UReCA: The NCHC Journal of Undergraduate Research and Creative Activity
2020 Edition

Periodontitis and Pregnancy Outcomes

By Leslie Abegglen, Madison College

Abstract

Periodontitis is an infection in which the pathogens associated with it and their toxic products such as lipopolysaccharides lead to systemic inflammation. The inflammatory process is strongly implicated in preeclampsia, a leading cause of pregnancy complications affecting 3-7% of pregnant women. The red complex bacteria involved with periodontal disease initiate profound intracellular damage that plays a part in many systemic diseases including adverse pregnancy and neonatal outcomes. Pregnant women are particularly susceptible to the immune-inflammatory response to periodontal infection due to the increased sensitivity of their immune system and the increase in hormones. The immune-inflammatory response is responsible for the release of cytokines which result in systemic inflammation allowing bacteria to move from the site of infection to the bloodstream and into chorionic tissue. The result is miscarriage, premature birth, preeclampsia, low birth weight, and perinatal morbidity and mortality. C-reactive proteins, free radicals, and prostaglandin E2 are additional chemicals produced during the inflammatory response that have negative consequences for pregnancies and fetuses. In addition, there is a link between periodontitis and metabolic syndrome in which over 50% of of women with MetS during early pregnancy developed complications. Lastly, periodontal disease is thought to contribute to infertility by delaying conception and by affecting the ovary, uterus, embryo, and implantation.

Keywords: Periodontal disease; pregnancy; adverse pregnancy outcomes

Periodontal disease is a disease of the oral periodontium, which includes the gingiva (gums), periodontal ligament (fibrous tissue connecting tooth cementum to bone), alveolar bone (ridge of bone that contains the tooth sockets), and the cementum (calcified substance covering the root of a tooth). These tissues are the support structures for the teeth. Periodontal diseases are prevalent worldwide with severe chronic periodontitis being the sixth most common medical condition according to the Global Burden of Disease Study (Kassebaum, Bernabé, Dahiya, Bhandari, Murray, & Marcenes, 2014).

Periodontal pathogens have been linked to many systemic diseases in addition to diseases of the oral periodontium. Examples of systemic diseases linked with periodontal disease are: cardiovascular disease, diabetes, respiratory disease, chronic obstructive pulmonary disease, rheumatoid arthritis, gastrointestinal disorders, Alzheimer's disease, osteoporosis, kidney disease, preterm birth, low birth weight, and cancer (Warner, 2017). Because there is an extensive link between polymicrobial periodontal pathogens and systemic diseases, it is important to keep the periodontium healthy and clean to reduce bacterial load. While the list of associated diseases is extensive, this paper concentrates on the link between periodontitis and its adverse effects on pregnancy such as preterm birth, preeclampsia, delayed conception, and spontaneous abortion. In addition to adverse pregnancy outcomes, there are adverse neonatal outcomes such as small fetal size/low birth weight, macrosomia, fetal distress, polyhydramnios, and the need for neonatal resuscitation, that this paper will explore.

The bacteria associated with periodontal disease are anaerobic, meaning they are able to live without oxygen in the gingival sulcus (space between teeth and gums). These anaerobic bacteria also have endotoxins known as lipopolysaccharides (LPSs) on the outer membrane of

their cell walls. LPSs assist bacteria by providing protection from chemical attack and also by contributing to the structural integrity of the cell (www.Wikipedia.org, 2019). The LPSs are released after the destruction of the bacterial cell wall. These LPS endotoxins are responsible for stimulating the host response and the destruction of collagen, alveolar bone and other tissue; the result being periodontal disease (Suzuki, Yoneda, & Hirofuji, 2013). Endotoxemia and a subsequent low-grade pro-inflammatory response result from exposure to LPS toxins (Pussinen, Paju, Mäntylä, & Sorsa, 2007). Exposure to LPS during pregnancy can also contribute to poor pregnancy outcomes (Patil, Kalburgi, Koregol, Warad, Patil, & Ugale, 2012).

Warner (2017) states that there are over 700 bacterial species that can live in the subgingival sulcus. Of special concern among these bacterial species are the extremely virulent and destructive red complex bacteria. These specific bacteria are strongly associated with periodontitis and known to be the most destructive bacteria in periodontal disease. The red complex bacteria are known high-risk pathogens and initiate profound intracellular damage wherever they are found (Warner, 2017). The red complex bacteria include *Porphyromonas gingivalis (P. gingivalis)*, *Treponema denticola (T. denticola)*, and *Tannerella forsythia (T. forsythia).* The red complex bacteria plus the bacterial species *Aggregatibacter actinomycetemocomitns (A. a.)* make up "the big four" bacteria known to cause periodontal disease (Warner, 2017).

