

# Exposure measurement in the association between periodontal disease and prematurity/low birth weight

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#### Abstract

**Aim:** To compare the use of different definitions for exposure measurement in cases of association between periodontal disease (PD) and prematurity and/or low birth weight (PLBW).

**Material and Methods:** A database from a previous case–control study was used to compare four different definitions for periodontitis: at least one site with probing depth  $\geq 4 \text{ mm}(1)$ ; at least one site with clinical attachment loss (CAL) $\geq 3 \text{ mm}(2)$ ; at least four teeth with one or more sites presenting probing depth  $\geq 4 \text{ mm}$ , with CAL $\geq 3 \text{ mm}$  at the same site (3); and at least four teeth with one or more sites with probing depth  $\geq 4 \text{ mm}$ , with CAL $\geq 3 \text{ mm}$  at the same site (3); and at least four teeth with one or more sites with probing depth  $\geq 4 \text{ mm}$ , with CAL $\geq 3 \text{ mm}$  at the same site and presence of bleeding on probing (4). The PD frequency, diagnostic values and adjusted association measurements were calculated. **Results:** PD frequency ranged from 33.1% to 94.7%. Odds ratio<sub>adjusted</sub> varied slightly according to the exposure measurement used.

**Conclusions:** The association between PD and PLBW weight was consistent, except for exposure measurement 1, i.e. using at least one site with  $CAL \ge 3 \text{ mm}$  for periodontitis diagnosis, while the magnitude of this varied according to the definition established.

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The association between periodontal disease (PD) and prematurity and/or low birth weight (PLBW) has been considerably investigated, and this is reflected in the increasing numbers of studies on this subject in the literature (Offenbacher et al. 1996, 2006, Jeffcoat et al. 2001, 2003, López et al. 2002a, b, Radnai et al. 2004, Cruz et al. 2005,

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Financial support for this research was provided by the Research Support Foundation of the State of Bahia (FAPESB) and Feira de Santana State University. Noack et al. 2005, Hujoel et al. 2006, Michalowicz et al. 2006, Sadatmansouri et al. 2006, Urbán et al. 2006).

The increase in the quantity of clinical and epidemiological research in this field is a consequence of the importance of this association as a public health matter, because of both the importance of the exposure (PD) and the outcome (PLBW). With regard to exposure, the search for knowledge is attributable to the high occurrence of this disease. Its prevalence in the general population is around 10–20% (Papapanou 1996). Moreover, the current evidence suggests that this disease, which is also associated with advanced age, presents an upward trend as a result of the increasing life expectancy in Brazil and around the world (Brasil. Ministério da Saúde. Projeto SB Brasil 2003). This further affects the stomatognathic system in large populations and gives rise to higher costs for dental care.

On the other hand, with regard to the outcome, investigations on PLBW, per se, are important for the field of public health, because such events are strong determinants of infant mortality and particularly neonatal mortality. Furthermore, such events contribute towards infant morbidity through neurological, respiratory and behavioural development problems and congenital anomalies (McCormick 1985, Yu 2000). Even though the importance of this topic for public health seems clear, research investigating the association between PD and PLBW presents divergent findings that do not allow categorical conclusions. It is, however, known that such results may arise from unsatisfactory internal validity in various studies, i.e. the dubious quality of the divergent methods utilized, including those for diagnosing PD.

Thus, it can be considered that the diagnostic criteria could interfere with the findings from studies on the association between PD and PLBW, thereby also causing difficulties regarding their comparability and trustworthiness because of the complexity of the clinical characteristics of periodontitis. The present study, using a database from a previous investigation (Cruz et al. 2005), makes an important contribution towards comprehending this subject by comparing the use of different definitions for measuring the exposure (periodontitis) in cases of association between PD and PLBW, in order to evaluate whether there is any distortion from the use of these measurements.

### Material and Methods

#### Study sample

The minimum sample size was calculated using the Epi Info software (version 6), with the assumptions of a power of 80% and a confidence interval (CI) of 95%. The following parameters available in the literature were used (Offenbacher et al.  $1996)^2$ : (1) frequency of 18% for PD among mothers whose children had low birth weight; and (2) frequency of 4.7% among mothers whose children had normal birth weight 95%.

