Periodontal disease treatment and risk of preterm birth: a systematic review and meta-analysis

Tratamento de doença periodontal e risco de parto prematuro: revisão sistemática e metanálise

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Abstract

The events leading to preterm birth are still not completely understood. A quantitative systematic review was performed to estimate the effects of periodontal care during pregnancy on preventing preterm birth and low birth weight. The meta-analysis included randomized trials with pregnant women with a diagnosis of periodontal disease before 20 weeks of gestation. Relative risk (RR) with 95% confidence intervals (95%CI) was calculated. We evaluated the reduction in preterm and low birth weight. Thirteen trials were included, comparing 3,576 women in intervention groups with 3,412 women receiving usual care. The meta-analysis of the effects of periodontal disease treatment during pregnancy indicated a non-significant reduction in preterm births (RR = 0.90; 95%CI: 0.68-1.19) and low birth weights (RR = 0.92; 95%CI: 0.71-1.20). The creation and examination of a funnel plot revealed clear evidence of publication bias. In summary, primary periodontal care during pregnancy cannot be considered an efficient way of reducing the incidence of preterm birth.

Periodontal Disease; Premature Birth; Low Birth Weight Infant; Review; Meta-Analysis

Introduction

Preterm labor complicates 10 to 15% of all pregnancies, is the leading cause of neonatal morbidity and mortality and causes 75% of neonatal deaths that are not due to congenital anomalies [1]. Preterm birth, defined as childbirth occurring at less than 37 completed weeks (or 259 days) of gestation, is a major determinant of neonatal morbidity and mortality and has long-term, adverse health consequences [2,3]. Estimates indicate that, in the United States alone, costs associated with preterm birth, in terms of medical, educational expenditure and lost productivity, were more than US$ 26.2 billion in 2005 [2]. Although the etiology is thought to be multifactorial, the events leading to preterm birth are still not completely understood. It is unclear whether preterm birth results from the interaction of several pathways or from the independent effects of each pathway [2].

There is convincing evidence that infections in pregnant women may alter normal cytokine and hormone-regulated gestation, which could result in preterm labor, premature rupture of membranes and preterm birth [4]. Periodontitis has been associated with pregnancy outcomes such as preterm birth, low birth weight deliveries and premature rupture of membranes [4]. The development of periodontitis involves the invasion of primarily Gram-negative bacteria through the periodontium, stimulating a chronic inflamma-

tory response and forming pockets that become infected [5,6]. However, according to Oliveira et al. [7], non-surgical periodontal treatment during the second semester of gestation did not reduce the risk of preterm birth, low birth weight, or preterm low birth weight.

The link between maternal periodontal disease and preterm birth or low birth weight is a grey area and it remains unclear whether adverse pregnancy outcomes have a causal relationship with periodontal disease or if they are a surrogate for another maternal factor.

The objective of the current work was to conduct a systematic review and meta-analysis of randomized, controlled trials to quantify the relationship between periodontal disease, preterm birth and low birth weight in order to explore the reasons for the ongoing controversies surrounding this issue.

Methods

The PRISMA guidelines were followed for the meta-analysis of randomized trials [8].

Inclusion and exclusion criteria

To be eligible for inclusion in our systematic review, studies had to examine specific treatments for periodontal disease during pregnancy, compare the results of usual care ("intensified") and specific treatment ("less intensified") and report on at least one outcome of interest (preterm birth, low birth weight, and/or preterm low birth weight). We included only randomized trials whose participants met the following criteria: women over the age of 18 with a single gestation at 22 weeks or less, who had gingival inflammation with ≥ 25% of sites bleeding upon probing and sites with clinical attachment loss > 2mm. The exclusion criteria included the following: having fewer than 18 natural teeth, indication of prophylactic antibiotics for invasive procedures, occurrence of diabetes prior to pregnancy, and the intention of giving birth at a hospital outside this study.

