ISSN No: 2455-7803

REVIEW ARTICLE

ORAL INFECTION & LOW BIRTH WEIGHT BABIES: A BIOCHEMICAL INTER RELATIONSHIP

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ABSTRACT:
Preterm low birth weight (PLBW) are the most relevant biological cause of new born survival both in developed and in developing countries. For adverse pregnancy outcomes, various risk factors have been defined in the studies. There are common etiological factors for adverse pregnancy outcomes like genitourinary tract infections along with various metabolic and genetic factors. It is well known from various literatures that sub-clinical infection sites which are away from genitourinary tract may also be the cause for pregnancy outcomes which are adverse for both mother and fetus. The periodontal infection has been reported in many studies as a possible risk factor for adverse pregnancy outcomes. Poor periodontal health status of the pregnant women is the potential risk factor for PLBW. Although this review found a consistent association between periodontal infection and PLBW. Education for the pregnant women and health care providers in respect of biological plausibility of association and the potential risks is indicated for the prevention of adverse pregnancy outcomes.
Keywords: Pregnancy; periodontal infections; periodontal status; premature; preterm; low birth weight and risk factors.

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This article may be cited as: Chadha V, Sharma V, Gill JS, Kansal G, Gupta G, Wadhwa R. Oral infection & low birth weight babies: A biochemical inter relationship. Int J Res Health Allied Sci 2017;3(2):15-20.

INTRODUCTION

PLBW is the serious health problem during pregnancy. The weight of the fetus at birth is the most important for the survival, growth and healthy development of a child. A birth is considered premature if the delivery occurs before the 37th gestational week and is commonly accompanied with low birth weight, which means a birth weight less than 2500 grams.[1] Of preterm births (PTB), "very low birth weight" is less than 1500g.[2,3]However extremely low birth weight (LBW), is defined as a weight, not more than 1000g, and "very premature birth" means delivery at less than 32 weeks' of gestation.[4] Although 25% to 50% of adverse pregnancy outcomes occur without any known cause, there is increasing evidence that infection may play a significant role in preterm (PT) delivery. It is considered to be a public health problem because of the higher morbidity and neonatal mortality rate. Low birth survivors face consequences like neuro-developmental abnormalities, congenital anomalies and respiratory problems.

RISK FACTORS FOR ADVERSE PREGNANCY OUTCOMES

Risk factors helps in the identification of high-risk group women, which allows the initiation of risk-specific treatment. Identification of risk factors would help in defining an appropriate population where particular interventions could study. There are several risk factors for adverse pregnancy outcomes like PLBW e.g. maternal age of <17 years, or >35 years, low socio-economic status, smoking, [5]alcohol[6],drug abuse, multiple pregnancies, genitourinary tract infections, uterine contractions, cervical length, biological and genetic markers, hypertension, metabolic and genetic disorders, inadequate prenatal care, malnutrition or poor general health of the pregnant woman. [7, 8]Women with early spontaneous PTB are more likely to have subsequent spontaneous PTB. The causative mechanism for the rate of increased PTB is uterine over-distension, resulting in contractions.

Localized infections of the genital, urinary systems, maternal medical disorders such as hypertension, diabetes, asthma, generalized infections like diarrhoea and malaria [9] can affect the gestational length.[10,11,12]The possible association between infection and adverse pregnancy outcomes suggested by subclinical infection, in which the micro-organism and their lipopolysaccharides (LPS) enter the uterine cavity during pregnancy by the ascending route from the lower genital tract or by the blood-borne route. It has been suggested that PLBW is commonly associated with bacterial vaginosis. These bacterias invade the choriodecidual space and activate or trigger the maternal immune system to produce a variety of cytokines and growth factors. Increased inflammatory burden results in placental damage and fetal growth restriction. Cytokines lead to stimulation of prostaglandin synthesis and release of matrix metalloproteinases (MMPs), results in uterine contractions and membrane rupture, leading to the induction of PLBW.

