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Periodontal Disease and Preterm Low Birth Weight-An Overview

[1]Dr. Swetalin Das, Master of Dental Surgery, Periodontology

[2]Dr. Teenu vijayan, Master of Dental Surgery, Public Health Dentistry

[3]Dr. Khushboo Rathod, Master of Dental Surgery, Periodontology

[4]Dr. Shruti Paradkar, Master of Dental Surgery, Periodontology

Corresponding Author: Dr. Swetalin Das, Master of Dental Surgery, Periodontology

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Abstract

Every year, about 15 million infants worldwide are born preterm (before 37 weeks of gestation), and these preterm babies typically have low birth weight, (<2,500 g). Preterm birth is one of the leading cause of neonatal mortality, morbidity, and developmental loss. Advances in obstetric care have not altered the rates of preterm birth, and it is estimated that about 9.6% of worldwide births are preterm. Of the multiple risk factors for preterm birth, maternal infection is identified consistent factor. Periodontal disease is considered as a highly prevalent infectious and inflammatory disease of tooth-supporting structures and if left untreated can lead to oral disabilities. In the last two decades, many studies have examined the relationship between periodontitis and preterm birth. Periodontitis is a chronic infection by anaerobic gram-negative organisms and may produce local and systemic infection, so a possible association between periodontitis and adverse pregnancy outcomes has been suggested. Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of preterm birth and, therefore, reduce the maternal and perinatal morbidity and mortality. Hence, this article is an attempt to review the relationship between periodontal condition and altered pregnancy outcome.

Keyword: Periodontitis, Preterm low birth weight.

Introduction

The term ‘periodontal diseases’ encompasses a wide variety of chronic inflammatory conditions of the gingiva, bone and periodontal ligament supporting the teeth. Periodontal disease begins with gingivitis, the localized inflammation of the gingiva that is initiated by bacteria in the dental plaque, which is a microbial biofilm that forms on the teeth and gingiva.[1] Periodontitis is a multifactorial disease with microbial dental plaque as the initiator of periodontal disease.[2] However, the manifestation and progression of periodontitis is influenced by a wide variety of determinants and factors, including subject characteristics, systemic factors, genetic factors, tooth-level factors, microbial composition of dental plaque and other risk factors.[3] Periodontal infection is associated with organ systems like cardiovascular system, endocrine system, reproductive system, and respiratory system which makes it a complex multiphase disease.

Periodontal disease influencing systemic health is not new concept. Miller’s focal infection theory in suggest that microorganisms or their waste products reach to parts of the body adjacent to or remote from the mouth. Periodontal infection acts as a bacterial reservoir that may exacerbate systemic diseases.[4] These organisms and their

products readily get access to the periodontal structures and to the circulation via the sulcular epithelium, which is frequently ulcerated and discontinuous. As the periodontal tissues induce an immunoinflammatory response to bacteria and their products, systemic challenge with these agents also induces a vascular response. This host response may help to explain mechanisms for the interactions between periodontal infection and a variety of systemic disorders.[5] Various researches provides proof that the periodontal diseases have been associated with many systemic diseases such as cardiovascular disease, diabetes mellitus, chronic respiratory diseases, rheumatoid arthritis and adverse pregnancy outcomes.

Preterm low birth weight (PLBW) is considered as a major medical, social, and economic problem accounting for a large proportion of maternal and especially neonatal mortality, acute morbidity, and long-term sequelae. Birthweight of "<2500 g" (up to and including 2499 g) was finalized in 1976 as the definition of low-birth weight by 29th World health assembly. Preterm birth (PTB) is defined as birth before 37 weeks of gestation. -PLBW considered as significant cause of infant morbidity and mortality whereas, pre-eclampsia is the common disorder associated with PLBW.

