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Periodontium in pregnancy: A systematic review

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***Abstract*---**Introduction: Periodontal diseases are advocated to show adverse pregnancy outcomes. Hence in our study we aim to conduct a systematic review of the previous systemic reviews studying the association between periodontal disease and adverse pregnancy outcomes. Material and methods: We searched online databases up to November 2016 for the previous Systematic reviews of studies comparing pregnancy outcomes among women with and without periodontal disease were eligible for inclusion. Primary outcomes were maternal mortality, preterm birth, and perinatal mortality. Results:

From the 23 none reported the association between periodontal disease and maternal or perinatal mortality. Systematic reviews with the lowest risk of bias consistently demonstrated positive associations between periodontal disease and preterm birth, low birth weight, preeclampsia, and preterm LBW. Based on these figures, estimated population- attributable fractions for periodontal disease were 5% to 38% for preterm birth, 6% to 41% for LBW, and 10%to 55% for preeclampsia. Due to substantial overlap in included primary studies, we could not combine results across reviews. Conclusion: We can conclude that pregnant women with periodontal disease are at increased risk of developing preeclampsia and delivering a preterm and/or LBW baby.

***Keywords*---**periodontitis, pregnancy, maternal morbidity, mortality.

Introduction

The prevalence of gingivitis varies between 50% to 90% in the world.[1] The increased risk of adverse pregnancy outcomes are seen in the Pregnant women with periodontal disease, comprising preeclampsia, preterm delivery, and low birth weight.[2-4] Assumed the global disease burden of periodontal disease and the range of adverse pregnancy outcomes that have been related with it, it is significant to clarify their relationship. This in turn will inform prioritizing of the development of preventive and therapeutic intercessions to lower the occurrence of adverse pregnancy outcomes among women with periodontal disease. Several systematic reviews have consequently been done to clarify the association between periodontal disease and adverse pregnancy results. Though, in keeping with the seemingly contrasting findings of individual studies, these systematic reviews also have important discrepancies in their conclusions. [5-10] Given the global health relevance of the subject, it is significant that the pertaining literature—which is thus currently clouded—is thoroughly assessed to classify possible sources of the apparently heterogeneous findings and to try to reach more reliable conclusions. Hence in our study we aim to conduct a comprehensive synthesis of findings from systematic reviews assessing the link between periodontal disease and a broad range of adverse pregnancy outcomes.

Material and Methods

We conducted an electronic data base search, from PUBMED, EMBASE, and Google for the articles from the earliest to till august 2020. Only the systemic studies in the English language were considered. We included prospective/retrospective cohort studies, cross-sectional studies, and/or case-control or nested case-control studies. Our primary objective was to assess whether differences in adverse pregnancy outcomes—in particular maternal mortality, perinatal mortality, and preterm birth—exist between 1) women diagnosed with periodontal disease within 6 months prior to or during pregnancy and 2) women without periodontal disease. Two reviewers independently screened resolved through discussion and later finalized the articles based on the PRISMA

guidelines. Risk of bias across systematic reviews was assessed with the use of a citation matrix.

Results

From a total of 6,916 articles 23 systematic reviews were finalized. A total of 120 individual studies were included in these systematic reviews. The primary studies were performed in 37 countries. Figure 1. None of the included systematic reviews varied between 1 and 9 points in AMSTAR. None of the reviews provided information about protocol for the review, conflicts of interest relevant to the primary included studies. Systematic reviews that included meta-analyses generally had a higher AMSTAR score than those that did not.

None of the included systematic reviews reported information about the association between periodontal disease and maternal or perinatal mortality. Seventeen systematic reviews reported on the association between periodontal disease and preterm birth (Table 1), of which 7 performed a meta-analysis. Six meta-analyses showed a statistically significant positive association between periodontal disease and preterm birth: odds ratios (ORs) and/or relative risks (RRs) ranging from 1.6 to 3.9. The seventh showed borderline significance (RR, 1.7; 95% confidence interval[95% CI], 1.0 to 2.8) but also delivered evidence for a dose-response association with more severe periodontal disease being associated with the strongest risk of preterm birth (RR, 2.0; 95% CI,1.3 to 2.9). The relationship between periodontal disease and preterm birth was consistent in sensitivity meta-analyses restricted to primary studies with the lowest risk of bias, which were performed in 3 reviews. Nine systematic reviews stated on the association between periodontal disease and preeclampsia. Of 5 reviews in which a meta-analysis was performed, 4 found a significant association between periodontal disease and preeclampsia, with ORs/RRs ranging from 2.2 to 2.8. All reviews that performed a meta-analysis stated a significant positive association among periodontal disease and preterm LBW, with ORs/RRs varying between 2.1and 5.3.