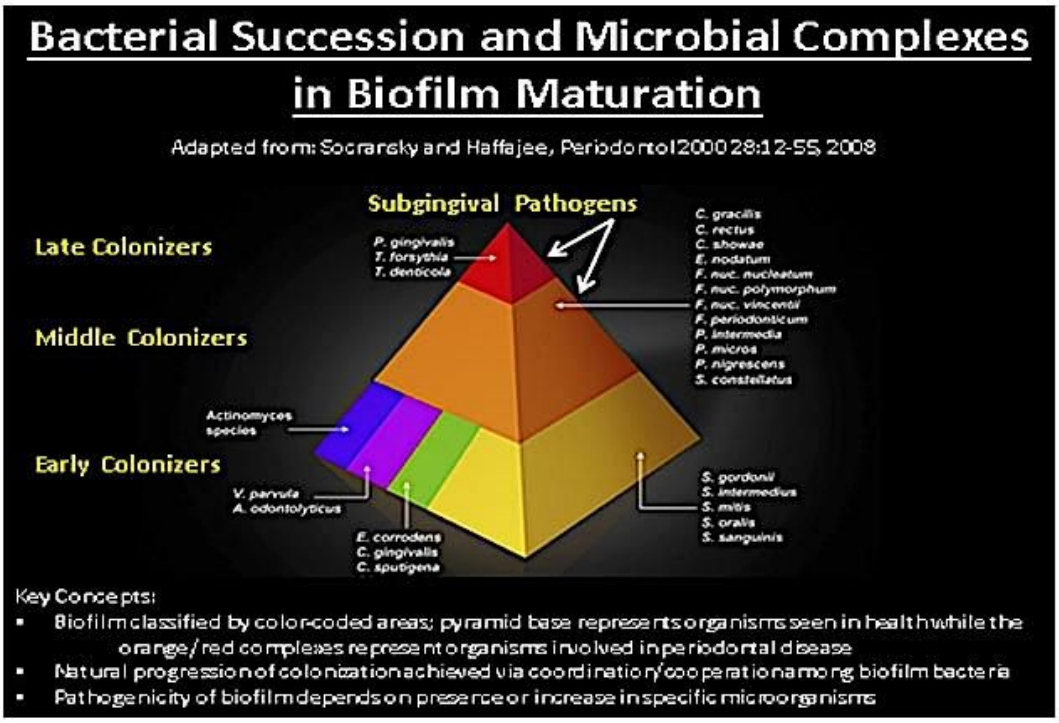

Figure 1. Bacterial succession and microbial complexes in biofilm maturation

Note that in the above figure the red complex bacteria are at the apex of the pyramid. These bacteria are the destructive "late colonizers" capable of causing tissue damage. The red complex bacteria appear when dental biofilm has been left undisturbed, meaning that the biofilm has not been mechanically removed by brushing, flossing and/or scaling.

As biofilm grows undisturbed, it develops three-dimensional micro-colonies that produce a matrix made of extracellular polymeric substance (EPS). The EPS anchors the bacteria to each other and to the tooth structure, making removal harder (Wilkins, 2017). In addition, the EPS protects the biofilm from the immune response of the host and from antimicrobial and antibacterial agents (Wilkins, 2017). Mature biofilm releases cells that colonize and proliferate in other areas of the mouth (Wilkins, 2017). The cells within the biofilm communicate via quorum sensing which increases the microbial virulence (www.sciencedirect.com, 2019). It is,

therefore, understandable how a biofilm community of red complex bacteria can be destructive to oral tissue.

The chart below illustrates the time period required for varying types of bacteria to accumulate. During days one and two, the dominant bacteria are the gram-positive streptococci, *Streptococcus mutans (S. mutans)* and *Streptococcus sanguis (S. sanguis)*. While they contribute to dental caries (cavities), these bacteria are not periodontal pathogens. Gram-positive filamentous forms of bacteria grow between days two and four and gradually replace the cocci as they increase in number. Next, between days four and seven, mixed flora of rods, filamentous, and fusobacteria emerge. Note that leukocytes, white blood cells of the immune system, appear during this time, indicating that the host's immune response has been activated. The thickening of mature biofilm at the gingival margin provides an anaerobic environment in the gingival sulcus where the gram-negative, anaerobic, periodontal pathogens thrive. Weeks one to two see the appearance of anaerobic spirochetes and vibrios along with histologic evidence of gingival inflammation. Gingivitis is clinically evident between 14-21 days (Wilkins, 2017). The movement of biofilm is apically, from supragingival to subgingival (from above to below the gingiva). From the subgingival sulcus, the pathogens may invade the underlying connective tissue resulting in alveolar bone and periodontal ligament loss (Wilkins, 2017). If supragingival biofilm is removed, it is possible to protect the periodontium altogether. Therefore, effective brushing techniques and frequent prophylactic visits to the dentist are crucial to maintaining good oral health.

Note that in the above figure the red complex bacteria are at the apex of the pyramid. These bacteria are the destructive "late colonizers" capable of causing tissue damage. The red complex bacteria appear when dental biofilm has been left undisturbed, meaning that the biofilm has not been mechanically removed by brushing, flossing and/or scaling.

As biofilm grows undisturbed, it develops three-dimensional micro-colonies that produce a matrix made of extracellular polymeric substance (EPS). The EPS anchors the bacteria to each other and to the tooth structure, making removal harder (Wilkins, 2017). In addition, the EPS protects the biofilm from the immune response of the host and from antimicrobial and antibacterial agents (Wilkins, 2017). Mature biofilm releases cells that colonize and proliferate in other areas of the mouth (Wilkins, 2017). The cells within the biofilm communicate via quorum sensing which increases the microbial virulence (www.sciencedirect.com, 2019). It is, therefore, understandable how a biofilm community of red complex bacteria can be destructive to oral tissue.

The chart below illustrates the time period required for varying types of bacteria to accumulate. During days one and two, the dominant bacteria are the gram-positive streptococci, *Streptococcus mutans (S. mutans)* and *Streptococcus sanguis (S. sanguis)*. While they contribute to dental caries (cavities), these bacteria are not periodontal pathogens. Gram-positive filamentous forms of bacteria grow between days two and four and gradually replace the cocci as they increase in number. Next, between days four and seven, mixed flora of rods, filamentous, and fusobacteria emerge. Note that leukocytes, white blood cells of the immune system, appear during this time, indicating that the host's immune response has been activated. The thickening of mature biofilm at the gingival margin provides an anaerobic environment in the gingival

sulcus where the gram-negative, anaerobic, periodontal pathogens thrive. Weeks one to two see the appearance of anaerobic spirochetes and vibrios along with histologic evidence of gingival inflammation. Gingivitis is clinically evident between 14-21 days (Wilkins, 2017). The movement of biofilm is apically, from supragingival to subgingival (from above to below the gingiva). From the subgingival sulcus, the pathogens may invade the underlying connective tissue resulting in alveolar bone and periodontal ligament loss (Wilkins, 2017). If supragingival biofilm is removed, it is possible to protect the periodontium altogether. Therefore, effective brushing techniques and frequent prophylactic visits to the dentist are crucial to maintaining good oral health.