Preterm low birth weight definitions

The following categories have been defined by the World Health Organization[6]

- Low birth weight (LBW) – Less than 2,500 g (5 lb 8 oz)
- Very low birth weight (VLBW) -- Less than 1,500g (3 lb 5oz)
- Extremely low birth weight (ELBW) – Less than 1000 g (2 lb 3 oz)
- Prematurity – Less than 37 weeks of gestation
- Very premature - Less than 32 weeks of gestation

Preterm birth is defined as babies born alive before 37 weeks of pregnancy are completed. Globally 15 million babies are born prematurely every year and account for 40% of under-five deaths. More than one in ten babies are born preterm, affecting families all around the world, and over 1 million children die each year due to complications of preterm birth.[7] India is among the top ten countries with maximum preterm births, a rate of 21% and of the 3.6 million preterm births, in India, 303,600 do not survive, in short, we have maximum deaths due to prematurity.[8]

Changes in Periodontal Status of Women during Pregnancy

An increase in the incidence of gingivitis and an exaggerated gingival response to dental biofilm among pregnant women has been reported in literature suggesting that hormonal changes can have varied manifestations in periodontal tissues. High plasma levels of estrogen and progesterone during pregnancy affects periodontal tissues through different mechanisms, such as interference in the subgingival microflora composition[9], the modulation of the maternal immune response, and the stimulation of the production of pro-inflammatory mediators.[10]

Lopatin et al. in their study observed an increase in the rate of occurrence of gingivitis during gestation with no alteration in the amount of plaque present as well as in the proportion of anaerobic and aerobic species in the subgingival flora.[11] It has been established that pregnant women have a tendency to develop clear signs of inflammation in the presence of relatively little plaque.[12]

Changes in periodontal clinical parameters, such as bleeding on probing and probing depth, and reported an increase in clinical attachment loss among pregnant women during gestation were observed by Lieff et al.[13]

In a study done by Ojanotko et al. it was seen that high concentrations of female sex hormones stimulated the production of prostaglandin E2 and may exacerbate the inflammatory response of periodontal tissues.[14]

Similarly, Raber-Durlacher et al. in their study reported a decrease in neutrophil chemotaxis, a depression of cell-mediated immunity and phagocytosis, as well as a reduced response of T-cells, associated with increased levels of ovarian hormones, especially progesterone.[15]

Lapp et al. also observed that high levels of progesterone during pregnancy alter the gingival protective response to bacterial challenge due to decreased production of IL-6.[16]

Etiopathogenesis of Preterm Births

The primary stimulus for the initiation of physiological labor arises from the fetal hypothalamopituitary-adrenal axis. This in turn stimulates steroid synthesis and prostaglandin production leading to dilation of the cervix and the onset of myometrial/uterine contractions. (figure-1)

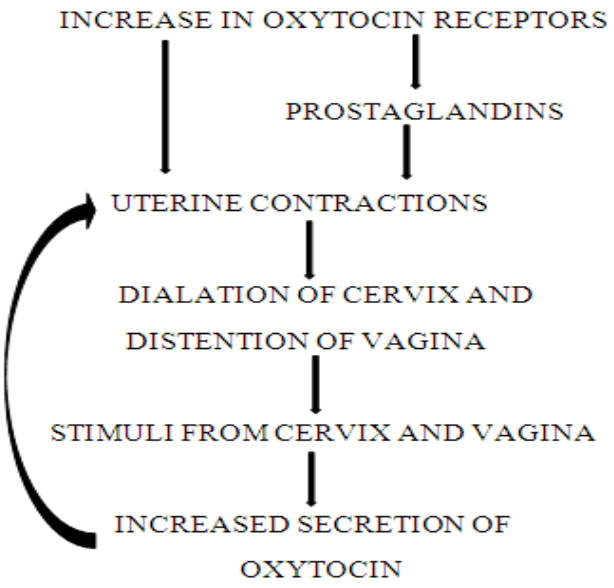

Figure1: Physiology of parturation

The involved mechanism of spontaneous preterm labor is inflammation, and similar processes are also responsible for the onset of labor at term. Several factors are implicated in preterm labor such as infection, uteroplacental ischemia, and hormonal abnormalities and comorbid conditions in mother including malnutrition, low immunity, fever, and stress.

