

The role of inflammation in preterm birth—focus on periodontitis

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It is universally accepted that acute inflammation is responsible for a substantial fraction of preterm births, particularly early cases. Much of this inflammation is caused by intrauterine infection. There is also evidence that infection and perhaps inflammation remote from the genitourinary tract can trigger preterm labour. Several studies have suggested that periodontitis during pregnancy increases the risk of preterm birth. Periodontitis may cause preterm birth by causing low-grade bacteraemia, which lodges in the decidua, chorion and amnion or by releasing endotoxin into the maternal circulation, which triggers intrauterine inflammation and preterm birth. Alternatively, it may release cytokines and other inflammatory products, which then trigger preterm labour. It is also conceivable that periodontitis might

serve as a marker for other unhealthy behaviours, or immune hyperresponsiveness and that hyperresponsiveness to low-grade intrauterine infection itself might cause preterm birth. Currently, there are few data available to distinguish these possibilities. Such distinctions are important since they have clear implications for whether treatment of periodontitis might reduce the incidence of preterm birth. Several clinical trials of treatment of periodontitis are continuing, but until their results are known there is currently little evidence that treatment of periodontitis during pregnancy reduces the incidence of preterm birth.

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Introduction

The immune system comprises two components: innate and adaptive. The phylogenetically primitive innate immune system is responsible for the stereotypical response of acute inflammation, and it is comprised of granulocytes, macrophages, complement and acute-phase proteins. Through a response that is rapid and non-specific, this is the first line of defence against pathogens. The adaptive immune system, characterised by specificity of response and immunological memory first appeared in cartilaginous fish, and was evolutionarily grafted onto the innate system. This system is usually recruited by innate immunity and is comprised of cells of the lymphoid line.

It is universally accepted that acute inflammation is responsible for a substantial fraction of preterm births, particularly the early cases.¹ Much of this inflammation is caused by intrauterine infection,¹ and this will not be reviewed here. There is also evidence that infection and perhaps inflammation remote from the genitourinary tract can trigger spontaneous preterm labour. Several studies have indicated that

periodontitis during pregnancy might be an important risk factor for preterm birth.^{2–4} If it is a risk factor, it will be important to ascertain whether it is the cause of the increased risk or merely acts as a confounding factor or marker. This is an important distinction, since treatment will only be effective in the former case. The aim of this article is to review the available data on periodontitis in pregnancy and discuss its possible role in preterm birth.

Periodontal disease and preterm birth

Periodontal disease is characterised by low-grade infection of the gums and tooth support structure by Gram-negative, predominantly anaerobic bacteria. This results in a build up of endotoxins and cytokines in the crevicular fluid, which results in tooth loss and bone destruction. While the host mounts an immune response, it is unable to clear the infection and substantial tissue damage ensues.²

One of the earliest suggestions of an association between periodontitis and preterm birth came from a case-control study of 124 pregnant or postpartum women with identifiable

periodontal disease, as determined postpartum, as a statistically and clinically significant risk factor for low birthweight (LBW), with an adjusted odds ratio (OR) of 7.9.³ A subsequent smaller case-control study by Goepfert *et al.*⁴ supported these findings, reporting that women with early spontaneous labour and preterm birth were more likely to have severe periodontal disease than women with iatrogenic preterm birth or term birth (OR 3.4; 95% CI: 1.5–7.7). In contrast, however, other case-control studies have found no such association. Davenport *et al.*⁵ found no evidence for an increased occurrence of preterm birth/LBW among women with periodontal disease in a case-control study of 236 women (OR 0.78; 95% CI: 0.64–0.99). Moore *et al.*⁶ conducted a case-control study of postpartum women, which evaluated periodontal disease and polymorphisms in the genes for the cytokines interleukin-1beta (IL-1 β) and tumour necrosis factor-alpha (TNF- α) as risk factors for preterm birth. They found no interaction between either of the genotypes and periodontal disease with preterm birth. The findings of the latter two studies would argue against a specific drive to improve periodontal health of pregnant women as a means of improving pregnancy outcomes.

A number of cohort studies also support a link between periodontitis and preterm birth. Dortbudak *et al.*⁷ found that women with periodontitis were at high risk of preterm birth (OR 20.0; 95% CI: 2.0–201.7, $P < 0.01$). A large prospective study involving more than 1300 women showed that those with severe or generalised periodontal disease were at increased risk for preterm birth (adjusted OR 4.45; 95% CI: 2.16–9.18), the risk increasing with increasing prematurity (to 5.28 [95% CI: 2.05–13.60], before 35 weeks of gestational age and to 7.07 [95% CI: 1.70–27.4] before 32 weeks of gestational age).⁸ In another large cohort of more than 1000 women, preterm birth occurred in 11.2% of those with good periodontal health and 28.6% of those with moderate-to-severe periodontal disease (adjusted risk ratio [RR] 1.6, 95% CI: 1.1–2.3).⁹ Moderate-to-severe periodontal disease was associated with 24.9% incidence of spontaneous preterm labour and preterm birth compared with 15.2% among women with good periodontal health (adjusted RR 2.0, 95% CI: 1.2–3.2). Progression of periodontal disease was significantly associated with an increased occurrence of very preterm birth (adjusted RR 2.4, 95% CI: 1.1–5.2).⁹ The interested reader is referred to a systematic review of this topic published in 2006.¹⁰

Periodontal disease—confounding factor, marker or cause of preterm birth?

