

Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases

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Sanz M, Kornman K, and on behalf of working group 3 of the joint EFP/AAP workshop. 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–S169. doi: 10.1111/jcpe.12083.

Abstract

Background: Pregnancy sometimes has adverse outcomes including low birthweight (<2500 g), pre-term birth (<37 weeks), growth restriction, pre-eclampsia, miscarriage and/or stillbirth. Maternal periodontitis directly and/or indirectly have potential to influence the health of the foetal–maternal unit.

Aims: To assess the epidemiological evidence for the impact of periodontal disease on adverse pregnancy outcomes and to identify potential underpinning mechanisms.

Epidemiology: Low birthweight, pre-term birth and pre-eclampsia have been associated with maternal periodontitis exposure. However, the strength of the observed associations is modest and seems to vary according to the population studied, the means of periodontal assessment and the periodontal disease classification employed.

Biological mechanisms: Two major pathways have been identified, One direct, in which oral microorganisms and/or their components reach the foetal–placental unit and one indirect, in which Inflammatory mediators circulate and impact the foetal–placental unit.

Interventions: Although periodontal therapy has been shown to be safe and leads to improved periodontal conditions in pregnant women, case-related periodontal therapy, with or without systemic antibiotics does not reduce overall rates of pre-term birth and low birthweight.

Guidelines: Given the current evidence, various treatment strategies could be evaluated that consider specific target populations, as well as timing and intensity of treatment.

Key words: adverse pregnancy outcomes; complications; intervention; low birthweight; mechanisms; periodontal disease; periodontitis; pre-eclampsia; pre-term birth; still birth

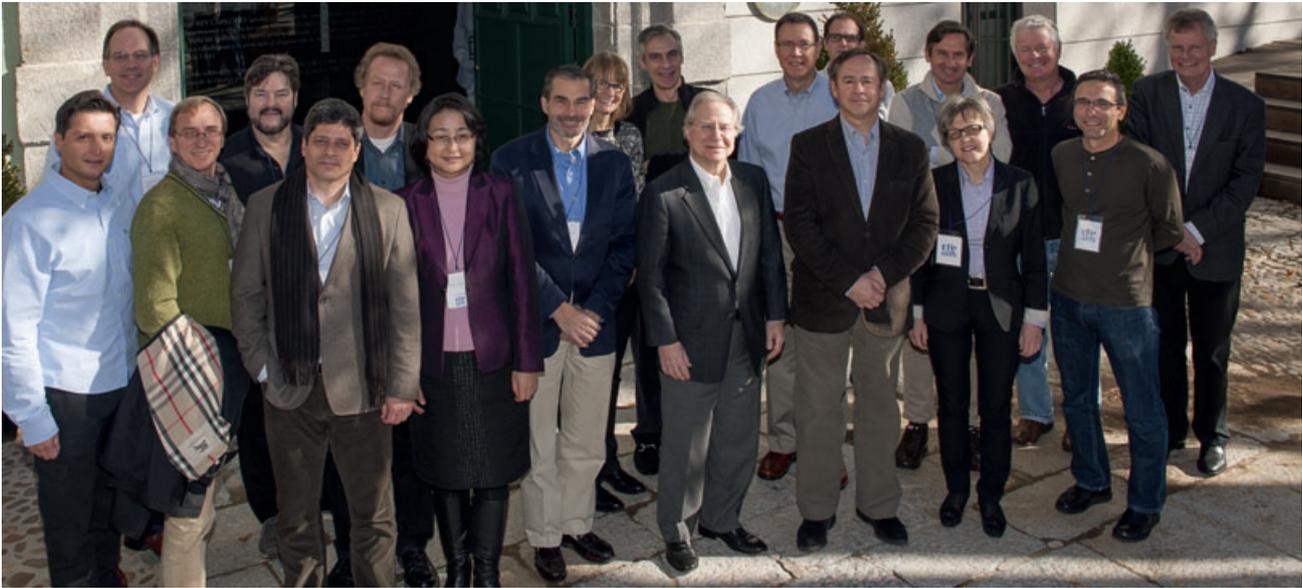
Accepted for publication 14 November 2012

The proceedings of the workshop were jointly and simultaneously published in the Journal of Clinical Periodontology and Journal of Periodontology.

Conflict of interest and source of funding statement

Group participants declare no conflict of interest. The workshop was funded by an unrestricted educational grant from Colgate-Palmolive to the European Federation of Periodontology and the American Academy of Periodontology.