PATHOGENESIS OF PRETERM LABOUR

There are many factors that lead to the events of preterm labour and are different from those that occur with term labour so in this way they represent a pathologic than that of a physiologic process. There are three main

biologic events central to all pathophysiologic pathways that lead to the onset of parturition, whether term or preterm. These are: cervical ripening, formation and expression of myometrial oxytocin receptors and myometrial gap junction formation. Prostaglandins E2 and tumor necrosis factor (PGE2 and TNF) are believed to be important factors involved in these events. [13]The evidence of this is based upon so many experimental findings. Firstly, the increased prostaglandin (PG) levels are present in amniotic fluid, urine and maternal plasma of the mother during labour. These prostaglandins have been shown to facilitate cervical ripening and also to promote myometrial gap junction formation. The important role of prostaglandins in the process of parturition is evident from the fact that various exogenous prostaglandins administered when given to the patient by various routes are very much effective in facilitating cervical ripening and in inducing labour in gestation at any point. So finally, the administration of PG synthetase inhibitors delays the onset of parturition, arrests preterm labour and delays abortions. [14]The inciting events which culminate in the release of prostaglandins and thus the onset of labour are not yet fully understood. [15]

Although, there are a number of theories that have been proposed. The most widely held theory is that which involves premature decidual activation. Decidual activation may in part be mediated by the fetal-decidual paracrine system, it appears that in many cases, especially those involving early preterm labour, this activation occurs in the context of an occult upper genital tract infection. [16,17,18]Indeed, there are lots of evidence that has established a strong link between upper genital tract infection and spontaneous preterm delivery.

Infection of the upper genital tract results in inflammation and disruption of the choriodecidual interface, initiating a cascade of events ultimately resulting in spontaneous labour.[17]The confirmationfor these events is well supported by the biochemical changes that have been observed within the amniotic fluid, trophoblast, and decidua of pregnant women with spontaneous preterm labour. Further support for this hypothesis comes from studies of mid-trimester amniotic fluid, obtained at the time of genetic amniocentesis, which demonstrate that elevated interleukin (IL)-6 levels are often associated with subsequent spontaneous abortion, fetal death or preterm labour.[19, 20]

4. ROLE OF CYTOKINES IN PATHOGENESIS OF PRETERM LABOR

4.1 IL-1β

It is a pro-inflammatory cytokine produced by macrophages and plays an important roles in the up and down regulation of inflammation, promotes bone resorption, stimulates PGE2 release by monocytes and fibroblast and stimulates the release of matrix metalloproteinases (MMP's) that degrade the proteins of the extracellular matrix and participates in many aspects of immune response. IL-1β levels are generally elevated in gingival crevicular fluid (GCF) from diseased, inflamed periodontal tissues. [21]

4.2 IL-6

Elevated IL-6 levels most likely result from a subclinical upper genital tract infection, which is often present many weeks before the eventual onset of preterm delivery or adverse pregnancy outcome. In addition to the levels of IL-6, amniotic fluid levels of the proinflammatory cytokines IL-1 and TNFα have been associated with intrauterine infection and preterm labour. [22,21]It is an inducer of acute phase reactions and stimulates specific cellular and humoral immune responses, including end-stage B cell differentiation, immunoglobulin secretion and T cell activation. The transition between acute and chronic inflammation, IL-6 plays an important role. It is secreted by lymphocytes, monocytes and fibroblasts. Its levels have been shown to be elevated more in GCF of periodontitis patients than in gingivitis patients. IL- 6–dependent hepatic biosynthesis leads to increase in the level of C-reactive protein (CRP) in the circulation, which is involved in acute and chronic inflammation. [23.24]

4.3 TNF-α

It is a cytokine involved in inflammation and stimulates the acute phase reaction. It is produced chiefly by activated macrophages and can also be produced by fibroblast, CD4+ lymphocytes, NK cells and neurons. The primary role of TNF-α is in the regulation of immune cells. TNF-α, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, inflammation and respond to sepsis by IL-1 and IL-6 production. [25, 26]

