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PERIODONTITIS AS A RISK FACTOR FOR PRETERM LOW-BIRTH WEIGHT BABIES: A LITERATURE REVIEW

Shaju Jacob*

Abstract

Periodontitis is reported to be associated with preterm low-birth weight (PLBW) and is claimed to be one of its risk factors. This literature review examines evidence supporting the role of periodontitis in the occurrence of PLBW. PubMed, medIND and WHO indices were searched for published studies, (cross-sectional, case-control, longitudinal, experimental) using the key words: pregnancy, periodontitis. There is enough evidence to implicate periodontitis as a risk factor for preterm low-birth weight even though recent studies haven't shown a significant relation. New researches with population-specific definitions of PLBW and periodontal diseases must be done for a better assessment of the relation between periodontitis and PLBW.

Key words: preterm birth – pregnancy - periodontitis.

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LA PARODONTITE COMME FACTEUR DE RISQUE POUR LES BÉBÉS PRÉCOCES À FAIBLE POIDS À LA NAISSANCE: REVUE DE LA LITTÉRATURE

Résumé

La parodontite a été associée aux prématurités de faible poids et est considérée parmi ses facteurs de risque. Cette revue de la littérature examine les éléments probants incluant le rôle de la parodontite dans les naissances prématurées de faible poids. Une recherche sur PubMed, medIND et l'OMS a été réalisée pour répertorier les études (cas-contrôles, transversales, longitudinales, expérimentales) publiées sur ce sujet, en utilisant les mots clés suivants: la grossesse, la parodontite. De nombreuses études ont défini la parodontite comme étant un facteur de risque des naissances prématurées de faible poids. Cependant, une association significative entre ces deux entités n'a pu être démontrée par des études récentes. De nouvelles recherches adoptant des définitions des prématurités de faible poids et de la maladie parodontale plus strictes et appropriées à la population étudiée doivent être réalisées pour une meilleure évaluation de cette relation.

Mots clés: prématurité - grossesse - parodontite.

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Introduction

Adverse pregnancy outcomes include low-birth weight babies, preterm babies, stillbirths, death of foetus and death of mother. Periodontitis is linked to two of the outcomes: low weight and preterm births. Preterm birth (PTB) is the major cause of perinatal morbidity and mortality as well as long term neurologic disability [1]. While the last several decades have seen great strides being made in the treatment of the most preterm infants

leading to reductions in mortality, the long term handicap rates have remained the same for nearly 30 years [2]. Offenbacher [3] in 1996 mentioned the possible role of periodontal infection in preterm low-birth weight (PLBW) events.

The article reviews published studies in order to examine the association of periodontitis with these adverse pregnancy outcomes.

Materials and methods

Published studies in English language only were searched in various databases including PubMed, medIND and WHO. Key words used were "pregnancy, periodontitis". 102 studies were identified. Non human studies, *in vitro* studies, anecdotes, case reports and studies with the main objective of identifying a biological mechanism were excluded (17 publications). 35 publications found fulfilling the objective were sourced and included.

Case-control studies with significant results
Offenbacher et al. 1996 [3]
Dasanayake et al. 1998 [8]
Radnai et al. 2004 [9]
Mokeem et al. 2004 [10]
Moliterno et al. 2005 [11]
Bosnjak et al. 2006 [12]
Zadeh-Modarres et al. 2007 [13]
Betleja-Gromada et al. 2007 [14]
Le et al. 2007 [15]
Gomes-Filho et al. 2007 [16]
Siqueira et al. 2007 [17]
Marakoglu et al. 2008 [18]
Khader et al. 2009 [19]
Cruz et al. 2009 [20]
Nabet et al. 2010 [21]

Table 1: Case-control studies showing significant results regarding the association of periodontal diseases and PLBW.

Case-control studies with non-significant results
Davenport et al. 2002 [22]
Buduneli et al. 2005 [23]
Noack et al. 2005 [24]
Hujoel et al. 2006 [25]
Skuldbøl et al. 2006 [26]
Bassani et al. 2007 [27]
Vettore et al. 2008 [28]

Table 2: Case-control studies showing non-significant results regarding the association of periodontal diseases and PLBW.

The review was divided into sections based on study design as cross sectional (4 publications), case-control (22), longitudinal (5) and experimental studies (4), all of which had original data that evaluated the association between maternal periodontal disease and adverse pregnancy outcome.