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Periodontitis and Adverse Pregnancy Outcomes

Pregnancy is normally a healthy physiological process that sometimes has adverse outcomes including low birthweight (<2500 g) or very low birthweight (<1500 g), pre-term birth (<37 weeks or very pre-term <32 weeks), growth restriction (weight for gestational age), pre-eclampsia (commonly defined as maternal hypertension and proteinuria after the 20th gestational week), miscarriage and/or still birth. Some of these outcomes occur together, and it is unclear whether they share common mechanisms.

Every year, 1.1 million babies die from prematurity, and many survivors are disabled. Worldwide, 15 million babies are born pre-term with two decades of increasing rates in almost all countries with reliable data. Pre-term birth is now worldwide the second most common cause of death in children younger than 5 years after pneumonia, and is decreasing at a much slower rate than pneumonia, even increasing in several countries. In addition, pre-term birth is the leading risk factor for deaths due to neonatal infections and contributes to long-term growth impairment and substantial long-term morbidity such as cognitive, visual and learning impairments (Chang et al. 2013)

Adverse pregnancy complications have been associated with a variety of general risk factors including

individual-level behavioural and psychosocial factors, neighbourhood characteristics, environmental exposures, medical conditions, infertility treatments, biological factors and genetics. Many of these factors occur in combination, particularly in those who are socio-economically disadvantaged or are members of racial and ethnic minority groups.

Adverse pregnancy outcomes are generally associated with elevated local and systemic inflammatory mediators and intra-uterine infections. Current evidence suggests that adverse outcomes primarily originate from ascending infections from the vagina or cervix or from haematogenous spread from known or unknown non-genital sources. Maternal periodontitis represents one potential source of microorganisms that are known to routinely enter the circulation, and directly and/or indirectly have mechanistic potential to influence the health of the foetal–maternal unit.

The scope of this Working Group will be:

- (a) Review current evidence for a role of periodontal diseases in adverse pregnancy outcomes,
- (b) Review the epidemiological evidence for an association between periodontal diseases and adverse pregnancy outcomes,
- (c) Identify the currently known potential mechanisms that may

explain the observed association and review the evidence,

- (d) Review and interpret the evidence from periodontal intervention trials, summarizing the overall interpretation of the combined evidence from epidemiological, mechanism and intervention studies and Identifying key issues for future research,
- (e) Provide general recommendations for the general oral health professional and the medical profession.

Epidemiological evidence

Are the currently used periodontal case definitions suitable in the study of the epidemiological association between periodontal infections and adverse pregnancy outcomes?

The currently used case definitions may not be deemed suitable for such investigations of potential associations. The majority of studies investigating this association have used a dichotomous definition based on the number of teeth or sites with pre-defined levels of probing depth and attachment loss.

These definitions do not capture “cases” with profound gingival inflammation in the absence of clinical attachment loss and associated pocketing, and may exclude individuals with significant oral inflammatory burden exacerbated during pregnancy. Other studies have employed a range of continuous variables to reflect peri-

odontal status, including probing depth, attachment loss and bleeding on probing. These variables have been expressed either as mean values or as total numbers/percentages of sites involved. This approach allows an exposure–response relationship analysis, and provides greater insight into the effects of a range of periodontal conditions that may be involved. However, in situations where there is a low extent of disease, mean values of probing depth or attachment loss may not fully reflect periodontal status and associated exposure.

Regardless of the choice of dichotomous or continuous classification, these studies have involved either full-mouth or partial mouth recording protocols. While the latter are known to underestimate/misclassify periodontal disease status, they have been adopted due to logistical challenges (e.g. recruitment of adequate numbers of women attending medical clinics). This is disadvantageous when assessing periodontal status in a population of younger adults with low prevalence/extent of periodontitis.

What are the features of periodontal infections that may be relevant to pregnancy outcomes?

Most epidemiological studies have thus far focused on clinical measures of periodontal disease, which may not adequately reflect the infectious/inflammatory burden present in pregnant women. Importantly, the recording of bleeding following probing has often been omitted. In addition, these measures have generally been assessed at a single time point, and hence do not allow determination of the impact of changes in and duration of exposures during gestation related to bacterial biofilm, and maternal and foetal inflammatory states. At least two assessments, carried out early in/preceding pregnancy and again close to parturition, are desirable.