5. ROLE OF INFLAMMATORY MEDIATORS IN PREGNANCY OUTCOME

The pro-inflammatory cytokines IL-1, IL-6 and TNF-α stimulate PGE_2 synthesis by the human placenta and chorioamnion. Prostaglandins have a role in regulating the normal physiology of pregnancy, and Gibbs et al. (1992) [27]summarized the evidence supporting the role of these inflammatory mediators in human labour:

- The administration of prostaglandins results in abortion or labour.
- Treatment with prostaglandin inhibitors delays the process of mid-trimester abortion and the onset of labour and can arrest preterm labor.
- Parturition at term is associated with elevated amniotic fluid and maternal plasma concentrations of prostaglandins.
- Arachidonic acid (prostaglandin precursor) concentration in the amniotic fluid increases during labour.
- Intra-amniotic administration of arachidonic acid results in labor.

The cytokines and lipid mediators are produced either at the infected site (i.e. periodontium) or at the placenta in response to infection. Several mediators produced

during gram-negative infection have been proposed to elicit a deleterious effect on the developing fetus, including TNF-α and PGE_2. [28]

6. PERIODONTAL DISEASES INFECTION AS A RISK FACTOR FOR PRETERM AND LOW BIRTH WEIGHT

Infection is nowa day's considered one of the major causes of PLBW, being responsible for more than 30% of all cases. [29] An association between infection of the pregnant woman and preterm delivery has been demonstrated by a number of studies. Maternal genitourinary tract infection has been linked also to an increased prevalence of PTB.[30]Bacterial infection of the chorioamnion, or extraplacental membrane, may lead to chorioamnionitis, which is strongly associated with preterm delivery.[31]However, it was demonstrated that in the case of chorioamnitis proven by histology, the placentas had in 18-49% negative bacterial cultures. The findings of further studies[32,33,34]led to the conclusion that an infection may be distant from the fetal-placental unit or the genitourinary tract, yet still present a risk for preterm birth, as a result of the indirect action of translocated bacterial products, like LPS or the action of maternally-produced inflammatory mediators. These findings directed the attention of researchers towards chronic periodontal infection, which can play a significant role as a possible risk factor for PTB.

In the early 1990's, Offenbacher and his group hypothesized that oral infections, like chronic periodontitis, could be a reservoir for inflammatory mediators, and may thus pose a potential threat to the placenta and fetus, so increasing the likelihood of PTB. [33]There is the potential risk that periodontitis causes bacteremias for different manipulations, like chewing, tooth brushing or dental treatment. In this respect, the surface area across which the bacteria or their products can invade the host tissues is very important. The incidence and magnitude of dentally induced bacteremia correlate with the severity of gingival inflammation and with the degree of traumatic dental procedures.[35]Fortunately, dental-induced bacteremia is mostly of a low-grade intensity and is of short duration, the blood becoming sterile again in less than 15-30 minutes. Nonetheless, in the case of a weaker host immune response, these repeatedly occurring bacteremias can have great influence on the systemic condition of patients. During pregnancy, there are changes in the gingival tissues, which result in the gingiva being less resistant to the bacteria and bacterial products. The early works of Loe & Silness showed that the first signs of gingival inflammation appear in the second month of pregnancy.[36]In the presence of plaque, the signs of inflammation are more severe, but in the absence of plaque and pre-existing inflammation, the gingiva may also bleed easily in women without the signs of gingival inflammation.[37]Hormonal changes during pregnancy have a special effect on the periodontium [38,39,40]as gingival capillaries dilate, and vascular permeability increases in the gingival tissues as a result of increased levels of circulating progesterone. As a consequence, bacteria and/or their products can diffuse into tissues more readily than normal. [41,42,43] which can further cause adverse pregnancy outcomes.

