Periodontal diseases comprise a variety of conditions affecting the health of the periodontium. These are among the most common chronic diseases of humans, affecting 5 to 30% of the adult population in the age group of 25 to 75+ years. They are also among the most important causes of pain, discomfort, and tooth loss in adults.[19]

They are a group of infectious diseases caused by predominantly Gram-negative, anaerobic and microaerophilic bacteria that colonize the subgingival area.[20] Clinically, bleeding on probing is the first predictor of presence of periodontal disease followed by development of periodontal pockets and loss of clinical attachment level. This occurs because of loss of periodontal ligament and disruption of its attachment to cementum, by migration of the epithelial attachment along the root surface. Also, resorption of alveolar bone occurs.[21]

Periodontitis can be considered a continuous pathogenic and inflammatory challenge at a systemic level, due to the large epithelium surface that could be ulcerated in the periodontal pockets. The total surface area of pocket epithelium in contact with subgingival bacteria and their products in a patient with generalized moderate periodontitis has been estimated to be approximately the size of the palm of an adult hand, with even larger areas of exposure in cases of more advanced periodontal destruction. Thus the subgingival microbiota in patients with periodontitis provides a significant and persistent gram-negative bacterial challenge to the host. These organisms and their products, such as lipopolysaccharides (LPS), have ready access to the periodontal tissues and to the circulation via the sulcular epithelium, which is frequently ulcerated and discontinuous.[22]

Even with treatment, complete eradication of these organisms is difficult, and their re-emergence is often rapid. Bacteremias are common after mechanical periodontal therapy and also occur frequently during normal daily function and oral hygiene procedures.[22] This fact allows bacteria and their products to reach other parts of the organism, creating lesions at different levels. Even some periodontopathogens, like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* can directly invade cells and tissues. This exposition to Gram-negative bacteria and their products can generate an immuno-inflammatory response with potential damages to different organs and systems.[2]

The last decade has witnessed a spectacular increase in the awareness of the association between chronic periodontitis and systemic diseases. Published studies have focused on the statistical relationship between periodontitis and systemic diseases and on pathophysiologic aspects of periodontitis having the potential to aggravate systemic disease. Knowledge about virulence factors of periodontal pathogenic bacteria and protective host immune responses has provided significant insights into the etiopathogenesis of periodontal diseases and into the potential for periodontal disease to contribute to medical pathosis.[23]

4.1 HISTORY

Throughout the history of mankind, there has been the belief that diseases which affect the mouth such as periodontal disease can have an effect on the rest of the body. Old wives' tales have also advocated keeping the mouth clean to prevent and cure a range of diseases, from painful joints to an upset stomach. Sound, healthy teeth were highly

valued by the early Hebrews. According to an Assyrian physician, ‘‘The pains in his head, arms and feet are caused by his teeth and must be removed.’’ The Greeks considered strong teeth indicative of good health.[24]

Thus the contribution of periodontitis, or the oral cavity, to systemic disease has been written about since ancient civilization. Until very recently, all information on the effect of periodontal disease on systemic health was anecdotal at best, and all the writings through the ages were for the most part mythological musings by a diverse group of dentists and physicians.[25] In 1891, Miller published a classic article entitled “The human mouth as a focus of infection.” In 1900, William Hunter wrote an article entitled “Oral sepsis as a cause of disease”. In 1911, Frank Billings, Professor of Medicine and head of the focal infection research team at Rush Medical College and Presbyterian Hospital in Chicago, replaced the term oral sepsis with ‘‘focal infection’’. He defined a focus of infection as a ‘‘circumscribed area of tissue infected with pathogenic organisms’’ and the term focal infection implied. [24]

Recent research that increasingly substantiates a role for periodontitis in affecting systemic health has brought the term “Periodontal medicine” to the forefront, and has fostered a new branch of periodontology.

4.2 PATHOGENESIS OF PERIODONTAL DISEASE

Nonspecific accumulation of bacterial plaque was once thought to be the cause of periodontal destruction, but it is now recognized that periodontitis is an infectious disease associated with a small number of predominantly gram negative microorganisms.[22]

According to Haffajee & Socransky[26], several specific subgingival oral bacteria including *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Tannerella forsythia, Campylobacter rectus, Fusobacterium nucleatum* and spirochaetes are associated with severe forms of periodontal disease. A group of pathogens, not normally found in the oral cavity, except as transients, has been associated with periodontal disease, including *Enterobacteriaceae, Pseudomonaceae, Klebsiella* spp, *Actinobacter* and others, such as *Staphylococcus aureus* and *Candida albicans*.[27] Periodontal disease is caused by bacteria in dental plaque, and evidence is increasing that specific periodontal pathogens are associated with the progressive form of the disease.

Furthermore, the importance of the host in disease initiation and progression is clearly recognized. Although pathogenic bacteria are necessary for periodontal disease, they are not in and of themselves sufficient to cause the disease. A susceptible host is also imperative. In a host who is not susceptible to disease, pathogenic bacteria may have no clinical effect. Conversely, the susceptible host experiences clinical signs of periodontitis in the presence of pathogenic bacteria.[22]

Histological studies by Seymour[28] support the concept that the immune system responds to plaque microorganisms. He found that the infiltrate in the periodontal lesion consists of lymphocytes and macrophages; whereas T lymphocytes predominate in the stable lesion, the proportion of B cells and plasma cells is increased in the progressive lesion.

Host hyper-responsiveness or reactivity is induced by periodontal infection and includes activation of neutrophils, which migrate to the area of periodontal infection, and

induction of antibodies, both of which appear to be protective. Extracellular degradation is usually thought to occur at neutral pH values. Consequently proteinases of the metallo and serine families will be optimally functional and seem to be most responsible for the initial phases of degradation.[29] This leads to connective tissue destruction and production of proinflammatory cytokines, such as IL-1, resulting in alveolar bone resorption. These cytokines can cause activation of fibroblasts, which then produce major metalloproteinases that destroy extracellular matrix. Pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, lead to activation of osteoclasts, thereby causing bone resorption. Genetic polymorphisms in the pro-inflammatory cytokines IL-1 and TNF α have been associated with adult periodontitis.[30] The oral pathogens and inflammatory mediators such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) from periodontal lesions immediately reach the blood stream inducing systemic inflammatory reactants such as acute phase proteins, and immune effectors including systemic antibodies to periodontal bacteria.[31]

Several mechanisms have been described to explain the interaction between periodontal disease and systemic diseases.[2]

- Periodontal bacteria may get introduced into the blood stream and cause infections after colonizing other sites of the organism (bacterial translocation that cause metastasic infections).
- Periodontal bacteria may also colonize the lower respiratory tract in individuals with predisposing factors, mainly through direct inhalation, without going first to the blood stream, originating pulmonary infections.