Additional relevant features include:

- (a) An assessment of the microbial composition of the oral biofilm,
- (b) Measures of host inflammatory response, including.

Biological markers of microbial challenge or maternal and foetal response, such as systemic inflamma-

tory markers and serum antibodies to oral microorganisms

What are the adverse pregnancy outcomes that are currently associated with maternal periodontitis exposure? What is the strength of the association?

Low birthweight, pre-term birth and pre-eclampsia have all been associated with maternal periodontitis exposure. However, the strength of the observed associations based on clinical parameters is modest and seems to vary according to the population studied, the means of periodontal assessment and the periodontal disease classification employed (Ide & Papapanou 2013).

Are there identifiable potential confounders, which may influence the association between periodontitis and adverse pregnancy outcomes demonstrated in epidemiological studies?

Studies have identified a range of relevant exposures, which include:

- (a) Socio-economic status,
- (b) Race and ethnicity,
- (c) Smoking and use of recreational drugs.

Attempts have been made to try to compensate for the potential impacts of these exposures in some analyses in high-quality studies. In addition, it has been postulated that several other exposures may have a role, although these have not been confirmed, and these may include:

- (a) Maternal age and weight, and weight gain during pregnancy,
- (b) Behavioural and lifestyle factors including alcohol use, nutritional status, exercise and stress,
- (c) Other medical conditions including obesity, metabolic syndrome and diabetes.

Biological mechanisms

What are the most likely mechanisms that may mediate an association between periodontal infections and adverse pregnancy outcomes?

Two major pathways have been proposed to trigger an inflammatory/immune response and/or suppression of local growth factors (such as IGF-2) in the foetal–placental unit

(myometrium, membranes, amniotic fluid, placenta, foetal circulation and tissues).

(1) Direct pathway

- (a) Oral microorganisms and/or their components reaching foetal–placental unit via haematogenous dissemination from oral cavity,
- (b) Oral microorganisms and/or their components reaching foetal–placental unit by an ascending route via genitourinary tract.

(2) Indirect pathway

- (a) Inflammatory mediators locally produced in periodontal tissues, for example, PGE₂, TNF α , circulate and impact the foetal–placental unit,
- (b) Inflammatory mediators and/or microbial components circulate to the liver, enhancing cytokine production (e.g. IL-6) and acute phase protein responses (e.g. CRP), which then impact the foetal–placental unit.

The strongest evidence from both animal and human studies supports the concept that periodontal infections provide a portal for haematogenous dissemination of oral microorganisms and their products, which reach the foetal–placental unit. This direct pathway is associated with inflammatory/immune responses in the foetal–placental unit that induce a range of adverse outcomes, which are dependent on timing and severity of exposure. Lower exposures may induce hyper contractility of the uterus, cervical dilation and loss of membrane integrity leading to pre-term delivery. Growth restriction and earlier pre-term delivery are associated with higher and/or earlier exposures. Even higher exposures may lead to spontaneous abortion, late miscarriage and stillbirth (Madianos et al. 2013).

What are the variables that provide an assessment of oral infectious exposure to the foetal–placental unit?

The main variables are presence and levels of microorganisms and microbial components in amniotic fluid, placental cord blood, neonatal respi-

ratory aspirates, placenta, foetal membranes, foetal tissues (still born), titres of antibodies to oral microorganisms in maternal serum (all isotypes) and foetal cord blood (IgM).

What are the variables that currently provide an assessment of inflammatory exposure or response relevant to a potential foetal-placental effect?

Inflammatory biomarkers in the maternal serum may include IL-6, TNF α , CRP, 8-isoprostane (oxidative stress), sICAM1

Inflammatory biomarkers in foetal cord blood may include IL-6, PGE₂, TNF α , 8-isoprostane, sICAM1

Inflammatory biomarkers in amniotic fluid may include MMPs (2,3,8,9,13), fibronectin, α -fetoprotein, IL-6, TNF α , IL-1, 8-isoprostane

Is there evidence of specific oral microorganisms being implicated in the pathobiology of adverse pregnancy outcomes?

Based on the amount of evidence such as frequency of detection of the microorganism and/or their respective antibodies in cases of adverse pregnancy outcomes and animal studies, the following bacterial species have been more strongly associated with adverse pregnancy outcomes: *Fusobacterium nucleatum*, *Campylobacter rectus*, *Porphyromonas gingivalis* and *Bergeyella* sp. Furthermore, additional oral bacterial species have been associated with adverse pregnancy outcomes in human and animal studies, but with less evidence.

