, as during pregnancy, HbA1c levels are influenced by other factors: 1) ferritin; 2) folic acid; 3) vitamins B6 and B12 levels; and 4) the amount of bleeding during labor.[2] Nevertheless, because HbA1c levels reflect changes in glycemic control during a period of 2 to 4 months before the exam,[1-4] this marker was selected in the present study in an attempt to reflect alterations in glycemic control in the 2 to 4 months leading up to delivery.

Another limitation of the current study is the sample-size calculation. Because there were no previous studies investigating this relationship among the mothers' glycemic level, periodontitis, and birth weight, the prevalence of periodontal disease was used to calculate the sample size.[6] Because this study is the first to explore the influence of maternal glycemic level on the relationship

between periodontitis and LBW, the subgroup analysis can reduce the power of the study. Thus, it is possible that the finding of no statistical significance achieved in the group with high glycemic levels (HbA1c ≥5.6 and <6.5%), when adjusted for the potential confounders, could be attributable to a reduction in the power of the study.

Conversely, other features strengthen the method, lending more quality to the study and granting it internal validity. The cutoff point established by the World Health Organization classification was used to define LBW,[20] and the criteria used for the classification of periodontal disease has good specificity and has been used in many other studies linking periodontitis to systemic conditions.[23,28,34-39] In this context, given the current evidence on reference values for gestational glycemic levels and the findings of this study that showed the overshadowing influence of maternal glycemic level in the relationship between periodontitis and LBW, mainly in mothers with an HbA1c <5.6 but also in those with an HbA1c ≥5.6 and <6.5%, it is important to highlight the need for accurate glycemic levels when studying the oral health status of females during pregnancy.

Moreover, additional studies are necessary to determine the actual causal pathway(s) by which glycemic levels and periodontal infection influence LBW. The current findings suggest that, depending on maternal glycemic level, the effect of periodontitis on birth weight may be camouflaged.

CONCLUSION

The current study shows that periodontitis and glycemic levels appear to have opposing influences on birth weight in that periodontitis was associated with LBW, but this was overshadowed, and the magnitude of the association was altered depending on maternal blood glucose level.

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