- Periodontal infection can promote an inflammatory and immune systemic response by releasing inflammatory mediators (pro-inflammatory cytokines).
- Liberation of proteins of the acute phase to a distant site, such as the liver, the pancreas, the skeleton or the arteries.
- Genetic elements as common risk factors.
- Environmental elements as common risk factors.
- Metastasic lesions due to the effects of oral microbial circulating toxins.

Thus the subgingival microbiota in patients with periodontitis provides a significant and persistent gram-negative bacterial challenge to the host.[22]

Thus the emerging science suggests periodontitis as a possible risk factor for several systemic diseases including cardiovascular disease, adverse pregnancy outcomes, diabetes mellitus, and bacterial pneumonia.[32]

4.3 PERIODONTAL DISEASE AND PREGNANCY OUTCOME

Pregnancy provides unique diagnostic and treatment challenges to the periodontal clinician. It is an opportunity to individualize care at a time when the patient may experience the most profound physiologic and psychologic changes in her life. Awareness exists regarding pregnancy and its effect on periodontal disease; however, recent evidence indicates an inverse relationship to systemic disease.[33] Adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth, low birthweight, miscarriage or early pregnancy loss, and pre-eclampsia.[32]

The proposed link between maternal periodontitis & preterm low birth weight (PLBW) infants is particularly compelling.

The World Health Organisation defines Preterm Birth as any live birth at less than 37 weeks gestation. Delivery at less than 32 weeks is termed very preterm, and delivery at less than 28 weeks extremely preterm. Birth weights are considered to be low if <2500g, very low if <1500g, and extremely low if <1000g.[34] Preterm birth (PTB) that occurs at less than 37 weeks gestation & associated low birth weight of less than 2500 grams (about 5 ½ grams) represents the major cause of neonatal morbidity and, among survivors, a major contributor to long-term disability.[35]

Low birth weight lower than that expected from the genetic potential might be caused by fetal, maternal or placental factors or a combination of risk factors, resulting in an impaired placental transport of nutrients or reduced growth potential of the fetus.[36]

The primary cause of LBW infant deliveries is preterm labour or premature rupture of membranes.[22] The etiology of preterm birth is clearly multifactorial, and a host of individual, environmental and genetic factors can affect risk. Risk factors can be considered primary if they are present before the pregnancy or secondary if they develop during the course of the pregnancy.[34]

4.4 RISK FACTORS FOR PRETERM AND LOW BIRTH WEIGHT

Maternal Age

Very young maternal age (younger than 18 years) and older maternal age (older than 36 years) are thought to affect intrauterine growth and gestational duration.[15]

In a study conducted by Sharma et al (2009) in India proportion of LBW was found to be comparatively higher among babies born to mothers who were below 20 years of age (50.0%).[14]

Race

Black women have twice the risk of preterm delivery compared to whites. The average length of gestation have been reported to be 5 days shorter in black than in white populations.[37] Further, in the US and the UK, Afro-American and Afro-Caribbean women have preterm birth rates of 15–18%, more than double than that of the white population.[38]

Demographic and psychosocial risk factors

Women with low body mass index and poor maternal weight gain in pregnancy are at increased risk. Poor education, women living alone, minimal or no pre-natal care and low socio-economic status are other factors associated with preterm labour.[35]

Low literacy level and low per capita income were found to be significant risk factors of LBW in a study done in India by Sharma et al (2009).[14]

Socio-economic factors associated with preterm labour include social class, (usually assessed by earnings and education), working conditions (professional status, ergonomic environment, working hours), physical and travelling activities, daily life activities, lifestyle, family status and psychosocial state as related to past and current pregnancy history together with current stress factors. The most stressful events were related to family illness, mortality, disruption, violence or financial distress. [39]

Domestic violence and injuries resulting from physical abuse are also associated with preterm birth.[40]

Poor maternal nutrition

Low weight and Body mass index (BMI) at conception or delivery, as well as poor weight gain during pregnancy, are associated with LBW, prematurity, and maternal delivery complications.[41]

Lack of weight gain in the second trimester specially correlates with decreased birthweight (Abrams and Selvin,1995).[42]

The growth of the fetus is affected by the nutrients and oxygen it receives from the mother. Maternal diet in pregnancy has little effect on birth weight but may program the infant. A fetus may adapt to undernutrition by modifying metabolism, this may take the form of changing rates of hormone production, slowing the growth rate.[15]

Toxic exposure

Cigarette smoking – more than 10 cigarettes per day and alcohol use – drinking more than 10 units of alcohol per day are important risk factors for pre-term low birth weight.[15]

Smoking during pregnancy has been linked to 20% to 30% of low-birthweight births and 10% of fetal and infant deaths.[8]

Maternal smoking during pregnancy is a risk factor for very preterm birth. The impact of maternal smoking on very preterm birth appears to be complex: it lowers the

risk of very preterm birth due to gestational hypertension, but increases the risk of very preterm birth due to other mechanisms. These findings might explain why maternal smoking is more closely related to preterm birth among multiparous women than among nulliparous women.[43]

Genetics

The recurrent, familial and racial nature of preterm birth has led to the suggestion that genetics may play a causal role.[44]

Maternal and foetal genotypes in the aetiology of pre-term birth.[45] A higher risk of spontaneous pre-term delivery has been associated with genetically driven excessive amniotic fluid IL-Iβ or with a disturbance of bioavailability and/or bio-response of this cytokine, which is central to the pro-inflammatory reaction to infectious stimulants.[46,47] The foetus also has a role in pre-term birth; the foetus recognizes a hostile intrauterine environment and may precipitate labour by premature activation of the foetal–placental parturition pathway (Gardosi 2005).[48]

Medical Risk Factors

Medical risk factors for LBW before pregnancy are chronic conditions like hypertension, renal insufficiency, cardio-respiratory, autoimmune, endocrine or infectious disorders. The risk factors for LBW during pregnancy are hypertensive disorders, diabetes, malnutrition, bleeding, anemia, infection, placental or fetal anomalies and multiple pregnancies.[36]

Vascular disease: Especially when complicated by superimposed preeclampsia, chronic vascular disease commonly causes growth restriction.[49]

Renal disease: Chronic renal insufficiency is often associated with underlying hypertension and vascular disease. Chronic nephropathies are commonly accompanied by restricted fetal growth.[49]