Based on the available evidence, there appears to be an association between periodontitis and preterm birth, but is it necessarily the cause? It could be argued that periodontitis is merely a confounding factor for preterm birth. Women

who have poor dental hygiene may tend to have other unhealthy habits and behaviours that could be the real cause of preterm birth. Although this is a possible scenario, the elevation in risk of preterm birth among women with periodontal disease appears to be of greater magnitude than that associated with most unhealthy habits. It seems unlikely that confounding by lifestyle factors explains the association between periodontal disease and preterm birth.

It is also possible that periodontitis is a marker for preterm birth—women with periodontal disease may have an immune system that overresponds to low-virulence anaerobic infections. Perhaps when these women also happen to have abnormal genital tract flora, they hyperrespond to the genital infection, thereby causing preterm birth.¹¹ In that setting, the periodontitis serves to identify a hyperresponding woman, but is not itself a cause of preterm birth. Other possibilities are that intermittent low-level bacteraemia as a result of periodontitis leads to infection of the decidua and chorion that subsequently results in preterm birth; or that periodontitis releases endotoxin or inflammatory mediators, such as cytokines, into maternal blood which initiate intrauterine inflammation.

A study by Bearfield *et al.*¹² investigated whether oral bacteria are also found in the amniotic fluid using polymerase chain reaction (PCR) in a group of women undergoing elective caesarean section at term. They found that the presence of *Streptococcus* spp. and *Fusobacterium nucleatum* in amniotic fluid paralleled their oral presence. Positive PCR results for *Streptococcus* spp. and *F. nucleatum* were significantly associated with an adverse obstetrical history, including miscarriage, intrauterine death, neonatal death, preterm birth and prelabour rupture of membranes ($P < 0.05$ and $P < 0.01$, respectively). No significant differences were found in the levels of prostaglandin E₂ (PgE₂) and cytokines, with the exception of IL-1 α , in women with and without evidence of infection.

In a case-control study of spontaneous preterm labour and preterm birth, Moore *et al.*⁶ found that the TNF-2 allele was associated with increased risk of preterm birth, but not with an increased risk of periodontitis. There was no interaction between TNF-2 allele and periodontitis in the risk of preterm birth. A cohort study of periodontitis in pregnancy showed that the presence of oral pathogens was similar in term and preterm births.¹³ Fetal immunoglobulin (Ig) M to oral pathogens was more commonly found in the cord blood of preterm infants, and a lack of maternal IgG to pathogens increased the risk of preterm birth. Boggess *et al.*¹⁴ also found that fetal exposure to oral pathogens, as evidenced by an IgM response, was associated with preterm birth, with the risk being greatest among fetuses that also show an inflammatory response. Although the case-control study of Goepfert *et al.*⁴ supported an association between severe periodontal disease and spontaneous preterm labour and preterm birth <32 weeks, neither histological chorioamnionitis, a positive placental culture nor

an elevated cord plasma IL-6 level was found to be significantly associated with periodontal disease. Periodontal pathogens were found rarely in culture, and the rates did not differ between preterm and term births.

Dortbudak *et al.*⁷ used PCR in addition to culture to analyse amniotic fluid and gingival plaque samples of women during early pregnancy (weeks 15–20). While all amniotic fluid samples were negative for bacteria, periodontal PCR and culture found more pathogens in women delivering preterm. Furthermore, periodontal PCR correlated with levels of IL-6 and PgE₂ in amniotic fluid. This implies that periodontitis can induce a primary host response in the chorioamnion leading to preterm birth. If this is the case, then treatment of periodontitis may be expected to lower the risk of preterm birth.

A pilot study was undertaken to determine the feasibility of conducting a trial to determine whether treatment of periodontitis may reduce the risk of spontaneous preterm labour and preterm birth. In this study, women (weeks 21–25) with periodontitis were randomised to one of three treatment groups: (1) dental prophylaxis plus placebo; (2) scaling and root planing plus placebo and (3) scaling and root planing plus metronidazole (250 mg three times a day for 1 week).¹⁵ The rate of preterm birth was 4.9% in the prophylaxis group compared with 3.3% in the scaling and root planing plus metronidazole group and 0.8% in the scaling plus root planing group plus placebo group. Although the differences were not statistically significant, the trial suggests that scaling and root planning may reduce the risk of preterm birth in women with periodontitis. Adjunctive metronidazole therapy did not improve pregnancy outcome. Several trials are underway to further clarify the potential role of periodontal treatment in reducing the incidence of preterm birth.

Conclusions

An association between maternal periodontitis and preterm birth has been consistently shown. Data on the mechanism of the association are sparse and inconsistent. Future studies using more sensitive (PCR based) tests to attempt to isolate oral organisms from decidua, membranes and placenta may provide further insights. In addition, measures of periodontal clinical and microbiological status, correlated with histological and biochemical measures of *in utero* inflammation may prove useful. Several clinical trials of treatment of periodontitis to prevent preterm birth are continuing, but until those

results are known there is currently little evidence to suggest that treatment of periodontitis during pregnancy reduces the incidence of preterm birth. ■

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