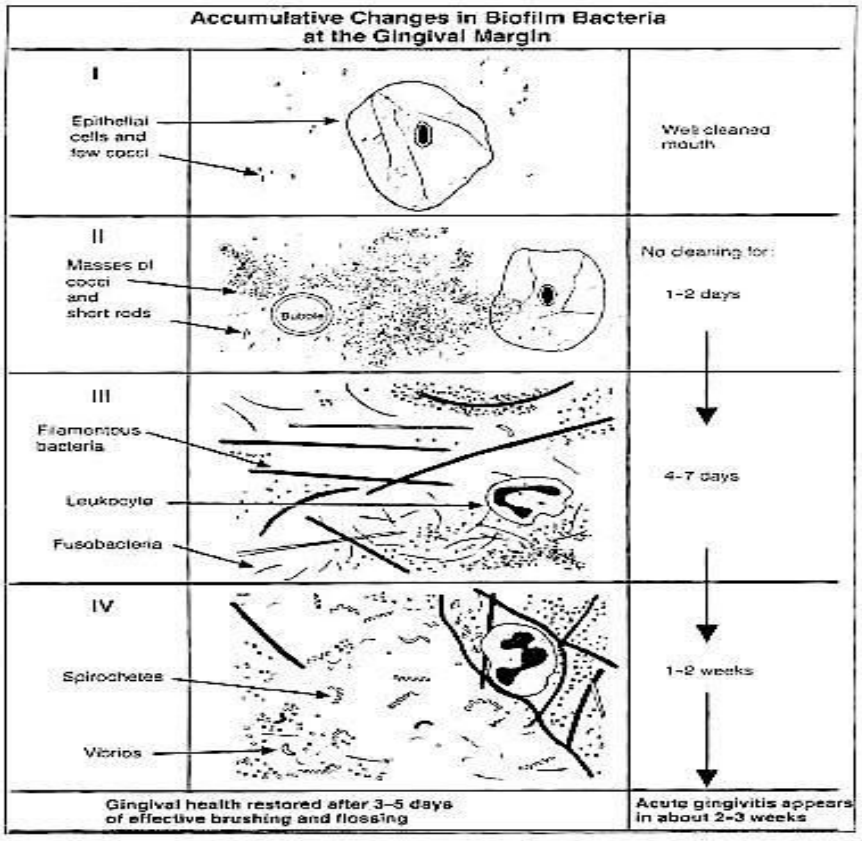

Figure 2. Accumulative changes in biofilm bacteria at the gingival margin

We see that bacteria play an important role in periodontal disease. The focus of this paper is how periodontal disease affects pregnancy and fetal health. It is known that hormonal changes during a woman's lifetime affect her periodontal health; especially during puberty, menstrual cycles, pregnancy, and menopause (Patil et al., 2012). In fact, evidence suggests that periodontal status deteriorates during gestation but improves postpartum (Chanomethaporn, Chayasadom, Wara-Aswapati, Kongwattanakul, Suwannarong, Tangwanichgapong et al., 2018). Pregnancy causes many hormonal changes that increase the risk to the expectant mother of developing gingivitis and periodontal diseases (www.periodontalhealth.com, 2019). Androgen, estrogen, and progesterone receptors are localized in periodontal tissues (Patil et al., 2012). The hormonal changes during pregnancy cause the gingiva to have an exaggerated response to the effects of bacteria, particularly in the eighth month of pregnancy (Gehrig, Shin, & Willmann, 2019). Elevated hormones can alter the host's immune-inflammatory response to bacteria present and increase inflammation of the gingival tissues (Moore & Blair, 2017). Moore and Blair (2017) state that some bacteroides species present with periodontal disease will, "metabolize estrogen and progesterone and if colonized in the oral cavity may become more prevalent during pregnancy with increased risk of disease". The specific bacteria associated with pregnancy gingivitis and periodontitis is *Prevotella intermedia (P. intermedia)* (Gehrig et al., 2019).

Progesterone and estrogen levels are elevated during pregnancy and reach levels 10 and 30 times greater, respectively, than during the menstrual cycle (Grodstein, Colditz, & Stampfer, 1996). A dramatic, visual example of the inflammatory effect of pregnancy hormones is the

presence of pregnancy tumors. In 9.6% of women, pregnancy granuloma (pregnancy tumors), similar in appearance to pyogenic granuloma are observed (Gornstein, Lapp, Bustos-Valdes, & Zamorano, 1999). These "tumors", or inflammatory hyperplasias, are due to irritation of the tissue brought on by hormonal changes during pregnancy. The tumors are lesions unrelated to infection and arise, instead, in response to various stimuli such as low-grade local irritation, traumatic injury, or hormonal factors (Gondivkar, Gadbail, & Chole, 2010). Pregnancy tumors are problematic because they may be painful and interfere with mastication.

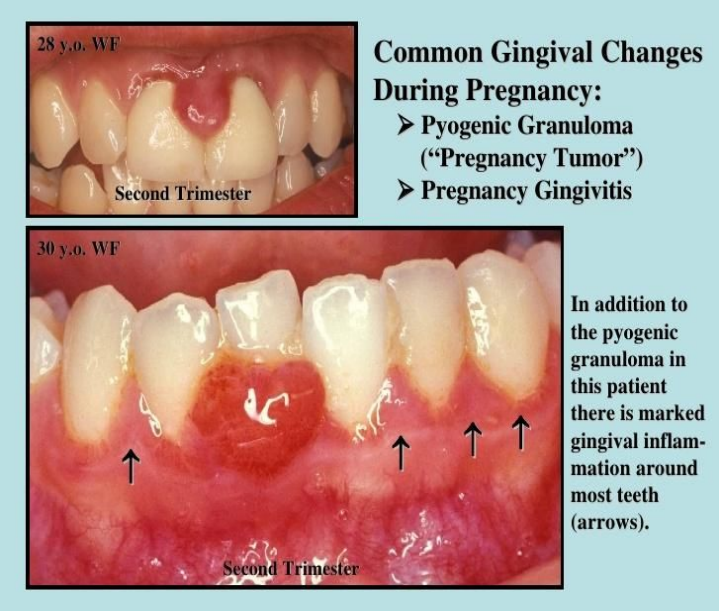

Figure 3. Common gingival changes during pregnancy

While bacteria and hormones are a major factor in periodontal disease, the damage associated with periodontal disease is a result of the host immune-inflammatory response which the bacteria and hormones stimulate. During pregnancy, the maternal immune system is

