Research Journal of Pharmaceutical, Biological and Chemical Sciences

Role of Estrogen and Progesterone in the Periodontium.

Jaiganesh Ramamurthy*.

Department of Periodontics, Saveetha Dental College and Hospitals, 162, Poonamalee High Road Velappanchavadi, Chennai – 77, Tamil Nadu, India.

ABSTRACT

The investing and supporting structures of the teeth, termed Periodontium is responsive to endogenous hormones of our body. Among the endogenous hormone Estrogen and Progesterone have direct influence on oral tissues. The periodontal status at a given time is a cumulative effect of sex hormone levels, their regulatory impact, and the effects of interventions. The two hormones act synergistically to regulate the periodontal processes. Alteration in the proportionate concentration levels of the two hormones results in jeoparadisation of the overall regulatory mechanism at work. Puberty, Menstrual cycle, Pregnancy and Menopause alters the level of the sex hormones thereby influencing the periodontal tissues. This article summarizes the role of Estrogen and Progesterone in the Periodontium.
Keywords: Estrogen, Progesterone, Periodontium, Periodontitis.

*Corresponding author

INTRODUCTION

The investing and supporting structures of the teeth are termed as Periodontium. It comprises of Gingiva, Periodontal ligament, Cementum and Alveolar bone. The gingiva is firmly attached to the underlying bone and is continuous with the alveolar mucosa. Gingiva is divided into Marginal, Attached gingiva and Interdental papilla. Between the teeth and the gingiva is a shallow space called gingival sulcus. Gingiva comprises of epithelium and connective tissue. Periodontal ligament fibers attach the tooth to the alveolar bone. The root portion of the teeth has a mineralized external surface called as Cementum. These tissues are responsive to endogenous hormones of our body. Of all the endogenous hormones, Estrogen and Progesterone have direct influence on these structures. Any change in the level of these hormones can affect the homeostasis of the periodontium.

The Steroid Hormones

Eukaryotic cells express many cell-specific proteins in response to hormonal stimuli. Many of these hormones are steroids. Steroid hormones are grouped into five categories:

- Progestins
- Glucocorticoids
- Mineralocorticoids
- Androgens
- Estrogens

These hormones mediate a wide variety of physiological functions. All contain the four ring structure of the steroid nucleus and are remarkably similar in structure despite enormous differences in their physiological effects [1].

**Figure 1: shows the pathway of estrogen and progesterone formation**
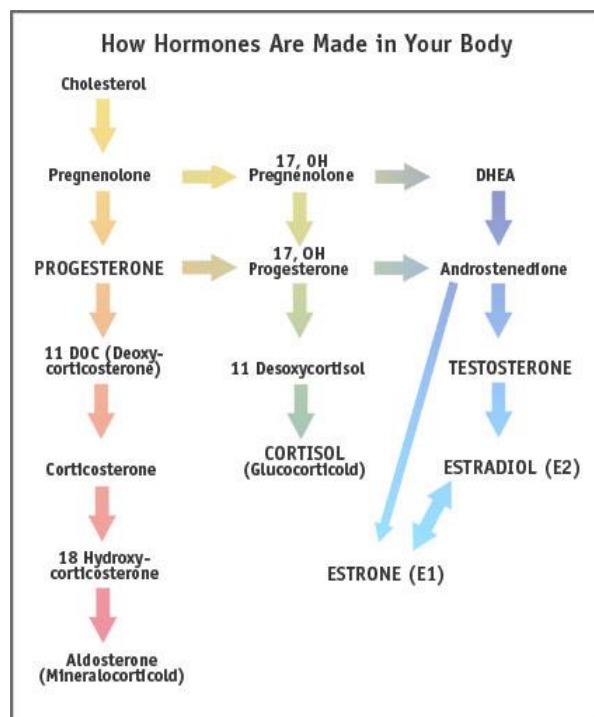
Estrogen

The term estrogen means 'estrus (Sexual season) producing substance' and hence, as applied to women and the higher primates, it is a misnomer sanctioned by historical reasons and common usage [2].

Estrogen occurs in three natural forms:

- 17 Beta - Estradiol
- Estrone
- Estriol

17 Beta - Estradiol is the major secreted primary estrogen and it is in equilibrium with estrone in circulation. Estrogens are secreted primarily by the granulosa cells of the ovarian follicles, corpus luteum, and the placenta [3].

**Figure 2: shows the structure of Estrogen**

HO... CH₃ OH structure
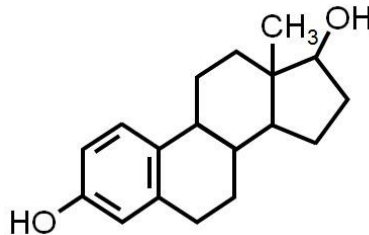
Progesterone

Hormones exhibiting progestational activity are the Progestins. They are also known as the luteal hormones, luteoids, or gestogens.They are C-21 pregnane group of steroid hormones of ovarian origin and they help mediate the menstrual cycle and pregnancy [1].