This was a case-control study on 302 puerperas (Cruz et al. 2005). (The present investigation used the database of Cruz et al. (2005), from the same authors, with a different objective.). The cases were mothers of premature newborns who were born with a gestational age of <37 weeks and/or low birth weight (< 2500 g). The controls were mothers of newborns with a birth weight  $\geq 2500 \,\text{g}$  and gestational age  $\geq$  37 weeks, in accordance with World Health Organization criteria (WHO 1976). Puerperas were excluded from the study if they had presented cardiopathy, diabetes or other systemic alterations during the pregnancy that required antibiotic prophylaxis, and also if the individuals were only identified more than 7 days after delivery.

The puerperas were selected at the women's Hospital in the city of Feira de Santana, Bahia, Brazil. After identifying the women for the case group, they were then invited to participate in the study. The puerperas of the control group were identified and formed a list that was drawn up every day, containing all the mothers of newborns with normal gestational age and weight. For each case identified, two women were drawn from this list every day, thus forming the proportions of two controls for each case. The data collection period was from February to July 2003, and during this period 102 cases and 200 controls were selected. The study was approved by the Research Ethics Committee of the Feira de Santana State University, Bahia, Brazil (Protocol no. 023/2005).

#### Data collection procedures

The complete periodontal examinations were conducted within 7 days of delivery, by a single observer who was chosen because of this individual's considerable previous experience in periodontics. It is emphasized that this examiner was unaware of the puerpera's gestational condition at the time of the examination. Intra-examiner calibration was performed before the start of the study. The reliability was confirmed by obtaining repeated measurements during the calibration sessions and from around 10% of the patients (selected randomly) during the study. The degree of intraexaminer concordance for the measurements made was classified as very good and ranged from 0.806 to 0.812 ( $\kappa$  test).

In addition to this, questionnaires were used with the aim of collecting sociodemographic, lifestyle and medical-dental information. Nursing auxiliaries were trained to follow the protocol for initially approaching, inviting and recruiting the puerperas for the whole study, and were also trained to be impartial in obtaining information. The data relating to the newborns' gestational ages and birth weights were collected from the mother's hospitalization card or, possibly, from the birth certificates. With regard to the information on gestational age, the ultrasound examination performed by doctors within the public health service was preferentially used. However, in its absence, the data

relating to the date of the last menstruation were used.

The mothers' periodontal condition was evaluated in the dental consultation office of the study hospital, by means of the clinical attachment loss (CAL) measurement, which was performed using a Williams probe graduated in millimetres. This was obtained as the sum of the probing depth and recession measurements, at six sites per tooth: mesiovestibular, mediovestibular, distovestibular, mesiolingual, mediolingual and distolingual. The probing depth was recorded at each location as the distance from the gingival margin to the most apical extent of probe penetration. Measurements of the height of the gingival margin in relation to the cement-enamel junction were made using the same probes (graduated in millimeters) as used for determining the probing depth. In cases of gingival recession, the reading in millimetres was taken to be positive and the gingival margin was located apical to the cement-enamel junction. In addition to this, the bleeding on probing index was determined at all the above-mentioned sites while obtaining the probing depth records, by observing whether bleeding was present within 10s after removing the graduated probe from the pocket or sulcus.

# **Classification of the PD**

Each puerpera was classified as presenting periodontitis or not. This was done in accordance with the literature on the subject of the association between PD and PLBW (Madianos et al. 2002), which classifies the measurement of the exposure (periodontitis) according to the clinical parameters obtained from periodontal examination of all the teeth. From this, the PD frequency was obtained in accordance with four types of exposure measurement, defined as follows:

- Measurement 1 (*EM1*): at least one site with CAL ≥ 3 mm (Noack et al. 2005).
- Measurement 2 (*EM2*): at least one site with a probing depth ≥4 mm (Hujoel et al. 2006).
- Measurement 3 (*EM3*): at least four teeth with one or more sites with a probing depth greater than or equal to 4 mm, with CAL≥3 mm, at the same site (López et al. 2002a, b).

