

PREGNANCY AND PERIODONTAL DISEASE: DOES EXIST A TWO-WAY RELATIONSHIP?

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SUMMARY

Periodontal disease (PD) is an inflammatory disease of the tissues supporting the teeth. PD affects 65 million adults over the age of 30 years in the USA, and worldwide 5 to 70% of adults. Women who develop PD during pregnancy, it's estimated 1 woman in 5, may have a higher risk of adverse pregnancy outcomes. PD during pregnancy starts by dental plaque and is increased by the action of pregnancy hormones. In order to study the effect of PD on adverse pregnancy outcomes, we have performed this narrative review summarising the current studies about the influence of PD on pregnancy. Periodontal pockets are a reservoir of oral microbiota. Modifications in oral microbiota may be considered as a potential mechanism for developing PD during pregnancy. PD is surely caused by bacteria, but the progression and worsening are due to a host immune response. The inflammation caused by PD is not limited to the oral cavity. It is hypothesized that episodes of bacteraemia and dissemination of endotoxins from periodontal pockets can induce the activation of the systemic immune response. In conclusion our narrative review shows that there's no relationship between PD and adverse pregnancy outcomes, and PD treatment during pregnancy does not confer a general protection against adverse pregnancy outcomes.

Key words: periodontal disease, periodontitis, pregnancy, adverse pregnancy outcome, preterm birth, perinatal mortality, maternal mortality, treatment, systematic review, overview.

Introduction

Periodontal disease (PD) is an inflammatory disease of the tissues supporting the teeth. PD affects 65 million adults over the age of 30 years in the USA (1-4), and worldwide 5 to 70% of adults. These percentages differ according to the geographical area and the definition of PD (5). Women who develop PD during pregnancy, it's estimated 1 woman in 5, may have a higher risk of adverse pregnancy outcomes (APOs) (6, 7).

Preterm delivery is the APO most often associated with PD (4). The prevalence of extremely preterm delivery (<28 weeks gestation) was estimated

11.1% in pregnant women with PD respect to women without PD (1.1 %) (8). Low birth weight (5), preeclampsia (6, 7) and being small for gestational age are considered other APOs associated with PD (8). The association between PD and APOs has been studied in many reviews and meta-analyses. These findings show important differences between the reviews considered (9, 10). Systematic reviews about the influence of periodontal treatment during pregnancy in reducing APOs have stated different conclusions (11-13). The studies about the relationship between PD and APOs as well as the potential benefits of periodontal therapy in pregnancy are very useful to establish clinical guidelines in daily dental practice.

Mechanism of action

PD during pregnancy starts by dental plaque and is increased by the action of pregnancy hormones (8). Since the Nineties, the two-way relationship between PD and systemic conditions has been investigated, leading to the definition of periodontal medicine. It is well known that PD can affect systemic diseases, including atherosclerotic cardiovascular disease, diabetes, APOs and chronic obstructive pulmonary disorder. APOs may manifest with a prevalence of approximately 2-3%, and are the leading causes of maternal morbidity and mortality in the Western world (8). Women with diseases associated with chronic low-grade inflammation, such as diabetes mellitus, hypertension, obesity and arterial diseases, have an increased risk of developing APOs (10). Because PD is also associated with low-grade inflammation, it can be hypothesized that patients with PD may have an increased risk of developing APOs. Many epidemiological studies have found a positive association between PD and APOs (12-17). However, these studies have used different measurement methods and investigated various populations. Therefore, the magnitude of the association has varied, and different studies have also reported conflicting findings. Thus, the possible role of PD in the pathogenesis of APOs remains an important but unresolved issue.

In order to study the effect of PD on APOs, we have performed this narrative review summarising the current studies about the influence of PD on pregnancy.

Oral microbiota

A direct relationship between worsening of PD and pregnancy has been demonstrated in many studies (12-17). During pregnancy, the classical manifestations of PD (bleeding on probing, increase of pockets depth) are exacerbated. These clinical signs are reduced after childbirth. Recent studies found that PD don't affect preg-

nant woman more than non-pregnant women and PD parameters showed no significant correlation with the progression of pregnancy.

PD is an inflammatory response of the host to the presence of dental plaque, leading to the loss of teeth, if untreated (18-33). Pregnancy-associated PD is similar, but oestrogen and progesterone can exacerbate gingival oedema and vasculature (34, 35). Recent studies established changes in putative pathogens of PD during pregnancy.

Periodontal pockets are a reservoir of oral microbiota. Modifications in oral microbiota may be considered as a potential mechanism for developing PD during pregnancy.

A recent study reported that the worsening in PD was associated with the increase of "red complex" bacteria like *Porphyromonas gingivalis* and *Prevotella* (34). However, the proportions of the "red complex" bacteria did not differ during pregnancy, although significant differences were found for all the pathogens after childbirth (34). A recent study reported that bacteria loading of *Porphyromonas gingivalis* and *Tannerella forsythia* at the 3rd month of pregnancy was associated with worsening in PD measured by bleeding on probing.

Another recent study measured bacteria loading of pregnant women and the relationship with estradiol levels. The results concluded that *Campylobacter rectus* was higher in pregnant women than in no pregnant women (35). This data can be explained considering that *Campylobacter rectus* loading is directly related to the level of estradiol in pregnant women.

Another study has shown that the bacteria, and in particular *Fusobacterium nucleatum*, originating from the periodontal pocket of pregnant women, cross the placental barrier and can cause acute infections and APOs.