In humans, *Fusobacterium nucleatum* has been detected in amniotic fluids in cases of pre-term birth and in the amniotic fluid and foetal tissues in cases of stillbirth. Anti-*F. nucleatum* IgM antibodies have also been detected in cord blood from cases of pre-term birth. *Campylobacter rectus*: approximately 1/3 of foetuses harbour positive IgM antibodies to oral bacteria. Anti-*C. rectus* IgM titres in foetal cord blood were the best predictor of adverse pregnancy outcomes. *Porphyromonas gingivalis* has been detected in placental tissues from pre-term deliveries and anti-*P. gingivalis* IgM antibodies have been frequently detected in foetal cord blood. *Bergeyella* sp. have been detected in amniotic fluids and cord blood in cases of pre-term birth.

Intervention studies

Based on the available evidence, do periodontal interventions improve adverse pregnancy outcomes?

Although periodontal therapy has been shown to be safe and leads to improved periodontal conditions in pregnant women, scaling and root surface debridement, with or without adjunctive care including systemic antibiotics, does not reduce overall rates of pre-term birth and low birthweight. Because some trials have shown an overall positive effect, there may be distinct patient populations that benefit from treatment. Previous pre-term birth history and baseline periodontal conditions may be associated with a treatment effect (Michalowicz & Gustafsson 2013).

In the context of improved pregnancy outcomes, which periodontal conditions should be targeted for intervention studies?

Oral health, and periodontal health in particular, should be maintained or re-established in pregnant women, with specific attention to reduction of the periodontal microbial infection and related inflammatory responses. However, available evidence does not provide clinical, microbiological or immunological parameters (or combinations of the above) that define patient subgroups whose pregnancy outcomes would be improved with periodontal treatment.

What clinical and other end points should be targeted with treatment protocols in intervention studies?

In the absence of clinical, inflammatory or microbiological thresholds that convey an increased risk for adverse pregnancy outcomes, intervention studies should strive to eliminate clinical signs of periodontal inflammation, which reflects control of the microbial biofilm load.

What would be the recommended oral health interventions for reducing adverse pregnancy outcomes?

Given the existing intervention trials, non-surgical periodontal therapy, delivered during the second trimester of pregnancy, cannot be recommended as a means of improving

pregnancy outcomes. However, based on epidemiological and plausibility studies that have associated periodontitis with adverse pregnancy outcomes various treatment strategies could be evaluated that consider specific target populations, as well as timing and intensity of treatment.

Recommendations for future research

The association of maternal periodontitis with adverse pregnancy outcomes has been investigated for the past 20 years. As reviewed above, epidemiological studies identified a modest but statistically significant association between maternal periodontitis and pre-term birth, low birthweight and pre-eclampsia, independent of other exposures.

In parallel, several studies in animals and humans contributed to a better understanding of the biological plausibility and the mechanisms that are involved in these associations.

On the other hand, several well-conducted, adequately powered intervention studies over the past decade demonstrated that non-surgical periodontal therapy delivered during the second trimester does not improve pregnancy outcomes.

It would be inappropriate to conclude that these seemingly contradictory findings from observational/mechanistic *versus* interventional studies indicate a lack of rationale for further research in this field that continues to have high public health importance. Experiences in medical research (notably the early trials on hypercholesterolaemia treatment and cardiovascular disease risk) underscore the possibility that interventional studies may still fail despite targeting true risk/causative factors. This could be due to several reasons related to the complexities of the clinical condition and of the interventions, including inappropriate timing and/or type of intervention, or inclusion of patients whose risk was not modifiable. These observations indicate that a more thorough understanding of the effects of treatment on the pathophysiology of the condition under study will provide important insights relevant to the design of future clinical trials. For example, knowledge that mechanical instrumentation of the periodontal tissues

results in a transient bacteraemia/ increased systemic inflammation may partly negate the longer term potential benefits of periodontal treatment associated with reduced maternal infectious and inflammatory burden.

Therefore, additional research is needed to better understand the pathophysiology and risk profile that underlie these associations, to develop the most appropriate treatment modalities with respect to type, time and intensity, as well as to identify subpopulations of pregnant women that will benefit most from these interventions.