Search strategy

We performed a literature search of studies published between 1980 and March 2012 using MEDLINE, Embase, BIOSIS, LILACS, Scopus, the Cochrane Central Register of Controlled Trials, the ISI Web of Science and IBECS. First, we derived three themes that were combined with the Boolean operator "AND". Each theme was created with the Boolean operator "OR" to search for terms appearing as either exploded medical headings (MeSH) or text words. The first theme was "randomized control trial". The second theme was "preterm birth", "low birth weight", "preterm delivery", "neonatal deaths", "intrauterine infection", "chorioamnionitis", "perinatal care", "LBW", and "PTB", and the third theme was "gingivitis", "periodontal treatment", "periodontitis" and "periodontal status". We then manually scanned the reference lists of all identified articles. No restrictions were placed on the language of the publications. All randomized controlled trials that allocated pregnant women to receive treatment with scaling and root planning, versus no treatment or prophylaxis, were eligible for inclusion. Trials were considered eligible if they included patients with documented periodontal disease (periodontitis or gingivitis), as defined by the International Workshop for Classification of Periodontal Diseases and Conditions in 1999. All trials were eligible regardless of the depth and the severity of the periodontal disease. We based our classification of severity of periodontal disease on the conclusions of the 2003 working group of the Centers for Disease Control and Prevention and the American Academy of Periodontology. Based on these classifications, we defined moderate and severe periodontitis in terms of probing depth and clinical attachment loss to enhance the case definitions and provide distinct categories. We excluded randomized trials that included patients with threatened preterm delivery who received tocolytic agents, non-randomized trials and pseudo-randomized trials.

Data extraction

Multiple teams consisting of four reviewers (M.I.R, L.R.M, M.I.E. and P.D.S.P) independently screened the title, abstract and key words of each reference identified by the search and applied the inclusion and exclusion criteria. The same procedure was applied to full text articles and potentially eligible references. Differences in reviewers' opinions were resolved by discussion or a by a fifth reviewer. Data on quality, patient characteristics, interventions and relevant outcomes were independently abstracted by two reviewers (J.M.-M. and M.L.S).

Risk of bias was assessed by considering the adequacy of randomization and allocation concealment, and the comparability of the women in the different study groups. Although periodontal disease is treated with complex interventions, outcome assessors could be blinded to the treatment status of participants, thus minimizing bias.

Outcomes of interest

The effects of interventions were compared with respect to the following outcomes: preterm birth (< 37 weeks), low birth weight (< 2,500g).

Statistical analysis

We measured the inter-rater agreement for study inclusion and methodological quality assessment (weighted κ) [9] and outcomes were reported using relative risk (RR) with 95% confidence intervals (95%CI). Pooled-effect estimates were derived using a random effects model with Mantel-Haenszel statistics [10]. Study heterogeneity was determined using the I^2 statistic, in which numbers greater than 75% suggest considerable heterogeneity [9], and p-values from the χ^2 test. In cases of considerable heterogeneity, no pooled-effect estimate was provided. A sensitivity analysis was planned *a priori* to compare study results and designs, and to report on study quality, focusing on those defined as "good quality" studies [11].

Meta-analysis was performed using version 5.0.17 of the Review Manager software (Nordic Cochrane Center, Copenhagen, Denmark).

