

Periodontal Disease and Preterm Delivery of Low-Birth-Weight Infants

(Les maladies parodontales et la naissance prématurée de bébés de faible poids)

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S o m m a i r e

La naissance prématurée de bébés de faible poids demeure un important problème de santé publique et une cause majeure de décès chez les nouveau-nés, ainsi que de troubles neurologiques du développement et de problèmes de santé de longue durée. Or selon des études épidémiologiques et des études microbiologiques et immunologiques récentes, les maladies parodontales pourraient être un facteur de risque indépendant de la naissance de bébés prématurés de faible poids. Au nombre des mécanismes mis en cause, mentionnons la translocation de pathogènes parodontaux vers l'unité fœto-placentaire, ainsi que l'action d'un réservoir parodontal de lipopolysaccharides ou de médiateurs de l'inflammation. Cependant, des facteurs sans lien de causalité pourraient aussi expliquer cette corrélation entre les maladies parodontales et les bébés prématurés de faible poids à la naissance. Donc, des études prospectives et, ultérieurement, des études interventionnelles, devront être menées avant que l'on puisse conclure à un lien de causalité entre les maladies parodontales et la naissance de bébés prématurés de faible poids.

Mots clés MeSH : *infant, low birth weight; periodontal diseases/complications; risk factors*

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The concept that periodontal disease might influence systemic health is not new. Miller originally published his "focal infection theory" in 1891,¹ suggesting that "microorganisms or their waste products obtain entrance of parts of the body adjacent to or remote from the mouth." Miller and subsequent proponents of the focal infection theory²⁻⁴ blamed oral foci of infection for a number of regional and systemic diseases, ranging from tonsillitis and middle ear infections to pneumonia, tuberculosis, syphilis, osteomyelitis, endocarditis, meningitis and septicemia. Before the development of modern periodontal treatments, many teeth were extracted prophylactically because of the focal infection theory.^{3,4}

Then, in 1952, an editorial in the *Journal of the American Medical Association* stated that "many patients with diseases caused by foci of infection have not been relieved of their symptoms by removal of the foci. Many patients with these same diseases have no evident focus of infection; also, foci of infection are as common in apparently healthy persons as

those with disease."⁵ The focal infection theory was not revisited for the next 50 years.

However, recent progress in identification and characterization of periodontal pathogens, as well as elucidation of potential systemic mechanisms of action of bacterial products and inflammatory cytokines, have opened the way for a more realistic assessment of the systemic importance of periodontal disease. Epidemiological and microbiological-immunological studies have lent credence to the concept that periodontal disease may be a separate risk factor for cardiovascular disease, cerebrovascular disease and respiratory disease, as well as preterm delivery of low-birth-weight infants.^{6,7}

Preterm Delivery of Low-Birth-Weight Infants

Low birth weight, defined as birth weight less than 2,500 g, continues to be a significant public health issue in both developed and developing countries. This obstetric complication is usually a direct result of preterm labour, in which case it is referred to as preterm delivery of low-birth-weight infants (PLBW). Introduction of neonatal intensive care methods

during the 1960s and the subsequent development of surfactant therapy in the 1980s resulted in improvements in the survival rates of PLBW neonates.⁸⁻¹¹ However, compared with infants of normal birth weight, PLBW infants are still 40 times more likely to die during the neonatal period.¹² PLBW births represent approximately 10% of all live births in North America, and medical care for these infants is estimated to exceed \$5 billion US annually.^{13,14}

PLBW infants who survive the neonatal period face a higher risk of several neurodevelopmental disturbances,^{15,16} health problems (such as asthma, upper and lower respiratory infections, and ear infections)^{17,18} and congenital anomalies.¹⁹ Although most PLBW children are normal on neurological examination, the rates of neuromotor dysfunction are higher than in control groups. The spectrum of neurological deficits ranges from subtle degrees of neuromotor abnormality to cerebral palsy, with rates of cerebral palsy approaching 20% in the subset of infants with very low birth weight (where very low birth weight is defined as birth weight less than 1,500 g).¹⁷

A higher prevalence of behavioural problems is reported for PLBW children, including attention deficit hyperactivity disorder and formal conduct disorder.²⁰⁻²² Learning problems among low-birth-weight children have been documented through teacher and parent ratings of school performance and direct assessments of academic skills in clinical settings; these children exhibit lower levels of achievement in reading, spelling and math.²³ Studies of intellectual and academic functioning during adolescence of children born in the 1960s and earlier indicated that the adverse consequences of low birth weight were still apparent at that age.²⁴ Thus, there is no reason to anticipate that current survivors will experience improvements in outcome with age.