characterized by a reinforced network of recognition, communication, trafficking, and repair; it can raise the alarm, if necessary, in order to maintain the well-being of the mother and the fetus (Mor, Cardenas, Abrahams, & Guller, 2011). Because gingivitis and periodontitis are infections, the body's immune system is activated. To fight infection, white blood cells must reach the infected site. To reach the infected gingival sulcus, the white blood cells migrate from the bloodstream into the infected tissue by producing pro-inflammatory chemicals called cytokines, which result in inflammation not only at the point of infection but throughout the body (Kulacz & Levy, 2002).

The inflammatory process is detrimental because while white blood cells can pass from the blood to the infected site, bacteria are able to move in the opposite direction; from the infected site into the bloodstream. (Kulacz et al., 2002). In fact, oral pathogens such as *Fusobacterium nucleatum (F. nucleatum)* and *P. gingivalis* have been detected in the chorionic tissues of high-risk pregnant women (Chanomethaporn et al., 2018). Bacteremia (bacteria in the blood) may result when periodontal pathogens and their by-products reach the placenta and infiltrate the fetal circulation and surrounding amniotic fluid (Moore et al., 2017). Pathogens in fetal circulation can trigger immune-inflammatory response in the fetal compartment which has been linked to miscarriage, premature birth, preeclampsia, low birth weight due to impaired transport of nutrients, and perinatal morbidity and mortality (Moore et al., 2017). The fetal immune-inflammatory response is characterized by immunoglobulin M (IgM) antibody production and the secretion of inflammatory mediators, which, in addition to the above conditions, may cause fetal tissue damage (Madianos, Bobetsis, & Offenbacher 2013).

The production of cytokines and inflammation brought on by infection cause the liver to produce C-reactive protein (CRP). This protein has been associated with adverse pregnancy outcomes including preeclampsia and premature birth (www.periodontalhealth.com, 2019). C-reactive protein has been found to be up to 65% higher in pregnant women where periodontal disease is present (Pitiphat, Joshipura, Rich-Edwards, Williams, Douglass & Gillman, 2006). Vecchie, Bonaventura, Carbone, Maggi, Ferraiolo, Carloni et al. (2018) performed a study comparing CRP concentrations in pregnant women during the middle phase of pregnancy. They found a correlation between elevated CRP serum levels (>1.86 µg/mL) and adverse maternal and neonatal pregnancy outcomes (Vecchie et al., 2018), defined as the following: gestational hypertension, premature delivery (prior to the 37th week of gestation), Cesarean delivery, macrosomia, fetal distress, polyhydramnios, small or large infant size, low Apgar scores, and the need for neonatal resuscitation (Vecchie et al., 2018). In women with significantly higher CRP serum levels, the most frequent complications were Cesarean delivery (50.6%), premature delivery (9.4%), small size for gestational age fetus (22.4%), macrosomia (2.9%), and the need for neonatal resuscitation (1.7%), in fact, all cases of neonatal resuscitation occurred in this group (Veccie et al., 2018).

While inflammation may cause havoc during mid-term pregnancies, it is essential during the early and late phases of pregnancy. During implantation and placentation, there is a strong inflammatory response to the actions of the blastocyst. The blastocyst breaks through the

epithelial lining of the uterus during implantation, while the trophoblast replaces endothelium and vascular smooth muscle of the maternal blood vessels during placentation, all of which Mor, Abrahams, and Guller (2011) liken to “an open wound”. Mor et al. (2011) state that:

> these activities create a veritable “battleground” of invading cell, dying cell, and repairing cells. An inflammatory environment is required to secure the adequate repair of the uterine epithelium and the removal of cellular debris. Thus, the first trimester of pregnancy is a pro-inflammatory phase. The second trimester is an anti-inflammatory state while the mother, placenta and fetus are symbiotic

A second pro-inflammatory stage occurs during the third trimester in order to promote “contraction of the uterus, expulsion of the baby and rejection of the placenta” (Mor et al., 2011). Because heightened immune response and inflammation are a normal part of pregnancy, it is important to have good oral health, with a low bacterial load, prior to pregnancy.

With infections, like periodontitis, the body’s natural defense mechanism includes the production of free radical and reactive oxygen species. If these species are produced in excess, the result is oxidative stress; a key driver for chronic inflammation and tissue damage including periodontal disease (Moore et al., 2011). This creates an ongoing cycle of infection leading to the production of free radicals leading to further tissue damage. During pregnancy, susceptibility to oxidative stress increases due to the high metabolic demand and increased need for oxygen by tissues (Hansson, Nã¤Ã¤V, & Erlandsson, 2015). The inflammatory process is strongly

implicated in preeclampsia which is a leading cause of pregnancy complications, affecting 3-7% of pregnant women (Hansson et al., 2015). Hansson et al. (2015) assert that oxidative damage to the placental barrier induces the accumulation of toxic free fetal hemoglobin and its metabolites in the placenta, which eventually leak over to the maternal circulation, resulting in vasoconstriction, generation of free oxygen radicals, activation of neutrophils and cytokines, and placental and kidney damage.