Figure 1. Flow diagram of study selection

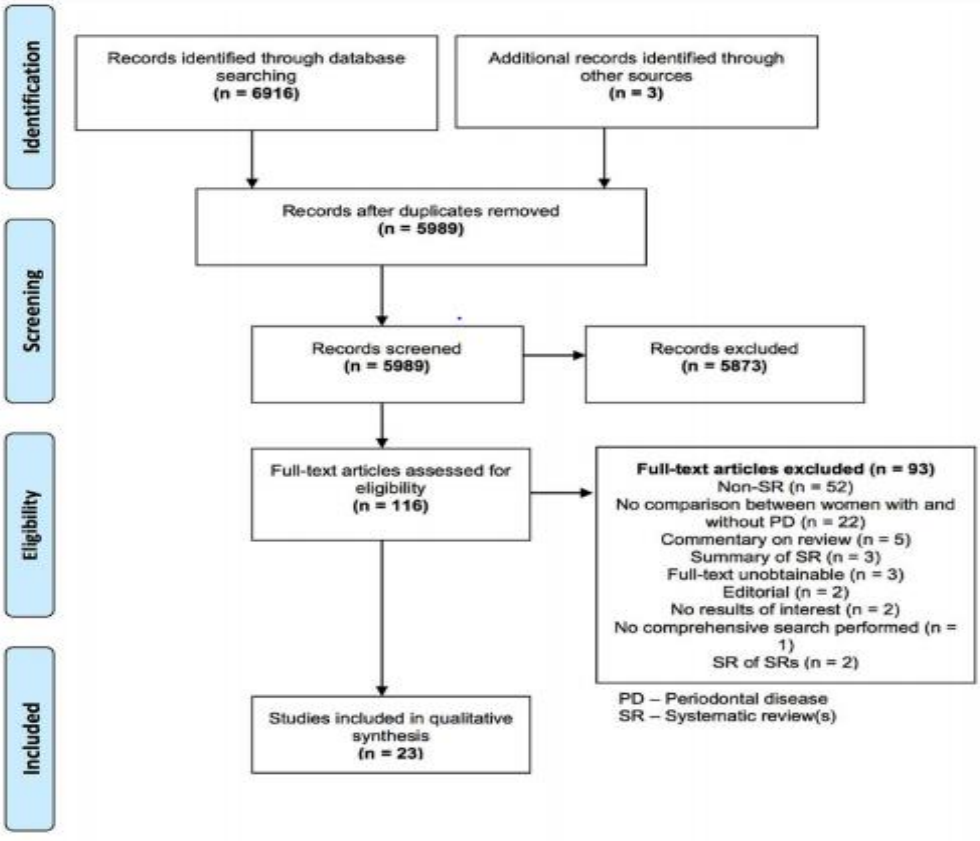

Table 2.Evidence of the Association between Periodontal Disease and Primary Outcome Preterm Birth

Systematic Review (Year); No. of Studies (Participants)	Main Findings 1. Results of Meta-Analysis: OR/RR (95%-CI) 2. Results of Subgroup Analysis: OR/RR (95%-CI)	Risk of Bias Assessment	Summary of Findings
Chambrone (2011) 8 (10,804)	**All studies** RR 1.7 (1.0-2.8) **Studies of high methodological quality** RR 1.8 (1.0-3.1) **All studies** PD defined by PPD and CAL: RR 1.4 (1.1-1.8) PD defined by CAL alone: RR 3.1 (0.2-45.1) PD defined by other methods: RR 1.3 (0.5-3.0) Studies of high methodological quality PD defined by PPD and CAL: RR 1.4 (1.1-1.8) PD defined by CAL alone: RR 3.1 (0.2-45.1) Mild PD defined by PPD and CAL: RR 1.3 (1.0-1.7) Moderate-severe PD defined by PPD and CAL: RR 2.0 (1.3-2.9) Jeffcoat (2001) was not included in the meta-analysis. This cohort study found a positive association between PD and PTB, with the following ORs: 4.5 (2.2-9.2) (<37 weeks of GA), 5.3 (2.1-13.6) (<35 weeks of GA) and 7.1 (1.7-27.4) (<32 weeks of GA).	Individual studies: NOS-scale (max. 14.0) Mean: 11.9 Range: 9.0-13.0 Systematic review: AMSTAR = 7	Overall analysis did not show a significant association between PD and PTB. PD was associated with PTB in studies where PD was defined by PPD and CAL. There was evidence of a dose-response association between severity of PD and risk of PTB.
Chambrone (2012b) 14 (8,588)	OR 1.8 (1.6-2.0) No subgroup analyses performed	Individual studies: Not reported Systematic review: AMSTAR = 6	PD showed a significant association with PTB.
Corbella (2016) 17 (6,741)	RR 1.6 (1.3-2.0) Low risk of bias studies RR 1.7 (1.3-2.2) Moderate risk of bias studies: RR 1.5 (1.1-2.1)	Individual studies: Cochrane Bias Methods Group (max. 5.0) Mean: 4.5 Range: 4.0-5.0 Systematic review: AMSTAR = 8	PD showed a significant association with PTB, which was consistent in studies with low and moderate risk of bias.
Ide (2013) 24 (18,626)	CC studies reporting PD as a categorical variable: OR 2.5 (2.2-2.8) CC studies reporting PD as a continuous variable (PD): WMD 0.04 (0.01-0.06) CC studies reporting PD as a continuous variable (CAL): WMD -0.04 (-0.07-0.02) CC studies reporting PD as a continuous variable (BOP): WMD 4.7 (2.8-6.7) Prospective cohort studies reporting PD as a categorical variable: RR 1.2 (0.9-1.5) Prospective cohort studies reporting PD as a continuous variable (PD): WMD 0.01 (-0.00-0.02) Prospective cohort studies reporting PD as a continuous variable (CAL): WMD -0.02 (-0.03, -0.01) Prospective cohort studies reporting PD as a continuous variable (POB): WMD -0.00 (-0.6-0.6)	Individual studies: NOS (max 8.0): Mean: 5.5 Range: 4-7 Systematic review: AMSTAR = 6	PD showed a positive association with preterm birth.

