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Periodontal Disease: A Risk Factor in Pregnancy Outcomes

Alka Waghmare*, Alkesh Shende, Alka Patil***, Anuradha Bhatsange****, Lalitha Shiggaon******

Author's Affiliation:
*Professor & Head, **Post Graduate Student, **** Reader, Department of Periodontics, JMF's A.C.P.M. Dental College, Dhule, Maharashtra, India. ***Professor & Hrad, Department of Obstetrics & Gynaecology, JMF's A.C.P.M. Medical College, Dhule, Maharashtra, India.

Reprint Request:
Alkesh Shende, 9/704 Premsagar Housing Complex, Near Indian oil Nagar, Mankhurd Link Road, Chembur, Mumbai-400043. Maharashtra, India.
E-mail: alkesh.s07@gmail.com

Abstract

Periodontal diseases arethe most common chronic disorders with a reported prevalence varying between 10 and 60% in the population, involving gingivitis and periodontitis.Periodontitis is an inflammatory disease of a multifactorial origin with anaerobic gram-negative organisms involved in the etiopathogenesisand may result in local and systemic inflammation, so a possible association between periodontitis and adverse pregnancy outcomes has been suggested. Adverse pregnancy outcomes have been linked to periodontal disease, that include preterm birth, low birthweight, miscarriage or early pregnancy loss, and preeclampsia. Preterm birth and low birth weight are world wide leading perinatal problems having evident public health implications. Due to the fact that their incidence doesn't decrease in spite of the many attempts at their prevention,pre-eclampsia and preterm births are the major causes of maternal and perinatal morbidity and mortality. This review is to understand the relationship between periodontal diseases and pregnancy related conditions affecting the overall health of the patient and its outcome.

Keywords: Periodontal Disease; Pregnancy; Inflammation.

Introduction

Periodontal diseases are distributed worldwide and represent a major oral health concern. The role of subgingival microbial species in the etiology of periodontal diseases has been extensively documented. In the last two decades, the scientificcommunity has demonstrateda growing interest indetermining whether periodontaldisease is associatedwith pregnancy complications. Inpart, this concern derives from thefact that despite the advances inprenatal care and increased publicawareness, adverse pregnancy outcomesstill present a major publichealth problem worldwide [1].

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

Periodontitis can be considered as 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 [2].

Periodontal Disease and Its Impact on Pregnancy

Periodontal infection is one of many infections that have been associated with adverse pregnancy outcomes. The hypothesis that periodontal conditions influence the outcome of a pregnancy is not a new idea. In 1931, Galloway identified that the focal infection found in teeth, tonsils, sinuses, and kidneys pose a risk to the developing fetus. Galloway summarized that removal of a known focal infection, which had clearly demonstrated to be a source of danger to any pregnant woman, was more beneficial than allowing the infection to harbour throughout the pregnancy. He went on to suggest that all foci of infection should be removed early in pregnancy [3].

It is widely recognized that good oral health maintains the structures within the oral cavity. However, it is not universally accepted that oral health may be an independent contributor to abnormal pregnancy outcomes. Many studies have been conducted and the literature is controversial on the role periodontitis has and its influence on adverse pregnancy outcomes [4].

Recognition and understanding of the importance of oral health for systemic health has led to significant research into the role of maternal oral health and pregnancy outcomes. During pregnancy, changes in hormone levels promote an inflammatory response that increases the risk of developing gingivitis and periodontitis. As a result of varying hormone levels without any changes in the plaque levels, 50%-70% of all women develop gingivitis during their pregnancy, commonly referred to as pregnancy gingivitis. This type of gingivitis is typically seen between the second and eighth month of pregnancy [5]. Increased levels of the hormones progesterone and estrogen can have an effect on the small blood vessels of the gingiva, making it more permeable [6,7].

This increases the mother's susceptibility to oral infections, allowing pathogenic bacteria to proliferate and contribute to inflammation in the gingiva. This hyperinflammatorystate increases the sensitivity of the gingiva to the pathogenic bacteria found in dental biofilm. Females often see these changes during other periods of their life, when hormones are fluctuating, such as puberty, menstruation, pregnancy, and again at menopause [6,7].