Periodontal disease can be associated with preterm labour via three mechanisms: (a) shared risk factors: factors that put individuals at risk for periodontal disease, may also put individuals at risk for preterm labour (examples of risk factors and indicators include: smoking, stress, age, ethnicity and gender); (b) subgingival biofilms: represent as a reservoir of bacteria with ready access to the periodontal tissues and the blood circulation; (c) periodontal sites as a reservoir of inflammation: the periodontium acting as a constant source of proinflammatory cytokines, which can reach the circulation and induce or perpetuate systemic effects.[44]

In periodontal disease the pathogenic bacteria and their virulence factors, found in the periodontal pockets, induce a local periodontal host-immune response that includes mainly the production of pro-inflammatory cytokines e.g. IL-1, PGE2, TNF-α, IL-6 and antibodies against the bacteria.[45] If this immune response and the neutrophils are not capable of keeping the infection localized (such as low maternal IgGresponse to bacteria), then the bacteria, the virulence factors and the inflammatory cytokines may gain access systemically via the circulation. Clinically, bleeding on probing and increased pocketing is seen during pregnancy. The presence of the bacteria in the circulation willtrigger the host to elicit a systemic inflammatory response, mainly by the production of more inflammatory cytokines and acute-phase reactants such CRP[38]from the liver. Eventually, bacteria, virulence factors and inflammatory cytokines may reach the placenta. This can create another site of bacterial challenge and possibly placental infection, which may lead to a new inflammatory response, localized at the fetal-placental interface, with the production of more inflammatory cytokines. As in periodontal tissues, these cytokines, although produced with the intention to combat the infection, also may cause local tissue destruction. The structural integrity of the placenta is vital for the normal exchange of nutrients between the mother and the fetus, this placental tissue damage may contribute to impaired fetal growth, which may lead to low birth weight. Also, structural damage in the placenta may disrupt the normal blood flow between the mother and the fetus, affecting the maternal blood pressure and leading to preeclampsia, which is a risk factor for PTB. The increase in the production of inflammatory cytokines such as IL-1β and PGE2 also may contribute to preterm rupture of the membranes and uterine contraction and lead to miscarriage or preterm delivery.[39] Finally, periodontal bacteria, their virulence factors and inflammatory cytokines may cross the placenta and enter the fetal circulation, and cause fetal toxicity resulting in preterm delivery and low birth weight babies (Figure: 1)

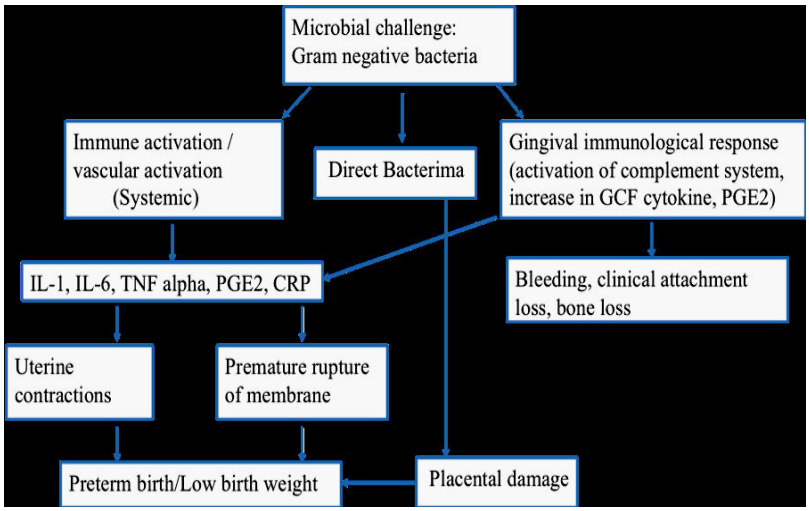

Figure: 1 Biological Plausibility: association between maternal periodontal disease andpreterm birth/low birth weight.

