POOR ORAL HEALTH AND PRE-TERM LOW BIRTH INFANTS

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Abstract:
Oral health though often considered as a distinct specialty that is separate from the body as a whole, but the health of the oral cavity can have wide-reaching effects on overall health. Poor oral health may occur concomitantly with a more serious underlying disease process or may predispose an individual to other health conditions. This article examines the relationship between poor oral health and increased risk for Pre-term low birth weight infants, underscoring that the oral cavity and its tissues are an integral part of the human body.

Introduction:
There is emerging interest and increasing amount of evidence that support the inter-relationship between oral health and systemic conditions.[1] The mouth is colonized by hundreds of different bacterial species that inhabit dental plaque. These species form firm clusters adhering in layers to oral surfaces that are not easily eliminated by the body's natural immune responses, and must be mechanically removed. [2] Therefore the mouth can be a major source of chronic or permanent release of toxic bacterial components in the bloodstream during chewing.[3] It has been found that individuals with severe periodontal disease had approximately 4 times more harmful bacterial products in their blood.[3] Recently, it has been recognized that oral infection, especially periodontitis, may affect the course and pathogenesis of a number of systemic diseases, such as diabetes, insulin resistance, respiratory diseases,[4] rheumatoid arthritis,[5] obesity,[6] osteoporosis,[7,8] complications of pregnancy, such as pre-term low birth weight infants, [9,10] and cardiovascular diseases such as atherosclerosis, heart attack, congestive heart failure, and coronary artery disease.[2,3,11,12] Some of these conditions may in turn increase the incidence and severity of periodontal disease by modifying the body's immune response to periodontal bacteria and their byproducts.[11-13] Thus, an increasing body of evidence suggests a bi-directional relationship between periodontitis and systemic diseases.

Periodontal diseases:
Periodontitis is a prevalent human disease with defined risk parameters that contributes to population morbidity in terms of edentulism and decreased oral function.[14] More teeth are lost due to periodontal (gum) disease than through caries (tooth

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decay).[15] Symptoms like tooth mobility, gingival tenderness, abscess formation and/or tooth loss generally occur in late stages of the disease; however, periodontitis for most persons remains an insidious but destructive inflammatory condition.[16] Often patients are unaware of the onset of periodontal disease, which can be symptomless, and only seek treatment when the situation is out of control. [15] Risk factors for destructive periodontitis have been extensively reviewed and include exposures such as specific bacterial pathogens, smoking and diabetes mellitus.[17,18] In addition, genetic factors based on polymorphisms and inflammatory responses have been recently identified.[19, 20]

Prevalence of periodontal disease varies with race and geographic region. It is not simple to compare the existing data from different studies. Most of the well-documented epidemiologic studies providing detailed information are from western countries while the majority of the studies from third world countries have used the CPITN system, which provides inadequate data.[21]

However, Epidemiologic surveys estimate that periodontitis affects roughly one third of adults.[22-24] Although advanced periodontal destruction affects only one in eight persons, its prevalence increases to over one third among older individuals (55 to 65 years of age). [16] Approximately 75% of US adults are affected by Periodontitis. [25]

Certain subgingival species, mostly Gram-negative bacteria, have been related to the etiology of destructive periodontal diseases; *Actinobacillus Actinomycetemcomittans, Porphyromonas Gingivalis, Prevotella Intermedia* and some *Bacterioides* species. These species can produce toxic products in dental plaques such as endotoxin, cell wall nucleopeptides, fatty and organic acids, amines and leukotoxines.[26-32] These products trigger sequences of host-mediated events that has an impact on the initiation and progression of periodontal diseases. It can be summarized that inflammatory and immune processes in periodontal tissues are a response, not simply to one microbial specie but to several of species and their products acting over a long period of time. [26] The host defense process can be divided into specific and non-specific responses.[33]

