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. 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...
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 progesterons (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.\(^9\)

**Periodontal Status in Menstrual Cycle**

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.\(^10\) 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.\(^11\)

**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.\(^12\) 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
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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.\(^13\)

**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.\(^14\)
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*.\(^15\) 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.\[^{18}\]\(^{18}\) 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 can possibly explain the presence of progesterone in medium.\[^{19}\]\(^{19}\)

**Plaque-induced periodontal infections in pregnancy**

Pregnancy gingivitis is extremely common condition occurring in a range between 30 and 100% of all pregnant women.\[^{20}\]\(^{20}\) Clinically, it is seen as mild inflammation to severe hyperplasia, pain and bleeding, increased gingival probing depths, increased gingival infiltration, 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.\[^{21}\]\(^{21}\)

**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%.\[^{22}\]\(^{22}\) It develops as a result of an exaggerated inflammatory response to local irritants 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.\[^{23}\]\(^{23}\) 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.\[^{24}\]\(^{24}\)

**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.\[^{25}\]\(^{25}\) 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.\[^{26}\]\(^{26}\) 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.\[^{27}\]\(^{27}\) 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. micro, 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.\[^{28}\]\(^{28}\)

**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.\[^{29}\]\(^{29}\) 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.\[^{30}\]\(^{30}\)

**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.\[^{31}\]\(^{31}\) 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.\[^{32}\]\(^{32}\) 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.\[^{33}\]\(^{33}\)

**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 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 stimulate 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 proteases 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 increased 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.\[40\]

**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 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 anti-catabolic and anabolic therapy, which, respectively, decrease bone resorption and stimulate new bone formation.\[42\] The anti-catabolic 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.\[43\] 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 farnesy pyprophosphate synthase.\[44\] 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.[43]

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 circulating halflife 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.

REFERENCES


26. Klebanoff M, Searle K. The role of inflammation in preterm...
birth – focus on periodontitis. BJOG 2006;113 Suppl 3:43-5.


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