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Preterm low birthweight and the role of oral bacteria

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Preterm and low birthweight (PTLBW) continues to be a major cause of mortality and morbidity across the world. In recent years, maternal periodontal disease has been implicated as a risk factor for adverse pregnancy outcomes. There is conflicting evidence to support such an outcome as illustrated by descriptive, case control and randomised controlled trials involving pregnant women from across the world, using different measurement tools to determine the level of periodontal disease. Whilst considering the literature, there is evidence for both arguments, based on the effect of periodontal inflammatory by products. Bacteria associated with periodontal disease are not dissimilar to those known to be associated with genito-urinary bacterial infections and adverse pregnancy outcomes. Several groups have demonstrated the apparent translocation of *Fusobacterium nucleatum*, *Prevotella nigrescens*, *Prevotella intermedia*, *Porphyromonus gingivalis*, *Treponema denticola* to the foetal placental unit whereby a maternal or foetal response has been detected resulting in premature birth or low birthweight. The normal process of parturition involves a cascade of events including a build-up of inflammatory mediators as linked to inflammation, whereby the maternal environment becomes hostile and threatens the well-being of the infant, and the foetus expelled. The question remains therefore, is there a greater risk of delivering a PTLBW infant when the mother has detectable periodontal disease, or is the release of inflammatory mediators and their translocation via the haematogenous route sufficient to induce a poor pregnancy outcome? The data investigated would suggest that there is a positive outcome when certain oral gram-negative bacteria create a cumulative effect sufficient to trigger early delivery, which represents the final straw to result in preterm or low birthweight delivery. There is equally sufficient epidemiological evidence that does not support this outcome, but it is agreed that maintaining oral health during pregnancy is beneficial to the mother and her infant.

Keywords: *preterm*; *low birthweight*; *periodontal disease*; *oral bacteria*

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Low birthweight (LBW) is a major cause of infant mortality and morbidity around the world. The reality being that 10% of all live births are preterm, 1 in 14 babies are born underweight or premature and preterm birth (PTB) accounts for two-thirds of all infant mortality. In addition to this, those premature or LBW babies who survive suffer health problems including neurological, asthma, cerebral palsy, poor motor skills, and functional disability, some of which are long-term and the associated costs have been estimated to be in the region of $17.2 billion per year (1). Hence, the need to fully understand which of the risk factors associated with preterm and low birthweight infants (PTLBW) are key, and being able to target aspects of poor pregnancy outcome to reduce the chances of such events occurring.

For the last 15 years or so, maternal periodontal disease has been implicated in poor pregnancy outcome. Offenbacher and his group in 1996 reported a sevenfold increased risk of a mother with periodontal disease delivering a PTLBW baby (2). This observation was difficult to ignore and since then many studies have been completed but with varying results. Since 2001, several systematic and non-systematic reviews have been published (3–7), which have more often than not concluded the data available to be inconsistent and recommended that more rigorously designed studies should be conducted (6).

There are aspects of the relationship that require careful consideration as part of understanding and unravelling its complexity. These include: the aetiology, natural history, and epidemiology of periodontal disease; the same for PTLBW or poor pregnancy outcomes; known and proven

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risk factors for both periodontal disease and PTLBW; and finally study design to include consideration of confounders.

Periodontal disease

Periodontal disease is a chronic, low grade, gram-negative anaerobic infection of the periodontal tissues that is associated with an increase in systemic levels of inflammatory cytokines that, in turn, causes destruction of soft and hard periodontal tissues characterised by gingivitis and periodontitis (8, 9). Of the many oral bacteria, those that are most often associated with poor pregnancy outcome include *Fusobacterium nucleatum*, *Campylobacter rectus*, *Peptostreptococcus micros*, *Prevotella nigrescens*, *Prevotella intermedia*, *Porphyromonus gingivalis*, *Bacteroides forsythus*, *Treponema denticola.* These bacteria have been divided into a series of complexes or clusters namely purple, yellow, green, orange, and red (10). The orange cluster is considered to be important in terms of the maturation of the biofilm and enabling the colonisation of the red-complex organisms such as *P. gingivalis*, *B. forsythus,* and *T. denticola*. It has been demonstrated by several groups that oral bacteria 'translocate' to the foetal placental unit and induce a maternal or foetal response that can result in the premature birth of an infant (11). The systemic dissemination via the haematogenous route of inflammatory mediators and prostaglandins such as IL-6, IL-8, and TNF-α, PGE_2 originating from the periodontal inflammatory process are not dissimilar to those associated with the onset of labour. Therefore, is the onset of labour a single or cumulative effect of the increased levels of inflammatory process originating from the infected periodontium that acts as a reservoir for microbial products and inflammatory mediators (12–15)?