Prostaglandin E2 (PGE2) is a labor-inducing compound that is an important mediator of uterine activity and also found in oral bacteria strains associated with periodontitis (O'Brien, 1995). O'Brien (1995) states that prostaglandins are even more critical to labor than oxytocin and are instrumental in the contraction of the smooth muscle of the uterus along with the biophysical changes associated with cervical ripening. Unlike oxytocin, prostaglandin receptors are always present in myometrial tissue (O'Brien, 1995). Therefore, prostaglandin can work on the uterine muscle anytime during a pregnancy. Most, if not all, events that induce labor can be attributed to the action of the PGE2 (Uriza, Roa, & Silva et al., 2018). During pregnancy, concentrations of PGE2 gradually increase reaching maximum levels near the end of pregnancy when it is induced by an inflammatory response promoting uterine contraction (Uriza et al., 2018). The inflammatory mediator, PGE2, is also triggered by the local and systemic infections due to periodontal disease. The high levels of PGE2 due to periodontal disease is a risk factor for preterm delivery (Uriza et al., 2018). In their study, Uriza et al. (2018) found that both PGE2 and cytokines levels increased with the severity of periodontitis, with chronic periodontitis

having the highest levels such that “in the presence of severe and generalized periodontitis, preterm delivery is 3.9 times more likely compared with women with a healthy periodontium”.

Another factor to consider is metabolic syndrome. Metabolic syndrome (MetS) is a condition in which metabolic, vascular, and inflammatory indicators are present in a cluster of 3 or more risk factors (Grieger, Bianco-Miotto, & Grzeskowiak et al., 2018). The following are risk factors for MetS: insulin resistance, high blood pressure, obesity, atherogenic dyslipidemia, high triglycerides, low high-density lipoprotein cholesterol, elevated fasting blood sugar, pro-thrombotic, and pro-inflammatory states (Gurav, 2014). In their study of MetS in pregnancy, Grieger et al., (2018) determined that over 50% of of women with MetS during early pregnancy developed complications, such as spontaneous preterm birth, gestational diabetes mellitus, preeclampsia, and large for gestational age infants, compared to 33% who did not have MetS.

There is a known connection between MetS and periodontitis. Women with periodontitis have inflammatory issues which is one of the criteria in diagnosing MetS. Subgingival bacteria associated with periodontitis are a significant and persistent challenge to the host. Periodontal bacteria, and their noxious products, gain access to the periodontal tissues and to the systemic circulation through the ulcerated sulcular epithelium of the gingiva in periodontitis (Gurav, 2014). The pro-inflammatory cytokines and periodontal bacteria enter the systemic circulation and produce a “low level systemic inflammation/infection” (Gurav, 2014). It has been reported that the association between periodontitis and MetS could be bi-directional. The inflammatory markers in various components of MetS can up-regulate the periodontal inflammatory process

and the persistent periodontal inflammation may worsen the inflammatory components of MetS (Gurav, 2014). Some believe that periodontal disease should be considered as a component of MetS as many studies point out the positive relation of MetS with periodontitis (Gurav, 2014).

Not only does periodontal disease result in harm to an existing pregnancy but it can also have negative effects on fertility. Infection and inflammation (which we know occur with periodontal disease) contribute to infertility by affecting the ovary, uterus, the embryo, and implantation (Weiss, Goldsmith, Taylor, Bellet, & Taylor, 2009). Inflammation may interfere with ovulation and hormone production as well as contributing to endometriosis (Weiss et al., 2009). Inflammation alters endometrial receptivity and affects the trophoblast and trophoblast—endometrial interaction (Weiss et al., 2009). Furthermore, women who have periodontal infection and inflammation have worse in vitro fertilization (IVF) outcomes than women with healthy periodontium (Pavlatou, Tsami, & Vlahos, 2013). In their paper, *The effect of in vitro fertilization on gingival inflammation according to women's periodontal status: clinical data*, Palatou et al., (2013) state that, "a poor pre-existing periodontal status seems to be associated with poorer outcomes of IVF treatment". Paju, Oittinen, Haapala, Asikainen, Paavonen, & Pussinen (2017), published a paper in the Journal of Oral Microbiology entitled *Porphyromonas gingivalis may interfere with conception in women*. In their paper, Paju et al., (2017) found that when *P. gingivalis* salivary antibody concentrations were in elevated concentrations, there was a significant increase in inability to get pregnant. On average it took

two months longer for women with periodontal disease to get pregnant than women with good oral health (Moore et al., 2017).

So, given this information, what is a pregnant woman to do? There are a few things a pregnant woman can do to safeguard herself, and her pregnancy, against the problems associated with chronic inflammation arising from periodontitis. A dental visit to determine periodontal health is something that is best done prior to pregnancy, since periodontitis can delay conception and x-rays can safely be taken before pregnancy to identify any underlying dental issues. Dental problems such as caries and overhanging restorations can ideally be dealt with prior to pregnancy. Maintaining a high level of dental hygiene before and during pregnancy is important and can be achieved by effective brushing and use of interdental aids at home to keep bacteria-laden plaque levels low. If you are unsure about how to effectively brush and/or floss, ask your dental hygienist to demonstrate correct methods of dental care. Visiting the dentist and hygienist regularly is crucial to keep teeth free of calculus (tartar). If the disease is identified during pregnancy, treatment should start immediately to minimize destruction of the periodontium (Moore et al., 2017).

In addition to assessing oral health prior to and during pregnancy, a woman can reduce the chances of oxidative stress by limiting refined sugars, carbohydrates, and saturated fats from her diet during pregnancy. Eating foods rich in vitamin C and E, such as leafy green vegetables and red, blue, and black berries can counter oxidative stress (Moore et al., 2017). Moore et al., (2017) assert that, “research increasingly links diet and nutrition with the countering of oxidative

stress and the role it plays in chronic inflammatory diseases". Eating high quality foods such as vegetables and lean meats will also help with cholesterol and other health issues associated with MetS. Smoking also increases oxidative stress and is a factor for periodontal disease (Moore et al., 2017) and should therefore be avoided. Adverse side effects of smoking on the periodontium include reduction of blood supply to tissue, increased tissue breakdown due to nicotine, and reduced tissue healing (Van der Vaart, Postma, Timens, Hylkema, Willemse, Boezen, et al., 2005). Smoking cessation should be started as soon as possible for the health of the mother and the growing fetus.