Chronic hypoxia: When exposed to chronically hypoxic environment, some foetuses have significantly reduced birthweight. Severe hypoxia from maternal cyanotic heart disease is frequently associated with severely growth restricted fetuses (Patton et al, 1990).[49]

Low birth weight in preterm infants remains a significant cause of perinatal morbidity and mortality. Compared to normal-birth-weight infants, low-birth-weight infants are more likely to die during the neonatal period, and low-birth-weight survivors face neurodevelopment disturbances, respiratory problems, and congenital anomalies. They also demonstrate more behavioral abnormalities as preschoolers and may have attention deficit hyperactivity disorder.[9]

Obstetric risk factors

Conditions that cause over-distension of the uterus predispose to preterm labour.[37] A previous history of: preterm birth, spontaneous abortion, stillbirth, cervical incompetence, extremely high parity and multiparity are risk factors for preterm delivery. Fetal distress, however caused also result in a preterm birth.[15] Multiple pregnancies carries one of the highest risk of preterm labour. About 50 % twins and nearly all higher multiple gestations deliver preterm.[37]

Primi mothers were comparatively at lower risk of delivering LBW babies as compared to multi-gravida mothers.[14] Apart from preterm premature rupture of

membranes(PPROM) and idiopathic preterm labour which are responsible for 2/3rd of the cases, the most important maternal condition associated with preterm births are pre-eclampsia and antepartum haemorrhage.[37]

Vaginal bleeding in early pregnancy is associated with increased adverse outcomes. Both light bleeding (described as spotting) and heavy bleeding (similar to menses) are associated with subsequent pregnancy loss prior to 24 weeks, preterm labour and placental abruptions.[49]

The etiologic analyses show that premature rupture of the fetal membranes and maternal-fetal problems are more frequent causes of low birth weight than preterm labour and that they cause significantly more severe neonatal morbidity.[50]

Preterm birth is often a result of assisted reproductive technology.[51,52] A number of placental abnormalities like placental abruption, extensive infarction, chorioangioma, marginal or velamentous cord insertion, circumvallate placenta or placenta previa may cause fetal growth restriction.[49]

Past obstetrics history

The previous history of preterm birth or second trimester pregnancy loss confers a very significant risk of preterm delivery. The recurrence risk from previous history of pre-term birth ranges from 17-40% depending on the number of previous preterm deliveries. Cervical length and fetal Fibronectin levels are significantly correlated with the recurrence risk of preterm birth. Cervical length was an independent risks factor with the risk inversely proportional to the length of the cervix.[37]

Previous abortion is a significant risk factor for LBW and PB, and the risk increases with the increasing number of previous abortions. Practitioners should consider previous abortion as a risk factor for LBW and PB.[53]

Constitutionally Small Mothers

Small women typically have smaller infants. If a women begins pregnancy weighing less than 100 pounds, the risk of delivering a SGA (Small-for-gestational-age) infant is increased at least twofold.[54] Brooks et al, 1995 concluded that the environment provided by the donor mother was more important than the genetic contribution to birthweight.[55]

Infections

Both generalized infections, including episodic illness such as viral respiratory infections, diarrhea and malaria, and more localized infections of the genital and urinary systems can affect the gestational period.[15] Bacterial vaginosis and intrauterine infection are now believed to be an important risk factor for preterm delivery.[56] These infections are more likely to occur in mothers in poor socioeconomic conditions.[15]

Trichomonas vaginalis also confers a modest risk of spontaneous preterm birth. Other micro organisms incriminated in the etiology of preterm labour includes *Chlamydia trachomatis*, *Mycoplasma hominis* and *Ureaplasma urealyticum*.[37]

A number of maternal bacterial infections are associated with preterm birth including pyelonephritis, asymptomatic bacteriuria, pneumonia, and appendicitis. Also periodontal disease has been shown repeatedly to be linked to preterm birth.[17]

Associations between chorioamnionitis, where sources of infection gain access to the extraplacental fetal membranes, and infection of the amniotic fluid and preterm low birth weight are now established.[15] Bacteria are recovered by transabdominal amniocentesis from as many as 20% of women in preterm labour without overt clinical infection and intact fetal membranes.[57, 58, 59] Viral products have also been recovered.[60] Hauth et al (1998) confirmed that recovery of organisms from the chorioamnion was significantly increased with spontaneous preterm birth.[61]

Periodontal disease, as a remote Gram negative infection, may have the potential to affect pregnancy outcome. It has been clearly demonstrated that intraoral manipulations, such as toothbrushing, have the potential to cause Gram-negative bacteremias and that these bacteremias occur more frequently in people with more plaque and gingival inflammation.[16]

During the second trimester of pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases with respect to aerobic bacteria.[9] Periodontal disease can affect pregnancy outcome either by the direct or indirect effect of periodontal pathogens on the developing fetus.[13]

Evidence of increased rates of amniotic fluid infection, chorioamnion infection, and chorioamnionitis supports an association between preterm birth or low birth weight and infection during pregnancy.[10] Vaginosis, caused by gram-negative, anaerobic bacteria, is a significant risk factor for prematurity and is usually associated with the smallest, most premature neonatal deliveries. The biological mechanisms involve bacterially induced activation of cell-mediated immunity leading to cytokine production

and the ensuing synthesis and release of PG, which appears to trigger preterm labor. Elevated levels of cytokines (IL-1, IL-6, and TNF-α) have been found in the amniotic fluid of patients in preterm labor with amniotic fluid infection. These cytokines are all potent inducers of both PG synthesis and labor. Intra-amnionic levels of PGE_2 and TNF-α rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery.[9]

As a remote gram-negative infection, periodontal disease may have the potential to affect pregnancy outcome. During pregnancy, the ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaque in the second trimester. The gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that can directly affect the host. One microbial component, LPS, can activate macrophages and other cells to synthesize and secrete a wide array of molecules, including the cytokines IL-1β, TNF-α, IL-6 and PGE2 and matrix metalloproteinases. If they escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of PGE2 and TNF-α in the amniotic fluid and induce premature labor.[9]