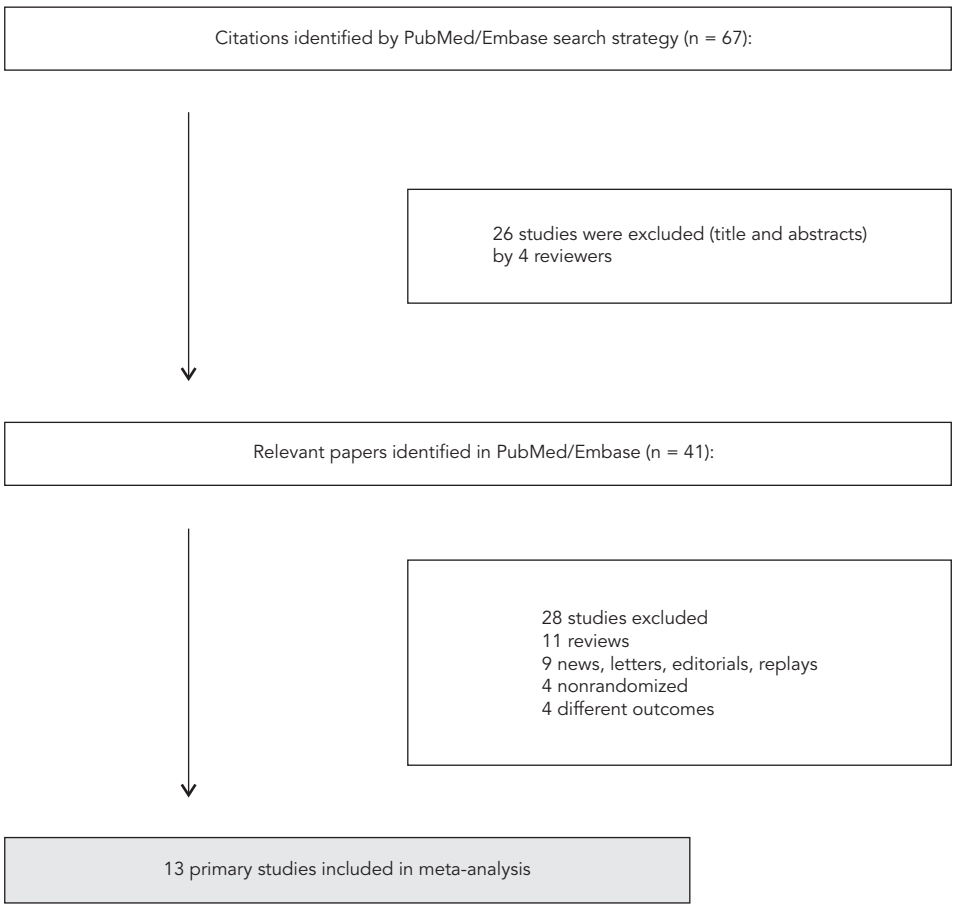
Results

Identification of eligible trials

The literature search yielded 62 potentially relevant publications, of which 13 were considered eligible for inclusion in this review (Figure 1) [3,5,6,7,12,13,14,15,16,17,18,19,20]. Reviews of the reference lists

Figure 1

Flow chart summarizing the literature search process.



yielded two further citations. The inter-rater reliability for study selection was good (κ = 0.9).

Characteristics of trials, participants and interventions

The 13 trials were conducted in seven countries from five different continents and included 6,988 patients (3,576 in the periodontal work group and 3,412 in the control group).

We excluded four randomized trials for the following reasons: one included patients hospitalized for threatened preterm birth that received tocolytic agents [21], another [22] was a duplicate of Michalowicz et al. [6], and in another [23] patients were randomized based on the efficacy of periodontal treatment that differed from other included studies.

All reviewed studies were published in English. Table 1 shows the details of the study populations, interventions, outcome assessments and data reporting. Table 2 presents the risk of bias for each trial. Inter-rater agreement of assessments of methodological quality ranged from 0.58 to 1.00 for the eight categories, with an overall agreement of 0.75. The lowest agreement was in the category other bias, whereas perfect agreement was achieved in the areas of adequate sequence generation and allocation concealment. Although all studies described randomization, nine did not adequately describe the random sequence generation methods [3,5,7,12,15,16,17,18,19,20] and nine did not adequately describe allocation concealment [3,5,7,12,15,16,17,18,19,20]. Twelve studies did not use blinding methods for adjudication outcomes [3,5,6,7,12,13,14,15,16,17,18,19,20]. Four trials described a modified intention-to-treat analysis [3,6,13,15]. Only two papers [3,6] distinguished between gingivitis and periodontitis (such as periodontal disease) and the remaining authors defined only periodontitis. Unfortunately, there is no universally accepted standard of periodontal disease [3]. Unlike gingivitis, periodontitis cannot be assessed by visual examination alone. The disease is diagnosed with the use of a probe that is inserted into the gingival crevice between the teeth and gums [6]. Therefore, the other authors establish the depth of each pocket (the insertion loss of the structure of the periodontium, i.e., the cementum, ligament and alveolar bone) according to their own criteria.

Table 1

Characteristics of included studies: treatment for periodontal disease versus usual care.