Definition of Terms

Apgar score- a test on infants at one and five minutes after birth to detect how well the baby tolerated the birthing process and how well the baby is doing outside of the womb respectively, the test criteria are: activity, pulse, grimace, appearance, and respiration (MedlinePlus Medical Encyclopedia, 2019).

Atherogenic dyslipidemia- refers to elevated levels of triglycerides and small-dense low-density lipoprotein and low levels of high-density lipoprotein cholesterol, all three elements have been recognized as an independent risk factor for cardiovascular disease (www.ncbi.nlm.nih.gov, 2019).

Biofilm- small, highly complex, well-organized, independent communities, containing thousands of compatible bacteria encapsulated in a self-protecting extracellular polymeric substance forming on solid, wet surfaces (Wilkins, 2017).

C-reactive protein- an acute phase reactant protein produced by the liver that increases in response to cytokines released from white blood cells during the inflammatory process (MedlinePlus Medical Encyclopedia, 2019).

Cytokines- small, pro-inflammatory secreted proteins released by leukocytes involved in the initiation and persistence of pathologic pain by directly activating nociceptive sensory neurons (www.ncbi.nlm.nih.gov, 2007).

Endometriosis- when the tissue that makes up the uterine lining is present on other organs inside the body, usually in the lower abdomen, or pelvis, women with endometriosis often have abdominal pain, and have a hard time getting pregnant (http://obgyn.ucla.edu, 2019).

Endotoxemia- the change in the permeability of the intestinal flora, which allows the passage of lipopolysaccharide derived from intestinal bacteria into the bloodstream (www.sciencedirect.com, 2019).

Extracellular polymeric substance- fundamental constituents of biofilms and can improve the biofilm community's ability to scavenge both water and nutrients from the environment (www.sciencedirect.com, 2019).

Free radicals- generated by our body by exposure to different physiochemical conditions or pathological states. A balance between free radicals and antioxidants is necessary for proper

physiological function. If free radicals there is an imbalance, oxidative stress ensues. Free radicals adversely alter lipids, proteins, and DNA and trigger a number of human diseases (www.ncbi.nlm.nih.gov, 2010).

Lipopolysaccharides- endotoxins derived from the outer membrane of Gram-negative bacteria (www.sciencedirect.com, 2019).

Macrosomia- a significantly larger than average newborn with a birth weight of more than 8 pounds, 13 ounces regardless of gestational age (www.mayoclinic.org, 2018).

Oxidative stress- a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses, has a role tissue damage (www.ncbi.nlm.nih.gov, 2000).

Periodontitis- a common and serious gum infection that damages the soft tissue and destroys the bone that supports the teeth leading to lost teeth. Periodontitis is preventable with good oral hygiene (www.mayoclinic.org, 2018).

Polyhydramnios- excessive accumulation of amniotic fluid (www.mayoclinic.org, 2017).

Prostaglandin E2- one of the prostaglandins, a group of hormone-like substances that participate in a wide range of body functions such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, control of blood pressure, and modulation of inflammation (www.medicinenet.com, 2019).

Pyogenic granuloma- a benign vascular tumor that occurs on the skin and mucous membranes (www.ncbi.nlm.nih.gov, 2017).

Quorum Sensing- a process of cell-to-cell communication that relies on the production and release of extracellular signaling molecules termed auto inducers, whose concentration increases as a function of cell density (Alouf, 2015).

Trophoblast- cells forming the outer layer of blastocyst which provide nutrients to the embryo and develop into a large part of the placenta (www.wikipedia.org, 2019).

Summary

Periodontal disease is a worldwide problem that has been linked with numerous systemic diseases. Periodontal infection results in the immune-inflammatory response in the host. With chronic infection, comes adverse health effects which wreak havoc on the human body. Pregnant women are particularly susceptible to adverse health effects due to their increased hormone levels and their heightened immune response.

The anaerobic bacteria associated with periodontitis include the virulent and destructive red complex bacteria as well as *Aggregatibacter actinomycetemocomitns*. These bacteria have endotoxins known as lipopolysaccharides. Lipopolysaccharide exposure leads to endotoxemia and a low-grade, chronic, pro-inflammatory response in the host. For this reason, exposure to lipopolysaccharides during pregnancy contributes to poor pregnancy outcomes.

There are many reasons why periodontal infections are detrimental to pregnancy. With periodontal infections, like other infections, the host immune system is activated to protect the body against infection. With periodontitis, periodontal bacteria gain access to systemic circulation through the ulcerated sulcular epithelium of the gingiva. A low-level, systemic inflammation and infection initiates in the body.

Cytokines are released which add to systemic inflammation and allows pathogens to move from the oral cavity into the fetal circulation. Pathogens in fetal circulation have been linked to miscarriage, premature birth, preeclampsia, low birth weight due to impaired transport of nutrients, and perinatal morbidity and mortality. Periodontal disease and the associated inflammation also lead to the production of C-reactive protein which has also been associated with adverse pregnancy many outcomes. Free radicals are also produced with periodontal infections and pregnant women are more susceptible to oxidative stress due to high metabolic demand during this time.

Prostaglandin, a labor inducing chemical, is found in oral bacteria strains associated with periodontitis. Prostaglandin levels increase with the severity of periodontitis. A high level of prostaglandin, which is seen in generalized and chronic periodontitis is a risk factor for preterm delivery. In addition to inflammation causing negative effects on pregnancies and fetuses, it may also interfere with ovulation, hormone production, and ability to conceive as well as contributing to endometriosis. It has been stated that women who have periodontal infection and inflammation also have worse in vitro fertilization outcomes. Studies have shown that when *P.*

gingivalis salivary antibody concentrations were in elevated concentrations, there was a significant increase in the inability to become pregnant. On average it took two months longer for women with periodontal disease to get pregnant than women with good oral health.