7. MICROBIOLOGY OF PERIODONTAL DISEASES

The microflora of the supra and subgingival plaque and the mechanism of the manifestation of periodontal disease have been investigated or analysed in detail over the past decades. Theperiodontal pathogens, predominant with adult periodontitis arePorphyromonas gingivalis, Bacteroides forsythus (now Tannerella forsythensis), Treponema denticola, Actinobacillus actinomycetemcomitans, Campylobacter rectus (C. Rectus), Eikenella corrodens(E. Corrodens), Eubacterium species(Eubacterium sp), Fusobacterium nucleatum(F. Nucleatum), Peptostreptococcus micros, Prevotella intermedia, Selenomonas sputigena, Streptococcus intermedius,[46,47]Actinobacillus actinomycetemcomitans (AA) is a Gram-negative, nonmotile rod, and has been strongly associated with localized aggressive periodontitis and its role in chronic periodontitis are viewed as significant. Actinobacillus actinomycetemcomitans has the ability to invade cultured human gingival epithelial cells and human vascular endothelial cells in vivo Porphyromonas gingivalis is a Gram-negative, anaerobic non motile rod and has been associated with periodontitis for many years. P. gingivalis has the ability to induce elevated systemic and local immune responses, and to invade human gingival epithelial cells in vitro. Bacteroides forsythus (now Tannerela forsythiensis) is also a Gram-negative, anaerobic, pleomorphic rod, and is found most commonly in subgingival plaque and in deep pockets. It also appeared that it is able to invade pocket epithelial cells, too.[48]

Subgingival flora may be modified during pregnancy and several studies have shown that the numbers of some microorganisms increase, though the role of any specific bacteria is difficult to determine. The ratio of anaerobic bacteria increased in subgingival plaque during pregnancy. These changes in the subgingival have an association with hormonal and immunologic effects of the pregnancy [49]which alsoshow the increased levels of progesterone and estrogen paralleled gingival conditions, [50]suggesting that hormonal changes play a role in the profile of specific microorganisms. Offenbacher and his group found[51] four bacteria present at a higher level in women with PTB than in normal birth controls. Bacteroides forsythus (Tannerela forsythiensis, Tf), Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Treponema denticola were detected in mature plaque more often in mothers with PTB infants than in controls.

8. CONCLUSION

The various literature which is so far published shows that a very special attention should be made to the pregnant women oral health. There is greatly prevalence and severity of oral infections, more swollen bleeding gums and also higher levels of putative periodontal pathogens in pregnant women. Women especially those who are at risk should be motivated to attain oral hygiene before pregnancy and throughout their pregnancies. The patients which remain untreated moderate to severe oral infections may have risk for adverse pregnancy outcomes. The motivation could be given through public policies and strategies that involve the dental health workers and lead maternity care workers to assist women with their oral health during pregnancy, particularly through the distribution of adequate information and encouragement of preventive measures. The services are to educate women for oral health problems and advice on balanced and healthy diets, avoidance of alcohol and smoking, advice on the importance of adequate oral hygiene. This is necessary to dispel myths and „old wives" tales such as those that suggest that tooth loss is normal during pregnancy. Pregnant women have to be properly informed about the changes they can expect in their mouth during pregnancy and what they can do to prevent problems and maintain oral health. They also should be encouraged to see a dentist before and during pregnancy, especially for routine check-ups, cleaning and other preventive measures. Sound oral health for women can also mean sound health for their children, due to

preventing periodontal disease and possible negative birth outcomes. Periodontal disease is a treatable and preventable condition. However, increasing access is not a guarantee for better health outcomes. It is necessary to understand women's, behaviour, beliefs, and attitudes about their oral health during pregnancy to best deliver health messages and services. This could start by increasing awareness about the importance of oral health for pregnant women within the whole population and to health professionals.

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Source of support: Nil **Conflict of interest:** None declared