The acute-phase reaction (non-specific) with characteristic features such as fever, neutrophilia, increased gluconeogenesis, and protein catabolism, hormonal changes etc is the primary defense reaction and protects against bacteria and their products. It is initiated by tissue macrophages through direct stimulation and secretion of various cell communication substances. An additional acute-phase response is modification of the vasculature with dilation and leakage of blood vessels, resulting in tissue edema, red blood cells

extravasation and associated redness. These immune reactions will result in release of cytokines and pro-inflammatory mediators, which in turn increases the inflammation and thus in time be more harmful to the host. [33]

Cytokines can be divided into three groups:

1) Pro-inflammatory cytokines (IL-1, IL-8, TNF)

2) Interleukine-6-type cytokines (IL-6, IL-11, leukemia inhibitory factor)

3) Anti-inflammatory cytokines (IL-4, TGF-b)

It has been shown that pro-inflammatory cytokines and mediators are significantly elevated with gingival inflammation during the destructive phase of periodontitis and thereby play a major role in the clinical symptom and tissue destruction associated with progression of periodontitis.[34] The cytokines IL-1 and TNF stimulate bone resorption and inhibit bone formation. [35] In the natural history of periodontitis, the chronic exposure to a pathogenic oral flora (e.g*., Porphyromonas gingivalis, Bacteroides forsythus, Actinobacillus actinomycetemcomitans* and *Treponema denticola*) remains a central pathophysiological event.[36,37] (Figure 2).

Dental plaque serves as a microbial biofilm whereby pathogenic bacteria coexist and interact within a matrix-enclosed environment. The plaque biofilm exposes the host to bacterial cell surface components such as lipopolysaccharide (LPS) that are shed within the gingival sulcus in the form of outer membrane vesicles. These bacterial products both bombard and penetrate tissues coming into contact with a variety of host cells including monocytes and macrophages. Accordingly, LPS forms a complex with a host binding protein (i.e., lipopolysaccharide-binding protein or LPB) which in turn binds to CD14 receptors on monocytes and macrophages.[38] These binding events lead to the expression and local release of immuno-inflammatory mediators like arachidonic acid metabolites (e.g., prostaglandin E_2) and cytokines (e.g., interleukin-1b and tumor necrosis factor a). These biochemical-cellular interactions mark the biologic onset of the disease and set into motion catabolic events which culminate in periodontal tissue destruction (pocket formation, clinical attachment loss and alveolar bone loss).[39]

Pre-term Low Birth Weight:

The international definition of low birth weight adopted by the 29th World Health assembly in 1976 is a birth weight <2500 g.[40] Growth in the uterus is a balance between the genetic potential of each individual fetus and the maternal environment. The maintenance of a normal pregnancy for approximately 9 months represents the balance of the maternal and fetal nutritional, hormonal and immunological systems. Low birth weight can

be a result of a short gestational period and/or retarded intrauterine growth.[1] This obstetric complication is usually a direct result of pre-term labor, in which case it is referred to as pre-term delivery (less than 37 weeks) of low birth weight infants (PLBW).[40,41]
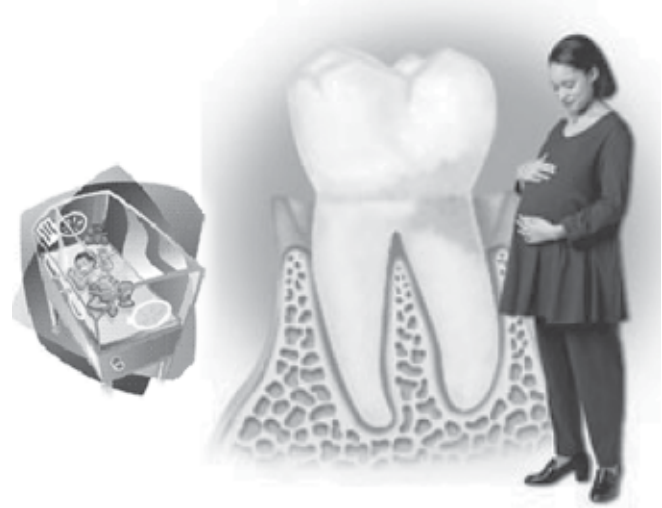
Low birth weight (LBW) continues to be a significant public health issue in both developed and developing countries. [42] It is the second leading cause of infant death in general, and the major cause of infant mortality among African-American infants. [43]These low birth weight infants are more likely to die during the neonatal period,[44] and low birth weight survivors are more likely to develop neuro-developmental problems,[45] respiratory problems [46] and congenital problems.[47] Respiratory distress, cerebral palsy and learning disorders are among the long-term disabilities of PLBW. [16] In addition, the neonatal and long-term healthcare cost of pre-term infants imposes a considerable economic burden both on individual families and taxpayers. [1] The societal burden of PLBW can be measured in terms of both economic and morbidity outcomes. Annual intensive care unit costs for treating PLBW infants total more than $5 billion.[48]