Recent research suggests that the presence of maternal periodontitis has been associated with adverse pregnancy outcomes, such as preterm birth,preeclampsia,gestational diabetes, delivery of a small-for-gestational-age infant,and fetal loss [8]. The strength of these associations ranges from a 2-fold to 7-fold increase in risk. The increased risks suggest that periodontitis may be an independent risk factor for adverse pregnancy outcomes.

In 1996, Offenbacherreported a potential association between maternal periodontal infection and delivery of a preterm or low-birthweight infant.The study was done over 124 pregnant women, and observations suggested that women who delivered at less than 37 weeks gestation or an infant weighed less than 2500g had significantly worse periodontal infection than control women [9].

In another case-control study conducted by Dasanayake, women who delivered a full-term infant weighing less than 2500g were matched to women who delivered full term infants weighing more than 2500g. All women received a periodontal evaluation after delivery, and poor periodontal health was determined to be an independent risk factor for delivering a low-birth-weight infant [10].

Periodontal Disease as Focal of Infection: (Inflammatory Response)

The ability of periodontal pathogens and their virulence factors to disseminate and induce both local and systemic inflammatory responses in the host has led to the hypothesis that periodontal disease may have consequences beyond the periodontal tissues themselves. Interestingly, this concept was reported by Miller in 1891, when he published the theory of "focal infection." On the basis of this theory, oral foci of infection were considered responsible for a number of regional and systemic diseases, such as tonsillitis, pneumonia, endocarditis and septicemia.[11] However, the lack of scientific evidence condemned this theory to dormancy.It was 100 years later, in the early 1990s, that Collins and colleagues [12,13] hypothesized that oral infection, such as periodontitis, could act as a source of bacteria and inflammatory mediators that could disseminate systemically to the fetal-placental unit, via the blood circulation, and induce pregnancy complications.

Periodontal diseases are a group of conditions that cause inflammation and destruction to the supporting structures of the teeth. These chronic oral infections are characterized by the presence of a biofilm matrix that adheres to the periodontal structures and serves as a reservoir for bacteria. Dental plaque biofilm is a complex structure of bacteria that is marked by the excretion of a protective and adhesive matrix [14].

Increased levels of the hormones progesterone and estrogen can have an effect on the small blood vessels of the gingiva, making it more permeable. This increases the mother's susceptibility to oral infections, allowing pathogenic bacteria to proliferate and contribute to inflammation in the gingiva. This hyperinflammatory state increases the sensitivity of

the gingiva to the pathogenic bacteria found in dental biofilm. Females often see these changes during other periods of their life, when hormones are fluctuating, such as puberty, menstruation, pregnancy, and again at menopause [14].

Systemic inflammation and its chemical mediators play a major role in the pathogenesis of preterm delivery,including pre-eclampsia, intrauterine growth restriction, and preterm delivery. Chronic infectionslike intrauterine infection and chorioamnionitis are linked to both preterm birth and elevated CRPlevels. Furthermore, periodontal disease has been associated with increased risk of preterm low birthweight, low birth weight, and preterm birth. Therefore, chemical mediators, principally CRP,might be a plausible mediator of the association between periodontitis and adverse pregnancy outcomes [15].

It appears that periodontal disease triggers increased levels of biological fluids that induce labour. It has been reported that periodontal infections cause a faster-than-normal increase in the levels of prostaglandin and tumor necrosis factor molecules that induce labour [15].

The Impact of Inflammation on FetalDevelopment

On the basis of the current evidence from both animal and human studies, a hypothetical model of the association between maternal periodontal inflammation and fetal development may be proposed. Periodontal bacteria and their virulence factors, found in the periodontal pockets, induce a local periodontal host-immune response, that includes mainly the production of inflammatory cytokines (IL-1, PGE2, TNF-α) and antibodies against the bacteria. If this immune response and the neutrophils are not capable of keeping the infection localized (such as low maternal IgG response to bacteria), then the bacteria and/or their virulence factors and the inflammatory cytokines may gain access systemically via the blood circulation. This would be particularly evident clinically by signs of bleeding on probing and increased pocketing during pregnancy. The presence of the bacteria in the blood circulation will trigger the host to elicit a second round of inflammatory response, systemic this time, mainly by the production of more inflammatory cytokines and acute-phase reactants such as C-reactive protein from the liver.