Progesterone or Progestin means "in favour of pregnancy". Progesterone and its inactivated metabolite Pregnanediol are the most important progestins besides the 17 alpha - hydroxy derivative of the former.17α - hydroxy progesterone is secreted along with the estrogens from the ovarian follicle and it parallels 17α - estradiol secretion [2].

The biosynthesis of the progestins parallels that of the estrogens. Cholesterol transported to mitochondria by a steroid carrier protein is converted to pregnenolone by the side chain cleavage enzyme cholesterol dismutase (Cytochrome P450).Pregnenolone moves to the smooth endoplasmic reticulum where some of it is dehydrogenated to form progesterone.

Figure 3: shows the structure of Progesterone
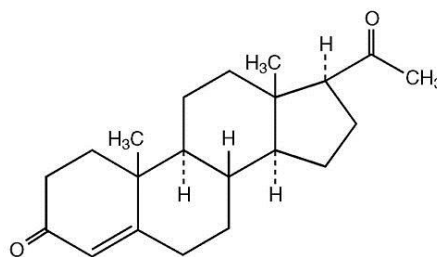
Effects of Estrogen and Progesterone

Progesterone primarily acts on estrogen primed tissues. The two act synergistically, though they can be antagonists. Estrogens increase progesterone receptors on the target tissues, but on the other hand progesterone reduces the number of estrogen receptors on the target tissues.

By affecting peripheral blood vessels, estrogens typically cause vasodilation and heat dissipation; they are anabolic and are required for the maintenance of metabolism in skin, bone and muscle; they have anabolic

effect on bone and cartilage and so they are growth promoting; Estrogens prevent osteoporosis probably by direct effect on osteoblasts.

Progestins reduce the proliferative activity of the estrogens on the vaginal epithelium and convert the uterine epithelium from being proliferative to secretory thus preparing the uterine epithelium for implantation of the ovum.

Mechanism of action

Estrogen binds with its receptors leading to active transformation of the receptors which involves loss of inhibitory proteins and dephosphorylation. Receptor dimerisation occurs which stimulates gene transcription [4,5]. ER alpha and ER beta are receptors for estrogen.

Progesterone receptor is bound to a heat shock protein in the absence of the steroid and progesterone binding releases the heat shock protein exposing the DNA binding domain of the receptor. The ligand - receptor complex is assumed to be the intracellular messenger in steroid hormone binding.

The hormone - receptor complex binds to a specific region of DNA and activates or inactivates specific genes; this DNA region is called hormone response element (HRE) and this is one regulatory element / control site in the DNA.

Homeostasis and Pathogenesis

The Ovarian steroid hormones, Estrogens and Progesterone, along with the androgens, are regulatory in protein metabolism and growth function.[6] Being regulatory, they have potent effects on the major determinants of the development and integrity of the skeleton and oral cavity including periodontal tissues.

They form part of the multifactoral relationships which contribute to the homeostasis of the Periodontium at different life stages like puberty, menstruation, pregnancy, menopause and postmenopause.

Periodontal manifestations in any stage are attributed to an imbalance of the steroid hormones. For Periodontal Pathogenesis to occur, besides the bacterial plaque, the susceptibility of the host is a pre-requisite. Estrogens and progesterone are systemic modifying factors which have a definite bearing on the susceptibility of the host in terms of prevalence, progression, and severity of the disease [7,8].

Figure 4: shows a clinical picture of Periodontitis

Hormone Receptors

To be effective in an organ system, a hormone should be able to effect genetic alterations and for this, as a pre-requisite, it should find its target cells with receptors and metabolizing factors in that system.

Estrogen and Progesterone receptors are located in the gingival tissues, periosteal fibroblasts, lamina propria fibroblasts, ligament fibroblasts, and osteoblasts.

RANKL stimulation studies have provided evidences for the presence of ERα in osteoclast progenitor cells [9.] Clinical reports of gingival enlargement concurrent with the onset of puberty and during pregnancy, or gingival atrophy, or surface desquamation during menopause have led some investigators to regard the gingiva as a secondary or 'another target organ' for the direct action of female sex hormones. Also, human gingiva has been shown to metabolise estrogens. [10]Clinical observations in humans have confirmed an increased prevalence of gingival disease with fluctuating plasma estrogen levels, even when oral hygiene remained unchanged [11].

Estrogen induced fibroblasts are found in cell culture indicating the fact that estrogen sensitive cell population is present in gingival fibroblasts. Progesterone competes either for the Osteoblast receptor along with the glucocorticoids or for the Glucocorticoid receptor itself. In both, bone resorption is inhibited.

