REVIEW ARTICLE

e-ISSN: 2349-0659 p-ISSN: 2350-0964
doi: 10.21276/apjhs.2018.5.2.26

Periodontal status in pre- and post-menopausal women: A review

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ABSTRACT

Life of a female itself can be termed as complex journey beginning biologically at puberty and terminating at menopause. Hormones are specific regulatory molecules that have potent effects on the major determinants of the development and the integrity of the skeleton as well as the oral cavity including periodontal tissues by modulating the periodontal tissue response. Periodontal manifestations occur when an imbalance of these steroid hormones take place. The aim of this article is to focus on the changes in periodontium that female experiences during beginning and cessation of her reproductive life and to inform and update practitioner's knowledge about the impact of these changes in the periodontium of a female.

Key words: Female, hormones, periodontal disease, periodontium

INTRODUCTION

Biological changes in a woman at specific phases in their life can be broadly divided into two phases, that is, premenstrual and postmenstrual phase; both of them being directly affected by changes in hormonal levels. Hormones are defined as specific regulatory molecules that have potent effect on the major determinants of the development and integrity of skeleton and oral cavity including periodontal tissues.[1] The homeostasis of the periodontium involves complex multifactorial relationships in which the endocrine system plays an important role, and it is well documented that periodontal manifestations occur when an imbalance of steroid hormones takes place. This review article will analyze how hormones influence the periodontium at different life stages such as puberty, menstruation, pregnancy, menopause, and postmenopause. Moreover, the effects of contraceptives and hormone replacement therapies (HRTs) on the periodontium will be discussed which could help the dental practitioner in better understanding and subsequently diagnosing and planning treatment of such conditions accordingly.

METHODS

Manual/electronic search was done from year 1965 to 2011 in English language for words such as "female and periodontium." Data from reputed journals were selected and compiled for review.

REVIEW OF LITERATURE

Reproductive life of a female begins with puberty which is a complex process of sexual maturation resulting in an individual capable of reproduction.[2] This begins with the secretion by the anterior pituitary of gonadotropin hormones (follicle-stimulating hormone and luteinizing hormone), which causes the ovaries to begin cyclical production and secretion of female sex hormones (estrogen and progesterone). It is also responsible for changes in physical appearance and behavior that are related to increased levels of the steroid sex hormones, testosterone in males, and estradiol in females. During puberty, the production of sex hormones increases to a level that remains constant for the entire normal reproductive period. After puberty follows menstrual phase where increased production and secretion of estrogen and progesterone in a cyclic pattern accompanies the onset of puberty and is referred to as the reproductive or menstrual cycle. The duration of normal reproductive cycle is 28 days and the monthly reproductive cycle has two phases: Follicular phase or proliferative phase and secretory or luteal phase. The first phase is the follicular phase, where the levels of follicle-stimulating hormone and estrogen are elevated and estrogen peaks approximately 2 days before ovulation. After ovulation, the secretory phase begins at approximately 14th day of the cycle. This phase is characterized by the synthesis and release of estrogen and progesterone by the follicular cells, which have become the corpus luteum. If fertilization does not occur, the corpus luteum will degenerate, plasma levels of estrogen and progesterone will decline, and menstruation will ensue.[3] During the menstrual cycle, progesterone peaks at approximately 10 days (increases from the 2nd week) and drops before menstruation.

Along with menstrual phase comes the course of a normal pregnancy, which is a series of profound and dynamic physiological changes occur in both the mother and developing baby. Some of the pregnancy-induced immunological modifications in the mother increase her susceptibility to a number of infections including

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Received: 15.02.2018 **Revised:** 28.04.2018 **Accepted:** 07.06.2018

periodontal disease. On fertilization and implantation, the corpus luteum continues to produce estrogen and progesterone while the placenta develops. Progesterone and estrogen reach their peak plasma levels of 100 mg/ml and 6 mg/ml, respectively, by the end of the third trimester, and the potential biological impact of estrogen and progesterone takes place in periodontal tissues during this period.[4]

During this phase, a female might as well start taking oral contraceptives these agents are based on the effects of gestational hormones that simulate a state of pregnancy to prevent ovulation. Current oral contraceptives consist of low doses of estrogens (0.05 mg/day) and progestins (1.5 mg/day), then comes menopause which is defined as permanent cessation of menstruation owing to loss of ovarian follicular activity.[5] Stages of the reproductive aging workshop developed a model to describe the seven stages of reproductive aging,[6] climacterium consisting of the transition period from fertility to infertility, of which menopause (the last menstruation) as well as perimenopause and postmenopause are parts. It is characterized by several symptoms such as night sweats and hot flushes which are observed in 75–80% of all women in the menopausal age.