• Measurement 4 (*EM4*): at least four teeth with one or more sites with a probing depth greater than or equal to 4 mm, with CAL≥3 mm at the same site, and the presence of bleeding on probing (Gomes-Filho et al. 2005).

#### Data analysis

To describe the study samples, the PD was distributed in accordance with each exposure measurement and all the covariables considered. Then, by means of stratified analysis, the existence of potential confounding factors and effect modification was investigated for the following covariables: number of prenatal consultations, occupation before and during pregnancy, weight before pregnancy, place of residence, number of children, number of people living in the home, presence of urinary infection during pregnancy, hypertension, smoking, alcohol use, age, level of schooling, family income, marital status, frequency of tooth brushing, use of dental floss, number of meals per day, number of visits to the dentist and height. The backward stepwise strategy was utilized in non-conditional logistic regression analysis to assess the statistical significance, taking 95% CIs. The possibility of effect modification was evaluated by means of the maximum likelihood ratio test. Potential confounding variables were selected on a theoretical or an empirical basis, or on both bases, and these variables were taken to be the ones that would produce a change of at least 20% in the association measurement. Additionally, the adjusted association measurements were calculated for each of the exposure measurements and expressed as odds ratios (ORs). Finally, EM4 was taken as the gold standard to make comparisons with the other measurements, using diagnostic sensitivity and specificity values and positive and negative predictive values.

The Stata (Version 8.0, Lakeway Drive, Texas, 2003) software was utilized for data processing and analysis.

#### Results

Table 1 shows that no statistically significant differences between the case and control groups were detected for any of the characteristics considered in this investigation. The two groups were therefore comparable with regard to all *Table 1.* Some sociodemographic and lifestyle characteristics (number and percentage) for the cases and controls, and the respective *p*-values. Women's Hospital, Feira de Santana, Bahia, Brazil, 2003 (n = 302)

Characteristics	Case* $(N = 102)$		$\text{Control}^{\dagger} (N = 200)$		$p^{\ddagger}$
	Ν	%	Ν	%	
Age (years)					
13–20	50	49.1	85	42.5	
21-35	44	43.1	105	54.5	0.28
36–48 <sup>s</sup>	8	7.8	10	5.0	
Place of residence	24	22.2	50	25.0	
Kural zone	54	33.3	50	25.0	0.20
Urban zone Marital status	08	00.7	150	/5.0	0.28
Single	21	20.8	16	22.0	
Siligle Married/aphabiting	21	20.8	154	23.0	0.60
Family income (minimum salaries)	80	19.2	154	77.0	0.00
	65	63 7	117	58 5	
<li>1</li>	37	36.3	83	41.5	0.38
Schooling level	51	50.5	05	41.5	0.56
	34	34.3	56	28.7	
+4	65	65.7	139	71.3	0.32
Occupation before pregnancy	05	05.7	155	/1.5	0.52
Self-employed/laborer/other	32	31.4	76	30.0	
Maid/student/housewife	70	68.6	124	70.0	0.45
Occupation during pregnancy	70	0010	12.	7010	0.10
Self-employed/laborer/other	33	24.5	74	31.5	
Maid/student/housewife	69	75.5	126	68.5	0.45
Height (cm)	0)	1010	120	0010	0.10
< 160	42	42.0	83	42.8	
≥160	58	58.0	111	57.2	0.86
Smoking					
Yes	21	20.8	46	23.0	
No	80	79.2	154	77.0	0.72
Urinary infection during pregnancy					
Yes	27	26.5	57	28.5	
No	75	73.5	143	71.5	0.71
Number of prenatal consultations					
0–3	33	32.3	57	28.5	
4–9	69	67.7	143	71.5	0.48
Weight before pregnancy (kg)**					
≤50	38	37.6	70	35.5	
>50	63	62.4	127	64.5	0.72
Number of children					
1	50	49.0	104	52.3	
>1	52	51.0	95	47.7	0.65
Number of people living in the home'		10			
0-4	47	48	93	47.7	
>4	51	52	102	52.3	0.93
Alcohol use**	10	0.0	15	7.5	
Yes	10	9.8	15	7.5	0.24
NO	90	90.2	185	92.5	0.54
Number of tooth-brushings	0	8.0	10	0.1	0.21
I per day	9	8.9	18	9.1	0.51
>1 per day	92	91.1	179	90.9	
Vas	82	82.2	156	70.6	
No	18	17.8	40	20.4	0.50
Hypertension	10	17.0	+0	20.4	0.59
Yes	15	177	21	10.5	
No	87	85 3	170	89.5	0.20
Visits to the dentist	07	05.5	1/2	07.5	0.29
Yes	2	1 96	14	7	
No	100	98	186	93	0.06
Number of meals per day <sup>¶¶</sup>	100		100	20	0.00
0-3	62	62.6	141	71.6	
>4	37	37.4	56	28.4	0.11