Eventually, bacteria and/or their virulence factors and inflammatory cytokines appear to reach the placenta, as about 40 percent of all pregnancies are associated with some fetal IgM antibody response to organisms of maternal oral origin. This will create another site of bacterial challenge and possibly placental infection, leading to a new inflammatory response, localized at the fetal-placental interface this time, with the production of more inflammatory cytokines [1].

As in periodontal tissues, these cytokines, although produced with the intention to combat the infection, also may cause tissue destruction. Because 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.

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 leading to miscarriage or preterm delivery. Finally, periodontal bacteria and/or their virulence factors and inflammatory cytokines may cross the placenta and enter thefetal circulation. Therefore, they may trigger a new fetal-host immune response, as evidenced by the observed elevated levels of fetal IgM to periodontal pathogens. If the fetus cannot control the infection, the bacteria and/or their virulence factors may gain access to various tissues and initiate local inflammatory responses and, consequently, structural damage to the fetal tissues and organ systems. Depending on the extent of this damage, the newborn may or may not survive the perinatal period. However, survivors may possess deficiencies that may compromise theirquality of life, even throughout adulthood [1].

Role of Periodontal Microbes in Pregnancy

The current body of knowledge indicates that specific microorganisms or groups of species, including Actinobacillusactinomycetemcomitans, Porphyromonasgingivalis,Tannerellaforsythensis, and Treponema denticolaoccur more frequently and/or in higher levels andproportions in periodontitis sites and subjects, whereas others, such as members of the Actinomyces genus, areprimarily associated with periodontal health [16]. The bacteria known as Fusobacterium nucleatum,has been linked with adverse pregnancy outcomes. Since F.nucleatumis associated with periodontal infectionsrather than genital or uterine infections. It is supposed that the infection doesn't enter the womb by an ascendant route coming up through the genital tract; rather it enters the mother's bloodstream making its way down

from the oral cavity [17,18].

When periodontal disease is present, the number of bacteria significantly increases by as much as 10,000 times the original population. The immune system relaxes slightly during pregnancy so as not to harm the fetus. More bacteria grow when the immune system is not working full throttle. Bleeding gums let bacteria enter the blood stream, travel through the mother's body, and enter the placenta [15].

The potential role of maternal infection with specific organisms within 2 bacterial complexes most often associated with periodontitis, conventionally termed "Orange" (Campylobacter rectus, Fusobacterium nucleatum,Peptostreptococcus micros, Prevotellanigrescensand Prevotella intermedia) and "Red" (Porphyromonasgingivalis, Bacteroidesforsythus, and Treponema denticola) complexes respectively, to prematurity was investigated by relating the presence of oral infection, maternal IgG, and fetal cord IgM, comparing full-term to preterm. There was a 2.9-fold higher prevalence of IgM seropositivity for one or more organisms of the Orange or Red complex among preterm babies, as compared to term babies. Specifically, the prevalence of positive fetal IgM to C. rectus was significantly higher for preterm as compared to full-term neonates. A lack of maternal IgG antibody to organisms of the Red complex was associated with an increased rate of prematurity; consistent with the concept that maternal antibody protects the fetus from exposure and resultant prematurity.

The highest rate of prematurity was observed among those mothers without a protective red complex IgG response coupled with afetal IgM response to orange complex microbes. These data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that translocate to the fetus resulting in prematurity. The high prevalence of elevated fetal IgM to C.rectus among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent eliciting prematurity [19].

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. Adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth, low birthweight, miscarriage or early pregnancy loss, and pre-eclampsia [10,20,21].

The placenta is a very good line of defense to protect a human fetus from the elements. But it is known for some time that it isn't an impenetrable barrier. Tobacco and alcohol, for example, can travel through the mother's system and into the baby's system causing illnesses and birth defects in many cases. For a long time, we have known that risk factors such as smoking, alcohol use and drug use may contribute to produce an alteration, disruption or teratogenic consequence. New research suggests a new risk factor – periodontal disease being related to many of the pregnancy related outcomes.