Risk Factors for PLBW

Approximately 25% of PLBW deliveries occur without any of the risk factors discussed in this section, which emphasizes the limited understanding of the causes and pathophysiology of the problem.²⁵ Furthermore, although efforts have been made to diminish the effects of these risk factors through preventive interventions during prenatal care, the incidence of PLBW deliveries has not decreased significantly over the past decade.⁷

Identified risk factors for PLBW include older (> 34 years) and younger (< 17 years) maternal age; African-American ancestry; low socioeconomic status; inadequate prenatal care; drug, alcohol and tobacco abuse; hypertension; genitourinary tract infection; diabetes mellitus; and multiple pregnancies. Smoking during pregnancy has been linked to 20% to 30% of low-birth-weight births and 10% of fetal and infant deaths.²⁵ No consistent associations have been observed between caffeine and low birth weight or preterm births.²⁵

Role of Infection in PLBW

Infection is now considered one of the major causes of PLBW deliveries, responsible for somewhere between 30% and 50% of all cases.^{13,26,27} Bacterial infection of the chorioam-

nion, or extraplacental membrane, may lead to chorioamnionitis, a condition strongly associated with premature membrane rupture and preterm delivery.^{28,29}

The biological mechanisms involve bacterially induced activation of cell-mediated immunity, which leads to production of cytokines (such as interleukins [IL-1 and IL-6] and tumour necrosis factor alpha [TNF- α]) and the ensuing synthesis and release of prostaglandins (especially prostaglandin E₂ [PGE₂]).^{28,30} During normal pregnancy, the intra-amniotic levels of these mediators rise physiologically until a threshold level is reached, at which point labour, cervical dilatation and delivery are induced.^{7,31} Abnormal production of these mediators in the setting of infection triggers preterm labour and low birth weight.^{28,30-35}

However, many cases of histologically confirmed chorioamnionitis are not associated with active infection of the genitourinary tract and the results of culture are negative, both of which indicate that local infection is not the sole cause of this condition.^{28,29} These findings led to speculation that an infection might be distant from the placental complex or the genitourinary tract and still present a risk for PLBW, as a result of the indirect action of translocated bacterial products such as endotoxins (specifically lipopolysaccharides [LPS]) or the action of maternally produced inflammatory mediators (or both).^{7,31,36}

Potential Role of Periodontal Disease in PLBW

The theory that remote sites of infection might contribute to PLBW was supported by a number of studies using the pregnant golden hamster model.³⁷⁻³⁹ Pregnancy outcomes were evaluated in these animals after either the establishment of experimental periodontitis,³⁸ the establishment of a non-disseminating subcutaneous tissue infection with *Porphyromonas gingivalis* (a common gram-negative periodontal pathogen)³⁷ or intravenous injection of LPS from *P. gingivalis*.³⁹ Fetal weights were significantly lower in the experimental animals, and the severity of the fetal effects was directly related to the levels of PGE₂ and TNF- α .

Drawing on the results of these animal studies, Offenbacher and his co-investigators developed a series of clinical studies to test the hypothesis that periodontal infections, serving as reservoirs for gram-negative bacteria, might pose a potential threat to the fetoplacental unit. The first investigation was a case-control study of 93 mothers of PLBW infants, which used clinical attachment level as a measure of periodontal health.⁷ Multivariate logistic regression models, controlling for other risk factors and covariates (tobacco and drug use, alcohol consumption, level of prenatal care, parity, genitourinary infections and nutrition), demonstrated a statistically significant correlation between periodontal disease and PLBW delivery. After adjusting for all other risk factors, the authors determined that mothers with periodontal infection had more than 7 times the risk of delivering a PLBW infant. Extrapolation from these data suggested that 18.2% of the PLBW deliveries occurring each year might be attributable to periodontal disease.