Cross sectional studies

In the study of Santos-Pereira et al. [4], 124 Brazilian women in the State of São Paulo were examined. Periodontal indicators, such as clinical attachment loss and bleeding on probing, were observed significantly more in the preterm labour (PTL) group. The presence of chronic periodontitis increased the risk for PTL (Odds Ratio = OR = 4.7), of preterm birth (PTB) (OR = 4.9) and of low-birth weight (< 2500 g) (OR = 4.2). However, Lunardelli et al. [5] did a population-based, cross-sectional study in Southern Brazil and the sample consisted of 449 parturients examined up to 48h post-partum. No statistically significant association was found between periodontal disease and preterm low-birth weight. Also, Marin et al. [6] found the incidence of low-birth weight (LBW) very low (4.6%), with no association with periodontal disease

in a study on 152 Caucasian pregnant women. Sánchez et al. [7] were unable to identify any statistically significant associations between the periodontal clinical parameters and PTB/LBW.

Case-control studies

22 case-control studies were identified, among which 15 reported significant results regarding the association of periodontal diseases and PLBW (3, 8-21], table 1). In a case-control study involving 124 women, Offenbacher et al. [3] found that women delivering PLBW infants had significantly worse periodontitis (OR = 7.5) than did those whose infants were of normal birth weight. Dasanayake et al. [8] conducted a matched case-control study using 55 cases (birth weight <2500g) and 55 controls at a hospital in Thailand, using the Community Periodontal Index for Treatment Needs (CPITN). Mothers with a more healthy gingiva (OR = 0.3) had a lower risk of giving birth to an LBW infant.

Moliterno et al. [11] conducted a case-control study on 151 mothers. Significant associations with LBW babies were found with periodontitis (OR = 3.48), arterial hypertension (OR = 9.65), haemorrhage during pre-

gnancy (OR = 10.88), frequency of prenatal examinations (OR = 0.10,) and genito-urinary infections (OR = 3.21). Betleja-Gromada et al. [14], in their study including 120 post-partum mothers in Pomerania, found a significantly higher percentage of women with periodontal disease having preterm newborns compared to the group who had term newborns. In a large case-control study, Siqueira et al. [17] studied the association of maternal periodontitis with pregnancy outcomes in 1305 Brazilian women. Cases with preterm birth (n = 238) had an OR = 1.77; for low-birth weight (n = 235), OR was 1.67 and for intra-uterine growth retardation (n = 77), OR was 2.06 when compared to a control group. Marakoglu et al. [18] conducted a case control study among a total of 48 Turkish mothers. Periodontitis (OR = 3.6) together with bacterial vaginosis (OR = 11.57) were independent risk factors of a preterm low birth weight.

7 case-control studies reported non significant results ([22-28], table 2). Davenport et al. [22], in a case-control study with a multi-ethnic group of pregnant women from the East End of London showed no association

between periodontal infection, PTB and LBW (OR = 0.83). In the study of Hujuel et al. [25] comparing 793 cases (infants <2,500 g) and a random sample of 3,172 controls (infants ≥ 2,500 g), the interruption of periodontal care during pregnancy did not lead to an increased risk for a low-birth weight infant when compared to women with no history of periodontal care (OR = 0.96). Bassani et al. [27] in an inclusive case-control design found that cases (n = 304) and controls (n = 611) had similar prevalence and severity of periodontitis.

Longitudinal Studies

Pregnant women who have moderate to severe periodontal diseases may be seven times more likely to deliver a premature child than women with healthy periodontium, according to a five-year study by Offenbacher et al. [29], conducted at the University of North Carolina. In a prospective study [30] on 1313 pregnant women, in Birmingham, complete periodontal, medical and behavioural assessments were made between 21 and 24 weeks of gestation. Patients with severe or generalized periodontal diseases had an OR of 4.45 for preterm delivery. The adjusted OR (aOR) increased with increasing prematurity to 5.28 before 35 weeks' gestational age and to 7.07 before 32 weeks' gestational age. Dortbudak et al. [31] who conducted a periodontal examination and collection of amniotic fluid (weeks 15–20 of pregnancy) in 36 women at risk for pregnancy complications found that periodontitis had an OR = 20.0. On the other side, Mitchell-Lewis et al. [32] investigated the relationship between periodontal infections and preterm low-birth weight in a cohort of pregnant and post-partum women and didn't find any association between women's periodontal status and birth outcomes. Also Moore et al. [33] conducted a prospective study involving 3738 women recruited at 12 weeks of pregnancy and found no significant relation between severity of periodontal disease and PTB or/and LBW.