Women with preterm labor often have culture-positive amniotic fluid, even in the absence of clinical infection. Of culture-positive patients, the most commonly isolated species is *Fusobacterium nucleatum*. Although *F. nucleatum* is occasionally isolated from the vaginal flora in bacterial vaginosis, its prevalence in women with preterm labor is much greater than in vaginosis and is even less frequently isolated from the vaginal flora of women without bacterial vaginosis. Many other isolated species are those commonly found in bacterial vaginosis. Thus an ascending route of infection is supported

by the presence of these bacterial vaginosis-associated species. However, the frequency of *F. nucleatum* detection suggests other possible routes of infection. Some investigators have suggested the possibility of infection via a hematogenous route from a location in which the organism is commonly detected. *F. nucleatum* is a common oral species and is highly prevalent in patients with periodontitis. It is possible that this organism reaches the amniotic fluid by hematogenous spread from the oral cavity. This route is also suggested by the occasional isolation of *Capnocytophaga* species in the amniotic fluid of women with preterm labor, an organism rarely isolated from the vagina but common in the oral cavity. Hill found that the species and subspecies of *F. nucleatum* isolated from amniotic fluid cultures in women with preterm labour more closely matched those found in subgingival plaque than strains identified from the lower genital tract. In addition to hematogenous spread, another possible route of infection is by oral-genital contact, with transfer of oral organisms to the vagina.[22]

Periodontitis shares some risk factors with preterm births and low birth weight. Recent studies have shown an association between these conditions, however it remains unclear whether or not there is a causal relationship between them. In any case, it has been shown that inflammatory mediators produced in periodontal diseases also play an important role in labour onset, and it is plausible that biological mechanisms may link both conditions. Some maternal factors, such as a short cervix, are more closely associated with preterm births when the woman has also bacterial vaginosis. It's probable that maternal periodontitis may interact synergistically with other maternal risk factors to induce preterm births.[2]

Lipopolysaccharide is a major component of the bacterial cell wall of Gram-negative cells. There is substantial evidence that LPS is associated with pregnancy complications in animals.[16]

4.5 ANIMAL STUDIES

Lanning et al (1983) noted that pregnant hamsters challenged with *Escherichia coli* LPS had malformation of fetuses, spontaneous abortions and low fetal weight. The work by Lanning and co-workers clearly demonstrated that infections in pregnant animals could elicit many pregnancy complications including spontaneous abortion, preterm labor, low birthweight, fetal growth restriction and skeletal abnormalities.[62] It was not clear, however, if these findings from *E. coli* would be similar if endotoxin from oral anaerobes was studied. First of all, LPS from Gram-negative enteric organisms differs in structure and biological activity from oral LPS. Secondly, the oral cavity represents a distant site of infection. Although pneumonia has been a recognized example of a distant site of infection triggering maternal obstetric complications, it was important to demonstrate that distant, non-disseminating infections with oral pathogens could elicit pregnancy complications in animal models. Thirdly, oral infections are chronic in nature. Increased obstetric risk is generally associated with acute infections that occur during pregnancy. Thus, in concept, maternal adaptation to a chronic infectious challenge was assumed to afford protection to the fetus, even during acute flare-ups that may occur during pregnancy.[32]

Collins' landmark hamster studies (Collins et al 1994a, b) demonstrated that chronic exposure to oral pathogens like *P. gingivalis* in a chamber model (Genco & Arko

1994) does not, in fact, afford protection, but actually enhances the fetal–placental toxicity of exposure during pregnancy.[32]

They described the effects of two gram-negative bacterial endotoxin (lipopolysaccharide, LPS) preparations on hamster pregnancy outcome variables. Single intravenous challenges with *Escherichia coli* and *Porphyromonas gingivalis* LPS on day 8 of pregnancy produced dose-dependent effects on fetal weight malformation and fetal resorption with E. coli LPS having potent embryolethal effects. Premating maternal exposure to *P. gingivalis* produced embryolethal effects similar to those of *E. coli*. The chronic exposition to *Porphyromonas gingivalis* lead to a decrease of over 15-16% of foetal weight with an increase of PGE2 and TNF-α. These data suggested that maternal exposure to *P. gingivalis* LPS prior to and during pregnancy can induce deleterious effects on the developing fetus.[63]

They also examined the effects of various localized, non-dissemination challenges of *Porphyromonas gingivalis* on inflammatory mediator production and pregnancy outcome in the golden hamster. Live or heat-killed (HK) organisms were inoculated into a previously implanted subcutaneous tissue chamber on the 8th day of gestation to determine the effects on fetal weight, viability, and resorption. In one group of animals, HK organisms were inoculated prior to mating to determine the effects of previous exposure on day-8 gestational challenges. Chamber contents were assayed at 1 and 5 days after challenge for prostaglandin E2 (PGE2) and tumor necrosis factor alpha (TNF-alpha). There was a statistically significant association between increasing levels of both PGE2 and TNF-alpha and fetal growth retardation and embryolethality. These data suggested that infections with gram-negative periodontal pathogens can elicit adverse

pregnancy outcomes and that the levels of PGE2 and TNF-alpha produced as a result of challenge are associated with the severity of fetal effect. [18]

More recently this group has focused on a possible role for *Campylobacter rectus* in contributing to adverse pregnancy outcomes.[64] In recent animal studies utilizing the BALB/C mouse model, *Yeo et al* (2005) have reported that remote maternal *Campylobacter rectus* infection mediates fetal resorptions and fetal growth restriction in pregnant mice.[65]

More recently, Offenbacher et al 2005 found that maternal *C. rectus* infection induced placental inflammation and decidual hyperplasia as well as a concomitant increase in fetal brain IFN-γ. Maternal infection with *C. rectus* increased mouse pup mortality and also affected the hippocampal region of the neonatal brain, suggesting that maternal infection with *C. rectus* may also affect perinatal neurological growth and development.[66]

4.6 CASE-CONTROL STUDIES

In a landmark human study, Offenbacher and colleagues (1996) conducted a case–control study on 124 pregnant or postpartum women. Preterm low birthweight cases were defined as a mother whose infant had a birthweight of less than 2500 g and also had one or more of the following: gestational age <37 weeks, preterm labor or preterm premature rupture of membranes. Controls were all mothers whose infant had a normal birth weight. Assessments included a broad range of known obstetric risk factors such as tobacco usage, drug use, and alcohol consumption, level of prenatal care, parity,

genitourinary tract infections, and weight gain during pregnancy. Each subject received a full mouth periodontal examination to determine clinical attachment levels. Mothers of preterm low birth weight (PLBW) cases and first birth PLBW cases had significantly more advanced periodontal disease as measured with attachment loss than the respective mothers of normal birth weight controls. Multi-variate logistic regression models, controlling for other known risk factors and co-variates, demonstrated that periodontitis was a statistically significant risk factor for preterm low birth weight, with adjusted odds ratios of 7.9 and 7.5 for all PLBW cases and primiparous PLBW cases respectively. This research was the first to demonstrate an association between periodontal infection and adverse pregnancy outcomes in humans.[7]