DISCUSSION AND SUMMARY

Various factors influence the effect of sex hormone periodontium:

a. Gender: Gender plays an important role in changes of the bone density throughout the entire skeleton, and it is well known that women are much more affected than men. When the influence of gender on periodontal disease was studied, females were considered for several years to be more affected than males, although contradicting data have also been reported. This disparity seems to be simply correlated with the fact that females are more likely to seek more dental care than males.[2]
b. Age: The biological changes on the periodontal tissues during different time points such as puberty, the menstrual cycle, pregnancy, oral contraceptive use, and menopause have generated interest to know the relationship between steroid sex hormones and the health of the periodontium. Females also seem to be more prone to hormone imbalance than males.

Periodontal Status in Puberty

Several cross-sectional and longitudinal studies have demonstrated an increase in gingival inflammation without accompanying an increase in plaque levels during puberty.[7] Increased gingival inflammation was positively correlated with an increase in serum estradiol and progesterone and was not accompanied by a significant change in the mean plaque index.[8] The subgingival microflora is also altered during this period since the bacterial counts increase in number. There is a higher incidence of black-pigmented *Bacteroides* and higher populations of other Gram-negative rods in the subgingival microflora compared with healthy sulci in puberty with increased prevalence of certain bacterial species such as *Prevotella intermedia* and *Capnocytophaga* species.[9] *Capnocytophaga* species, which often increase during puberty, have been associated with the increased bleeding tendency observed during this period of time, whereas *P. intermedia* has been shown to possess the ability to substitute estrogen and progesterone for menodione (Vitamin K).

Periodontal Status in Menstrual Cycle

Progesterone increases permeability of microvasculature, altering the rate and the pattern of collagen production in the gingival tissue, increases folate metabolism, stimulates the production of prostaglandins, and enhances the chemotaxis of polymorphonuclear leukocytes.[10] As a result, significant gingival inflammatory changes have been documented in association with the menstrual cycle and gingival inflammation seems to be aggravated by an imbalance and/or increase in sex hormones.[11]

Bleeding and swollen gingival increase in gingiva exudates and a minor increase in tooth mobility have all been demonstrated during menses.[12] A gradual increase in gingival fluid occurs during the proliferation phase just before menstruation, where an increase in the production of estrogen and progesterone is observed.[13] During the luteal phase of the cycle, when progesterone reaches its highest concentration, intraoral recurrent aphthous ulcers, herpes labialis lesions, and candida infections may also occur in women.[14]

Periodontal Status in Pregnancy

Effect of hormones on pregnancy

Sex steroid hormones have been shown to have effects on cellular growth, proliferation, and differentiation of target tissues including keratinocytes and fibroblasts in the gingival tissues and may also modulate the production of cytokines.[11] Increased sex steroid hormones have effects on gingival vasculature, subgingival microbiota, specific cells of periodontium, and local immune system during pregnancy. Increased edema, erythema, gingival crevicular exudate, and hemorrhagic gingival tissues may also be observed due to the effects of estrogen and progesterone on the gingival vasculature. Progesterone has been shown to downregulate interleukin 6 (IL-6) production by human gingival fibroblasts which, in turn, may affect the development of localized inflammation, and gingiva becomes less efficient at resisting the inflammatory challenges produced by bacteria.[15]

Pregnancy and its microbiology

Several standard cultural microbiological studies have shown that estrogen and progesterone changes associated with pregnancy have an effect on the composition of the subgingival microbiota.[16] Some of the periodontal pathogens that apparently blossom under the selective pressure of pregnancy-associated steroids are *P. intermedia*, *Bacteroides species,* and *Campylobacter rectus*. Using DNA probes, it has been shown that pregnant and parous women harbor a diverse array of pathogens that have the potential to cause periodontal damage (i.e. periodontitis) including *Actinomyces odontolyticus*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Prevotella nigrescens*, *Fusobacterium nucleatum*, *Eikenella corrodens*, *Selenomonas noxia,* and *Aggregatibacter actinomycetemcomitans.*[17] Quantitative differences were detected in the subgingival bacterial composition between the pregnant and the non-pregnant women with the higher proportions of periodontal pathogens in pregnant versus non-pregnant women. Proportions of *P. intermedia* were significantly higher at the first trimester visit in pregnant group than in non-regnant group. Proportions of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* were significantly higher at the third

trimester visit in the pregnant group than at the 6 months visit in non-pregnant group.[18] Proportions of *Porphyromonas gingivalis* in positive patients tend to increase progressively during pregnancy with a peak at the third term and an abrupt decrease after delivery. The increase in *P. gingivalis* it can possibly explain the presence of progesterone in medium.[19]