Experimental studies

López et al. [34] randomly assigned 400 pregnant women with periodontal disease, aged 18 to 35, to either an experimental group (n = 200), which received periodontal treatment before 28 weeks of gestation or to a control group (n = 200) which received periodontal treatment after delivery. They found that periodontal disease was the strongest factor related to PLBW (OR = 4.70). In the study of Jeffcoat et al. [1], 366 pregnant women (between 21 and 25 weeks of gestation) with periodontitis were divided into 3 treatment groups and received 1) dental prophylaxis plus placebo capsule; 2) scaling and root planing (SRP) plus placebo capsule and 3) SRP plus metronidazole capsule (250 mg t.i.d. for one week). An additional group of 723 pregnant women meeting the same criteria for periodontitis served as an untreated reference group. The rate of preterm birth (PTB) at < 35 weeks was 4.9% in the prophylaxis group, 3.3% in the SRP plus metronidazole group and 0.8% in the SRP plus placebo group with no significance found when compared with the non SRP group. The rate of PTB at < 35 weeks was 6.3% in the reference group. Offenbacher et al. [35] realized a randomized delayed-treatment, controlled pilot trial to evaluate the effects of scaling and root planing and the use of a sonic toothbrush performed at the second trimester of pregnancy. Periodontal intervention resulted in a significantly decreased incidence for preterm delivery.

Cruz et al. [36] conducted a non-randomized study including 339 pregnant women to evaluate whether periodontal therapy would reduce the incidence of low-birth weight. The experimental group received periodontal treatment throughout pregnancy, whereas the control group was only monitored over the same period. The frequency of low-birth weight among the women with treated periodontitis was 9.22%, while it was 13.10% in the group without periodontal disease. However, the difference was not statistically significant.

Discussion

In 1996, Offenbacher et al. [3] suggested a correlation between periodontitis and the preterm (< 37 weeks gestation) low-birth weight infants. They proposed that periodontal infections that serve as reservoirs for gram-negative anaerobic organisms, lipopolysaccharides and inflammatory mediators (including PGE-2 and TNF- α) might pose a threat to the foetal-placental unit through haematogenous transmission. Since then, much research has gone to decipher this association and identify the involved mechanism.

The use of various definitions to identify the adverse pregnancy outcomes in the different studies hampers the comparison of the results. In fact, the World Health Organization [37] has defined pregnancy outcomes according to the following categories:

- Low-birth weight (LBW): less than 2,500 g (5 lb 8 oz).
- Very low-birth weight (VLBW): less than 1,500 g (3 lb 5 oz).
- Extremely low-birth weight (ELBW): less than 1,000 g (2 lb 3 oz).
- Prematurity: less than 37 weeks of gestation.
- Very premature: less than 32 weeks of gestation.

Most studies [5-8, 10-13, 34] have considered preterm labour (PTL) as when a baby is delivered before the 37th gestational week and a low-birth weight (LBW) when the newborn is < 2500g (WHO).

Though the definition of PLBW seems homogeneous among studies, it has to be mentioned that the size of babies at birth vary considerably among populations [38]. The mean weight of infants born in India is about 2,900 g (6 lb 6 oz) [40], while that of infants born in Sweden is 3,500 g (7 lb 11 oz). In the United States, African-American babies weigh on average 250 g (9 oz) less at birth than do Caucasian-American babies [39]. This notion should be taken into account especially that low-birth weight is a contributor to infant mortality and

morbidity. Also, the studies analyze infant birth weight as a dichotomized variable (LBW versus normal birth weight) without taking into account that this variable is a continuous variable.

Research on periodontitis has and is being plagued by the use of a variety of case definitions. For example, Radnai et al. [9] used bleeding on probing (BOP) in her definition of periodontitis as bleeding indicates active phases of periodontitis as well as it is associated with pregnancy, whereas Marin et al. [6] classified women having more than 5% gingival bleeding, with clinical attachment loss higher than 6mm in ≥ 2 sites and with ≥ 1 site with probing depth ≥ 5 mm as having periodontitis. The stricter case definition of periodontitis probably made the relation to PLBW insignificant. Dasanayake et al. [8] and Davenport et al. [22] used the CPITN and found that the relation between PLBW and periodontal disease was significant. But the use of CPITN doesn't seem appropriate as it is recommended for the estimation of treatment needs and can underestimate the prevalence of bleeding and periodontal pockets.