On the contrary, in another study no differences were noted in *Fusobacterium* species between pregnant and no pregnant women (36). In conclusion, there is no evidence of correlation between the pregnancy hormones and an increase in putative pathogens of PD. Further studies are needed to determine the changes of the oral microflora in pregnancy.

Host response

PD is surely caused by bacteria, but the progression and worsening are due to a host immune response. The inflammation caused by PD is not limited to the oral cavity. It is hypothesized that episodes of bacteraemia and dissemination of endotoxins from periodontal pockets can induce the activation of the systemic immune response. Bacteria or bacterial endotoxins in the systemic circulation may induce pro-inflammatory cytokine production. These cytokines, then further activate the inflammatory response, which results in a chronic low-grade systemic up-regulation of the inflammatory molecules involving IL-6 and C-reactive protein (37). The inflammatory response also activates inflammatory and endothelial cells and may result in endothelial dysfunction. In pregnancy, the immune response plays a pivotal role in maintaining a healthy equilibrium between the mother and fetus. During a normal pregnancy, the specific immune response is shifted towards a Th2-type immune response, and the inflammatory response is also activated (38). The increased expression of activation markers on monocytes and granulocytes, differences in monocyte cytokine production, and increased circulating levels of pro-inflammatory cytokines and inflammatory markers, such as C-reactive protein, characterizes this activation of the inflammatory response during pregnancy.

Periodontal treatment

Recent reviews show that periodontal treatment does not seem to prevent APOs. Strong evidence for PD influencing APOs will ever be reached, whilst possible harmful effects cannot be ruled out. Only for high-risk populations, PD appeared potentially related to the onset of APOs, supporting results from previous analyses (16, 39), whilst trial sequential analysis indicated that firm evidence for this relationship has not been established so far. In addition, treatment of PD

was generally not found efficacious for preventing APOs, but this data are very sparse and not significant.

Considering these limitations and our results, the summarized evidence is insufficient to support or refute the hypothesis that PD treatment could reduce APOs. Our findings add weight to previous studies (40), which doubted the association between PD and APOs found by observational studies.

Attempts at PD treatment during pregnancy, to improve pregnant women oral health, have had no definitive conclusions. Recently, several large clinical randomized controlled trials failed to establish that standard PD therapy during pregnancy reduced the incidence of APOs. The question is when to perform PD treatment to reach the better outcomes during pregnancy.

Pregnancy may not be an appropriate period for PD treatment (40). PD treatment during pregnancy may be non-effective to decrease the local and systemic inflammation caused by periodontal pathogens (20, 41-46). PD treatment may cause bacteraemia triggering systemic inflammation, leading to APOs. Because of safety concerns on the frequency of PD treatment during pregnancy, the treatments are often restrict to 1 or 2 courses, which may not be effective in preventing the progression of PD.

On the contrary, the pre-conception period may be optimal for PD treatment (40). Pre-conception PD treatment may allow reaching better clinical outcomes, as it can be more intensive compared with PD treatment during pregnancy. Pre-conception PD treatment may provide more evidence as to whether PD is a causal risk factor for APOs. If pre-conception PD treatment is shown to be effective, it may highlight the biological mechanism of how subclinical infections such as PD lead to an increased risk of APOs. PD is preventable and curable. If the effect of pre-conception PD treatment is confirmed, this treatment will lead to improved pregnancy. Therefore, PD treatment either before pregnancy (for nulliparous women) or in the period between pregnancies (for multiparous women) may reduce APOs (47-57).

These are non-surgical PD treatment and can be performed by oral health professionals after receiving appropriate training. In addition, since PD treatment is performed before pregnancy, it will avoid potential risks to the pregnancy (fetus) and will be less stressful to women. PD treatment is effective, so it will be proposed to pre-conceptional women and be extended after childbirth. In addition, we would propose a protocol for pre-conception PD treatment promote mother and child's oral health.

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%. Our narrative review showed that PD treatment during pregnancy does not confer a general protection against APOs.

The prevalent periodontal symptoms in pregnancy such as swelling and bleeding could have been related to hormonal changes and not to PD. The dental team could play a major role in the prevention of PD and educate their patients about the benefits of good oral hygiene practices, and clinicians should educate pregnant women about the importance of maintaining a good standard for oral health.

In addition, the reviews we included, considered only the relationship between PD and APOs. We didn't consider other factors such as age, obesity, smoking and alcohol consumption, suggesting that the association between PD and APOs is robust and less likely to be greatly attenuated by unmeasured factors, although the residual confounding effects of the measured variables, particularly obesity, may not be completely removed. In summary, our review suggests that PD may not increase the risk of APOs. Further investigations should assess the underlying biological links between PD and APOs.

Periodontal diseases has an impact not only on pregnancy but overall on implant outcome (1-3,18-27, 29, 41-53, 55, 56, 58-77) as well as in after bone reconstruction (78-82) and in syndromic diseases (83-85).

Pregnancy is a critical time to prevent future defects or diseases of the mother of the newborn,

so it is mandatory to maintain good oral and general health.

Conclusion

This narrative review will provide a synthesis of the existing systematic reviews on the association between PD and APOs as well as on the impact of interventions to prevent or treat PD on these outcomes.

We conducted our review using existing guidelines, and our aim will be to formulate recommendations for dental team caring for pre-conceptional and pregnant women. In doing so, our review has the potential to contribute to reducing the significant global burden of APOs. We will furthermore identify the key knowledge gaps in the field and accordingly propose future research priorities.

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