Because we know that bacteria initiate the infections that lead to inflammation and the resulting adverse effects, it is crucial to keep these bacteria counts low. If dental biofilm is left undisturbed, gingivitis is evident within two to three weeks and, if left untreated, periodontitis follows. Periodontitis can be avoided altogether by maintaining good oral hygiene through regular dental visits and effective brushing and flossing methods at home. In addition, pregnant women can protect themselves and their fetuses from oral infections by limiting refined sugars, carbohydrates, and saturated fats from her diet, by eating foods rich in vitamin C and E, such as leafy green vegetables and red, blue, and black berries and by quitting smoking.

References

Apgar score: MedlinePlus Medical Encyclopedia. (n.d.). Retrieved June 29, 2019, from https://medlineplus.gov/ency/article/003402.htm

Betteridge, D. J. (2000, February). What is oxidative stress? Retrieved October 5, 2019, from https://www.ncbi.nlm.nih.gov/pubmed/10693912.

C-reactive protein: MedlinePlus Medical Encyclopedia. (n.d.). Retrieved June 29, 2019, from https://medlineplus.gov/ency/article/003356.htm

Chanomethaporn, A., Chayasadom, A., Wara-Aswapati, N., Kongwattanakul, K., Suwannarong, W., Tangwanichgapong, K., Sumanonta, G., Matangkasombut, O., Dasanayake, A., Pitiphat, W. (2018). Association between periodontitis and spontaneous abortion: A case-control study. *Journal of Periodontology,90*(4), 381-390. doi:10.1002/jper.18-0174

Endometriosis. (n.d.). Retrieved October 5, 2019, from http://obgyn.ucla.edu/endometriosis.

Endotoxemia. (n.d.). Retrieved October 5, 2019, from https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/endotoxemia.

Extracellular Polymeric Substance. (n.d.). Retrieved October 5, 2019, from https://www.sciencedirect.com/topics/immunology-and-microbiology/extracellular-polymeric-substance.

Fetal macrosomia. (2018, May 19). Retrieved June 23, 2019, from https://www.mayoclinic.org/diseases-conditions/fetal-macrosomia/symptoms-causes/syc-20372579

Gehrig, J. S., Shin, D. E., & Willmann, D. E. (2019). *Foundations of periodontics for the dental hygienist* (4th ed.). Philadelphia: Wolters Kluwer.

Gondivkar, S. M., Gadbail, A., & Chole, R. (2010). Oral pregnancy tumor. Retrieved June 24, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3220110/

Gornstein, R. A., Lapp, C. A., Bustos-Valdes, S. M., & Zamorano, P. (1999). Androgens Modulate Interleukin-6 Production by Gingival Fibroblasts in Vitro. *Journal of Periodontology,70*(6), 604-609. doi:10.1902/jop.1999.70.6.604

Grieger, J. A., Bianco-Miotto, T., Grzeskowiak, L. E., Leemaqz, S. Y., Poston, L., Mccowan, L. M., Kenny, L. C., Myers, J. E., Walker, J. J., Dekker, G. A., Roberts, C. T. (2018). Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: A prospective cohort of nulliparous women. *PLOS Medicine,15*(12), 1-16. doi: 10.1371/journal.pmed.1002710

Grodstein, F., Colditz, G. A., & Stampfer, M. J. (1996). Post-Menopausal Hormone Use and Tooth Loss: A Prospective Study. *The Journal of the American Dental Association,127*(3), 370-377. doi: 10.14219/jada.archive.1996.0208

Gurav, A. N. (2014, January). The association of periodontitis and metabolic syndrome. Retrieved July 21, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955301/

Hansson, S. R., Nã¤Ã¤V, Ã, & Erlandsson, L. (2015). Oxidative stress in preeclampsia and the role of free fetal hemoglobin. *Frontiers in Physiology, 5*. doi:10.3389/fphys.2014.00516

Jr, W. C. S. (n.d.). Definition of Prostaglandin E2. Retrieved October 5, 2019, from https://www.medicinenet.com/script/main/art.asp?articlekey=24892.

Kassebaum, N. J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C. J., & Marcenes, W. (2014, November). Global burden of severe periodontitis in 1990-2010: A systematic review and meta-regression. Retrieved July 26, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293771/

Kulacz, R., D.D.S., & Levy, T., M.D., J.D. (2002). Periodontal Disease. In *The roots of disease: Connecting dentistry & medicine* (pp. 133-140). Xlibris Corporation.

Lipopolysaccharide. (2019, June 12). Retrieved June 18, 2019, from https://en.wikipedia.org/wiki/Lipopolysaccharide

Lipopolysaccharide. (n.d.). Retrieved October 5, 2019, from https://www.sciencedirect.com/topics/neuroscience/lipopolysaccharide.

Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010, July). Free radicals, antioxidants and functional foods: Impact on human health. Retrieved October 5, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3249911/.

Madianos, P. N., Bobetsis, Y. A., & Offenbacher, S. (2013). Adverse pregnancy outcomes (APOs) and periodontal disease: Pathogenic mechanisms. *Journal of Clinical Periodontology, 40*. doi:10.1111/jcpe.12082

Moore, J., & Blair, F. (may 2017). Periodontal health and pregnancy. *British Journal of Midwifery,25*(5), 289-292.