Plaque-induced periodontal infections in pregnancy

Pregnancy gingivitis is extremely common condition occurring in a range between 30 and 100% of all pregnant women.[20] Clinically, it is seen as mild inflammation to severe hyperplasia, pain and bleeding, increased gingival probing depths, increased gingival inflammation, increased gingival crevicular fluid flow, increased bleeding on probing, and increased tooth mobility. The anterior region of the mouth is more commonly affected and the interproximal sites tend to be the most involved areas.[21]

Pyogenic granuloma and pregnancy

It is also known as pregnancy tumor or pregnancy-associated granuloma or *granuloma gravidarum*. Pyogenic granuloma is a non-specific inflammatory lesion of skin and mucous membranes that may occur in both males and females and appears most commonly during the second or third month of pregnancy with the prevalence of 0.2–9.6%.[10] It develops as a result of an exaggerated inflammatory response to local irritations as a rapidly growing gingival mass that may bleed profusely when touched. Based on histological features, it is a highly proliferative vascular lesion resembling granulation tissue. When there are lobular aggregates of blood vessels, the lesion may be called a lobular capillary hemangioma.[22] Clinical complaints associated with pregnancy-associated pyogenic granulomas are relatively minor and usually include gingival bleeding, tenderness, and esthetic problems. Treatment may include surgical removal, especially if the lesion is large and symptomatic. However, in many cases, the lesions undergo partial or complete resolution after delivery, especially if local irritants are removed.[23]

Impact of periodontal infections on pregnancy outcomes

In most studies, preterm birth is defined as a pregnancy of <37 weeks and a low birth weight of <2500 g.[24] However, other outcomes that have been used include low birth weight babies, preterm birth, preterm low birth weight babies, preterm birth <35 weeks, spontaneous preterm birth <32 weeks, small-for-gestational-age babies, and preeclampsia.[25] The presence of infection, particularly in the cervical area of the uterus increases the risk of delivering a preterm low birth weight baby. A suggested mechanism is that endotoxin from Gram-negative bacteria enters the circulation at high enough levels to stimulate the production of inflammatory mediators such as prostaglandin E_2 by the amnion.[26] Prostaglandin E_2 and other inflammatory mediators are potent inducers of labor. Periodontal pathogens (or their antigens) such as *C. rectus, P. intermedia, F. nucleatum, P. micra, P. gingivalis, T. forsythia, T. denticola,* and *P. nigrescens* cross the placenta and reach the developing fetus in high enough levels to stimulate the fetus to produce IgM antibody against these bacteria. Infection of amniotic fluid by oral microorganisms has been shown to be a possible complication of pregnancy as well as the probable cause of some cases of preterm birth. Among these bacteria are *Streptococcus spp., F. nucleatum,* and *P. gingivalis*. It is noteworthy that elevated subgingival levels *of P. gingivalis, T. forsythia, P. intermedia,* and *P. nigrescens* have been detected in the oral microbiota during pregnancy, which may increase the chances of their hematogenous translocation to the amnion.[27]

Periodontal infections and preeclampsia

A serious complication of pregnancy linked to periodontal infections is preeclampsia. This complication is characterized by hypertension, with blood pressure ≥140/90 mmHg, peripheral edema, and proteinuria.[28] Failure to control these physiological abnormalities can lead to eclampsia, in which convulsions, coma and death of the mother may occur. The link between periodontal disease and risk of preeclampsia has not been confirmed in all populations.[29]

Periodontal Status and Oral Contraceptives

Gingival tissues may have an exaggerated response to local irritants in which inflammation ranges from mild edema and erythema to severe inflammation with hemorrhagic or hyperplastic gingival tissues. It has also been reported that there may be a spotty melanotic pigmentation of the skin with the use of oral contraceptives.[30] A 50% increase in gingival fluid volume has been reported in women using oral contraceptives for 12 months compared to those who were not on birth control pills. Kalkwarf reported that the response might be due to alterations of microvasculature, increased gingival permeability and the increasing synthesis of prostaglandins.[31] There are no significant differences in plaque index and gingival index scores and attachment level between the oral contraceptive group and the controls. However, a 16-fold increase in *Bacteroides* species has been noted in the oral contraceptive user group. 2-fold increases in the incidence of localized osteitis following extraction of mandibular third molars due to the effects of oral contraceptives on clotting factors. The estrogen in the oral contraceptives causes a variation in the coagulation and fibrinolytic factors in women taking them, leading to a greater incidence of clot lysis.[12]

Periodontal Status in Menopause and Postmenopause

The following changes are seen in periodontium in menopause:

Hormones and menopause

Estrogen inhibition occurs after which female may complain of dry mouth because of decreased salivary secretion as well as a burning sensation of the mouth and tongue. Some women develop a condition known as menopausal gingivostomatitis, which is characterized by gingiva that is dry and shiny, bleed easily, and range in color from abnormally pale to erythematous.