Dasanayake (1998) in a 1:1 matched case control study (n = 55 pairs) evaluated the hypothesis that poor oral health of the pregnant woman is a risk factor for LBW. The effect of periodontal and dental caries status of the woman at the time of delivery on the birth weight of the infant was evaluated by using conditional logistic regression analyses, while controlling for known risk factors for LBW. Mothers of LBW infants were shorter, less educated, married to men of lower occupational class, had less healthy areas of gingiva and more areas with bleeding and calculus, and gained less weight during the pregnancy. Conditional logistic regression analyses indicated that mothers with more healthy areas of gingiva had a lower risk of giving birth to an LBW infant. Risk of LBW was higher in mothers who had no or late prenatal care (OR = 3.9). They concluded that poor periodontal health of the mother is a potential independent risk factor for LBW.[13]

Dasanayake et al (2001) followed a predominantly African American and socioeconomically homogeneous group of 448 women from the second trimester of their

first pregnancy and observed the periodontal pathogen-specific maternal serum IgG levels in relation to birth weight of the infant, while controlling for known risk factors for LBW. *Porphyromonas gingivalis* (*P.g.*)-specific maternal serum IgG levels were higher in the LBW group compared to the normal birth weight (NBW) group (p=0.004). Women with higher levels of *P.g.*-specific IgG had higher odds of giving birth to LBW infants (odds ratio [OR] = 4.1; 95%; confidence interval [CI] for odds ratio = 1.3 to 12.8). This association remained significant after controlling for smoking, age, IgG levels against other selected periodontal pathogens and race. Thus they concluded that low birth weight deliveries were associated with a higher maternal serum antibody level against P. gingivalis at mid-trimester.[67]

Konopka et al (2003) assessed the relationship between periodontal diseases and PLBW in the population of women from the Lower Silesian Region (Poland), and the evaluation of prostaglandin E2 (PGE2), interleukin-1 beta (IL-1 beta) levels in gingival cervicular (GCF) and blood serum in women with PLBW and women giving birth on time as well as secretion of these proinflammatory mediators in whole blood after bacterial lipopolysaccharide stimulation. In the studied population women over 28 years and exposed to medical risk factors had more frequent PLBW occurrence probability. In primiparous over 28 there was a 4 times greater probability of preterm labor, and in case of the severe and generalized periodontitis presence there is 3.9 times higher possibility of PLBW compared to women with healthy periodontium. In all women with PLBW there is a significantly higher PGE2 and IL-1 beta concentration in GCF, and in primiparous also PGE2 level in blood serum, compared to controls.[68]

Mokeem et al (2004) examined the prevalence and relationship between periodontal disease and preterm low birth weight (PLBW) among Saudi mothers at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. The prevalence of the PLBW was found to be 11.3%, and the prevalence of periodontal disease was high among the study population. The risk of PLBW remained high with increasing periodontal disease (odds ratio [OR] 4.21, 95% confident interval [CI] 1.99-8.93) despite controlling the other risk factors such as age, smoking, and social class. They concluded that there is a correlation between periodontal disease and PLBW in KKUH.[69]

Moliterno et al (2005) examined 150 mothers. The periodontal examination included measurements of probing pocket depth (PPD) and clinical attachment loss (CAL) in six sites from all existing teeth, except for third molars. There was significant associations found with low birth weight (LBW) babies with periodontitis (odds ratio (OR) 3.48) Periodontitis was considered a risk indicator for LBW in this sample, similar to other risk factors already recognized by obstetricians.[70]

Jarjoura et al (2005) in an observational study involving 83 preterm cases (<37 weeks gestation) and 120 term delivery controls found preterm birth to be associated with severe periodontitis, i.e. five or more sites with clinical attachment loss ≥3 mm, adjusted OR = 2.75, (95% CI 1.1–7.54).[71]

Alves et al 2006 assessed the periodontal status of purpura and determined its possible relationship with preterm low birth weight (PLBW) delivery. The sample included 59 women seen at two maternity hospitals The Periodontal Screening and Recording (PSR) was used for periodontal assessment. Nineteen mothers had premature

and low birth weight babies (gestational age below 37 weeks and birth weight below 2,500 g – group I), and 40 had mature, normal weight babies (gestational age over 37 weeks and birth weight over 2,500 g – group II). There was a higher rate of periodontal disease in group I (84.21% – 16/19) as compared with group II (37.5% – 15/40) The data also showed a significant association between periodontal disease and PLBW (OR = 8.9 – 95% CI: 2.22 - 35.65; p = 0.001). It was concluded that maternal periodontal disease was an associated factor for prematurity and low birth weight in that sample.[72]

Radnai et al (2006) undertook a case–control study to detect whether initial chronic localized periodontitis could be a risk factor for preterm birth (PB) and foetal growth restriction. A significant association was found between PB and initial chronic localized periodontitis, the criteria being bleeding at ≥50% of the examined teeth and having at least at one site at >4mm probing depth (p = 0.0001). The adjusted odds ratio for initial chronic localized periodontitis was 3.32, 95% CI: 1.64-6.69. The average weight of newborns of mothers with periodontitis was significantly less than that of the women without periodontitis (p = 0.002). The results support the hypothesis that initial chronic localized periodontitis of pregnant women could lead to PB, and birth-weight reduction.[73]

4.7 COHORT STUDIES

Jeffcoat and co-workers (2001a, b) also found a positive association between maternal periodontal disease and preterm birth in a comparable US cohort study involving 1313 pregnant subjects. Complete periodontal, medical, and behavioral assessments were made between 21 and 24 weeks gestation for each subject. Gestational

ages of the infants were determined following delivery, and logistic regression modeling was performed to assess any relationship between periodontal disease and preterm birth while making adjustments for other known risk factors. Notably, subjects with severe or generalized periodontal disease had an adjusted OR of 4.45 (95% CI: 2.16–9.18) for preterm delivery (<37 weeks) as compared with periodontally healthy subjects. The adjusted OR increased with advancing prematurity to 5.28 (95% CI: 2.05–13.60) before 35 weeks gestational age and to 7.07 (95% CI: 1.70–27.4) before 32 weeks gestational age. Hence, mothers with severe periodontal disease were four to seven times more likely to deliver a preterm infant relative to mothers with periodontal health.[17, 74]