Various epidemiological studies have shown many risk factors for preterm labour such as increasing the age of women giving birth, ethnic origin, tobacco, socioeconomic disparities, maternal body-mass index, or multiple pregnancies. Cervical incompetence or short cervical length, preeclampsia and numerous maternal infections, systemic like toxoplasmosis, and local infections such as bacterial vaginosis, chorioamnionitis, or urogenital tract infections increase the risk of preterm birth. In the year 1996 Offenbacher et al. introduced the hypothesis that periodontal diseases could be a potential risk factor for preterm birth. Since then many epidemiological or interventional studies have been performed to explore this relationship.[17]

Preterm Low Birth Weight and Periodontal Infection

Based on biological plausibility, it is believed that periodontitis can contribute to adverse pregnancy outcomes through bacteraemia, where toxins and their products derived from maternal periodontitis can reach the bloodstream and induce injury to the placenta / fetal unit. Furthermore, maternal immune response to periodontal infection activates the release of inflammatory mediators, growth factors, and other potent cytokines that can induce the occurrence of preterm birth. (figure-2)

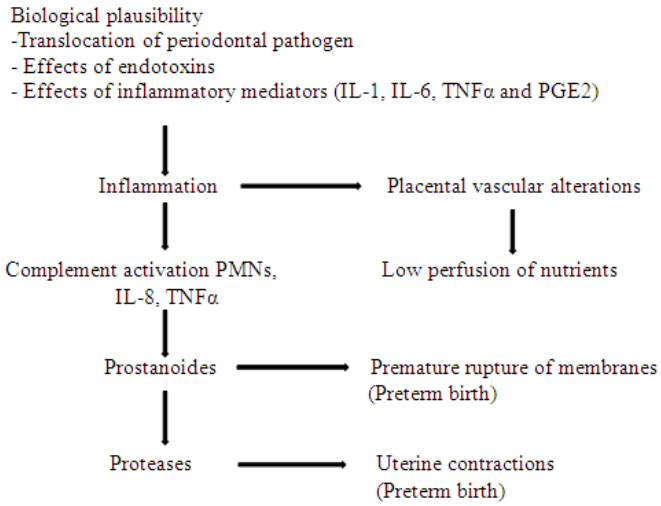

Figure 2: Biological plausibility: association between maternal periodontitis and preterm birth

Preterm low birth weight represents a major public health problem, ranking among the leading causes of infant mortality. It increases the chance of death during perinatal period and it can also results in severe debilitating disorders, such as neurological problems, lung and respiratory problems, blindness, as well as anomalies and complications due to neonatal intensive care. Preeclampsia, which affects around 10% of pregnant women remains among the most important disorders in obstetrics. It can lead to deterioration of various organs and systems, as well as maternal and fetal death.[18,19]

The Potential Mechanisms for How Periodontitis Can Affect Preterm Low Birth Weight Are –

Bacterial Spreading

Periodontal microorganisms act as pathogens that can affect not only the oral cavity but also other body areas. This is due to the following characteristics of bacteria: (1) the ability to rapidly colonize, (2) the ability to elude the host's defence mechanisms, and (3) the ability to produce substances that directly contribute to the destruction of tissue. Periodontal pathogens and their by-products may reach the placenta and enter the amniotic fluid and fetal circulation, serving to activate inflammatory signalling pathways.

Periodontitis is mainly caused by gram-negative bacteria and it may have the potential to influence on pregnancy. During the second trimester of pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases respect to aerobic bacteria. The Gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that may directly affect the host.[20]

Microorganisms associated with preterm labor, preterm delivery, and preterm premature rupture of the membranes are *Treponema pallidum*, *Neisseria gonorrhoeae*, Group B Streptococci, *Mycoplasma hominis*, *Chlamydia trachomatis*, *Gardnerella vaginalis*, *E-Coli* and *Fusobacterium sp*. Although various organisms are implicated in the causation of preterm low birth weight, *Fusobacterium nucleatum*, a common oral species, is the most frequently isolated species from amniotic fluid cultures among women with preterm labor and intact membranes.[21]

Venterpool et al. reported that *P. gingivalis* was only detected within the villous mesenchyme in the preterm cohort, but not the term group.[22] Thus, the detection of *P. gingivalis* in the placenta may be related to preterm birth.