Cytokines, periodontitis, and skeletal bone loss

Estrogen deficiency leads to upregulation of immune cells (macrophages and monocytes) and osteoclasts (OCs), which are responsible for a greater production of bone-resorbing cytokines[32] such as IL-1, 6, and TNF (1, 2). IL-1 and TNF are the most powerful locally produced stimulators of bone resorption and are well-recognized inhibitors of bone formation. These cytokines promote bone resorption *in vitro* and cause bone loss and hyperglycemia when infused *in vivo*. Lipopolysaccharide released byproducts related to periodontal tissues and bacterial plaque biofilm stimulates the production of inflammatory

cytokines, which further activates the OCs that resorb the bone. Inflammatory cytokines include IL-1, IL-8, IL-6, IL-10, tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), and the granulocyte colony-stimulating factor, which stimulate mature OCs, alter bone cell proliferation, and activate resorption of both the skeletal and alveolar bones, by triggering tissue proteinases and degradative enzymes, leading to the destruction of the connective tissue, alveolar bone resorption, and finally tooth loss.[33]

Periodontal diseases and menopause

Menopausal women also exhibit symptoms of periodontal diseases which refer to both gingivitis and periodontitis. Gingivitis is an inflammatory condition of soft tissues gums which can often be controlled by removing the hard and soft deposits from the tooth surface. If unchecked gingivitis progresses to periodontitis (which is a chronic inflammatory process that occurs in response to a predominantly gram-negative bacterial infection originating in dental plaque) leading to progressive and irreversible loss of bone and periodontal ligament attachment (as inflammation extends from gingiva into adjacent bone and ligament). Signs and symptoms of progressing periodontitis include red, swollen gums that may appear to have pulled away from the teeth, persistent bad breath, pus between the teeth and gums, and loose or separating teeth.

Osteoporosis and menopause

Osteoporosis is more common in women than in men. Women are at a greater risk for osteoporosis after menopause because estrogen levels decline rapidly leading to systemic bone loss.[34] Bone turnover rate is higher in alveolar bone than long bones. Therefore, it was suggested that a systemic imbalance in bone resorption and deposition might be manifested earlier in the alveolar process than in other sites.[35] Kribbs reported that postmenopausal women with osteoporosis had decreased mandibular bone density, thinned cortex at the gonion, and more tooth loss than healthy postmenopausal women. Type I osteoporosis occurs in postmenopausal women and has been related to estrogen deficiency associated with menopause. It leads to cascade of accelerated bone loss by decreased secretion of parathyroid hormone, increased secretion of calcitonin, and decreased calcium absorption which further aggravates bone loss. The possible mechanism by which postmenopausal osteoporosis leads to more periodontal destruction may be due to the presence of less crestal alveolar bone per unit volume, this bone of lesser density may be more easily absorbed which can be due to estrogen which reduces OC activity and increases its apoptosis. Studies suggest that low estrogen production after menopause is associated with increased production of IL-1, IL-6, IL-8, IL-10, tumor necrosis factor-alpha, granulocyte CSF, and GM-CSF, which stimulates mature OCs, modulates bone cell proliferation, and induces resorption of both skeletal and alveolar bone.[36] Serum osteocalcin is presently considered a valid marker of bone turnover (when resorption and formation are coupled) and a specific marker of bone formation (when formation and resorption are uncoupled).[37] Studies conducted by Bullon *et al*. reported that low serum osteocalcin concentration is associated with a significantly higher percentage of decrease in probing depth and clinical attachment level after periodontal treatment in postmenopausal women. Low saliva osteocalcin concentrations are significantly associated with a higher percentage of decrease in probing depth.[38]

Oral implants and menopause

Estrogen deficiency leads to decrease in trabecular bone volume around the implants and a decrease in contact between the implant and the trabecular bone.[39] Recent studies using animal models have examined the effects of a paucity of estrogen on the initial osseointegration of dental implants. These studies showed that when new implants (without functional occlusion) are placed in previously ovariectomized animals, the trabecular bone volume around the implant and contact between the implant and new trabecular bone are markedly decreased in comparison with non-ovariectomized animals.[41]