\*Mothers of children that were born with weight of under 2500 g and/or gestational period below 37 weeks. \*Mothers of children that are born with weight equal to or over 2500 g and gestational period equal to or above 37 weeks.

<sup>‡</sup>Statistical significance,  $p \leq 0.05$ .

<sup>§</sup>Because the observations were insufficient in number to analyze the association, this stratum was grouped with the preceding one.

<sup>¶</sup>One observation was lost. <sup>∥</sup>Eight observations were lost.

\*\*Four observations were lost.

<sup>††</sup>Nine observations were lost.

<sup>‡‡</sup>Two observations were lost.

<sup>§§</sup>Five observations were lost.

<sup>¶¶</sup>Six observations were lost.

Exposure	Absolute	Frequency	Sensitivity	Specificity (%)	Positive predictive	Negative predictive
measurement	frequency	of PD (%)	(%) 95% CI	95% CI	value (%) 95% CI	value (%) 95% CI
EM1*	286	94.7	100 [95.4–100]	7.9 [4.7–12.8]	35 [29.5–40.8]	100 [75.9–100]
EM2 <sup>†</sup>	150	49.7	100 [95.4–100]	75.2 [68.6–80.9]	66.7 [58.4–74]	100 [96.9–100]
EM3 <sup>‡</sup> EM4 <sup>§</sup>	110 100	36.4 33.11	100 [95.4–100]	95 [90.8–97.5]	90.9 [83.5–95.3]	100 [96.6–100]

Table 2. Distribution of periodontal disease (PD, %) and diagnostic values for exposure measurements 1–3, in comparison with exposure measurement 4 (taken as the gold standard). Women's Hospital, Feira de Santana, Bahia, Brazil, 2003 (n = 302)

\*Exposure measurement 1 (EM1): at least one site with clinical attachment loss  $\ge 3 \text{ mm}$ .

<sup>†</sup>Exposure measurement 2 (EM2): at least one site with a probing depth  $\ge 4$  mm.

<sup>4</sup>Exposure measurement 3 (EM3): at least four teeth with one or more sites with a probing depth  $\ge 4$  mm, with clinical attachment loss  $\ge 3$  mm, at the same site.

<sup>§</sup>Exposure measurement 4 (EM4): at least four teeth with one or more sites with a probing depth  $\ge 4$  mm, with clinical attachment loss  $\ge 3$  mm at the same site, and the presence of bleeding on probing.

the characteristics evaluated in this study.

The results also show that the PD frequency ranged from 33.1% to 94.7%, according to the measurement utilized. When using EM1 (at least one site with a CAL  $\geq 3$  mm), the relative frequency of PD was the highest:  $\sim 95\%$ . When using EM2 (at least one site with a probing depth  $\ge 4$  mm), the frequency decreased to about half of the studied group: 49.7%. Likewise, when EM3 (at least four teeth with one or more sites with a probing depth  $\ge 4 \text{ mm}$ , with CAL  $\ge$  3 mm, at the same site) was used, decreased PD frequency was observed: 36.4%. Finally, when using EM4 (at least four teeth with one or more sites with a probing depth  $\ge 4 \text{ mm}$ , with  $CAL \ge 3 \text{ mm}$  at the same site. and the presence of bleeding on probing), the frequency of PD was the lowest: 33.11%. This means that the more strictly the PD was defined, the lower the occurrence of the disease was.