The prevalence of LBW in the United State is about 7.3%.[49] In the United Kingdom 6% of all live births are classified as LBW and 6.7% as PLBW.[50] In Africa the average LBW is around 12% and around 15% in Asia.[51] Globally, about 16% of the infants born in the world are LBW infants.[52] Across industrialized nations, an estimate of 10% of annual births is PLBW.[1]

Many risk factors have been proposed for pre-term rupture of membranes and preterm labour, including infection and inflammation.[53] Twenty-five per cent to 50% of PLBW deliveries occur without any known aetiology. Maternal risk factors include: age, height, weight, socioeconomic status, ethnicity, smoking, genetics, the use of alcohol, nutritional status, and

stress.[54] In addition parity, birth intervals, previous complications, pre- and ante-natal care, maternal hypertension, generalized infections, localized infections of the genital and urinary system, and cervical incompetence may also be important.[55,56] The major factor among all these is infection, whose role is increasingly receiving more attention.[42] Both generalized infections, including viral respiratory infections, diarrhea and malaria,[57] and more localised infections of the genital and urinary systems can affect the gestational length.[58-60] Associations between chorioamnionitis, infection of the amniotic fluid and PLBW have been established.[61] It has been suggested that spontaneous pre-term labour is commonly associated with bacterial vaginosis, a vaginal condition characterised by a prevalence of anaerobes.[62-64] Bacterial invasion of the choriodecidual space can activate the fetal membranes or trigger the maternal immune system to produce a wide variety of cytokines and growth factors. This has been shown to elicit an inflammatory burden resulting in placental damage and distress and, hence, fetal growth restriction.[65,66] In addition, the cascade of disordered cytokine response can lead to the stimulation of prostaglandin synthesis and the release of matrix metalloproteinases (MMPs), which account for the uterine contractions and membrane rupture, respectively, leading to the induction of labour.[67-69]

Gibbs,[62] in his review article, provided an excellent outline of the possible association between infections and adverse pregnancy outcomes. The infection hypothesis suggests that during a subclinical infection, the micro-organisms and their lipopolysaccharides enter the uterine cavity during pregnancy by the ascending route from the lower genital tract or by the blood-borne route from a non-genital route, hence causing pre-term birth. In summary, the evidence that supports this hypothesis includes:[62]

1. The prevalence of histologic chorioamnionitis is increased in pre-term birth.

2. Clinically evident infection is increased in mothers and newborns after pre-term birth.

3. Epidemiologically, there are significant associations of some lower genital tract infections with pre-term births or pre-term rupture of membranes.