Recommendations for the Dental Profession

Pregnancy is a unique period during a woman's life and is characterized by complex physiological changes, which may affect oral health. At the same time, oral health is key to overall health and well-being. It is therefore essential for oral health professionals (OHP) (e.g. dentists, dental hygienists, periodontists) to provide pregnant women with appropriate and timely oral health care, which includes oral health education.

These are the preventive, diagnostic and therapeutic recommendations for the oral health professionals in regards to periodontal health and periodontal treatment. It is important to emphasize that all oral preventive, diagnostic and therapeutic procedures are safe throughout pregnancy and these measures are usually effective in improving and maintaining oral health. General obstetric guidelines, however, suggest that elective procedures should be avoided in the first trimester due to the possible stress to the foetus and preferably rendered during the second trimester.

Every OHP evaluating a female patient in childbearing age should always ask whether they are currently pregnant or are trying to become pregnant and if the patient responds affirmatively, the OHP should always consider this pregnancy status before any oral health intervention is recommended.

With regards to periodontal health the OHP should:

- (a) Identify the stage of pregnancy,
- (b) Perform a comprehensive oral evaluation including a periodontal examination. The periodontal

evaluation should include periodontal probing and evaluation of the periodontal inflammatory status (bleeding on probing).

The result of this periodontal examination will render as periodontal diagnosis:

- (a) Healthy,
- (b) Gingivitis,
- (c) Periodontitis.

These are the specific recommendations according to the obtained diagnosis:

In presence of a pregnant female with healthy periodontium

- (a) Health Promotion: In addition to providing pregnant women with oral health care, educating them about preventing and treating periodontal diseases is critical, both for women's own oral health and for the future oral health of their children. The OHP should inform the patient on the periodontal physiological events usually occurring during pregnancy (increase in vascularity, possibility of higher incidence of bleeding and gingival enlargement). The OHP should also undertake a general health assessment emphasizing the history of hypertension, diabetes, cardiovascular disease, etc. The OHP should try to include as part of the general patient examination the evaluation of blood pressure and in case of perceived medical risk the patient should be referred to the physician,
- (b) An important component in oral health education should be training and motivation in periodontal self-assessment and in oral hygiene practices, with special emphasis on inter-dental cleaning,
- (c) The patient should be scheduled for a re-evaluation at a later stage during pregnancy

In presence of a pregnant female with Gingivitis:

- (a) The same health promotion measures as discussed above,
- (b) The professional intervention aimed to treat gingivitis should have the goal of reducing the

bacterial load and the signs of inflammation,

- (c) Once periodontal health is re-instituted, frequent monitoring of the periodontal status should be maintained throughout pregnancy and recurrence occurs, a similar intervention should be indicated.

In presence of a pregnant female with Periodontitis

- (a) The same health promotion measures as discussed above
- (b) The professional intervention aimed to treat periodontitis should be the standard non-surgical periodontal therapy with the goal of reducing the subgingival biofilm and the signs of periodontal inflammation. If possible, extensive traumatic interventions should be avoided.
- (c) In presence of localized gingival enlargements, surgical excision should be delayed if possible until the inflammation has been controlled. Recommend supportive measures (oral hygiene instruction) and re-evaluation after delivery.

Recommendations for the Medical Profession

Health professionals as part of their regular care should provide oral health care to pregnant women. At the same time, pregnant women, should have the knowledge of the obvious signs of oral disease and try to seek or receive the appropriate oral care.

The health professionals (HP) should include an oral health history as part of the patient's general health history. These types of questions should always be asked: do you have swollen gums? Do you have problems eating or chewing food? Are you suffering from oral pain or other oral problems? The health professionals should inform the pregnant females that periodontal disease is associated with a higher risk for adverse pregnancy outcomes and therefore recommend them to visit an oral health professional for a check-up early during gestation.

The HP should include an oral examination as part of their regular initial examination. This examina-

tion may consist of the use of a tongue depressor assessing for presence of bleeding in the margin between the teeth and the gingiva and overt gingival inflammation. In presence of these signs, the physician should refer to an oral health professional for seeking diagnosis and care.

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Clinical Relevance

Adverse pregnancy outcomes are the most common cause of death in babies. Several epidemiological

studies have shown a significant association between chronic periodontitis and prematurity and low birth weight. It is therefore very rele-

vant to fully understand the extent of these associations, their possible biological mechanisms and the implications for healthcare.