Moreover, the following diagnostic values were obtained for all measurements (EM1-EM3) in relation to the gold standard (EM4): sensitivity 100% (95% CI: [95.4-100]); specificity 7.9% (95% CI: [4.7-12.8]); positive predictive value 35% (95% CI: [29.5-40.8]); and negative predictive value 100% (95% CI: [75.9-100]) for EM1; sensitivity 100% (95% CI: [95.4-100]); specificity 75.2% (95% CI: [68.6-80.9]); positive predictive value 66.7% (95% CI: [58.4-74]); and negative predictive value 100% (95% CI: [96.9-100]) for EM2; sensitivity 100% (95% CI: [95.4-100]): specificity 95% (95% CI: [90.8-97.5]); positive predictive value 90.9% (95% CI: [83.5-95.3]); and negative predictive value 100% (95% CI: [96.6-100]) for EM3 (Table 2). In this Table 2,

*Table 3*. Distribution of periodontal disease between case and control groups, unadjusted and adjusted odds ratios (ORs) and confidence intervals (CI) for the association between maternal periodontal disease (exposure measurements 1-4) and prematurity/low birth weight. Women's Hospital, Feira de Santana, Bahia, Brazil, 2003 (n = 302)

Exposure measurement	Frequency of PD (%)		Unadjusted	95% CI	Adjusted OR*	95% CI
	case $(N = 102)$	$\begin{array}{c} \text{control} \\ (N = 200) \end{array}$	on			
EM1 <sup>†,‡</sup>	94.1	95	_	_	_	_
EM2 <sup>§</sup>	62.7	43	2.24	[1.35-3.68]	2.23	[1.36-3.63]
EM3 <sup>¶</sup>	48	30.5	2.11	[1.27–3.47]	2.10	[1.28–3.44]
EM4	43.1	28	1.96	[1.18–3.23]	1.95	[1.17–3.21]

\*Age and schooling level.

<sup>†</sup>Inadequate number of observations for expressing the association measurement. High frequency of PD both in the case and in the control groups.

<sup>‡</sup>Exposure measurement 1 (EM1): at least one site with clinical attachment loss  $\ge 3$  mm.

<sup>§</sup>Exposure measurement 2 (EM2): at least one site with a probing depth  $\ge 4$  mm.

<sup>6</sup>Exposure measurement 3 (EM3): at least four teeth with one or more sites with a probing depth  $\ge 4$  mm, with clinical attachment loss  $\ge 3$  mm, at the same site.

Exposure measurement 4 (EM4): at least four teeth with one or more sites with a probing depth  $\ge 4$  mm, with clinical attachment loss  $\ge 3$  mm at the same site, and the presence of bleeding on probing.

it is important to highlight that there was an increasing trend in specificity and positive predictive value from EM1 to EM3. This means that, from EM1 to EM3, there was an increasing capacity to identify individuals without the disease and an increasing probability of correctly identifying individuals with the disease, for the measurements tested in relation to the gold standard.

Finally, Table 3 presents the distribution of PD between case and control groups and the measurements for the association between PD and PLBW, unadjusted and adjusted for age and schooling. It is emphasized that age was taken as a confounding factor from a theoretical point of view, given that it was associated simultaneously with both PD and PLBW. Schooling was taken to be a source of confounding, because it was the only covariable that,

when eliminated from the saturated model, led to a change of more than 20% in the regression coefficients when compared with that of the principal association, thereby satisfying the empirical criterion. The relative frequency between the case and control groups decreased from EM1 to EM4. This means that the more strictly the PD was defined, the lower the occurrence of the disease was in both groups. Furthermore, it can be highlighted that, regardless of the exposure measurement utilized, the strength of the association was significant, ranging from 1.96 to 2.24 (OR<sub>unadiusted</sub>). In the case of EM1, it was not possible to generate an association measurement because the PD was common to all subjects and nondiscriminating with respect to the disease (94.1% of the cases and 95% of the controls). The adjustment for age and

schooling yielded slightly lower ORs for the association between PD and PLBW: 2.23 (95% IC: [1.36–3.63]) for EM2; 2.10 (95% IC: [1.28–3.44]) for EM3; and 1.95 (95% IC: [1.17–3.21]) for EM4, but all remained statistically significant. Moreover, it was observed that the more strictly PD was defined, the lower the estimates of the association were. The possibility of effect modification was evaluated, but no interaction factors were identified.