In a subsequent case-control study, Offenbacher and others⁴⁰ measured levels of PGE₂ and IL-1 in the gingival crevicular fluid (GCF) of 48 mothers of PLBW infants. In addition, the levels of 4 periodontal pathogens (*Bacteroides forsythus*, *P. gingivalis*, *Actinobacillus actinomycetemcomitans* and *Treponema denticola*) were measured with microbe-specific DNA probes. GCF levels of PGE₂ were significantly higher in mothers of PLBW infants than in mothers of infants with normal birth weight (controls). The 4 periodontal pathogens, characteristically associated with mature plaque and progressing periodontitis, were detected at significantly higher levels in the mothers of PLBW infants. Furthermore, among the primiparous mothers of PLBW infants, a significant inverse association was demonstrated between birth weight (as well as gestational age) and GCF PGE₂, which suggests a dose-response relationship for increased GCF PGE₂ as a marker of current periodontal disease activity and decreasing birth weight.

More recently, Offenbacher's group⁴¹ analyzed blood samples from fetal cords for the presence of immunoglobulin M (IgM) antibody against various periodontal pathogens. Of the PLBW samples, 33.3% tested positive for IgM against the test bacteria, whereas only 17.9% of the normal birth weight samples tested positive. Of the 13 periodontal pathogens included in the analysis, IgM antibodies against *Campylobacter rectus*, *P. gingivalis* and *Fusobacterium nucleatum* were most often encountered. Although both preterm and normal birth weight infants had fetal cord IgM directed against specific bacteria, these fetal immune responses indicate that maternal periodontal infections can provide a systemic challenge to the fetus in utero.

Collectively, these animal and clinical studies clearly indicate an association between periodontal infection and adverse pregnancy outcomes. Although no definitive causal relationship has been established, and other explanations for the correlation might be offered, a model can nevertheless be envisaged wherein chronic periodontal infection could mediate this systemic effect through one or more of the following mechanisms:

- translocation of periodontal pathogens to the fetoplacental unit,
- action of a periodontal reservoir of LPS on the fetoplacental unit, or
- action of a periodontal reservoir of inflammatory mediators (IL-1, IL-6, TNF- α , PGE₂) on the fetoplacental unit.

Translocation of Periodontal Pathogens to the Fetoplacental Unit

No bacterial organisms are identified in 18% to 49% of histologically inflamed chorioamniotic membranes.²⁸ As a

result, it is generally maintained that the role of periodontal infection as a possible risk factor for PLBW more likely involves translocation of bacterial products (specifically LPS) or inflammatory mediators (specifically IL-1, IL-6, TNF- α and PGE₂) rather than bacteremic spread and translocation of the bacteria themselves.³¹ Most bacteria associated with progressive periodontitis are anaerobes, which find aerobic settings so inimical that they would rarely survive to enter the bloodstream,⁴² let alone establish an infection in the fetoplacental unit.

A curious footnote, however, involves *F. nucleatum*. As noted previously, IgM (which cannot cross the placenta and therefore represents a fetal rather than a maternal immune response)

directed against *F. nucleatum* is found more frequently in the fetal cord blood of PLBW samples than IgM directed against other bacteria.⁴¹ Furthermore, among cases of PLBW in which amniotic fluid was cultured, almost one-third of culture-positive women had far more *Fusobacterium* (*F. nucleatum*, whenever identification was to the species level) than other genera.⁴³ This high frequency of *F. nucleatum* does not reflect its prevalence among the microflora typical of bacterial vaginosis.⁴⁴ These observations led to speculation that the prevalence of *F. nucleatum* (a common periodontal pathogen) in cases of PLBW with culture-positive amniotic

fluid could reflect hematogenous spread of *F. nucleatum* from endogenous oral microflora or might represent an ascending route of infection introduced by oral-genital sexual contact with a partner.⁴³

