Reviewer’s report

Title: Effect of Intra-Pregnancy Nonsurgical Periodontal Therapy on Inflammatory Biomarkers and Adverse Pregnancy Outcomes: A Systematic Review with Meta-Analysis.

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Reviewer: Gustavo Nascimento

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Effect of Intra-Pregnancy Nonsurgical Periodontal Therapy on Inflammatory Biomarkers and Adverse Pregnancy Outcomes: A Systematic Review

Authors have conducted a systematic review on the effect of intra-pregnancy periodontal therapy on inflammatory markers and adverse pregnancy outcomes. It is a well-designed review. Authors are encouraged to clarify some points of their study, as diagnosis used for "chronic periodontitis" and the reason for including studies that collected inflammatory markers from GCF.

A more detailed review is presented below:

Introduction

It is a strong assumption to state that dental biofilm causes periodontitis based on the current knowledge. I agree that dental biofilm induces and maintains the periodontal destruction; however, I am not convinced that dental biofilm per se causes periodontitis.

Authors should be careful when stating: "Therefore, anti-infective periodontal therapies that reduce exposure to subgingival pathogenic microorganisms have an anti-inflammatory potential, being considered an anti-inflammatory intervention [8]", since the cited systematic review demonstrated that periodontal therapy promotes a modest short-term reduction in CRP levels systemically.

"A systematic review was conducted to evaluate association between periodontal inflammatory biomarkers from GCF, as IL-1β, PGE2, and TNF-α and APO, suggesting that a positive association between GCF inflammatory biomarkers level and APO might exist [18]." It is important to emphasize that the results of the aforementioned systematic review should be carefully considered, since there are relevant limitations among the studies included in this review.

"Some interventional studies on the effects of IPPT on APO also tested periodontal inflammatory biomarkers as prognostic markers to predict pregnancy outcomes, [10, 13, 16, 19, 20]. However, there is no systematic review available on the potential association between biomarkers and APO.
after IPPT." Why is a systematic review on the topic needed? Are there conflicting results on the topic? Please clarify the rationale of the study.

Methods

As a condition to be included, should the articles present both inflammatory markers and APO? Why have the authors not included studies that presented at least one of the outcomes: inflammatory markers or APO? The exclusion of studies without inflammatory biomarkers, effectively excludes some (maybe many) studies addressing the effects of non-surgical periodontal therapy on poor pregnancy outcomes. This introduces selection bias with regards to this particular question of the systematic review.

Inclusion criteria comprised: "randomized and non-randomized clinical trials in which pregnant women diagnosed with chronic periodontitis by clinical examination, underwent nonsurgical periodontal therapy (treated group) compared with those untreated (untreated group), tested for inflammatory biomarkers and followed till delivery were selected. Preterm birth (<37 weeks), low birth weight (≤2500 grams) and preeclampsia (140-160mm / Hg to 90-110 mm / Hg) were considered primary outcomes." It is unclear which the contribution of non-randomized clinical trials is, taking into account that some randomized clinical trials were excluded for not including measurements of inflammatory markers.

Authors stated that "Studies considering any periodontal condition other than chronic periodontitis" were excluded. How have the authors assured that the studies only included "chronic periodontitis"? How could the authors define "chronic periodontitis"? All included studies in this review present different definitions of periodontitis. Authors are encouraged to clarify this point.

Results

"All papers evaluated PTB [16,19,20]…" Please include the reference of all included studies.

How have the authors classified the studies into low, moderate and high risk of bias? Have the authors used a cut-off point of "Yes"/"No" answers? Please clarify.

Authors are encouraged to present a meta-analysis of PTB and LBW, since available data for such analyses are available.

According to my understanding, authors hypothesize that periodontal therapy would reduce the burden of systemic inflammation, and consequently, the number of adverse pregnancy outcomes. If that is the case, why have the authors included studies, which measured inflammatory markers in GCF?
In Table 1, please clarify the criteria used by Offenbacher and colleagues to define pre-eclampsia.

Discussion and conclusion

The considerable heterogeneity found in the studies included for appraisal warrants more discussion.

The authors write on conflicting results on the topic of interest: "… Alternative explanations include variations in the populations assessed, the presence of a range of potential confounding factors, variations in the definition of periodontitis across studies, relative obstetric risk and other factors which are known to influence the prevalence of APO, irrespective of oral status." It is unclear how this study addressed these alternative explanations, please elaborate on this.

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An article whose findings are important to those with closely related research interests

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