Offenbacher and co-workers conducted a prospective cohort study, entitled Oral Conditions and Pregnancy (OCAP), which was designed to determine whether maternal periodontal disease contributes to the risk for prematurity and growth restriction in the presence of traditional obstetric risk factors. Full-mouth periodontal examinations were conducted at enrollment (prior to 26 weeks gestational age) and again within 48 hours postpartum to assess changes in periodontal status during pregnancy. Maternal periodontal disease status at antepartum, using a 3-level disease classification (health, mild, moderate-severe) as well as incident periodontal disease progression during pregnancy were used as measures of exposures for examining associations with the pregnancy outcomes of preterm birth by gestational age (GA) and birth weight (BW) adjusting for race, age, food stamp eligibility, marital status, previous preterm births, first birth, chorioamnionitis, bacterial vaginosis, and smoking. Interim data from the first 814 deliveries demonstrate that maternal periodontal disease at antepartum and incidence/progression of periodontal disease are significantly associated with a higher

prevalence rate of preterm births, BW < 2,500 g, and smaller birth weight for gestational age. For example, among periodontally healthy mothers the unadjusted prevalence of births of GA < 28 weeks was 1.1%. This was higher among mothers with mild periodontal disease (3.5%) and highest among mothers with moderate-severe periodontal disease (11.1%). The adjusted prevalence rates among GA outcomes were significantly different for mothers with mild periodontal disease (n = 566) and moderate-severe disease (n = 45) by pair-wise comparisons to the periodontally healthy reference group (n = 201) at p=0.017 and P < 0.0001, respectively. A similar pattern was seen for increased prevalence of low birth weight deliveries among mothers with antepartum periodontal disease. For example, there were no births of BW < 1000 g among periodontally healthy mothers, but the adjusted rate was 6.1% and 11.4% for mild and moderate-severe periodontal disease (P = 0.0006 and P < 0.0001), respectively. Periodontal disease incidence/progression during pregnancy was associated with significantly smaller births for gestational age adjusting for race, parity, and baby gender. In summary, the present study provided evidence that maternal periodontal disease and incident progression are significant contributors to obstetric risk for preterm delivery, low birth weight and low weight for gestational age.[75]

Lopez et al (2002) investigated whether the maintenance of the mothers' periodontal health after 28 weeks' gestation reduces the risk of PLBW. The incidence of PLBW was 2.5% in periodontally healthy women, and 8.6% in women with PD (p=0.0004, relative risk = 3.5, 95% CI: 1.7 to 7.3). Risk factors significantly associated with PLBW were previous PLBW, PD, fewer than 6 pre-natal visits, and low maternal

weight gain. PD was associated with both preterm birth and low birth weight, independent of other risk factors.[1]

Romero et al conducted a study to determine whether maternal periodontal disease (PD) could be associated with the nutritional condition of newborns. After controlling for traditional risk factors for premature childbirth and low birth weight, 69 mothers were selected: 13 were periodontally healthy and 56 had varying stages of PD. A decrease in the average newborn's weight and gestational age was observed as the mother's level of PD increased. Correlation analysis demonstrated a highly significant clinical relationship between more severe PD and lower birth weight ($r = -0.49$; $P < 0.01$); a highly significant relationship was also clinically demonstrated between increasing PD severity and decreasing gestational age of the newborn babies ($r = -0.59$; $P < 0.01$). There were significant differences in the weight and gestational age of the newborns of mothers with PD. These data suggest that PD in pregnant women could be a clinically significant risk factor for preterm deliveries and low birth weight.[76]

Marin et al undertook a study to evaluate the proposed association between periodontal disease and infant birth weight. Periodontal disease in normal Caucasian pregnant women, older than 25 years was found to be statistically associated with a reduction in the infant birth weight.[77]

The purpose of the study done by Moreu et al (2005) was to determine the influence of periodontal status on low-birth-weight pre-term delivery. 96 pregnant women were examined in their first, second and third trimester to record plaque scores, clinically assessed gingival inflammation and probing depth (mean depth and percentage

of sites with depth of > 3 mm). No statistically significant association was found between gestational age and periodontal parameters. No significant relationship was found between low-weight delivery and plaque index measurements, although the association with gingival index was close to significant. A relationship was observed between low-weight birth and probing depth measurements, especially the percentage of sites of > 3 mm depth, which was statistically significant ($p = 0.0038$) even when gestational age was controlled for. According to these results, periodontal disease was found to be a significant risk factor for low birth weight but not for pre-term delivery.[78]

A study was conducted to assess if periodontitis predicts premature gestation and to study amniotic fluid cytokines and periodontitis variables in early-stage pregnancy. Periodontal examination and collection of amniotic fluid was performed (weeks 15–20) of pregnancy in 36 women at risk for pregnancy complications. Amniotic fluid (bacteria), vaginal smears and intra-oral plaque samples were studied. Cytokine levels in amniotic fluid were studied in relation to other study variables. Periodontitis was diagnosed in 20% of normal and in 83% of preterm birth cases ($p<0.01$). Bacteria were never found in the amniotic fluids studied. Sub-gingival plaque samples including bacteria in the orange and red complexes were found in 18% of full-term 100% of preterm cases ($p<0.001$) and total colony-forming units (CFUs) were higher in preterm birth ($p<0.01$). Amniotic levels of interleukin (IL)-6 and prostaglandin-E2 (PGE2) were higher in preterm cases ($p<0.001$). Amniotic IL-6 ($r=0.56$, $p<0.01$) and PGE2 ($r=0.50$, $p<0.01$) cytokine levels were correlated with CFU from sub-gingival plaque samples ($r2=0.44$).The odds ratio of preterm delivery and having periodontitis was 20.0 (95% confidence interval (CI): 2.0–201.7, $p<0.01$). The odds of >60 CFU in sub-gingival plaque and preterm birth was

32.5:1 (95% CI: 3.0–335.1, p<01). Thus the pregnant women with findings of elevated amniotic fluid levels of PGE2, IL-6 and IL-8 in the 15–20 weeks of pregnancy and with periodontitis were found to be at high risk for premature birth. The implication of this is that periodontitis can induce a primary host response in the chorioamnion leading to preterm birth.[79]