4. Positive cultures of amniotic fluid or membranes are common in some patients with pre-term births.

5. There are numerous biochemical markers of infection in pre-term births.

6. Bacteria or their products induce pre-term births in animal models.

7. Some antibiotic trials have shown a lower rate of pre-term births or have prolonged gestation.

Intrauterine Growth Restriction:
On the other hand, Intrauterine growth restriction (IUGR) refers to insufficient fetal growth diagnosed either by direct intrauterine growth assessment (ultrasonography) or insufficient fetal growth in length. It is not a disease entity, but a manifestation of several possible maternal and fetal disorders. Risk factors involving the fetus include chromosomal abnormalities,[70,71] multifactorial congenital malformations,[72] multiple gestations [73] and fetal infections. In a recent animal study, results suggested that challenge with an oral pathogen *Campylobacter rectus (C. rectus)* in a mouse chamber model showed significantly more growth-restricted fetuses in the challenged groups than the controls.[74]

Periodontal health Vs systemic health:
The notion that oral or periodontal infection can influence systemic health is not new to dentistry and has been proposed at various times throughout the centuries.[16] Willoughby Dayton Miller proposed this relationship in an 1891 commentary published in *Dental Cosmos*.[75] Miller described the mouth as a "focus of infection" through which "microorganisms or their waste products obtain entrance to parts of the body adjacent to or remote from the mouth." This commentary listed several systemic diseases including gangrene, tuberculosis, meningitis, syphilis, septicemia and pneumonia, all thought to originate from an oral focus of infection. In a 1900 *British Medical Journal* report, William Hunter used the term "oral sepsis" and blamed it for causing "diseases such as tonsillitis, glandular swellings, middle ear infections, ulcerative endocarditis, empyema, meningitis and osteomyelitis."[76]

A landmark 1989 paper by Mattila and coworkers reintroduced the association between oral infection and systemic disease using sound, scientific methods.[77] Later studies by DeStefano, Beck, Offenbacher and others have provided exciting support that periodontitis may confer independent risks for systemic conditions, in particular cardiovascular disease and preterm low birth weight.[78-83]

Periodontal health Vs Pre-term Low Birth Weight:
The possibility periodontal infections may constitute remote maternal infections that may adversely influence the birth outcome was raised for the first time in the late 1980s.[84,85] Ever since the pivotal study performed by Offenbacher et al, there has been a considerable interest in identifying the potential association between periodontal disease and pregnancy outcomes, such as PLBW.

Historical, Experimental and Epidemiological Evidence
In the early 1990s, Offenbacher et al hypothesised that oral infections, such as periodontitis, could represent a significant source of both infection and inflammation during pregnancy.[86,87] They noted that periodontal disease is a gram-negative anaerobic infection, which may lead to bacteraemia and induce pregnancy complications. In a series of landmark animal studies, they demonstrated that in a hamster chamber model, chronic exposure to *Porphyromonas gingivalis (P.*

gingivalis) led to a 15% to 18% decrease in fetal weights along with a local increase of prostaglandin E 2 (PGE 2) and tumour necrosis factor (TNF-??) within the chamber fluid.[86] Later, they studied the association between infection and pregnancy by inducing periodontal disease in the hamster model. Four groups of animals were fed either control chow or plaque-promoting chow for an 8-week period to induce experimental periodontitis prior to mating. Two additional groups received exogenous *P. gingivalis* via oral gavage. On the day of sacrifice, animals receiving both plaque-promoting chow and exogenous *P. gingivalis* challenge resulted in a significant 22.5% reduction in mean fetal weight.[87] These animal studies provided vital proof-of-principle experiments and suggested the possibility that low-grade oral infections may trigger off maternal-fetal inflammation and result in adverse pregnancy events In a subsequent landmark human study, Offenbacher et al [79] studied 124 pregnant or postpartum women. After controlling for known risk factors, the results of the study were the first to show that periodontitis was a significant risk factor for PLBW. The adjusted odds ratios were 7.9 and 7.5 for all PLBW and primiparous PLBW cases, respectively.