Mor, G., Cardenas, I., Abrahams, V., & Guller, S. (2011, March). Inflammation and pregnancy: The role of the immune system at the implantation site. Retrieved June 29, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078586/

O'Brien, W. F. (1995, December). The role of prostaglandins in labor and delivery. Retrieved July 20, 2019, from https://www.ncbi.nlm.nih.gov/pubmed/8665768/

Paju, S., Oittinen, J., Haapala, H., Asikainen, S., Paavonen, J., & Pussinen, P. J. (2017). Porphyromonas gingivalis may interfere with conception in women. *Journal of Oral Microbiology,9*(1), 1330644. doi:10.1080/20002297.2017.1330644

Patil, S. N., Kalburgi, N. B., Koregol, A. C., Warad, S. B., Patil, S., & Ugale, M. S. (2012, April). Female sex hormones and periodontal health-awareness among gynecologists - A questionnaire survey. Retrieved June 24, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3723266/

Pavlatou A, Tsami A, Vlahos N, et al. The effect of *in vitro* fertilization on gingival inflammation according to women's periodontal status: clinical data. J Int Acad Periodontol. 2013;15:36–42.

Periodontal Disease and Pregnancy. (2019, May 19). Retrieved June 24, 2019, from https://www.periodontalhealth.com/periodontal-disease-and-pregnancy/

Periodontitis. (2018, March 6). Retrieved October 5, 2019, from https://www.mayoclinic.org/diseases-conditions/periodontitis/symptoms-causes/syc-20354473.

Pitiphat, W., Joshipura, K., Rich-Edwards, J., Williams, P., Douglass, C., Gillman, M. (2006). Periodontitis and plasma C-reactive protein during pregnancy. *Journal Periodontol* 77(5): 821-25. doi: 10.1902/jop.2006.050193

Polyhydramnios. (2017, November 18). Retrieved June 23, 2019, from https://www.mayoclinic.org/diseases-conditions/polyhydramnios/symptoms-causes/syc-20368493

Pussinen, P. J., Paju, S., Mäntylä, P., & Sorsa, T. (2007). Serum microbial- and host-derived markers of periodontal diseases: A review. Retrieved July 26, 2019, from https://www.ncbi.nlm.nih.gov/pubmed/17896988

Quorum Sensing. (n.d.). Retrieved June 24, 2019, from https://www.sciencedirect.com/topics/immunology-and-microbiology/quorum-sensing

Suzuki, N., Yoneda, M., & Hirofuji, T. (2013). Mixed red-complex bacterial infection in periodontitis. Retrieved June 20, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3606728/

Trophoblast. (2019, August 31). Retrieved October 5, 2019, from https://en.wikipedia.org/wiki/Trophoblast.

Uriza, L., Juliana, Roa, Lara, Q., Margarita, S., Silva, . . . Maria, F. (2018, August 01). Periodontal Disease, Inflammatory Cytokines, and PGE2 in Pregnant Patients at Risk of Preterm Delivery: A Pilot Study. Retrieved July 20, 2019, from https://www.hindawi.com/journals/idog/2018/7027683/

Van der Vaart, H., Postma, D. S., Timens, W., Hylkema, M. N., Willemse, B. W., Boezen, H. M., Vonk, J. M., de Reus, D. M., Kauffman, H. F., ten Hacken, N. H. (2005, March 01). Acute effects of cigarette smoking on inflammation in healthy intermittent smokers. Retrieved July 27, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC554761/

Vecchie, A., Bonaventura, A., Carbone, F., Maggi, D., Ferraiolo, A., Carloni, B., Andraghetti, G., Bonabello, L., Liberale, L., Dallegri, F., Montecucco, F., Cordera, R. (Nov. 7, 2018). C-Reactive Protein Levels at the Midpregnancy Can Predict Gestational Complications. *Hindawi BioMed Research International,2018*(1070151), 1-8.

Warner, T. (2017, November 13). Define Periodontal Disease by Its Pathogens. Retrieved June 20, 2019, from https://www.dentistrytoday.com/news/todays-dental-news/item/2614-define-periodontal-disease-by-its-pathogens?tmpl=component&print=1

Weiss, G., Goldsmith, L. T., Taylor, R. N., Bellet, D., & Taylor, H. S. (2009, February). Inflammation in reproductive disorders. Retrieved July 26, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3107847/

Wilkins, E. M., Wyche, C. J., & Boyd, L. D. (2017). *Clinical practice of the dental hygienist* (12th ed.). Philadelphia: Wolters Kluwer.

Wollina, U., Langner, D., França, K., Gianfaldoni, S., Lotti, T., & Tchernev, G. (2017, July 13). Pyogenic Granuloma - A Common Benign Vascular Tumor with Variable Clinical Presentation: New Findings and Treatment Options. Retrieved October 5, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5535648/.

Zhang, J.-M., & An, J. (2007). Cytokines, inflammation, and pain. Retrieved October 5, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785020/.

Figure 1. Bacterial Succession and Microbial Complexes in Biofilm Maturation [Digital image]. (2017, November 13). Retrieved June 20, 2019, from https://www.dentistrytoday.com/news/todays-dental-news/item/2614-define-periodontal-disease-by-its-pathogens?tmpl=component&print=1

Figure 2. Accumulative Changes in Biofilm Bacteria at the Gingival Margin. (2017). Wilkins, E. M., Wyche, C. J., & Boyd, L. D. (2017). *Clinical practice of the dental hygienist* (12th ed.). Philadelphia: Wolters Kluwer.

Figure 3. Common gingival changes during pregnancy [Digital image]. (n.d.). Retrieved June 24, 2019, from https://images.search.yahoo.com/yhs/search;_ylt=AwrExo4vlBFdgBIA5X82nIlQ?p=pregnancy granuloma&fr=yhs-Lkry-SF01&hsimp=yhs-SF01&hspart=Lkry&fr2=p:s,v:i#id=8&iurl=https://image.slidesharecdn.com/effect-of-periodontal-infections-on-fetal-development-pregnancy-outcomes-1192827947171157-2/95/effect-of-periodontal-infections-on-fetal-development-pregnancy-outcomes-7-728.jpg? cb=1192802748&action=click