Poor pregnancy outcome

Poor pregnancy outcomes may include PTB that is a gestational age of less than 37 weeks with very premature at less than 32 weeks; LBW when a baby is born weighing less than 2,500 g; very or extremely LBW of under 1,500 g or 1,000 g, respectively; or premature birth or early onset of physiological pregnancy with or without obstetric complications such as premature labour, miscarriage, or early pregnancy loss and stillbirth (16).

Parturition is a normal process and characterised by coordinated uterine contractions leading to cervical dilatation and delivery of the foetus. Neurogenic reflexes stimulated by the stretch of the uterine muscle, foetal activation of the hypothalamic-pituitary-adrenal axis, and production of oxytocin and prostanoids lead to the event of labour and delivery of an infant. Additionally, endocrine mediators, prostaglandins, cytokines, and chemokines also play an important role in the labour process (17).

Infections from whichever source during pregnancy, maternal haemorrhage, placenta ischaemia, and stress may cause alterations to normal cytokine and hormone regulated gestation and result in preterm labour, premature rupture of membranes, or preterm birth (18–20). Romero and Mazor characterise the event of preterm labour as when the intrauterine or maternal environment becomes hostile and threatens the well-being of the host and, hence, expulsion of the foetus (18). Whereas Challis and colleagues regard PTB to be when there is asynchrony and the normal process of parturition takes place early and foetal maturation is delayed (17).

Link between periodontal disease and preterm low birthweight (PTLBW)

Periodontal disease is no different to any other infection in its outcome; it is therefore plausible that oral bacteria could contribute to poor or adverse pregnancy outcomes. Opportunistic pathogens including *Prevotella, Porphyromonus, Bacteroides, Peptostreptococcus* species are known to be associated with and found in the lower genital tract and detected in pelvic infections such as bacterial vaginosis, the clinical syndrome based on altered genital microflora. Hence, the extrapolation that similar oral microbial species might be associated with and have a role in the labour process. This can be justified by the premise that increased numbers of oral gram-negative anaerobic bacteria elicit inflammatory responses, induce tissue destruction, and produce a wider systemic impact (21, 22). The question is how and by which route oral bacteria and their resulting inflammatory products reach the foetal-placental unit? The accepted pathways for intrauterine infection include: ascending through the vagina and cervix, haematogenous dissemination through the placenta, retrograde seeding from the peritoneal cavity, and by accidental introduction during intrauterine procedures such as amniocentesis (18). The haematogenous route is the most likely route in terms of oral bacteria and has been implicated in the delivery of PTB and or LBW infants, threatened labour, miscarriage, or stillbirth (2, 15, 23, 24). Using an animal model, Collins and colleagues have demonstrated that by implanting a subcutaneous chamber containing *P. gingivalis* into a hamster, foetal weight of the hamster 'pups' was significantly reduced in the test group, and TNF-α and PGE_2 levels increased in the chamber (13). Hill further demonstrated that *Fusobacterium nucleatum* can be isolated from amniotic fluid cultures of women with preterm labour and intact membranes suggesting the transient bacteraemia had originated from the mouth via haematogenous spread and infection of the amniotic fluid through the placenta (25). More recently, Han and colleagues have reported a term stillbirth case by association was caused by *F. nucleatum* (24), she had previously demonstrated that *F. nucleatum* induced premature and term stillbirths in pregnant mice (26).

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Risk factors

Risk factors associated with both periodontal disease and poor pregnancy outcomes that might result in early parturition include maternal age, ethnicity, social class, education, socio-economics, nutrition, illness, gram-negative anaerobic microorganisms, and smoking (21, 23, 27–30). However, there are other specific risk factors, for example, poor oral hygiene for periodontal disease, antenatal care, parity, previous poor pregnancy outcome (miscarriage, stillbirth, PLB, prematurity), cervical incompetence, or intrauterine inflammation are all associated with PTLBW, PTB, and LBW (18, 19). Risk factors associated with poor pregnancy outcomes occur in combination and not alone and, therefore, developing preventive strategies can be challenging to be effective (31).