# Discussion

The findings from the present casecontrol study demonstrate the existence of a statistically significant association between PD and PLBW, except for EM1, i.e. the use of at least one site with CAL  $\ge 3 \text{ mm}$  for PD diagnosis. Moreover, it was found that the magnitude of the association and the frequency of PD could be influenced by these different measurements.

With regard to the different estimates for the association found in this study for these puerperas evaluated, such observations were already expected, given that it was believed that there would be interference from the type and robustness of the criteria utilized for diagnosing PD as a measurement of exposure to PLBW.

From this perspective, EM2 (one site with probing depth  $\geq 4$  mm) was the one that presented the greatest estimated association (adjusted OR = 2.23; 95% CI: [1.36-3.63]). On the other hand, when compared with the gold standard, the specificity value obtained demonstrated that this measurement could also have added a large number of puerperas with a false-positive diagnosis of periodontitis to the PD classification. Furthermore, according to the positive predictive value, the probability that this exposure measurement would correctly classify the PD was  $\sim 67\%$  of the puerperas evaluated.

With regard to EM3 (CAL  $\geq$  3 mm and probing depth  $\geq$  4 mm), this has already been utilized in other studies in the literature on the same subject (López et al. 2002a, b, Offenbacher et al. 2006, Sadatmansouri et al. 2006). Utilizing the combination of these two clinical parameters has the objective of identifying dental sites with a true periodontal pocket, and this may consequently distinguish individuals with the disease from those who do not have the

disease but present gingival recession (Andriankaja et al. 2006). The estimated association between PD and PLBW [adjusted OR = 2.10; 95% CI: (1.28– 3.44)] was less than that for EM2, but this corroborates the findings from other studies that utilized this exposure measurement (López et al. 2002a, b, Offenbacher et al. 2006, Sadatmansouri et al. 2006). It needs to be emphasized that the more rigorous the criterion for defining PD, the lower the frequency of this disease. Furthermore, the high specificity value obtained reinforces the understanding that the possibility of making false-positive diagnoses of periodontitis among puerperas is relatively small, with the addition of high probability that this measurement would correctly classify the PD in these puerperas (positive predictive value).

Consequently, EM4 (CAL $\geq$ 3 mm, probing depth  $\geq 4 \text{ mm}$  and bleeding on probing) was the one that presented the lowest-estimated association, which had been expected and was maintained [adjusted OR = 1.95; 95% CI; (1.17-)3.21)]. The addition of the clinical parameter of bleeding on probing to the combined criteria of CAL and probing depth was justified by the greater rigor obtained. This diagnostic criterion for PD had the objective of reinforcing the specific characteristic of tissue inflammation in periodontitis, because the use of radiographic examination during pregnancy is avoided, although such examinations would be important for confirming the diagnosis of periodontal support loss. Other studies on this subject (Radnai et al. 2004, Urbán et al. 2006) also utilized bleeding on probing as a diagnostic parameter for PD, thereby confirming the association between PD and PLBW. On the other hand, Michalowicz et al. (2006), in a clinical trial, using these clinical parameters, did not find this association. It could be probably due to the cut-off point used for the CAL (2mm) and bleeding on probing index (35%). In this sense, the choice of EM4 is reinforced by the need to validate more precise criteria for diagnosing periodontitis in studies evaluating this association, thereby making the results more consistent through the use of a more rigorous exposure measurement with very precise criteria, and thus avoiding falsepositive diagnoses.

Finally, EM1 (one site with  $CAL \ge 3 \text{ mm}$ ) was defined in this study as the weakest means of classifying PD,

because it presented the highest frequency of periodontitis both for cases and for controls and did not distinguish PD cases among the puerperas, thereby giving rise to an insufficient number of analysis parameters for generating an association measurement. Moreover, when it was compared with the gold standard measurement, the low specificity value obtained represented a large number of puerperas with a false-positive diagnosis of periodontitis that was added to the PD classification in this study. It is important to highlight that EM1 was not a good criterion for PD definition in this investigation. On the other hand, there are conflicting results in the literature from investigations that utilized this type of definition for PD as an exposure measurement, such that both the presence of an association (Offenbacher et al. 1996) and its absence (Noack et al. 2005) have been found.