Reference	Year of publication	Country	Design	Patients	Patient age in years [mean (SD)]	Diagnosis (periodontal disease was defined as)	Participants	Outcomes
López et al. [12]	2002	Chile	Randomized	400	Treatment: 28 (± 4.5) Control: 27 (± 4.3)	Presence of 4 or more teeth with probing depth > 4mm. Patients separated into two categories: < 2.5mm and > 2.5mm depth	Treatment: 200 Control: 200	Preterm birth; preterm/low birth weight
Jeffcoat et al. [13]	2003	USA	Randomized	366	Treatment: 22.0 (± 4.6) Control: 22.2 (± 4.3)	Presence of 4 or more teeth with 1 or more sites with probing depth > 4mm	Treatment: 246 Control: 120	Preterm birth < 37 weeks; preterm/low birth weight
López et al. [14]	2005	Chile	Randomized	870	Treatment: 25.5 (± 5.4) Control : 29.9 (± 4.5)	Gingival inflammation with ≥ 25% of sites with bleeding upon probing and no sites with clinical attachment loss > 2mm	Treatment: 580 Control: 290	Preterm birth; preterm/low birth weight
Michalowicz et al. [6]	2006	USA	Randomized	812	Treatment: 26.1 (± 5.6) Control: 25.9 (± 5.5)	≥ 4 teeth with a probing depth of ≥ 2mm and bleeding upon probing at ≥ 35% of tooth sites	Treatment: 413 Control: 410	Preterm birth; preterm/low birth weight

(continues)

Table 1 (continued)

Reference	Year of publication	Country	Design	Patients	Patient age in years [mean (SD)]	Diagnosis (periodontal disease was defined as)	Participants	Outcomes
Offenbacher et al. [16]	2006	USA	Randomized	74	Treatment: 26.8 (± 5.5) Control: 25.7 (± 5.5)	≥ 2 sites with probing depth≥ 5mm and periodontal attachment loss of 1 to 2mm at one or more depth ≥ 5mm	Treatment: 40 Control: 34	Preterm birth
Sadatmansouri et al. [18]	2006	Iraq	Randomized	30	Treatment: 28.4 (± 4.1) Control: 29.1 (± 4.3)	Having ≥ 4 teeth with ≥ 1 site with pocket depth ≥ 4mm	Treatment: 15 Control: 15	Preterm birth; preterm/low birth weight
Tarannum & Faizuddin [5]	2007	India	Randomized	200	Treatment: 23 (± 3.3) Control: 22 (± 3.6)	Bleeding index treatment group (%): 81.54 (37-100) Bleeding index control group (%): 83.63 (40-100)	Treatment: 100 Control: 100	Preterm birth; preterm/low birth weight
Newnham et al. [15]	2009	Australia	Randomized	1,087	Treatment: 30.5 (± 5.5) Control: 30.5 (± 5.5)	The presence of periodontal pockets ≥ 4mm in depth at ≥ 12 probing sites in fully erupted teeth	Treatment: 546 Control: 541	Preterm birth; low birth weight
Offenbacher et al. [17]	2009	USA	Randomized	1,806	Treatment: 25.4 (± 5.5) Control: 25.3 (± 5.5)	≥ 2 sites of chronic inflammatory response to tooth-associated microbial biofilm (plaque) with > 5mm probing depths	Treatment: 903 Control: 903	Preterm birth; preterm/low birth weight
Macones et al. [3]	2010	USA	Randomized, multicenter	756	Treatment: 24.1 (± 5.2) Control: 24.2 (± 5.7)	Attachment loss ≥ 3mm in ≥ 3 teeth	Treatment: 376 Control: 380	Preterm birth; low birth weight
Oliveira et al. [7]	2010	Brazil	Randomized	246	Treatment: 29.9 (± 4.3) Control: 26.5 (± 3.98)	Presence of ≥ 4 teeth with ≥ 1 site with probing depth > 4mm	Treatment: 122 Control: 124	Preterm birth; preterm/low birth weight
Sant'Ana et al. [19]	2011	Brazil	Randomized	31	Treatment: 29.1 (± 4.3) Control: 26.5 (± 3.9)	Presence of 4 or more teeth with one or more sites with pocket depth ≥ 4mm	Treatment:16 Control: 15	Preterm birth; preterm/low birth weight
Weidlich et al. [20]	2012	Brazil	Randomized	527	Treatment: 28.8 (± 4,7) Control:25.8 (± 4.6)	Full-mouth, excluding third molars, six sites per tooth, periodontal examination was carried out. Unclear how periodontal disease was defined	Treatment:145 Control: 154	Preterm birth; preterm/low birth weight

Table 2

Assessment of study quality.

