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Review Article

Periodontal & Oral-Systemic Relationships: Reproductive Health

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Abstract

The mouth is a part of the human body and thus it follows that when the mouth is not healthy, the body is not healthy. Periodontal disease is a common, chronic inflammatory disease affecting the supporting structures of the teeth. It has been proposed that periodontal disease is a risk factor for systemic diseases and conditions such as fertility issues, pregnancy complications: fetal mortality, preterm, low-birth weight deliveries, preeclampsia and male reproductive issues such as prostatitis and erectile dysfunction.

Keywords: Periodontitis; Systemic Disease; Reproduction; Female; Male

Introduction

The human body is a complex structure composed of many parts and biological processes whose interactions affect one another. The mouth is a part of the human body and is "the window to your body's health" [1]. It follows then that oral health is inextricably linked to general systemic health. Health is defined not only as the absence of disease or infirmity but a state of complete physical, mental and social well-being [2]. When the mouth is not healthy, the body is not healthy. In 1900, William Hunter, MD, first introduced the concept of oral sepsis to the medical literature in a paper entitled, "Oral Sepsis as a Cause of Disease" [3]. Dr. Hunter wrote of the association of oral infection and systemic disease.

It is through a thorough examination of the oral cavity that one can not only detect oral diseases, lesions and abnormalities but also detect systemic diseases and disorders, nutritional deficiencies, disorders of the immune system and cancers [4]. In 1996, Offenbacher coined the term "Periodontal Medicine" [5]. This is a branch of Period ontology that focuses on the strong relationships between periodontal health or disease and systemic health or disease. Furthermore, Miller, another periodontist, initiated the American Academy of Oral Medicine in 1945 and later the American Board of Oral Medicine in 1956 [6].

Periodontal disease is perhaps the most common chronic infections of humankind [7]. It is an infection caused by dental plaque or plaque biofilm. Dental plaque or the plaque biofilm is the well-organized, heterogeneous structure composed of microbial pathogens which is the primary etiologic agent for periodontal diseases. It is estimated the prevalence of periodontal disease in adults in the United States (age 20-64) is 8.5% and is 17.20% in seniors over the age of 65 [8].

There are two main forms of periodontal disease: gingivitis and periodontitis. Both are pathologic periodontal inflammatory processes that are the result of an accumulation of dental plaque. The most common is the plaque-induced gingival disease called gingivitis, which is a reversible form of periodontal disease [9]. The second most common form of periodontal disease is periodontitis. Periodontitis is a destructive, irreversible, chronic inflammatory process due to dental plaque, which results in atrophy or loss of the underlying bone and connective tissue support around the teeth [9].

It is believed that there are over 500 species of microbial species that are the primary etiologic agents for periodontal disease [10]. Despite the potential for many pathogen to be associated with periodontal disease, there is a small number most frequently associated with active periodontal disease. Socransky et al. divided the pathogens into two main clusters of microorganisms and deemed them the "red" and "orange" complexes [11]. The red complex include the following gram negative, anaerobic pathagens: *Porphrymonas gingivalis, Tanneralla denticola, Tanneralla forsythia*. The orange complex pathogens include: *Fusobacterium nucleatum, Prevotella intermedia, Prevotella nigrescens, Peptostreptococcus micros, Campylobacter rectus, Centruroides gracilis, Campylobacter showae, Eubacterium nodatum,* and *Streptococcus constellatus. Other microbial pathogens highly associated with periodontal disease are Aggregatibacter actinomycetemcomitans and Eikenella corrodens.*

In disease, the putative periodontal pathogens reside in and colonize the gum tissue collar that surrounds the tooth; forming a niche called the periodontal pocket. Periodontal plaque biofilm's access to the gingival circulation through ulceration of the periodontal gum pocket is a pathway for spread of the biofilm into the systemic circulation. The activation of an inflammatory response, due to the plaque biofilm, results in the production of inflammatory cytokines and mediators, such as Interleukin-1 (IL-1β), IL-6, and Tumor Necrosis Factor-alpha (TNF-α) [12].

These mediators, whose effects are also systemic in nature,

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are all means by which periodontal disease may affect a person's susceptibility to systemic diseases and conditions.

Periodontal disease is thought to be a risk factor associated with several systemic diseases and conditions such as fertility issues; pregnancy complications: fetal mortality, preterm and low-birth weight deliveries and preeclampsia and male reproductive issues such as prostatitis, erectile dysfunction.