Recent Epidemiological Evidence
Jeffcoat et al [88] conducted a prospective cohort study of 1313 pregnant women with severe or generalised periodontitis. The subjects were aged 20 to 30 years old; 83% of the subjects were African-Americans and the remaining 17% were Caucasians. There was an adjusted ratio of 4.45 for preterm delivery before 37 weeks' gestation age, 5.28 before 35 weeks and 7.07 for delivery before 32 weeks. In an ongoing large prospective cohort study from an initial 812 patients, it was reported that maternal periodontal disease represents a significant risk factor for pre-term birth and low birth weight.

The adjusted prevalence of moderate to severe periodontal disease increased with reducing gestational age. They reported a prevalence of 9% before gestational age of 37 weeks, 10.2% before 35 weeks, 13.6% before 32 weeks and 18.4% before 28 weeks.[89] Another study, which investigated the relationship between maternal periodontal status and nutritional condition of the newborns, yielded similar conclusions. It was concluded that the average newborn's weight and gestational age were inversely proportional to the maternal periodontitis status.[90] Despite a growing trend of studies showing positive correlation of the possible link between periodontal disease and low birth weight, a recently published study reported otherwise. In the case-control study of 236 cases of PLBW and 507 controls, the authors found no association between maternal periodontal disease and an increased risk for PLBW.[91] On the contrary, they found that increasing mean probing depths at the time of delivery was associated with a reduction in the risk of PLBW. Interestingly, another recent study that investigated the methods used to study periodontal health in a large cohort of pregnant women concluded that an increase in probing depths is observed consistently during pregnancy. However, the authors reported that although this increase of the probing depths from 1.6 mm to 1.7 mm was statistically significant, it was not clinically relevant as the slight change could be accounted for by gingival alterations that occur during pregnancy.[92]

Interventional Studies
The need for randomised intervention trials is necessary to further evaluate the causal relationships between periodontal disease and PLBW. There have been promising data on intervention trials to further evaluate the impact of periodontal therapy on pregnancy outcomes. (Table I)

Table- I: *Contribution of Periodontal Disease to Abnormal Pregnancy Outcomes* [93]

Multivariate Regression Models (n=357)		Odds Ratio	P	Cases
Periodontal disease at baseline	*Increased incidence of* • Prematurity < 34 weeks • Low birth weight < 2500 grams • Prematurity < 37 weeks	3.0* 2.6* 1.9*	.03 .01 .03	26 42 72
Periodontal disease at baseline with worsening periodontal status during pregnancy	• Preeclampsia	6.3**	.027	36
Post-partum mothers with periodontitis and low levels of maternal IgG antibodies to selected periodontal pathogens†	• Preeclampsia • Prematurity	6.0 3.0	.02 < .01	N/A N/A
Case-control subset analysis of fetal IgM antibody responses††	• Prematurity < 34 weeks	5.8**	.04	N/A

* Adjusted for age, race, smoking, vaginosis treatment history, previous pre-term delivery and marital status.
** Adjusted for age, race and smoking. † *e.g., Campylobacter rectus.* †† Against *C. rectus.* N/A Not available.