Reference	Year of publication	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Intention-to-treat	Free of other bias	Description of other bias
López et al. [12]	2002	Unclear	No	No	No	Yes	No	No	Post-randomization exclusion
Jeffcoat et al. [13]	2003	Unclear	No	Unclear	No	Yes	Yes	No	Baseline imbalance
López et al. [14]	2005	Unclear	No	No	No	Unclear	No	No	Baseline imbalance, post-randomization exclusion
Michalowicz et al. [6]	2006	Yes	Yes	No	Yes	Yes	Yes	Yes	-
Offenbacher et al. [16]	2006	Unclear	No	Unclear	Unclear	No	No	No	Poorly described statistical methods
Sadatmansouri et al. [18]	2006	Unclear	No	No	Unclear	No	Yes	No	Poorly described statistical methods
Tarannum & Faizuddin [5]	2007	Unclear	No	No	No	No	No	No	Poorly described statistical methods
Newnham et al. [15]	2009	Yes	Yes	No	Yes	Yes	Yes	Yes	-
Offenbacher et al. [17]	2009	Yes	Yes	Unclear	No	Unclear	No	Yes	-
Macones et al. [3]	2010	Unclear	No	No	No	Yes	No	No	Post-randomization exclusion
Oliveira et al. [7]	2010	Unclear	No	No	No	Unclear	No	No	Poorly described statistical methods
Sant'Ana et al. [19]	2011	Unclear	No	No	Yes	Unclear	No	No	Poorly described statistical methods
Weidlich et al. [20]	2012	Unclear	No	No	No	Unclear	No	No	Poorly described methods

None of the authors discussed the effectiveness of periodontal treatment in the treatment group.

Effects of interventions

Preterm births < 37 weeks: a meta-analysis of 13 studies [3,5,6,7,12,13,14,15,16,17,18,19,20] showed that periodontal disease treatment during pregnancy had no significant effect on the overall rate of preterm birth (RR = 0.90, 95%CI: 0.68-1.19; p = 0.45; I^2: 74%) (Figure 2).

Low birth weight < 2,500g: a meta-analysis of nine studies [3,5,6,7,12,14,15,17,20] showed a weak association between periodontal disease treatment during pregnancy and decreases in low birth weight, with no significant effect (RR = 0.92, 95%CI: 0.71-1.20; p = 0.55; I^2: 56%) (Figure 3).

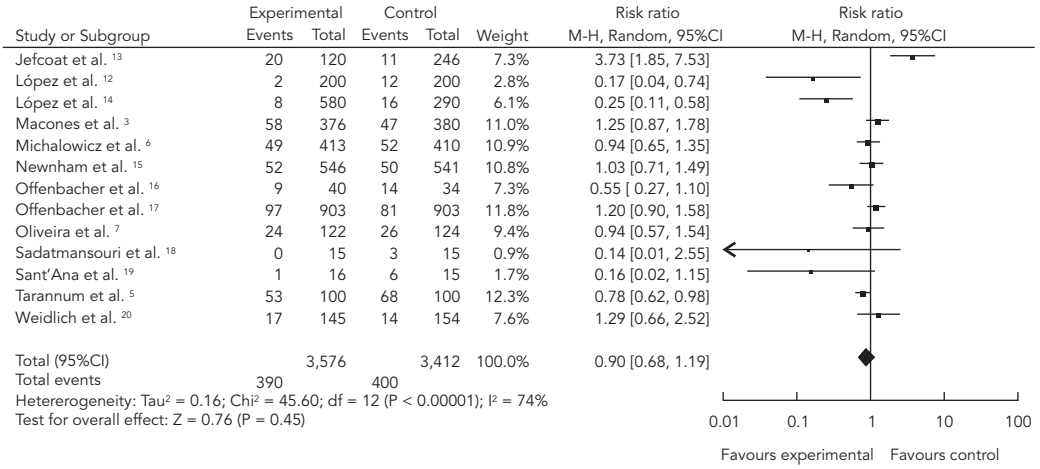
Heterogeneity was confirmed by the χ^2 test, which produced a p-value of 0.00001 and 0.02 for preterm birth and low birth weight, respectively.

Assessment of publication bias

An examination of the funnel plot for our data suggests strong evidence of publication bias for the preterm birth and low birth weight outcomes in the meta-analysis. This bias was confirmed by the results of tests proposed by Steichen [24], which produced p-values of 0.001 and 0.072 for preterm birth and low birth weight, respectively (Figure 4).