Study design

The variability of study design has created uncertainty about the validity of studies (32, 33), it has been suggested that this may be in part due to the many definitions and parameters used in the measurement of periodontal disease and pregnancy outcome (7). Such discrepancies are mainly associated with the diagnostic measurement of periodontal disease, either using periodontal indices such as CPITN or BPE, clinical attachment levels, bleeding on probing, and pocket depth compounded by the use of different periodontal probes. These inconsistencies are often driven by the need for simplicity, pragmatism, and the availability of mothers and accuracy of birth data. For example, mothers may only be accessible at the time of delivery and on the post-natal ward (30) or attending antenatal or ultrasound clinics (34). The acquisition and viability of clinical samples such as dental plaque, gingival crevicular fluid (14), blood serum, vaginal swabs, amniotic fluid, chorioamnion tissue (35), and umbilical and foetal cord blood (11, 18, 36) are crucial to the hypothesis testing. Timing is also significant in terms of the stage of pregnancy such as at parturition, including caesarean section (35), during the neonatal period (23, 37), or earlier in the pregnancy at 26 weeks or less gestation (9, 34, 38). The transferability of study outcomes across populations may also be limited because of the difficulties with replication of population demographics and sample collection (15, 30, 39).

Despite these perceived problems, work continues to eliminate the inconsistencies that have arisen, if only to identify unknown risk factors that might account for why 50% of mothers delivering a preterm baby do not have any known risk factors (11).

The original work carried out by Offenbacher and colleagues, as reported in 1996 and 1998 and as mentioned earlier, promoted the need to investigate further the link between gram-negative oral bacteria and poor pregnancy outcomes (2, 14). Offenbacher and colleagues reported a sevenfold risk of mothers with periodontal disease delivering a preterm low birth infant weight (2). A very small study followed in 1998 and provided early data supporting the oral bacteria and foetal-placental link. Here, 40 women volunteered either immediately before or within 3 days post-partum, gingival crevicular fluid levels of PGE_2 and Il-1β were increased, and *P. gingivalis, Actinobacillus actinomycetencomitans,* and *T. denticola* were also detected at higher levels in PTLBW mothers as compared to normal birthweight controls (14). These studies were small and opportunistic rather than adequately designed to demonstrate a reliable outcome.

In response, a prospective 5-year study titled The Oral Conditions and Pregnancy (OCAP) was designed to investigate the relationship between maternal periodontal disease and poor pregnancy outcomes such as preterm birth (<37 weeks gestation), and very preterm birth (<26 weeks gestation), LBW (<2,500 g), and pre-eclampsia. These studies have provided a means to unpick the apparent oral infection link to the foetal-placental unit and subsequent poor pregnancy outcomes but sample a particular population. Resulting subsets of data involving 640 to 1,224 women enrolled from prenatal clinics in Durham, North Carolina, at 26 weeks pregnancy have been reported by Offenbacher's group and provide evidence to support the relationship between maternal periodontal disease and poor pregnancy outcome (9, 11, 36, 38, 40).

Lieff and co-workers described the oral health of pregnant women enrolled in the prospective OCAP study. Where 58.7% of the women were primaparous, 45.9% were black, and 48.7% were unmarried. The clinical and delivery differences were found to be minimal over the time period; however, incident periodontal disease was noted in 23% of the 903 women indicating a continuum of periodontal disease during pregnancy (9).

Further exploration of 763 women enrolled in the OCAP study revealed those with severe periodontal disease or where periodontal disease had progressed and were significantly more likely to develop pre-eclampsia adjusted OR 2.4, 95% CI 1.1–5.3 and OR 2.1, 95% CI 1.0–4.4, respectively (41). In this same cohort, preterm birth (preterm adjusted RR 1.6, 95% CI 1.1–2.3) and spontaneous or very preterm birth (preterm adjusted RR 2.0, 95% CI 1.2–3.2) was higher among the women (28.6%) with moderate to severe periodontal disease than those with mild (19.0%) or periodontal health (11.2%), where adjustment was made for age, race, first birth, previous preterm delivery, smoking during pregnancy, marital status, food stamps, health insurance, and presence of chorioamionitis (38).