It is emphasized that the choice of which measurement to take as the gold standard was not arbitrary. It is known that there is a tendency in the literature to utilize the measurement of CAL for diagnosing periodontitis, allied with the probing depth, and that the precision of this is increased when information on the bleeding status upon probing is also utilized (Radnai et al. 2004, Gomes-Filho et al. 2005, Urbán et al. 2006), furthermore reinforced by the necessity to validate more precise criteria for diagnosing periodontitis in studies evaluating the association between PD and PLBW, because the false-positive subjects classified as diseased would contribute towards the inference of spurious findings.

With regard to the effect measurement, it is emphasized that the source of gestational age data described had limitations. The method for collecting gestational age data was not uniform, because the ultrasound examination was used as the first choice and, in its absence, the data relating to the date of the last menstruation were used. The gestational age data were obtained by doctors within the public health service.

Another point to be highlighted relates to the factors associated with PLBW. It is understood that conditions like the preterm history, vaginosis, subclinical urinary infections and the gain in maternal weight over the gestational period are important for evaluating the association under examination. However, the pilot study for this investigation indicated a lack of knowledge among the mothers regarding these conditions, thus leading to notable losses of data on these variables. This would contribute towards possible distortions. Furthermore, it is believed that there was uniformity in the pre-natal care, although this cannot be categorically stated. This entire follow-up was all carried out in municipal health units at the same location, which have standardized attendance. The limitation that memory bias represents in relation to self-reported information is ultimately among the disadvantages attributed to the case-control design.

Moreover, it is emphasized that this study had the main objective of evaluating whether different exposure measurements would affect the association under examination. Thus, although the limitations indicated are strictly very important, they are attenuated in that the effect measurements and the covariables of interest were the same, independent of the exposure measurement evaluated.

In the light of the analyses for each type of exposure measurement utilized in this study, it can be inferred that, independent of the interpretation of this epidemiological measurement, the OR varied slightly according to the type of exposure measurement utilized, except for EM1, i.e. the use of at least one site with CAL  $\geq$  3 mm for periodontitis diagnosis. Furthermore, it can be inferred that the choice of definition for PD must be made in accordance with the study design and the questions to be raised. In the specific case of studies on the association with PLBW, the definition of the exposure measure must be more rigorous, with a combination of clinical parameters, such as the one suggested by EM4, considering that by including bleeding on probing with the criteria of probing depth and CAL, this measurement becomes very specific.

### Conclusions

Even though the results from this study have demonstrated that the ORs changed slightly with different definitions of PD, except for EM1, i.e. the use of at least one site with CAL  $\ge 3 \text{ mm}$  for periodontitis diagnosis, this situation may not be generalized to other populations. Furthermore, in the event that other studies are conducted on the association between PD and PLBW, it is important to use an a priori definition of periodontitis, in accordance with the prevalence and severity of PD in the study population, and/or to perform a sensitivity analysis, as in the present study, in order to examine the effects of different definitions of PD. Precise selection of exposure measurement will make the results consistent and confer greater safety in determining the association.

From a methodological viewpoint, the choice of diagnostic criterion partly reflects the internal validity of the study, given that the classification of the disease may introduce errors that cause bias in measuring the association and compromise the quality of this measurement. This consequence reinforces the importance of choosing the criteria for measuring exposure in studies investigating the association between PD and PLBW, especially considering that knowledge of PD makes different diagnostic criteria available (which may or may not be validated), thereby impeding a consensus between periodontal classification systems.

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# **Clinical Relevance**

Scientific rationale for the study: The lack of consensus in the specialized literature regarding the criteria for defining exposure measurements in studies on the association between PD and PLBW causes difficulties in

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comparing and validating the findings from these studies.

*Principal findings*: Depending on the type of exposure measurement used, the association between PD and PLBW may or may not exist (with different magnitudes).

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*Practical implications*: To reinforce the importance of choosing the criteria for measuring exposure in studies investigating the association between PD and systemic diseases/ conditions, such as PLBW. This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.