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Microbial Evidence

As mentioned earlier in the previous reports, periodontal disease is an infectious disease caused by anaerobic gram-negative bacteria. These bacteria have been previously divided into 2 main clusters or complexes of micro-organisms, namely, the "Red" and the "Orange" complex, as described by Socransky et al.[94] The authors examined over 13,000 subgingival plaque samples from 185 adult subjects. Bacterial species were clustered using cluster analysis and community ordination techniques. Six closely associated bacterial species were consistently recognized and subsequently colour-coded into their respective complexes. The "Blue", "Green", "Yellow" and "Purple" complexes were described to be early colonisers of the tooth surface and form the conditioning film before the multiplication of the more pathogenic "Orange" and "Red" complexes. It has been shown that during the maturation of the biofilm in dental plaque, organisms from the "Orange" complex are required for the further establishment and colonisation of the "Red" complex. The presence of these 2 complexes, in particular the "Red" complex have been shown to be strongly correlated to severe and advanced periodontal disease.[94] Madianos et al [95] continued to identify the microbiological and biological mechanisms of this association between clinical periodontal disease and prematurity. From the subjects involved in the study, 386 maternal plaque samples, 367 maternal serum samples and 339 fetal serum samples were collected and analysed. A significant finding from this study was the highest prematurity rate in mothers who did not mount a robust immunoglobulin (IgG) response to the bacteria from the "Red" complex, such as *P. gingivalis, Bacteriodes forsythus (B. forsythus)* and *Treponema denticola (T. denticola)*. Strong fetal immunoglobulin (IgM) response to periodontal pathogens in the "Orange" complex, especially *C. rectu*s, was noted in pre-term compared to full-term neonates. The potential of *C. rectus* and *P. gingivalis* in mediating adverse pregnancy outcomes was recently studied in a mouse model. In this proof-of-concept mouse chamber model, maternal *C. rectus* challenge at a distant site results in adverse pregnancy outcomes. Pregnant mice receiving *C. rectus* had more fetal resorptions after challenge with 10 7 or 10 9 colony forming unit (CFU)/mL (24.1% and 30.1%, respectively) than controls (9%). Higher numbers of growth-restricted fetuses were also observed in the *C. rectus* challenged groups (21%) as compared to controls (2.3%). Fetuses from the dams challenged with 10 9 CFU/mL weighed less (0.49 g) and had shorter crown-rump lengths (14.69 mm) than controls (0.53 g and 15.54 mm, respectively).[74] Another study from the same group investigated the effects of *P. gingivalis* infection in the mouse model reported similar findings.[96] The data from these studies suggest that, at least in the mouse model, infection with the periodontal pathogen at a distant site affects fetal development and viability. This may have resulted from the dissemination and translocation of the periodontal pathogen into the circulatory system of the pregnant mice, as well as a possible induction of maternal and fetal immune/inflammatory responses.

Recent data from the North Carolina group further clarifies the microbial dimension of the periodontitis-PLBW association. Fetal cord blood samples from 21 PLBW and 39 NBW infants were collected and analyzed for the presence of IgM specific antibody against 13 periodontal pathogens using checkerboard immunoblotting.[83] While 17.9% of fetal cord blood samples from NBW infants tested positive for IgM directed against the tested pathogens, 33.3% of PLBW samples tested positive. Overall, IgM was most commonly specific for *Campylobacter rectus* followed by *P. gingivalis* and *Fusobacterium nucleatum*. These early data indicate that fetal cord blood IgM directed against specific periodontal pathogens could be detected in both PLBW and NBW infants; nevertheless, these specific fetal immune responses to periodontal pathogens provide direct evidence that maternal periodontal infection can provide a systemic challenge to the fetus in utero.

Periodontal disease mechanisms leading to Pre-term Low Birth Weight:

The mechanisms by which periodontal disease may cause preterm LBW or PTB have still not been elucidated, but the biological plausibility of the association between periodontal disease and adverse pregnancy outcomes can be identified.[79] It has been suggested that the effect of periodontal disease on PLBW could result from stimulation of fetal membranes on prostaglandin synthesis by cytokines produced by inflamed gingival tissues, or through the effect of endotoxin derived from periodontal infection. [1] Endotoxin can stimulate prostaglandin production by macrophage amnion [97] and decidua *in vitro.* [98] In animal models, it has been shown that endotoxin produces fetal growth retardation [82,99] On the other hand, peripheral monocytes obtained from some patients with periodontal disease showed enhanced release of inflammatory mediators such as PGE_2, IL-ß, and TNF-Ü , when challenged with bacterial endotoxin.[100,101] Endotoxin derived from periodontal pathogens in women with periodontal disease might signal preterm labor through primed monocyte-macrophage activation in peripheral blood and decidua. [102]