In contrast, there are a number of studies that do not support the relationship between maternal periodontal disease and the delivery of PTLBW infants. As outlined above, different populations and different parameters have been used, but better study design has provided

evidence that is sufficient to contradict but, at the same time, suggest that the premise is not straightforward. For example, Davenport and colleagues demonstrated that the risk for delivery of a PTLBW infant in a large population of 747 women where the majority were Bengali (53%) decreased with increasing pocket depth (OR 0.78 [95%] CI 0.64–0.99) having adjusted for maternal age, ethnicity, maternal education, smoking, alcohol consumption, infections, and hypertension during pregnancy. They considered it not necessary to increase periodontal health to improve pregnancy outcomes, but thought it was still important to maintain oral health during pregnancy (30). Bassini and colleagues examined 304 cases and 611 controls for periodontitis using attachment loss and information on perinatal outcome and general health in Brazil. They reported periodontitis was not significant for either LBW (OR 0.93, 95% CI 0.63, 1.41) or PTLBW (OR 0.92, 95% CI 0.54, 1.57) and concluded that their results did not uphold the hypothesis that maternal periodontal disease and PTLBW were linked (23). A further but small case control study conducted in Brazil of 116 post-partum women found that the non-PTLBW controls had significantly higher periodontal pocket depth 2.5 (sd 0.5) than either of those with LBW and or PTB (42).

Meanwhile with increasing inconsistency between study results, Mitchell-Lewis and his team reported the birth outcome in a minority group of young women 60% African American and 39% Hispanic aged between 16 and 19 years old, after intervention of oral prophylaxis there were no differences in periodontal status despite higher levels of *B. forsythus* and *C. rectus* in the plaque samples of PTLBW mothers (44). More recently a multi-centred randomised blinded control trial of the effects of non-surgical periodontal treatment during pregnancy on gestational age and birthweight has been reported, where 823 women were randomly selected to either receive scaling and root planning before 21 weeks or after delivery. Periodontal treatment improved periodontal health, but the risk of preterm delivery (OR 0.93, 95% CI 0.63, 1.37), birthweight ($p = 0.64$), or gestational age (OR 1.04, 95% CI 0.68, 1.58) was not significantly altered (45). This same group established that in this population they did not reduce the systemic markers of inflammation and concluded not to be associated with infant birthweight and gestational age (37).

Pathogenic response

By sampling dental plaque, high vaginal swab, amniotic fluid, and chorioamnion tissue from 48 East London women attending for elective caesarean section at full term, Bearfield and colleagues detected S*treptococcus species* and *F. nucleatum* in the amniotic fluid using PCR for the presence of the 16S rRNA gene specific to eubacteria and not by culture. An association between microbial DNA and complications during pregnancy such as previous miscarriage, intrauterine death, neonatal death, preterm delivery, and premature rupture of membranes were also noted as an incidental finding (35).

Furthermore the OCAP study demonstrated the detection of a number of oral microorganisms in 812 women at two points in their pregnancy; <26 week gestation and 48 hours post-partum using foetal cord and maternal blood samples to detect the systemic dissemination of oral bacteria and inflammatory components or products such as maternal IgG and foetal expression of IgM to 15 oral pathogens found in the red and orange complexes. These have been shown as key to the imbalance between the foetus and the mother resulting in PTB or LBW. For the same group of mothers, the resulting infection is linked as a trigger for prematurity as observed in those without protective red-complex IgG response coupled with foetal IgM response to orange-complex microorganisms (11).

Boggess and colleagues (36) further examined 640 umbilical cord blood samples to detect cord serum levels of C-reactive protein, IL-1β, IL-6, TNF-α, PGE_2, and the presence of foetal IgM antibody against five oral pathogens (*C. rectus*, *P. micros*, *P. nigrescens, P. intermedia,* and *F. nucleatum*). No significant risk for PTB was detected for oral pathogens alone or specific IgM response, unless a foetal inflammatory response was found as demonstrated by IgM and the additional presence of mediators C-reactive protein OR 5.0 (95% CI 1.9, 16.4), high 8-isoprostane OR 3.7 (95% CI 1.4, 9.3), and high PGE_2 OR 3.0 (95% CI 1.1, 8.1) significantly increased the risk of PTB that persisted when adjusted for race, infant gender, and presence of labour. All TNF-α strata after adjustment were found to be significant, underpinning a possible independent exposure to oral pathogens. Although this is important, the authors considered the study to be flawed because the number of useable samples was just over half of the original sample and therefore results were less tenable (36).