A case of acute chorioamnionitis was also reported by Bohrer et al. caused by *F. nucleatum* that caused maternal sepsis in a term patient with intact membranes.[23]

The presence of periodontal pathogen *Treponema denticola* in the vagina, regardless of the amount, increased risk of preterm birth as shown by the study done by Cassini et al.[24]

Hematogenous Dissemination of Inflammatory Products

Clinical attachment loss is considered as one of the important periodontal measure and is associated with plasma levels of IL-1β and TNF-α in pregnant women, which may induce labor activation through placental and chorion–amnion production of PGE2.[25]

Women with preterm birth showed significant increase in GCF levels of IL-6 and PGE2 compared with those who had full-term births as reported by Perunovic et al.[26] In their systematic review Stadelmann et al. established an association between GCF inflammatory mediator levels and adverse pregnancy outcomes.[27] In a subset of patients with severe periodontitis, locally produced proinflammatory mediators—such as IL-1β, IL-6, and TNF-α—can enter systemic circulation and induce an acute-phase response in the liver that is characterized by an increased level of C-reactive protein (CRP).[28] Serum

CRP level was observed to be elevated in subjects with periodontitis. An increased CRP level can increase the risk of cardiovascular disease, cerebrovascular accidents, and preterm low birth weight infants.[29]

Clinical studies support the association between enhanced levels of circulating proinflammatory mediators and preterm birth and have implicated IL-1β and IL-6 as major players in the onset of preterm birth.[30] Moreover, polymorphisms in proinflammatory genes, including the above-mentioned cytokines, have been associated with preterm birth. In addition, elevated amniotic fluid level of IL-6 in the second trimester was associated with the initiation and timing of preterm birth.[31]

The potential link between periodontitis and preterm birth can be explained by the following mechanisms. First, periodontal pathogens and their by-products can disseminate toward the placental and fetal tissues. Immune/inflammatory reactions within the placental tissues of the pregnant woman may occur, and the release of proinflammatory mediators in the amniotic fluid may increase and further contribute to preterm birth. Second, systemic inflammatory changes induced by periodontitis may exacerbate local inflammatory responses within the fetoplacental unit to increase the risk for preterm birth. (figure-3)

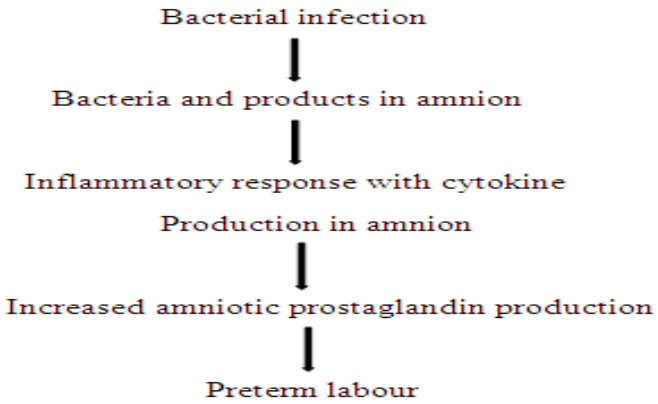

Figure-3 Effect of periodontal infection on pregnancy outcome

Role of Fetomaternal Immune Response

The immune and genetic characteristics of the fetus and pregnant women also play a role in linking periodontal diseases to preterm birth. It is clear from various studies, that the fetal and maternal antibodies directed against oral pathogens during pregnancy. Boggess et al. in their study observed that 35.2% of samples are IgM positive for at least one oral pathogen, and 26.6% are positive for more than one. The presence of IgM is associated to an increased risk of PB. The presence of fetal IgM to oral pathogens suggests that fetal exposure occurs, this fetal exposure to oral pathogens may result in a fetal inflammatory response that increases the risk of preterm birth.[32]

In the blood samples analyzed by Madianos et al. which was taken from the umbilical cord in 351 newborns, it was observed that premature babies showed levels of specific IgM against oral pathogens significantly higher than term babies. These results suggest a direct intrauterus foetal exposition to these bacteria that may be the responsible of the premature birth.[33]

Hongyo Ren and Minquan Du proposed two new therories about the role of periodontitis in preterm birth[34]-

i) Severe and/or generalized periodontitis promotes preterm birth-

Periodontal disease is considered as a chronic, multifactorial oral infection occurring in 5% to 40% of pregnant women that has been associated with adverse pregnancy outcomes such as miscarriage, preeclampsia and preterm birth.[35]

A study done by Jeffcoat et al. concluded that pregnant women with worse periodontal disease early in pregnancy had a 4-fold increased risk for preterm delivery at 37 week's gestation.[36]

Nabet et al in their case–control multi-center study of singleton live births conducted periodontal examinations

after delivery and identified generalized and localized periodontitis. Generalized periodontitis was identified in 13.4% of preterm birth women and in 10.8% of control women, and localized periodontitis was identified in 11.6 and 10.8%, respectively. A significant association was observed between generalized periodontitis and preterm birth.[37]

A case–control study by Resende et al. confirmed that only the presence of gingival recession for more than two teeth increased the risk of PTB.[38] In addition, several studies reported greater risk for PTB for mothers if periodontitis progressed during pregnancy.