Khader (2005) 4 (2,156)	OR 3.9 (2.1-7.0) PTB regardless of BW: OR 4.3 (2.6-7.0) PTB regardless of BW excluding the study with the lowest quality score: OR 4.3 (2.5-7.4)	Individual studies: Margetts et al.[a] (max 100%) Mean: 60 Range: 35-71 Systematic review: AMSTAR = 7	PD showed a positive association with PTB.
Konopka (2012) 7 (3,253)	OR 2.7 (2.1-3.6) No subgroup analyses performed	Individual studies: Margetts et al.[a] (max 100%) Mean: 46 Range: 31-68 Systematic review: AMSTAR = 6	PD showed a positive association with PTB.
Vergnes (2007) Not reported	OR 2.3 (1.1-4.9) No subgroup analyses performed	Individual studies: Margetts et al.[a] (max. 100%) Mean: 54.9 Range: 30.0-82.0 Systematic review: AMSTAR = 7	PD showed a positive association with PTB.
Corbella (2012a) 25 (19,493)	Fifteen studies found a significant positive association between PD and PTB (OR/RR 1.8-20), of which seven did not report an OR/RR, or reported an OR/RR without 95%-CI (OR/RR 1.1-1.9). Two studies found a significant association between PD and moderate-severe PTB only. Eight studies found no significant association (OR/RR 0.7-1.9).	Individual studies: Not reported Systematic review: AMSTAR = 2	The vast majority of included studies identified a positive association between PD and PTB, albeit with highly variable OR/RRs.
Madianos (2002) 1 (1,313)	One cohort study included which found a positive association between PD and PTB: OR 4.5 (2.2-9.2) (<37 weeks of GA), 5.3 (2.1-13.6) (<35 weeks of GA) and 7.1 (1.7-27.4) (<32 weeks of GA).	Individual studies: Not reported Systematic review: AMSTAR = 4	One cohort study included which showed a positive association between PD and PTB.
Oliveira (2009) 11 (4,982)	8/11 studies reported a positive association between PD and PTB (OR/RR 2.0-8.1), no 95%-CI were reported. Three studies showed no association.	Individual studies: Not reported Systematic review: AMSTAR = 2	The vast majority of included studies identified a positive association between PD and PTB.
Sanchez (2004) 1 (1,313)	One cohort study included which reported a positive association between PD and PTB, with the following ORs: 4.5 (2.2-9.2) (<37 weeks of GA), 5.3 (2.1-13.6) (<35 weeks of GA) and 7.1 (1.7-27.4) (<32 weeks of GA).	Individual studies: Not reported Systematic review: AMSTAR = 1	One study included which showed a positive association between PD and PTB.