Treatment modalities in menopause and postmenopausal women

a. Peri or postmenopausal women take HRT to relieve climacteric symptoms and increase their quality of life. Hormone replacement in adequate dosage can slow or prevent bone loss. HRT includes oral administration, estrogen-containing dermal patches, and tibolone.[40] Estrogen replacement improves bone density in postmenopausal women. In a 3-year randomized trial in postmenopausal women with moderate or advanced periodontal disease, estrogen therapy significantly increased alveolar bone mass compared with placebo, and it increased bone density in the femur but not the lumbar spine.[41] Furthermore, women receiving hormonal therapy had significantly less gingival inflammation, lower plaque scores, and less loss of attachment. Marcos reported that the response to the HR therapy in periodontal disease is probably due to the existence of estrogen receptors localized in the gingiva and the periodontal ligament. Some studies have suggested that postmenopausal women using HRT have increased tooth retention[47] and decreased periodontal destruction. Alex *et al*. found that postmenopausal HRT women had a 2 times greater likelihood of having periodontitis than premenopausal women. In contrast, postmenopausal HRT+ women did not have a greater chance of having periodontitis than premenopausal women. Although postmenopausal HRT- women showed significantly greater tooth loss than postmenopausal HRT+ women. In a study conducted by Engeland *et al*., it was observed that premenopausal women aged 50–54 years healed similarly to women aged 18–43 years, whereas age-matched postmenopausal HRT women showed delayed healing. The data indicated that HRT may improve mucosal wound healing in postmenopausal women.

b. The two main pharmacological approaches to osteoporosis are the anticatabolic and anabolic therapy, which, respectively, decrease bone resorption and stimulate new bone formation.[42] The anticatabolic agents comprise bisphosphonates: Etidronate, alendronate, risedronate, and zoledronic acid; estrogen and the selective estrogen receptor modulator (SERM) raloxifene; salmon calcitonin; and denosumab. The only anabolic agent currently available is teriparatide.[53] The treatment with bisphosphonates reduces fracture risk, which is not shown for other available agents. Bisphosphonates accumulate in the mineral phase of bone and reduce OC activity by inhibiting farnesyl pyrophosphate synthase.[54] They can be administered orally (daily, weekly, or monthly) or I.V. (quarterly or yearly). Since their initial introduction in the United States in 1995, questions have

been raised about their association with possible side effects (osteonecrosis of the jaw, musculoskeletal pain, atrial fibrillation, atypical fractures, and esophageal cancer) that appear to be rare and may not be causally related.[45]

c. A new therapeutic advance in the treatment of osteoporosis is denosumab, a fully human monoclonal antibody to soluble RANKL.[46] Denosumab is the newest antiresorptive agent, with a novel mechanism of action.[47] It acts like OPG, preventing RANKL from binding to OC receptor RANK as a result, OC recruitment, maturation, and action are inhibited and bone resorption decreases. Unlike bisphosphonates, denosumab does not accumulate in bone. It has a circulatory half-life of approximately 26 days, and like other monoclonal antibodies, the clearance of denosumab is through the reticuloendothelial system and does not depend on renal clearance.[48]

Clinical Significance

Buencamino *et al.* reviewed the association between menopause and periodontal disease and suggested that postmenopausal women can be managed, in part, by returning to the basics suggested by the ADA:

i. Regular dental examinations; regular professional cleaning to remove bacterial plaque biofilm under the gumline where a toothbrush will not reach.
ii. Daily oral hygiene practices to remove biofilm at and above the gumline including brushing twice daily with ADA accepted toothpaste.
iii. Replacing the toothbrush every 3–4 months (or sooner if the bristles begin to look frayed).
iv. Cleaning interproximally (between teeth) with floss or interdental cleaner.
v. Maintaining a balanced diet.
vi. No smoking.

CONCLUSION

It is clear that endogenous sex steroid hormones play significant roles in modulating the periodontal tissue responses and may alter periodontal tissue responses to microbial plaque, and thus directly may contribute to periodontal disease. They can influence the periodontium at different lifetimes such as puberty, menstruation, pregnancy, menopause, and postmenopause. A better understanding of the periodontal changes to varying hormonal levels throughout life can help the dental practitioner in the diagnosis and treatment. The influence of sex hormones on periodontal wound healing is still largely unclear. Recent discoveries have a potential for developing new therapeutic strategies for the treatment of hormonal and bone disorders and can be present a promising role in future for same.

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How to cite this Article: Singh M, Singhal R, Negi R, Gupta R, Dahiya P, Kumar M, Bhardwaj R. Periodontal status in pre- and post-menopausal women: A review. Asian Pac. J. Health Sci., 2018; 5(2):136-141.

Source of Support: Nil, **Conflict of Interest:** None declared.