According to Pattanashetti et al. study, pregnant women with preeclampsia are at greater risk for preterm delivery if periodontal disease is present during pregnancy or progress during pregnancy and rate of preterm delivery is more in preeclamptic women having moderate to severe periodontal disease.[39]

ii) Periodontitis only promotes preterm low birth weight for pregnant women who are young or HIV-infected or have preeclampsia, pre-pregnancy obesity, or susceptible genotypes-

A positive risk of PTB, LBW, and PLBW in HIV-infected pregnant women with periodontitis was reported by Pattrapornnan et al. There are positive risks of having adverse neonatal outcomes in HIV-infected women who had moderate periodontitis.[40]

Lee et al. found that pregnant women with periodontitis were 5.56 times more likely to have PTB with preeclampsia than women without periodontitis and that the association was much stronger in women with both periodontitis and obesity.[41]

Genetic is also considered as a factor involved in altered immune response against bacterial infections and also influence the effect of periodontitis in pregnancy. A significant relation between a specific polymorphism of prostaglandin E receptor 3 and both periodontitis treatment failure and spontaneous PTB was found in a study by Jeffcoat et al.[42]

Effect of Periodontal Treatment on Ptb Incidence

Periodontal treatment usually refers to non-surgical periodontal therapy that helps to improve periodontal health and is consists of plaque removal, plaque control, supragingival and subgingival scaling, root surface debridement, and the adjunctive use of chemical agents.

In their study Khairnar et al reported that the mean gestational age in the periodontal treatment group was 35.57 ± 2.40 versus 34.17 ± 2.92 weeks in the non-treated group. The treatment group showed a statistically significant reduction in mean CRP levels after delivery compared to baseline values; the control group showed no significant reduction in CRP levels. They concluded that the nonsurgical supportive periodontal therapy may lower the risk of preterm birth in women affected with periodontitis by reducing CRP level.[43]

A randomized controlled trial was conducted by Lopez et al. to determine the effect of routine plaque control and scaling on the pregnancy outcomes in women with gingivitis. They concluded that periodontal treatment significantly reduced the preterm low birth weight rate in population of women with pregnancy-associated gingivitis[44]

Bilinska et al. concluded that periodontal treatment during pregnancy is safe for both the infant and the mother, and it also provides beneficial effects for pregnancy and embryo-fetal development, leading to reduced morbidity and mortality in PTB infants.[45] Macedo et al. also found an association between a low number of daily tooth brushings and PTB.[46]

Similarly Radnai et al. observed that periodontal treatment performed before the 35th week of gestation seems to

have a beneficial effect on birth weight and gestational age.[47]

However, some research has yielded contradictory results which state periodontal therapy is not related to the outcome of pregnancy. According to these studies the periodontal therapy in pregnant women improved only the periodontal condition, but not incidences of preterm low birth weight deliveries.[48] In most of these studies, periodontal treatment was given during the second trimester of pregnancy, ultimately leading to preterm low birth weight deliveries due to a delay in diagnosis. Periodontal treatment, if provided before pregnancy, may produce more beneficial results. Furthermore, the appropriate time for providing periodontal treatment should be researched and the results applied to pregnant women to ensure a successful and safe delivery.[49]

Studies Showing Association Between Maternal Periodontitis And Preterm Birth

Animal Studies

A study was conducted on mice by Miyoshi et al. where they found high levels of contractile-associated proteins and ion channels in the myometrium of PTB model mice with chronic odontogenic *P. gingivalis* infection.[50]

Another study by Ebersole et al. using a baboon model, found a significantly greater frequency of the periodontitis group neonates had decreased gestational age and LBW. Spontaneous abortion/stillbirth/fetal demise was increased in the periodontitis group versus the control group.[51]

Offenbacher et al. observed that *Campylobacter rectus* induced infection lead to structural placental abnormalities and signs of inflammation in the brain, with a 2.8-fold increase in expression of IFN-Y in fetal brain.[52]