A subsequent analysis of OCAP data further indicated that maternal periodontal disease is associated with small-for-gestational-age births (Boggess et al 2006). Defining "small-for-gestational-age" as birthweight less than the tenth percentile for gestational age, Boggess et al (2006) reported that its prevalence was significantly higher among women with moderate or severe periodontal disease, compared with those with health or mild disease (13.8% versus 3.2%). Indeed, mothers with moderate or advanced periodontal disease were 2.3 times (RR, 95% CI: 1.1–4.7) more likely to have small-for-gestational-age infants as compared to mothers with periodontal health even after adjusting for age, smoking, drugs, marital/ insurance status, and pre-eclampsia (i.e. pregnancy related hypertension with proteinuria or edema).[80]

The goal of the study done by Toygar et al (2007) was to correlate maternal periodontal disease with birth outcomes in a Turkish population and evaluate maternal periodontal health. The study consisted of 3,576 Turkish women who gave birth within 24 hours of the onset of labour. The adjusted odds ratio was generated from various logistic regression models. The mean birth weight and weeks of gestation decreased as the CPITN level increased (P<0.001 for both). They concluded that maternal periodontal disease may be a risk factor for an adverse pregnancy outcome.[81]

One hundred and twenty-four women were investigated by Santos-Pereira and colleagues between December 2003 and May 2005. Sixty-eight women had pre-term labour (PTL) and 56 had term labour A periodontal examination was carried out to identify the presence of CP CP was found to be strongly associated with PTL, PTB and low birth weight in a group of Brazilian pregnant women. These data point to the necessity of regularly investigating CP during pregnancy.[82]

The aim of this study done by Agueda et al (2008) was to determine the association between periodontitis and the incidence of preterm birth (PB), low birth weight (LBW) and preterm low birth weight (PLBW). One thousand and ninty-six women were enrolled. Periodontal data, pregnancy outcome variables and information on other factors that may influence adverse pregnancy outcomes were collected. Data were analysed using a logistic regression model. The incidence of PB and LBW was 6.6% and 6.0%, respectively. The incidence of PLBW was 3.3%. PB was related to mother's age, systemic diseases, onset of prenatal care, previous PBs, complications of pregnancy, type of delivery, the presence of untreated caries and the presence of periodontitis (odds ratio 1.77, 95% confidence interval: 1.08–2.88). LBW was related to mother's smoking habits, ethnicity, systemic diseases, previous LBW babies, complications of pregnancy and type of delivery. PLBW was related to mother's age, onset of prenatal care, systemic diseases, previous LBW babies, complications of pregnancy and type of delivery. The factors involved in many cases of adverse pregnancy outcomes have still not being identified, although systemic infections may play a role. This study found a modest association between periodontitis and PB.[83]

Pitiphat et al evaluated periodontitis in relation to preterm birth (<37 weeks' gestation) and small-for-gestational-age (SGA, birth weight below the 10th percentile of birth weight for gestational age) among a group of medically insured women. The odds ratio (OR) associated with periodontitis was 1.74 (95% CI 0.65–4.66) for preterm delivery and 2.11 (95% CI 0.76–5.86) for SGA individually. When preterm delivery and/or SGA were combined, the OR was 2.26 (95% CI 1.05–4.85) relating periodontitis with poor pregnancy outcome. Within the limitations of the study, the results suggested that periodontitis is an independent risk factor for poor pregnancy outcome among middle-class women.[84]

The aim of the study conducted by Alson et al was to compare periodontal parameters in non-smoking pregnant women in Madagascar. A cohort study with 204 pregnant women (mean age: 25.6 years) was conducted in public prenatal care health clinics in Madagascar. Socioeconomic and obstetric information was obtained. Periodontal parameters, such as periodontal probing depth and clinical attachment loss (AL), were recorded during the second semester of pregnancy. Periodontitis (at least three sites from different teeth with clinical AL ≥4 mm) was found to be significantly associated with preterm birth (PB) (P <0.001), low birth weight (LBW) (P <0.001), and preterm low birth weight (PLBW) (P <0.01). The rates of periodontitis were considerably higher in PB (78.6%), LBW (77.3%), and PLBW (77.8%) groups than in the full-term (8.6%), normal weight (16.5%), and normal birth (2.7%) groups. The strong association among periodontitis, PB, and LBW found in this study highlights the need to consider the periodontal status of pregnant women.[85]

4.8 INTERVENTIONAL STUDIES

Mitchell-Lewis et al investigated the relationship between periodontal infections and preterm births and/or low birth weight in a cohort of young, minority, pregnant and post-partum women. Periodontal treatment was provided to 74 pregnant women and the incidence of preterm and/or low birth weight was compared with the 90 women studied after the birth of their babies. Although the incidence of adverse pregnancy outcomes was higher in women without periodontal treatment, this difference was not statistically significant (the authors consider that it is could be due to the small sample size.) However, preterm and/or low birth weight mothers had significantly higher levels of *Tannerella forsythensis* and *Campylobacter rectus*.[86]

López et al. found a reduction in the rate of preterm births and/or low birth weight in women that have received periodontal treatment before the 28th gestation week when they were compared with women that have not received any treatment. This reduction was significant for healthy periodontal women compared with women with gingivitis[87] and with periodontitis.[88]

Jeffcoat et al, in a pilot study, studied 366 women with periodontitis between the 21st and 25th gestation weeks in three intervention groups: 1-dental prophylaxis plus placebo capsule; 2-scaling and root planning plus placebo capsule; and 3-scaling and root planning plus metronidazole capsule. They conclude that performing scaling and root planning in pregnant women with periodontitis may reduce preterm births in that population, but adjunctive metronidazole therapy did not improve pregnancy outcome.[89]

Michalowicz et al studied the effect of scaling and root planning before the 21st gestation week, plus monthly tooth polishing in 823 pregnant women. They did not find

significant differences between treatment and control groups in birth weight or in the rate of delivery of infants that were small for gestational age, although there were more spontaneous abortions or stillbirths in the control group.[90]

On the other hand, in a pilot study by Offenbacher et al, it was observed that periodontal treatment significantly reduced the incidence of preterm births, in spite of the small size of the sample (53 women). The authors found a surprisingly high rate of preterm births in the intervention group (27.2%) and in the control group (45.8%).[91]

The goal of the research conducted by Sadatmansouri et al was to determine the effects of periodontal treatment on PLBW incidence among women with moderate or advanced periodontitis. The clinical trial research was conducted on 30 pregnant women age ranging from 18-35 years old, with moderate or advanced periodontitis. Fifteen subjects randomly underwent the first phase of periodontal treatment including scaling, root planning and the use of 0.2% chlorhexidine mouth rinse for one week. None of these steps were taken for the controls. After necessary follow ups, the effect of periodontal treatment on birth term and birth weight were analyzed statistically. In the control group, the observed rate of PLBW was 26.7% whereas among periodontally treated group, phase I, PLBW infant was not observed ($P < 0.05$). Infants birth weight were (3059.3 ± 389.7) gms in study group and (3371 ± 394.2) gms in the control group respectively ($p<0.05$). Periodontal therapy, phase I, results in a reduction in PLBW incidence rate. Therefore, the application of such a simple method among periodontally diseased pregnant women is recommended.[92]