Reproductive Health

Numerous studies have assessed a potential association between a woman's periodontal status and pregnancy complications such as fetal morality, preterm and low-birth weight babies and the development of preeclampsia, as well as infertility issues. There are also studies that have looked at the impact of periodontal infection on male's reproductive health, such as prostatitis and erectile dysfunction.

Female reproductive health

Pregnancy complications and adverse outcomes: A developing embryo and fetus have little to no immune system to stave off infection. They depend on the immune system of the mother. There are some pathogens that can cross the placenta from the mother and enter the embryo and fetus causing a perinatal infection. These infections can potential result in adverse outcomes. Examples of such outcomes would be fetal mortality, preterm and low-birth weight babies. Infection is considered to be a major factor associated with preterm and low-birth weight deliveries. It is thought to contribute to 30-50% of all preterm and low-birth weight babies [13].

Fetal mortality

Fetal mortality is defined as spontaneous intrauterine death at any time during the pregnancy [14]. When it occurs early on in the pregnancy, it is referred to as miscarriage. When it happens at 20 weeks of gestation or later, it is referred to as stillbirth [14]. Approximately 1 million fetal deaths occur at any gestational age in the United States each year [14].

Pregnancy imposes multiple changes on a woman's body. One such change is a change in her gingival condition. The increases in hormonal levels associated with pregnancy increase her risk for developing pregnancy gingivitis or inflammation of the gingival gum tissues secondary to pregnancy. Hormonal changes may affect the oral microbial population during pregnancy. It is common to see an increase in the following periodontal pathogens during pregnancy: *Porphyromonas gingivalis, Prevotella intermedia and Campylobacter rectus* [15-17]. A common complaint is bleeding gums during pregnancy, even in women who normally have healthy gum tissues. Pregnancy gingivitis affects 30-75% of the pregnant population [18]. This is a transient condition that usually resolves after delivery. In patients with periodontitis prior to pregnancy, it is speculated that pregnancy may increase the risk for further periodontal destruction [15].

The gingival inflammation associated with pregnancy provides a portal of entry for oral bacteria associated with gingivitis and periodontal disease to enter the blood stream causing a bacteremia. Once in the bloodstream, the periodontal microbial pathogens can cross the placental barrier and a perinatal infection can occur in the fetus and embryo. Such infections can contribute to adverse pregnancy outcomes. *Fusobacterium nucleatum*, a periodontal pathogen, was reported as the causative agent in the stillbirth of a baby that was already full term (39 weeks) [19]. The mother reported having bleeding gums during her pregnancy and developed an upper respiratory infection at the end of her pregnancy. It is theorized that the upper respiratory infection weakened her immune system, allowing the oral bacteria associated with her periodontal gingival disease to flourish and cause a bacteremia that ultimately infected her unborn child [19].

Preterm and low birth weight babies

Preterm (premature) births affect nearly 500,000 babies, approximately 1 in 8 or 11.6% infants born in the U.S. [20,21]. These are births of an infant prior to the 37th weeks of pregnancy [20]. Preterm labor is made between the 20th and 36th week of gestation [22]. Preterm birth is a major cause of infant mortality and morbidity. In 2009, preterm-related causes of deaths accounted for 35% of all infant deaths [20]. Preterm births are the leading cause of long-term neurological disabilities in children and cost the U.S. health care system more than $ 26 billion in 2005. Children born prematurely are at an increased risk for developing breathing and feeding problems, cerebral palsy, developmental delays and vision and hearing problems [20]. These children often require ongoing medical care, early intervention services and special education services [23].

A low birth weight is a child born less than 5.5 pounds [24]. A low birth weight baby may be born too small or too early (premature birth) or both [24]. Low birth weight is a major risk factor for neonatal and infant morbidity as well as mortality. These children may be at an increased risk for developing delayed motor and social skills, as well as developing learning disabilities [24]. Approximately 315,700 or 8.0% infants born in the United States are low birth weight [21].

Studies have shown that the risk factors for preterm low birth deliveries are similar to those who have periodontitis; such as smoking, low socio-economic status, lower levels of education and ethnicity [15]. Researchers have found that women that delivered prematurely had poorer oral health and worse periodontal disease compared to those without periodontal disease [25]. Offenbacher et al. found that mothers of preterm and low-birth weight babies had significantly worse periodontal disease than mothers of normal weight babies [26]. Studies have shown that mothers of preterm babies also had higher levels of PGE_2 and higher levels of periodontal microbial pathogens, such as *Campylobacter rectus, Fusobacterium nucleatum* and *Porphrymonas gingivalis* in the amniotic fluid than those without periodontal disease [25,27,28]. Researchers cannot rule out however; the possibility that a source of fusobacteria, in particular, could be acquired through cunnilingus from a new partner which may also contribute to its presence in amniotic fluid [29].