Figure 2

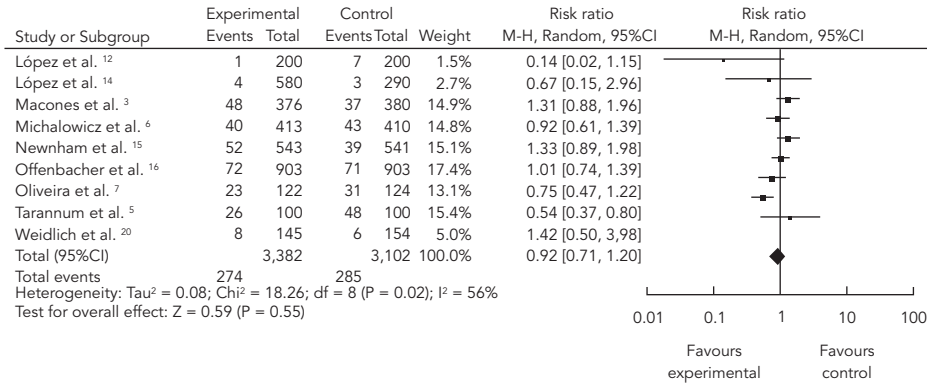
Meta-analysis plot for preterm birth < 37 weeks of gestation.



M-H: Mantel-Haenszel model; 95%CI: 95% confidence interval

Figure 3

Meta-analysis plot for low birth weight < 2,500g.



M-H: Mantel-Haenszel model; 95%CI: 95% confidence interval

Sensitivity analysis

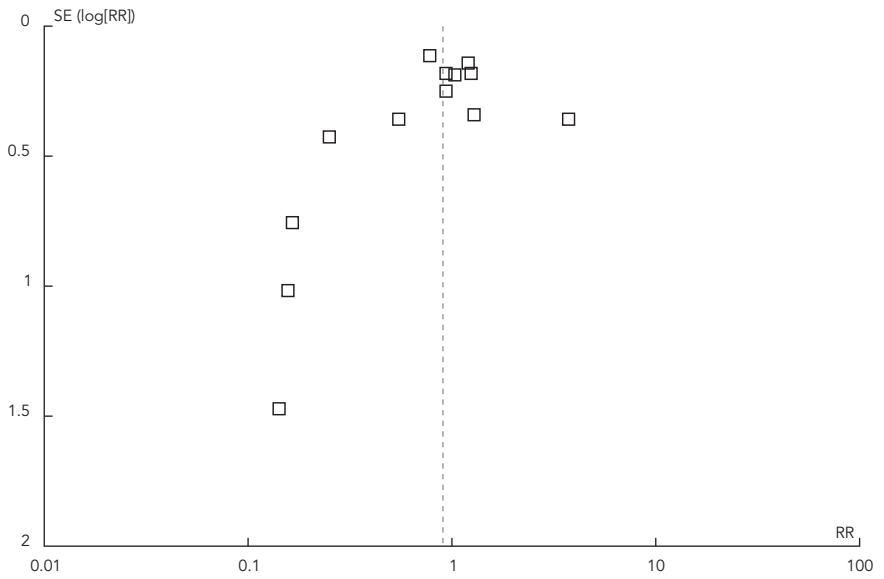
A sensitivity analysis was performed to test the robustness of the findings [24,25,26,27]. Pooled treatment effect estimates from studies with adequate sequence generation, randomization and allocation concealment were analyzed [6,17,18].

Discussion

The World Health Organization (WHO) reported an estimated 12.9 million annual worldwide preterm births between 1997 and 2007, representing an incidence of 9.6% [28]. This meta-analysis showed that periodontal disease treatment during pregnancy does not confer a general protec-

Figure 4

A funnel plot of publication bias of the studies included in this systematic review.



tion against preterm birth and low birth weight. Our systematic review identified 13 randomized [3,5,6,7,12,13,14,15,16,17,18,19,20], relevant studies published between 2002 [13] and 2012 [20]. These studies provided evidence from 6,988 pregnant women with periodontal disease who experienced a total of 790 preterm births. A second and equally important finding is that most of the studies included found no association between the subjects of study. In fact, the studies that rejected the alternative hypothesis were the most controlled and had the largest sample sizes.

Strengths and limitations of this review

Many aspects of this review lead us to believe that our results are valid. Firstly, we formulated a clinical question and then performed comprehensive searches that encompassed multiple online databases and searched the reference sections of relevant studies. No language restrictions were imposed and we used broad search terms to avoid making our question too specific to be adequately sensitive.