As severe gingivitis and pseudo-pockets may be present during pregnancy, Dortbudak et al. [31] used both clinical and microbiological data for the diagnosis of periodontitis, requiring at least four sites with a probing depth ≥ 5 mm and the presence of key pathogens associated with periodontitis.

The results of the studies were influenced by the case definition adopted. Gomes-Filho et al. [16] stated that the use of less strict definition leads to an insignificant association. When a strict definition of periodontitis is adopted, the number of cases is bound to become less for analysis. Hence it is important to use a priori definition [16] in accordance with the prevalence and severity of periodontitis in the studied population and/or to perform a sensitivity analysis in order to examine the effects of different definitions of periodontitis.

Also, precise selection of exposure measurement will make the results consistent and confer greater safety in determining the association. In many studies [3, 5, 10, 18, 22], the periodontal examination of women was accomplished within a few days post-partum. The oral hygiene of the women would be less than optimum and hence more gingival inflammation can be expected. The risk magnitude can increase when gingival bleeding is used to define periodontal disease. Mokeem et al. [10] showed that all the mothers in his case-control study had gingival inflammation and the high prevalence of CPITN score 3 reflects increased probing depth due to enlarged gingiva.

According to current knowledge [8], there are several risk factors for preterm low-birth weight (PLBW), e.g. maternal age of <17 years or >35 years, low socioeconomic status, alcohol/drug abuse, smoking, multiple pregnancies or poor general health of the pregnant woman. High-risk gestation, hypertension, gestational diabetes and systemic disease, placenta previa and maternal thinness defined by a low body mass index are also considered as risk factors [1]. Urinary tract infections, infections of the genital tract, such as bacterial vaginosis (BV) and intra-uterine infections are believed to be etiologic for many PTBs [1]. The other main risk factors for PTL are previous PTL, chronic intra-uterine infection and non-white ethnicity [40]. Pregnant women with a history of previous PTL presented a 15–80% risk of having another PTL in future pregnancies [41]. However, a significant proportion of low-birth weight is of unknown aetiology [22].

The validity of case-control studies can be affected by sample size, especially if the latter is not determined based on the prevalence of risk factors among the studied population. According to Lunardelli et al. [5], the use of a small sample size, the analysis of specific populations, the lack of appropriate statistical analysis or the omission of possible confounders represent methodological limitations.

Some studies [3, 8, 11, 30, 32] were carried out on samples including mostly African Americans mothers, a racial group that presents 2.4 times more risk of LBW (11.4%) than the Caucasian group (4.7%) and three times more risk of very LBW (<1500 g) than the Caucasian group [42]. This leads to a definite confounding as the African American race has various other risk factors [42] for adverse pregnancy outcomes. In countries like Denmark [26], comprehensive health care and public dental treatment are accessible for all citizens until the age of 18, which may not be the case for many of the participants in the reported studies carried out in North-American populations. As periodontal disease and adverse pregnancy outcomes share several common factors, it is mandatory to control confounder variables through both restriction criteria to eligibility and adequate statistical models.

The following observations should be taken into consideration when a case-control study is planned, especially in a rural population with a high infant mortality rate:

Researches must be done at a population level with a representative sample.

The case definition for PLBW should be decided based on the characteristics of the studied population, such as gestation age and weight of infants at birth.

Infant birth weight and gestation age should be analyzed as a continuous variable.

Proper sample size for the case-control study should be calculated based on the least prevalent risk factor.

All potential risk factors for PLBW should be included in the design.

Case definition for periodontitis should include probing depth and clinical attachment level. A relatively strict definition of periodontitis should be used in order to exclude false positives.

Conclusion

Preterm deliveries [6] and associated low-birth weight represent the major causes of neonatal mortality and, among survivors, a major contributor to long-term disability, including neuro-developmental, respiratory and behavioural problems as well as congenital anomalies. There is evidence to implicate periodontitis as a risk factor for periodontitis. However a stricter

case definition in recent studies has shown the relation to be non-significant. It is necessary to standardize the case definition and selection criteria, so that reasonable conclusions can be drawn when comparing various studies. Further researches with a population specific definition are mandatory for a better assessment of the relation between periodontitis and preterm low-birth weight.

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