Author’s response to reviews

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

Authors:

HELBERT EUSTÁQUIO CARDOSO DA SILVA (helbertcardososilva@gmail.com)
Cristine Stefani (cmstefani@gmail.com)
Nilce Melo (nilce@unb.br)
Adriano de Lima (adadlima@gmail.com)
Cassiano Rösing (ckrosing@hotmail.com)
André Porporatti (andreporporatti@yahoo.com.br)
Graziela Canto (graziela.canto@ufsc.br)

Version: 1 Date: 01 Jul 2017

Author’s response to reviews:

Responses to the reviewers

SYSR-D-17-00092


HELBERT EUSTÁQUIO CARDOSO DA SILVA, M.D.; Cristine Miron Stefani, PhD; Nilce de Santos Melo, PhD; Adriano de Almeida de Lima, PhD; Cassiano Kuchenbecker Rösing, PhD; André Luís Porporatti, PhD; Graziela De Lucca Canto, PhD

Reviewer #1:

1. Reference # 15 is not a Systematic Review.

Indeed, it is not a systematic review.

Text has been corrected (page 3).
2. INTRODUCTION: general comment.

Indeed, Systematic Reviews of observational studies show conflicting results (although the majority of them suggest an association)

However, when it comes to Systematic Reviews of INTERVENTIONAL STUDIES, there is little conflict. The results of most of the reviews (including one of our group) show that periodontal treatment is NOT associated with a reduction in adverse pregnancy outcomes (APO).

As indicated by Michalowicz et al (2013), when only larger and high-quality trials are considered, "there is no significant effect of non-surgical periodontal treatment on rates of preterm birth or low birthweight".


Obviously, SRs of RCTs are more important, since randomization controls for all confounding factors, including "relative obstetric risk and other factors which are known to influence the prevalence of APO".

Thus:

- Considering the limitations of observational studies in demonstrating effect of interventions
- Considering that many systematic reviews of interventional studies have shown no evidence of effect of periodontal therapy on APO,
- and considering that this is a SR of INTERVENTIONAL STUDIES, in my opinion, introduction should be re-written. Introduction should focus on SRs of interventional studies and the effect of periodontal therapy on periodontal inflammatory biomarkers (mainly on pregnant women).

Introduction was modified (page 1)

3. In this context, the aim of this SR should also be changed. Assessing the effect of periodontal therapy on APOs only in trials that ALSO assessed biomarkers can lead to a bias in the results and conclusions.

Only 04 trials were selected (trials that assessed BOTH pregnancy outcomes and biomarkers). However, one not-so-recent SR (Kim et al. 2012) identified 12 trials. Many important publications, such as Michalowicz et al (2009), were not included in the present SR, because biomarkers were not tested.
In my opinion, this review should focus on inflammatory biomarkers, only.

One of the recommendations of the Joint EFP/AAP Workshop of Periodontal Medicine in 2013 was the identification of serum inflammatory biomarkers to improve knowledge of the possible association between adverse pregnancy outcomes and periodontitis. (Sanz M, Kornman K, Working group 3 of joint EFP/AAPw. Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol. 2013; 40(Suppl 14):S164–169. doi:10.1111/jcpe.12083). So the aim of this systematic review was to correlate periodontal inflammatory biomarkers changes with the adverse pregnancy outcomes occurrence after nonsurgical periodontal therapy, and focus exclusively in inflammatory biomarkers excludes the main outcome (APO) from this equation.

Reviewer #2:

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.

Text was revised. Page 3 paragraph 1.

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.

Introduction was reformulated.

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.

The hypothesis of the article was to study the effect of the intervention (Intra-Pregnancy Nonsurgical Periodontal Therapy) on the reduction of the biomarkers and consequently on the occurrence of the adverse outcomes of the pregnancy. Therefore, it is necessary for the articles to present the two conditions, biomarkers and APO, being evaluated the effectiveness of Intra-Pregnancy Nonsurgical Periodontal Therapy on the reduction of biomarkers and the influence on the occurrence of APO's

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.

Since the authors did not find non-randomized clinical trials in the search of databases and in the selection of articles, it was removed from methods and considered an exclusion criteria.

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.

Considerations on this topic were included in the discussion.
Results

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

The reference was included.

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.

The cut-off point for the risk of bias tool was explained.

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

The meta-analysis was included in the paper as suggested.

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?

The subject was properly assessed in discussion.

In Table 1, please clarify the criteria used by Offenbacher and colleagues to define preeclampsia.

This reference was revised and in fact preeclampsia was considered as Baseline Characteristics of Study Participants by Intervention Group and not a primary outcome. Therefore, preeclampsia was not APO in any included study of this systematic review.

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.

Discussion was reformulated.