Although we did not seek any unpublished data, there is a risk of publication bias. However, we included only randomized, controlled trials to minimize selection bias. Many of the I^2 estimates calculated in this meta-analysis may be considered high. This is a drawback, and may be the result of considerable heterogeneity between studies [9].

Comparisons with other studies

Jeffcoat et al. [23] performed a randomized, controlled trial but included an intervention analysis based on the efficacy of periodontal treatment that differed from other studies. They found that successful, routine periodontal treatment was associated with decreased incidence of spontaneous preterm birth in the study population. We did not include this study in our systematic review because the intervention group included two subgroups (successful and unsuccessful) that were not found in other studies. According to Di Mario et al. [29], the applied study design of Jeffcoat's [23] study does not permit the control of confounders and bias and, therefore, the lack of randomization and control for previous preterm birth affects the validity of this study.

Polyzos et al. [30] conducted a meta-analysis of randomized clinical trials to determine whether periodontal treatment during pregnancy reduced preterm birth. After examining eleven trials that included 6,558 patients, they found that

periodontal treatment during pregnancy had no significant effect on the overall rate of preterm birth (OR = 1.15, 95%CI: 0.95-1.40; p = 0.15). In 2011, two meta-analyses were published by Chambrone et al. [31] and Fogacci et al. [32], including 11 and 10 trials, respectively, neither of which supported the hypothesis that periodontal therapy reduces preterm birth and low birth weight indices.

In contrast, a meta-analysis published in 2011, including ten eligible trials with 5,645 pregnant women, found that periodontal treatment significantly lowered preterm birth (OR = 0.65; 95%CI: 0.45-0.93; p = 0.02) [33].

The differences reported can be explained by the different strategies employed in the meta-analysis. George et al. [33] pooled all the trials together, while Polizos et al. [30] conducted the review by analyzing the high and low-quality trials.

Our study included 6,988 patients, all items covered by Polyzos et al. [30] and two other clinical trials published in subsequent years [20,29]. Our results corroborate Polyzos's and Chambrone's findings [30,31]. Two other systematic reviews were published in 2006 and 2007, but used case-control, cohort and controlled trials [34,35].

Conclusions

Primary periodontal care during pregnancy cannot reduce the rate of preterm birth or low birth weight. Although this review found no benefits of periodontal care during pregnancy, future research is needed to address this important question.

Resumo

Os eventos que levam à prematuridade ainda não são completamente compreendidos. Foi realizada uma revisão sistemática quantitativa para avaliar os efeitos do tratamento de doença periodontal durante a gravidez para prevenir o nascimento prematuro e baixo peso ao nascer. A metanálise incluiu estudos randomizados de grávidas com diagnóstico de doença periodontal antes de 20 semanas de gestação. O risco relativo (RR) com intervalos de 95% de confiança (IC95%) foi calculado. Avaliou-se os desfechos prematuridade e baixo peso ao nascer. Foram incluídos 13 estudos, comparando 3.576 mulheres em grupos de intervenção com 3.412 mulheres que receberam tratamento habitual. A metanálise mostrou uma redução não significativa nos partos prematuros (RR = 0,90; IC95%: 0,68-1,19) e baixo peso ao nascer (RR = 0,92; IC95%: 0,71-1,20). O gráfico de funil revelou clara evidência de viés de publicação. Em resumo, o tratamento periodontal em mulheres grávidas não pode ser considerado uma forma eficiente de reduzir a incidência de parto prematuro ou baixo peso ao nascer.

Doenças Periodontais; Nascimento Prematuro; Recém-Nascido de Baixo Peso; Revisão; Metanálise

Contributors

M. I. Rosa contributed to the study conception, literature search, data extraction and analysis, statistical analysis, preparation and revision of the manuscript and definition of intellectual content. P. D. S. Pires contributed to the literature search, data extraction and interpretation and editing of the manuscript. L. R. Medeiros contributed to the study conception, data analysis, statistical analysis, preparation and revision of the manuscript and definition of intellectual content. M. I. Edelweiss contributed to the study conception, preparation of the manuscript and definition of intellectual content. J. Martínez-Mesa contributed to data interpretation. All authors approved the final version of the manuscript.

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