Pre-Eclampsia

Preeclampsia is a rapidly progressive condition observed during pregnancy, characterized by hypertension and the presence of protein in the urine. At least 3% to 5% of pregnancies are affected, resulting in high morbidity and mortality around the world. Altered vascular-related conditions have been proposed as the main pathogenic mechanisms leading to placental endothelial damage [22,23,24].

Preeclampsia is also associated with short and long-term abnormal cytokine responses in the mother and the fetus, related to high circulating levels of tumor necrosis factor (TNF)-α, interleukin (IL)-10, and IL-6 [25]. Thus, the result is an inflammatory vascular damage that induces preeclampsia and other pregnancy complications such as low birth weight (LBW) or preterm births. Understanding the initiating etiologic factors may serve to properly design preventive and therapeutic strategies.

Recently, Herrera et al. [26] established that the early identification of risk factors, the administration of nutritional supplements, and the treatment of asymptomatic infections lowered the preceding incidences of preeclampsia in 15,354 pregnant women from low socioeconomic status in Colombia, where preeclampsia is a prevalent disease (8%). These authors hypothesized that chronic subclinical infections may cause increased maternal cytokine levels sufficient to affect vascular endothelial function, thereby making pregnant women prime individuals for the subsequent development of preeclampsia.

Preterm Low Birth Weight Infants

The World Health Organisation (WHO) 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. Preterm birth that occurs at less than 37 weeks gestation & associated low birth weight of less than 2500g represents the major cause of neonatal morbidity and, among survivors, a major contributor to long-term disability [27].

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.The primary cause of LBW infant deliveries is preterm labour or premature rupture of membranes. 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.

Preterm infants are immature and small factors that contribute to the increased risk of neonatal mortalityand morbidity. Low birth weight (LBW); a weight less than 5 pounds 8 ounces (2.5 kilograms) may be used as a surrogate for preterm birth in developing nations, where adequate ultrasound technology for dating of gestation is not readily available. Infants also may be born small for gestational age (SGA), a condition usually defined as birth weight of less than the 10th percentile of normal weight for gestational age. Thus, even full-term infants may be SGA, reflecting poor intrauterine growth and development [1].

Interestingly, because periodontal disease is characterized by periods of exacerbation and remission, one recent cohort study evaluated, whether the presence of active disease poses a greater risk to pregnancy. The investigators in this study concluded that women with progressing periodontal disease during pregnancy indeed are more likely to have more preterm deliveries compared with women whose disease does not progress [28].

Discussion

The majority of the studies, especially those carried out ineconomically disadvantaged populations, suggest that periodontal disease is associated with increased risk of variousadverse pregnancy outcomes such as preterm birth and low birthweight. There is a large body of evidence pointing to infection as a key factor in adverse pregnancy outcomes [29-33]. Oral mechanical manipulation (e.g. tooth brushing, dental procedures, and even routine mastication) can cause bacteremia [34]. Chronic periodontal infections can produce local and systemic host responses leading to transientbacteremia. Lipopolysaccharide (LPS) endotoxins and other bacterial substances can gain access to gingival tissue, initiate and perpetuate local inflammatory reactions, and consequently produce high levels of proinflammatory cytokines. Such activations of maternal inflammatory cell responses and cytokine cascades play important roles in the pathophysiological processes of preterm labour, low birthweight, and preeclampsia [31,33]. In addition, LPS, bacteria from subgingival plaque, and proinflammatory cytokines from inflamed periodontal tissue can enter the bloodstream, reach the maternal-fetal interface, trigger or worsen maternal inflammatory response, and increase plasma levels of prostaglandin andcytokines [35]. Thus, it appears that periodontal disease may play a nonspecific role in various adverse pregnancy outcomes.

Conclusion

There is evidence of an association between periodontal disease and increased risk of preterm birth and low birthweight, especially in economically disadvantaged populations, but potential biases (especially in terms of inconsistent definitions of periodontal disease) and the limited number of randomised controlled trial studies prevent us from offering a clearconclusion. Several randomised controlled trials are under way to test the hypothesis that periodontal treatment can reduce rates of certain adverse pregnancy outcomes. More studies are also needed to examine potential associations between periodontal disease and increased risk of pre-eclampsia, gestational diabetes, early pregnancy loss, and intrauterine growth restriction.

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