According to Fogacci et al. there were no statistically significant differences between groups in relation to prematurity, fetal, or birth weight. Regarding cytokines, there were no statistically significant differences in concentrations that were measured in each tissue between the groups with periodontitis and controls. Furthermore, all cytokine levels in the placenta, except interleukin-6, were diminished compared with the amniotic fluid or maternal serum, which suggested that the cytokines cannot easily be transferred via this tissue in maternal-fetal or fetomaternal direction. The fertility rate was reduced significantly in the group with periodontitis. Periodontitis that is induced in rats is not a risk factor for preterm birth or low birthweight.[53]

Intervention 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 and the effect of periodontal interventions on pregnancy outcome. Out of 164 pregnant women, periodontal treatment was provided to 74 pregnant women and remaining 90 pregnant women received no prenatal periodontal treatment. They concluded that the incidence of adverse pregnancy outcomes was higher in women without periodontal treatment, but this difference was not statistically significant. However, preterm low birth weight mothers had significantly higher levels of *Tannerella forsythensis* and *Campylobacter rectus*.[54]

In a pilot study done by Jeffcoat et al., 366 women with periodontitis were studied 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.[55]

López et al. concluded that 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 and with periodontitis.[56]

Negative results for the association between periodontal disease and PTB and LBW were also found in the intervention study conducted by Michalowicz et al. They concluded that, the distribution of gestational age at labor and mean birth weight did not differ significantly between women with and without progression of periodontitis and also treatment of periodontitis in pregnant women improves periodontal disease and is safe but does not significantly alter rates of preterm birth, low birth weight, or fetal growth restriction.[57]

Though Oliveira et al. failed to show the beneficial effects of periodontal treatment during the second trimester of pregnancy on adverse pregnancy outcomes. They concluded that there was no significant difference between the intervention group(women with periodontitis undergoing non-surgical periodontal treatment during pregnancy) and control group (124 women without periodontitis with no periodontal treatment during pregnancy).[58]

Systematic Review

Scannapieco et al. published a systematic review with 12 studies, three of which were intervention studies and one was randomized. They concluded that periodontal disease may be a risk factor for preterm birth and low birth weight but additional longitudinal, and intervention studies were needed to validate this association and to determine whether it was a causal relationship.[59]

A systematic review based on 36 studies was also published by Vettore et al. Twenty-six of the studies in this showed positive associations between periodontal disease and adverse pregnancy outcomes and 10 did not show any association. The authors concluded that, although 26 of the 36 studies showed 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 to reduce such outcomes.[60]

A meta-analysis developed by Khader and Ta'Ani indicate that periodontal diseases in the pregnant mother significantly increase the risk of subsequent preterm birth or low birth weight. They concluded that there is no convincing evidence, based on existing case control and prospective studies, that treatment of periodontal disease will reduce the risk of preterm birth. Therefore, large randomized, placebo-controlled, masked clinical trials are required.[61]

Polyzos et al. also developed a meta-analysis to examine whether treatment of periodontal disease with scaling and root planing during pregnancy is associated with a reduction in the preterm birth rate. They concluded that treatment of periodontal disease with scaling and root planing cannot be considered to be an efficient way of reducing the incidence of preterm birth. But women should be advised to have periodical dental examinations during pregnancy to test their dental status and should receive the treatment for periodontal disease. However, they should be also informed that such treatment during pregnancy is unlikely to reduce the risk of preterm birth or low birthweight infants.[62]

Meta-analysis by Chambrone et al. also concluded that periodontal treatment during pregnancy did not decrease the risk of preterm birth or low birthweight infants.[63]

Conclusion

Preterm births occur due to rupture of membranes or preterm labor. Several risk factors for adverse pregnancy outcomes have been identified and they include smoking and alcoholism, previous pre-term birth, low maternal

body mass index, high physical and psychological stress, low socio-economic status, poor maternal nutrition, genitourinary infections and periodontal infections.

Altogether, the majority of the intervention studies conducted supports the hypothesis that there is a causal relationship between periodontitis in pregnant women and adverse pregnancy outcomes, but few studies have also shown negative results. Therefore, more studies will be necessary to confirm that periodontitis in pregnant women is an independent risk factor for adverse pregnancy outcomes.

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