Dortbudak and colleagues (46) demonstrated a relationship between red and orange complexes and poor pregnancy outcome but others have not demonstrated similar relationships (11, 29).

The systemic inflammatory impact of periodontal disease involves the release from periodontal bacteria cytokines Il-1, IL-6, TNF-α, and PGE_2; transported via the haematogenous migration of oral bacteria in periodontal biofilm; and contributed to various maternal disturbances during pregnancy such as miscarriage, placental damage, premature birth, and LBW. The evidence of this effect whether direct, indirect, or a culmination of events continues to be debated. DePaoloa (47) made reference to a 'silent epidemic of oral disease,' which implicates periodontal disease and dental caries having a profound effect on systemic disease including adverse pregnancy outcomes. This complexity has led to

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many workers measuring the effect of risk factors (30, 38, 41, 45), some have argued that once the inflammatory cascade is activated during pregnancy it is difficult to target the pathway and prevent a PTB outcome.

The impact of intervention studies on poor pregnancy outcomes

There are mixed responses to treatment of periodontal disease during pregnancy that can reduce the chances of delivery of a preterm or LBW infant. Lopez and his colleagues, using a randomised control trial to investigate the effect of periodontal maintenance after 28 weeks gestation, demonstrated that 8.6% of the women with gingivitis and treated before 28 weeks gestation and 2.5% of those healthy and not treated until after delivery delivered a PTLBW infant (RR 3.5, 95% CI 1.7, 7.3, $p = 0.0004$) independent of usual risk factors. There was criticism in terms of selection bias and residual confounding associated with smoking, which illustrates problems associated with but not necessarily accounting for all confounders and taking care with selection (39). Jeffcoat and colleagues carried out a feasibility study to determine whether or not treatment of periodontal disease reduced poor pregnancy outcome in terms of spontaneous PTB in 366 women with periodontitis between 21 and 25 weeks gestation. The outcome of treatment for periodontitis was thought to reduce PTB in a predominantly African American population but adjunctive metronidazole had no effect. They concluded that a larger trial would be necessary to achieve statistical significance for a positive outcome of reducing poor pregnancy outcomes (43).

Conclusion

The question still remains, are women with periodontal disease any more at risk of having a poor or adverse pregnancy outcome than those whose periodontal health is good? Periodontal disease is an inflammatory process that occurs in the tissues surrounding the teeth in response to bacterial accumulations. The inflammatory response can be detected locally within the periodontal tissues and at the systemic level, which is not dissimilar to other inflammatory conditions and includes the process of parturition where similar 'inflammatory' processes play a part in a good pregnancy outcome with the delivery of a term infant.

Evidence supports the theory that dental plaque biofilm with its potential for increased risk of bacteraemia (infectious burden) and resulting inflammatory response may adversely affect distant sites and various organ systems. Therefore, periodontal-derived bacteraemia may have a role in increasing the risk of systemic disease and disorders. Periodontal disease can be modified when the public health impact is, therefore, predicated on public education for effective daily oral hygiene.

Why is this important to understand and devise simple preventive programmes? Finding a solution is just as important to clinicians as to mothers and their infants. The impact of preterm and LBW can be devastating for a mother and her family. In England and Wales, 7.6 and 1.2% of all live births weigh less than 2,500 g or less than 1,500 g, respectively; in areas of social deprivation those born with LBW increase to at least 9.3%, 0.5% of births are stillbirths, and less than 0.5% die within their first year (28). Additionally, of those babies born between 22 and 25 weeks gestation, half grow up with some form of neurological abnormality or development disability. The burden and impact on the children as they grow up, their families, and the health service is huge and, therefore, understanding the causes of poor pregnancy outcomes remains pressing (1).

Some would say as far as oral health care is concerned it is imperative to ensure that everyone at whatever stage in their lives brushes their teeth properly to maintain gingival and periodontal health and be caries free. By doing this, the risk of poor periodontal health and consequences of poor pregnancy outcomes may be averted but the evidence remains conflicting. However, there is probably sufficient evidence to support the haematagenous translocation of periodontal pathogens to the foetal-placental unit associated with a cumulative inflammatory response. This periodontal inflammatory response may well be the final straw and result in an adverse pregnancy outcome. It remains important to recognise the need for improvement in oral health during pregnancy, for the maintenance of good general health, and to provide the necessary mechanism promotion of the same.

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There is no conflict of interest in the present study for the author.

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