In the study done by Tarannum and colleagues in India the effect of non-surgical periodontal therapy on pregnancy outcome was determined. A total of 200 pregnant

women with periodontitis were randomly assigned to treatment and control groups. Detailed data about previous and current pregnancies were obtained. All women received a full-mouth periodontal examination, including oral hygiene index-simplified, bleeding index and clinical attachment level. The women in the treatment group received non-surgical periodontal therapy during the gestational period, and those in the control group received periodontal treatment after delivery. Periodontal therapy included plaque control instructions and scaling and root planing performed under local anesthesia. The outcome measures assessed were gestational age and birth weight of the infant. PTB was recorded when delivery occurred at <37 weeks of gestation, and low birth weight (LBW) was recorded when the infant weighed <2,500g. The difference in the mean gestational ages and mean birth weights in the treatment and control groups were found to be statistically significant thus concluding that non-surgical periodontal therapy can reduce the risk for preterm births in mothers who are affected by periodontitis.[93]

4.9 SYSTEMATIC REVIEWS

The first systematic review, published by Madianos et al in 2002, analyzed the association between periodontitis and an increased risk of coronary heart disease and preterm and/or low birth weight deliveries. Only one cohort study and four case-control studies met the established criteria. Of these four studies, two considered periodontitis clinical indicators, and the other two only microbiological data. Of the three studies that clinically evaluated periodontitis, two found a significant association between periodontitis and adverse pregnancy outcomes. However, the multivariate model in both studies was not adjusted adequately for the confounding variables, and both studies were

carried out in a predominantly Afro-American population, which interfered with the extrapolation of the results to others racial groups. The study with negative results inadequately measured the exposition (CPITN). The conclusion of the authors was that better designed observational and intervention studies were needed.[94]

In 2003, Scannapieco et al published a systematic review with 12 studies, three of which were intervention studies, although only one was randomized. The authors concluded that periodontal disease may be a risk factor for preterm birth and low birth weight but there was no clear evidence that periodontal disease has a causal role in adverse pregnancy outcomes. Hence additional longitudinal, and intervention studies were needed to validate this association and to determine whether it was a causal relationship.[95]

Xiong et al (2006) identified 25 studies (13 case–control, nine cohort, and three controlled trials) that focused on pre-term low birth weight, low birth weight, pre-term birth, birth weight by gestational age, miscarriage or pregnancy loss, and pre-eclampsia. Of these, 18 suggested an association between periodontal disease and increased risk of adverse pregnancy outcome and seven found no evidence of an association. The conclusion was that although there is evidence of an association between periodontal disease and increased risk of preterm birth and low birth weight, especially in economically disadvantaged populations, potential biases and the limited number of randomised controlled trials prevents a clear conclusion.[96]

Also in 2006, Vettore et al published a systematic review based on 36 studies. Twenty-six showed positive associations between periodontal disease and adverse pregnancy outcomes and 10 did not show this association. They noted clear differences

between studies concerning measurement of periodontal disease and adverse pregnancy outcomes. Moreover, they reported that most studies did not control for confounders, thus raising doubts about conclusions that can be made from them. The authors concluded that, although 26 of the 36 studies included in this review consider a positive relationship between periodontal disease and adverse pregnancy outcomes, there is no sound scientific justification to recommend screening of periodontal disease in pregnant women as a means to reduce such outcomes.[97]

4.10 META-ANALYSES

In 2005, Khader and Ta'ani, identified 40 articles but only five met the quality criteria to be included in their analysis. The authors concluded that periodontitis in pregnant women significantly increases the risk of preterm birth or low birth weight, but without convincing evidence that treatment of periodontal disease will reduce the risk of preterm birth. This meta-analysis has important limitations due to the reduced number of articles and their heterogeneity.[98]

Vergnes & Sixou (2007) pooled data from 17 observational studies totalling 7151 women, 1056 (14.8%) of whom delivered a pre-term and/or low birth weight infant. The pooled estimate for the risk of mothers with periodontal disease to have a pre-term and/or low birthweight infant was 2.83 (95% CI: 1.95–4.10, $p < 0.0001$). For the outcome ''pre-term birth'' alone, the overall OR was 2.27 (95% CI: 1.06–4.85, $p < 0.05$), and for the outcome ''low birth weight'' alone the OR was 4.03 (95% CI: 2.05– 7.93, $p < 0.0001$). It was concluded that there was a probable association between periodontal disease and

these adverse pregnancy outcomes, but it should be noted that they found significant statistical heterogeneity across studies.[99]

The meta-analysis conducted by Xiong et al included 44 studies (26 case–control studies, 13 cohort studies, and five controlled trials). Of these, 29 suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (OR: 1.10-20.0) and 15 found no evidence of an association. A meta-analysis of the five clinical trials suggested that oral prophylaxis and periodontal treatment may reduce the composite outcome of pre-term low birth weight [pooled risk ratio (RR): 0.53, 95% CI: 0.30–0.95, $p<0.05$], but did not significantly reduce the rates of pre-term birth (pooled RR: 0.79, 95% CI: 0.55–1.11, $p<0.05$) or low birth weight (pooled RR: 0.86, 95% CI: 0.58–1.29, $p<0.05$). It was concluded that periodontal disease may be associated with increased risk of adverse pregnancy outcomes, but currently, there was insufficient evidence to support the provision of periodontal treatment during pregnancy for the purpose of reducing adverse pregnancy outcomes.[100]

Fogacci et al (2011) collected data from only RCTs on the effect of periodontal therapy on preterm birth and LBW. The search resulted in 14 clinical studies. Ten articles met the inclusion criteria for preterm birth and four for LBW. Five meta-analyses on preterm birth were performed according to different criteria: 1) use of probing depth and attachment loss for periodontitis definition 2) controlling for multiparity 3) controlling for previous preterm birth, 4) controlling for genitourinary infections and 5) all the previous criteria. In all meta-analyses, the effect of periodontal treatment on preterm birth and LBW was not statistically significant. Results of this meta-analysis did not support the hypothesis that periodontal therapy reduces preterm birth and LBW indices.[101]