Systematic Review (Year); No. of Studies (Participants)	Main Findings 1. Results of Meta-Analysis: OR/RR (95%-CI) 2. Results of Subgroup Analysis: OR/RR (95%-CI)	Risk of Bias Assessment	Summary of Findings
Scannapieco (2003) 1 (1,313)	One cohort study included which reported a positive association between PD and PTB, with the following ORs: 4.5 (2.2-9.2) (<37 weeks of GA), 5.3 (2.1-13.6) (<35 weeks of GA) and 7.1 (1.7-27.4) (<32 weeks of GA).	Individual studies: Not reported Systematic review: AMSTAR = 3	One study included which showed a positive association between PD and PTB.
Teshome (2016) 4 (809)	Three studies reported a significant positive association between PD and PTB (4.2-137.5). One study found no association.	Individual studies: NIH checklist Mean: 10.3 Range: 9-12 Systematic review: AMSTAR = 5	The vast majority of included studies identified a positive association between PD and PTB.
Vettore (2006) 12 (7,370)	Four studies reported a significant positive association between PD and PTB (OR/RR 2.2-7.1). Another two studies reported a positive association between PD and PTB but OR/RR was not provided. Six studies showed no association.	Individual studies: Not reported Systematic review: AMSTAR = 4	Half of the included studies identified a positive association between PD and PTB
Wimmer (2008) 28 (15,822)	16/28 studies reported a positive association between PD and PTB (OR/RR 1.1-20). 12 studies showed no association.	Individual studies: Not reported Systematic review: AMSTAR = 2	The majority of included studies identified a positive association between PD and PTB.
Xiong (2006) 11 (7,629)	Seven studies reported a significant positive association between PD and PTB (OR/RR 2.1 to 20). One study reported only a significant association between moderate/severe PD and PTB (2.1 [1.3-3.4]) and not between mild PD and PTB (1.2 [0.9-1.7]). Four studies showed no association.	Individual studies: Not reported Systematic review: AMSTAR = 3	The vast majority of included studies identified a positive association between PD and PTB.
Xiong (2007) 20 (13,246)	10/20 studies reported a positive association between PD and PTB (OR/RR 2.1 to 20.0), whereas 10 found no association.	Individual studies: Not reported Systematic review: AMSTAR = 3	Half of the included studies identified a positive association between PD and PTB

Discussion

In our study we observed a strong evidence for a link between periodontal disease and various adverse pregnancies. Systematic reviews that did a meta-analysis generally had the lowest risk of bias. Given aggregate estimates from the highest-quality reviews, we assessed PAFs.[7] This highlights the essential global health significance of periodontal disease as well as the crucial need to classify the underlying mechanisms and therefore improve preventive strategies intended at decreasing its substantial disease burden. This highly all-inclusive review is the first to systematically produce the available suggestion from published systematic reviews on the relationship between periodontal disease and numerous adverse pregnancy outcomes. Subsequently a comprehensive prespecified and peer-reviewed protocol.[11] Outcomes clearly support strong positive relations between periodontal disease and these outcomes and were extremely consistent across

systematic reviews with low risk of bias. For a number of outcomes, there was supplementary evidence from within reviews that higher-quality chief studies supported this link.[8-10]

Dependent on the specific bacterial strain, *P. gingivalis* dental infection encourages preterm delivery and fetal growth restriction with abnormal placental vascularization in mice, *P. gingivalis* DNA in human chorionic villous tissue or amniotic fluid has been linked to recurrent early miscarriage or premature labor with preterm LBW, respectively.[6-12] Presence of *P. gingivalis* in the placenta or umbilical cord has been associated with preterm birth and preeclampsia. Published guidelines on oral health care during pregnancy note that it is an underdeveloped area and that the relevance of oral hygiene during pregnancy is insufficiently recognized by dental and obstetric health professionals.[13-15] The traditional segregation between dental and general medical education and services may in part be accountable for this. Guidelines also differ in their conclusions about the relationship between periodontal disease and adverse pregnancy outcomes, while discussion of this aspect of oral health during pregnancy is even absent in some. Our summary demonstrates strong evidence for a link between periodontal disease and adverse pregnancy outcomes, with substantial proportions of preeclampsia, preterm birth, and LBW cases being estimated to be attributable to periodontal disease. Given the high global prevalence of periodontal disease and the adverse pregnancy outcomes associated with it, it is pivotal that preventive and therapeutic strategies be developed to prevent adverse pregnancy outcomes via improving oral health.[15] Although randomized trials and systematic reviews of antibiotics and dental procedures during pregnancy usually validate a positive impact on periodontal disease, the indication for improvement of pregnancy outcomes is conflicting. There is thus a need to evaluate novel strategies of preventive and therapeutic approaches at earlier stages of pregnancy, perhaps even pre-conceptionally.[14,15] The limitations of our study are that several included systematic reviews reported that primary included studies did not adjust for confounders in a consistent manner.

Conclusion

From our study we propose that the association between periodontal disease and various common and severe adverse pregnancy results is now adequately recognized. There is now a necessity to focus on explaining the mechanisms fundamental the link between periodontal disease and adverse pregnancy outcomes to update the development of targeted therapies and precautionary strategies.

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