It is believed that poor oral health and periodontal disease may contribute to preterm and low-birth weight deliveries in the following manner. The oral infection, periodontal disease, activates a systemic cell-mediated inflammatory response that results in the production of pro-inflammatory cytokines such as IL-1 and TNF-α which triggers the synthesis and release of PGE_2. PGE_2 not only stimulates bone resorption, associated with periodontal disease, it also has an effect on labor by softening the cervix, relaxing smooth muscles and causing contractions [30].

Bacterial Vaginosis (BV) is a pelvic infection of the vagina caused when there is a shift in the normal balance of bacteria in the vagina which is predominated by facultative *lactobacilli* [31]. Microbial pathogens associated with bacterial vaginosis include *Gardnerella vaginalis*; anaerobic species primarily among *Prevotella*, *Porphyromonas*, *Bacteroides*, *Peptostrepococcus*, and *Mobiluncus*; *Mycoplasma hominis*; and *Ureaplasma urealyticum* become predominant in vaginal secretions [29]. The microbial pathogens associated with bacterial vaginosis are associated with a significant increase in the risk for preterm labor, preterm premature rupture of membranes, preterm birth cases and other perinatal infections and complications [29] Studies have found that there is a small but significant association between periodontal disease and bacterial vaginosis and a possible trend between receptive oral sex and periodontal disease [32]. Risk factors for bacterial vaginosis include douching and having new and/or multiple sex partners [31].

There is conflicting data regarding the effectiveness of periodontal therapy reducing the incidence of preterm delivery. Periodontal treatment may improve periodontal health and/or pregnancy outcome but it may not [15,33-35]. In 2009, however, Offenbacher et al. reported that periodontal therapy did not reduce the incidence of preterm delivery [35]. In their study, they evaluated 1,760 patients in a randomized treatment masked study carried out at four separate cites. The results were that 13.1% of the patients treated for periodontal disease experienced preterm births, and that 11.5% of the control group experienced preterm births. There was no statistical significance between the treatment group and the control group. Therefore, they demonstrated within a randomized controlled study with a sufficient statistical population that there doesn't appear to be a cause and effect relationship between active periodontal disease and preterm birth rates. The results of the 2009 Offenbacher study tend to demonstrate that correlation, odds ratio, and association data, do not necessarily demonstrate cause and effect which would demonstrate positive clinical therapeutic strategies. It has been suggested that periodontal therapy does reduce periodontal inflammation and improves periodontal status. This is beneficial in any population that is susceptible to periodontal disease, including a pregnant woman. Preventive treatment, especially before pregnancy, is the best way to reduce the risk of periodontal disease, particularly for those at risk for preterm delivery or any pregnancy complication.

Preeclampsia

Preeclampsia as defined by the American Congress of Obstetricians and Gynecologists as blood pressure > 140/90 mmHg and > or = 1 + proteinuria on a catheterized urine specimen [36,37]. Preeclampsia may be a risk factor for preterm labor and typically occurs after the 20th week of gestation. Preeclampsia is a significant cause of maternal and perinatal illness affecting approximately 5-10% of all pregnancies [38]. It has been demonstrated that a relationship exists between periodontal disease and preterm delivery as induced by preeclampsia where periodontal disease increases the risk for the development of preeclampsia and thus preterm delivery [22,38,39].

Intervention, to achieve optimal oral health, is crucial in reducing the risk for the developing pregnancy complications such as preterm, low birth weight deliveries and preeclampsia. Studies have suggested the time of this intervention is most important. Rendering dental treatment once the mother has periodontal disease and is pregnant may be too late to reduce the effects of the local and systemic inflammatory responses triggered by the infection [40,41]. Perhaps it is not only better to treat the periodontal infection before the woman becomes pregnant but to strive for oral and periodontal health preventing the initiation of the disease process from even occurring.

Fertility Issues

Researchers have also begun to look at the possibility that periodontal disease may also influence the "time taken to conceive" [42]. It has been suggested in a non-Caucasian population, periodontal disease has been associated with an increased time to conceive [42]. They have suggested two theories. One being perhaps this might be due to the low-grade systemic inflammation associated with periodontal disease that may have an effect on the endometrium, disrupting implantation; the other possibility is that periodontal disease is a marker for systemic inflammation affecting the entire body, including the endometrium [42]. Further studies are needed to help answer questions on the matter. Researchers recommend that treating periodontal disease early, before pregnancy, is best and that couples considering fertility treatment should consider waiting a period of time after completion of periodontal treatment to begin fertility treatment [42].