The interactions between prostaglandins and cytokines are important mediators that influence both normal and abnormal pregnancy and delivery. There is strong evidence that suggests the disturbances in the physiological balance and production of these intrauterine mediators may affect the pregnancy outcome.[103] These mediators can also be produced

within the periodontal diseased environment, escape into the systemic circulation and possibly to the maternal-placental compartment. These changes will affect the normal homoeostasis and balance of the maternal-fetal nutritional, hormonal and immuno-logical systems. Studies suggest a possible sequence of events: the presence of disease exposure, such as periodontitis, may present first as an infectious insult, leading to an inflammatory burden to the host, resulting in the pregnancy complications as described. [82,104]

Systemic inflammation is believed to be an important risk factor for poor pregnancy outcomes, including PLBW.[105]Elevated plasma C-reactive protein (CRP) levels are a marker for systemic inflammation, and have been linked to preeclampsia, intrauterine growth restriction, and preterm birth.[111] In addition, increases in CRP are associated with periodontal inflammation.[106] One study reported that women with periodontitis had 65% higher plasma CRP levels in early pregnancy than healthy matched controls (95% confidence interval - 2% to 180%, p=0.06).[106] Further investigation revealed that the median concentration of plasma CRP in early pregnancy tended to be higher in women with subsequent preterm delivery (n=117) than in matched controls who delivered at term (2.8 mg/L vs. 2.4 mg/L).[106] Compared to women with normal CRP levels, those with CRP levels e"8 mg/L had a 2-fold higher risk of subsequent preterm delivery (odds ratio 2.67, 95% confidence interval 1.04-6.86). The risk of preterm delivery increased even further in women with CRP levels e"12 mg/L (odds ratio 4.12, 95% confidence interval 1.12-15.15).[106] Taken together, these studies suggest that CRP may mediate the relationship between periodontitis and poor pregnancy outcomes.

A proposed mechanism (Fig.-1) by which periodontal disease may trigger pathways leading to PLBW through direct and indirect effects of oral bacteria.
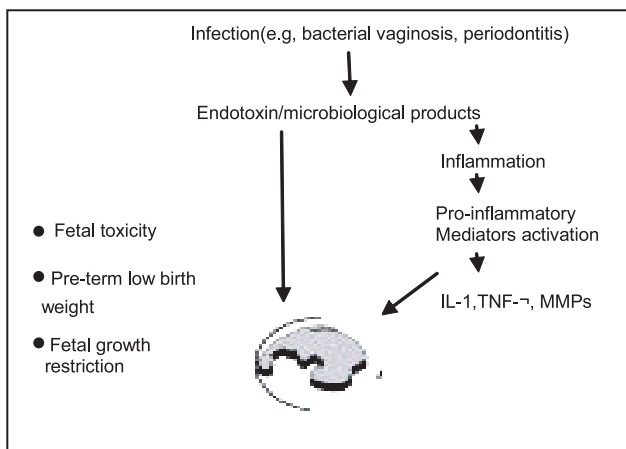

Fig.1. Proposed hypothetical model of the association between periodontal disease and adverse pregnancy outcomes: both the conditions are initiated by a microbial infection and share common patho-physiological reactions. While it appears likely that bacterial vaginosis is the major source of infectious challenge that contributes to PLBW, the potential of oral pathogens being involved in intra-amniotic infection have been demonstrated and may act as an additional risk factor that may contribute to PLBW for some of the cases.[64] Microbiological products like endotoxin will trigger off the host-immune response causing inflammation and activation of pro-inflammatory mediators like interleukin-1, TNF-Ü and MMPs which, in turn, may cross the placenta barrier and cause fetal toxicity resulting in pre-term delivery and low birth weight babies.

Conclusion:

Good oral health is an important component of overall health and well-being. When oral health is compromised, as in conditions such as periodontitis, consequences may reach far beyond the oral cavity. Periodontitis is associated with an increased risk of illnesses that affect the entire body. Protecting oral health is therefore critical to maintaining overall health.

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