Periodontal Reservoir of LPS

As noted previously, in many cases of PLBW with histological evidence of chorioamnionitis the results of culture are negative, which indicates that local infection is not a requirement for the triggering of inflammatory mediators of preterm labour.^{28,29} This finding suggested the possibility of indirect action of translocated bacterial products such as endotoxins (specifically LPS).^{31,36} LPS stimulate production of prostaglandins by the placenta and chorioamnion, and elevated concentrations of LPS have been measured in the amniotic fluid in cases of PLBW.^{32,45}

It is reasonable to suggest that the gram-negative anaerobic bacteria responsible for progressive periodontitis provide a chronic reservoir of LPS that could contribute to PLBW. This hypothesis has been supported by the results of the pregnant hamster experiments discussed above.³⁷⁻³⁹

Periodontal Reservoir of Inflammatory Mediators

The proinflammatory cytokines IL-1, IL-6 and TNF- α stimulate PGE₂ synthesis by the human placenta and chorioamnion,³¹⁻³³ and the amniotic fluid levels of these

After adjusting for all other risk factors, the authors determined that mothers with periodontal infection had more than 7 times the risk of delivering a preterm low-birth-weight infant.

cytokines are often elevated in women with preterm labour.³⁰ These cytokines can cross human fetal membranes, and it is plausible that the high concentrations of these cytokines that are generated at sites of chronic periodontitis and measured at higher levels in the plasma of patients with periodontitis⁴⁶ could influence the fetoplacental unit and contribute to PLBW.^{47,48}

Sites of chronic periodontitis are also associated with high tissue concentrations of PGE₂ and, as discussed above, the clinical studies of Offenbacher and his co-investigators have suggested a possible dose-response relationship between maternal levels of PGE₂ in the GCF and low birth weight.⁴⁰

Possible Non-Causal Explanations for Correlation between Periodontal Disease and PLBW

Given that the inflammatory mediators that play a role in periodontal diseases also play an important part in the initiation of labour, there certainly are plausible biological mechanisms that could link severity of periodontal disease with risk of PLBW. However, the association between periodontal disease and PLBW demonstrated by the studies described in this paper does not confirm a linear causal relationship. Perhaps the link relates, instead, to some commonality between these 2 disorders, based on an individual's genetically determined predisposition to mount a hyperinflammatory response in the presence of a bacterial challenge.^{13,36,49-51} This possibility gives rise to new questions. For example, to what extent is advanced periodontitis a susceptibility marker for PLBW, rather than playing a significant causal role? Is the association between periodontal disease and PLBW a reflection of some alteration in the patient's inflammatory phenotype, which places the patient at risk for both conditions?

In the pivotal case-control study by Offenbacher and others,⁷ the mean age for the PLBW mothers was 25 years. The mean periodontal attachment loss for this group exceeded 3 mm. As Zachariassen and Dennison⁴⁹ have pointed out, this degree of attachment loss would be categorized as early-onset periodontitis. It is known that certain patients with early-onset periodontitis, and those with refractory periodontitis, have peripheral blood monocytes that secrete up to 10-fold greater amounts of PGE₂, IL-1 β and TNF- α when exposed to LPS.^{50,52} Is the prevalence of this hyperactive-monocyte phenotype higher among mothers of PLBW infants? Does a genetically determined trait that predisposes an individual to periodontal disease also predispose to other multifactorial diseases of which inflammation is a component?

Conclusions

Although substantial efforts have been made to diminish the effects of known risk factors through preventive interventions during prenatal care, the frequency of PLBW deliveries has not decreased over the past 2 decades. Approximately 25% of PLBW cases occur without any of the known risk factors,²⁵ which has prompted continuation of the search for other possible causal factors.

Collectively, the studies summarized in this paper suggest a model wherein chronic periodontal infection, serving as a reservoir for bacterial products (such as LPS) or various inflammatory mediators (or both), may play an important role in the development of PLBW. However, larger prospective studies, and eventually interventional studies, will be necessary before periodontitis can be considered as a causal factor for PLBW. ♦

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Les vues exprimées sont celles de l'auteur et ne reflètent pas nécessairement les opinions et les politiques officielles de l'Association dentaire canadienne.

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