Male Reproductive Health

Prostatitis

Prostatitis is defined as inflammation of the prostate gland [43]. It may be classified into acute, chronic, asymptomatic inflammatory prostatitis and chronic pelvic pain syndrome [43]. Inflammation in the body is often associated with the body's response to an infection. An elevated Prostate-Specific Antigen, (PSA), level is a marker for many prostate diseases such as benign prostatic hyperplasia, prostatitis and prostate cancer. Researchers have found that periodontitis may contribute to an increase in PSA levels in those with prostatitis through an inflammatory response with the dissemination of inflammatory cytokines [44].

Erectile dysfunction

Erectile dysfunction also known as ED or impotence is characterized by the male's inability to develop or maintain an erection during sexual activity [45]. It is estimated that in the United States, nearly 30 million men are affected by erectile dysfunction [45]. Although the incidence increases with age, it is a treatable condition at any age. Common causes include side effects of medications, chronic illnesses such as diabetes, cardiovascular disease, atherosclerosis, hypertension, obesity, metabolic syndrome, cancer, Parkinson's disease, and inadequate blood flow to the penis, alcohol consumption in excess, smoking, physical exhaustion and stress [46].

Researchers have found a relationship between chronic periodontitis and the presence of erectile dysfunction [47,48]. It is theorized that the erectile dysfunction is associated with damage from endothelial dysfunction and systemic inflammatory changes associated with periodontal disease [47-49]. They have also suggested that improving periodontal and thus oral health in conjunction with other therapies may be a means to treat erectile dysfunction [47,50].

Conclusion

Many studies and researchers have established an association

between periodontal disease, and its potential effect on reproductive health, specifically associated adverse pregnancy outcomes; however, a cause and effect relationship has yet to be established [34]. It has been suggested that periodontal therapy does reduce periodontal inflammation and improves periodontal status. This is beneficial in any population that is susceptible to periodontal disease, including a pregnant woman and men. Preventive treatment, in any population, is the best way to reduce the risk of periodontal disease, particularly for those at risk for adverse pregnancy complications and/or outcomes and in men at risk for erectile dysfunction.

Periodontal disease is a chronic infection that contributes to a chronic inflammatory response in the oral cavity of those that are susceptible. Support has been provided describing plausible biological mechanisms by which periodontal disease may also contribute to issues related to females and males reproductive health. There is a vast amount of data which demonstrates an association relationship between periodontal disease and these medical entities. Further powered, randomized, controlled studies are needed to determine causality between periodontal disease and issues related to females and males reproductive health such as fetal mortality, preterm, low birth weight babies, preeclampsia, infertility, prostatitis and erectile dysfunction. Additionally, the gold standard in determining whether or not periodontal therapy will have a positive influence on medical outcomes associated with these medical conditions is prospective randomized controlled efficacy studies. Future studies may demonstrate the efficacy of periodontal therapy related to positive outcomes with regard to these medical conditions. However, current data and risk benefit ratios support the importance of periodontal therapy utilized to support periodontal health.

It should be noted that many of associations linking periodontal disease to systemic conditions and diseases are biologically complex conditions, such as those associated with adverse pregnancy complications and outcomes, infertility, prostatitis and erectile dysfunction. Periodontal disease is often modified by systemic diseases. The associations between poor oral health, particularly periodontal disease, and various systemic diseases and disorders provide ideal opportunities for greater communication and the development of more interprofessional relationships between dentists, periodontists, hygienists, primary care physicians, specialists, nurses, therapists and other health care providers. These relationships should begin to be established in health professional educational programs with continued emphasis to further strengthen and solidify them in practice settings and beyond.

There are many that do not regularly see their primary care physician for an annual exam yet may see their dentist for an annual check-up and vice versa. There are many factors which contribute to inadequacies and limitations associated with access to care issues which prevent people for seeking medical and dental care that are beyond the scope of this paper. Thus we should take any and every patient encounter as an opportunity to educate about the risks and hazards of oral and systemic diseases. As health care providers our goal is to provide comprehensive care to the "total patient".

The mouth is a part of the body and as suggested what happens in the mouth may have a crucial impact on the rest of the body. It thus becomes our duty to educate and inform our dental patients not only about their oral health but the potential increased risk for systemic diseases secondarily associated with poor oral health. We must also take the opportunity to communicate with our fellow health care practitioners and make appropriate referrals when we suspect our dental patients are at risk for systemic disease. Likewise, our fellow physicians equally share an obligation to educate and inform their patients who present with health problems of the potential risk for chronic oral infections and make appropriate referrals to their dental colleagues.

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