Action on Fibroblasts

Estrogen sensitive cell population is present in gingival fibroblasts. Specific Estrogen and Progesterone receptors have been found to exist in gingival tissues. This is direct biochemical evidence that this tissue makes periodontium a target organ for the sex hormones [12]. Hormone receptors have been identified in basal and spinous layers of the epithelium and connective tissue.Estrogens enhance the secretion of the fibroblast growth factor from the stromal cells and modulate androgen metabolism.

Action on Collagen and Non - collagenous proteins

Estradiol stimulates cellular proliferation in culture and it leads to the anticipation that protein production would also be enhanced in premenopausal fibroblasts incubated in the presence of estradiol. On the contrary, both collagen and non-collagen protein production has been found to be below control values. This means that there has been no effect of estrogen on the relative amount of collagen synthesized by gingival fibroblasts. Similar effects on protein synthesis are reported in other tissue culture studies. In human periodontal ligament cells, estrogen triggered an in vitro reduction in fibroblast collagen synthesis [13].

Estrogens modulate androgen metabolism and stimulate the conversion of testosterone and 14 C-4 androstenedione to DHT which has anabolic effect on matrix synthesis in connective tissue and bone [14]. Thus estrogens are indirectly involved in the maintenance of fibrous collagen.

Inflammation and Hormone action

An environment of inflammation could alter the expression of steroid hormone receptors on fibroblasts, partly mediated by growth factors that modulate their metabolism and effects on tissues.

In inflamed gingiva, the metabolism of Progesterone is 2 to 3 times greater than in healthy gingiva indicating a very low, negligible amount of biologically active hormone in inflamed tissue. However in normal, healthy human gingiva and during sustained chronic inflammation, Progesterone metabolizes only slightly and is therefore in an active form.

In pregnancy gingivitis and granuloma, Progesterone functions as an immunosuppressant in the gingival tissue of pregnant women, preventing the rapid type of inflammatory reaction against plaque, but allowing an increased chronic type of tissue reaction resulting clinically in an exaggerated appearance of inflammation [15].

Estradiol shows a bidirectional effect - being inhibitory at a lower concentration and stimulatory at a higher concentration on PGE2 production.[16]Clinically Estrogen sufficient patients have been reported to have more periodontal plaque without increased gingival inflammation when compared to patients with deficient levels of estrogen. This suggests that inflammatory mediators may be affected by Estrogen hormone level, which may be attributed to the production of prostaglandins by the involvement of estradiol and

progesterone. The amount of circulating estradiol is inversely correlated with the prevalence of periodontal disease.

Estrogens inhibit pro-inflammatory cytokines release by human marrow cells. They reduce T-cell mediated inflammation. They suppress leukocytes production from the bone marrow. They inhibit PMN chemotaxis. They stimulate PMN phagocytosis.

Effect on Alveolar Bone

Estrogen receptors found in osteoblast -like cells provide a mechanism for the direct action on bone [17]. Estrogens stimulate DHT formation and, thereby, contribute to matrix synthesis in connective tissue and periosteal bone and the maintenance of fibrous collagen. [18]There is evidence that estrogens maintain bone volume not only by combination of bone resorption but also by stimulating bone formation. Decreased estrogen level causes negative calcium balance leading to loss in bone mass as against volume causing osteoporosis.

Activation of estrogen receptors in osteoclast progenitor cells decreases osteoclast formation and activation of estrogen receptors in terminally differentiated osteoclasts inhibits the bone resorbing activity. Prostaglandins are arachidonic acid metabolites.

Role of cytokines in bone resorption

The group of bone resorbing cytokines currently includes IL-1, IL-6, IL-11, IL-17 and TNFα [19]. The effects of cytokines that stimulate osteoclast formation and bone resorption seem to be counteracted by other cytokines that inhibit the same processes. Thus IL-4, IL-10, IL-12, IL-13, IL-18, interferonγ (IFNγ) are all able to inhibit either osteoclast formation or bone resorption or both [19]. It is likely that it is the balance between stimulatory and inhibitory cytokines, will determine the quantity of osteoclasts formed and their activity, and thus the degree of bone loss. The cytokines involved in bone resorption are all RANKL stimulating cytokines and they enhance OPG expression. It is possible that the effect of estrogen on bone resorption could be due to the inhibition of RANKL - stimulating cytokines [20].

Alteration in sub gingival microflora

The hormonal variations affect the physiology of host-parasite interaction in the oral cavity. Gram-positive aerobic organisms predominate in normal pre-pubertal children and in non-periodontal gingivitis. There is an increased prevalence of the bacterial species Prevotella inter media (Pi) and Capnocytophaga during puberty. Both estrogens and progesterone are shown to be accumulated by Pi as a substitute for Vitamin K as an essential growth factor. The subgingival bacterial flora of pregnancy individuals changes as pregnancy progresses and causes an increase in the ratio of anaerobic to facultative bacteria and the proportional levels of Prevotella inter media. It is also observed that the increased proportions of Prevotella inter media are concomitant with an increase in gingivitis and elevated serum ovarian hormone level during pregnancy.

Factors Influencing Harmone Effect

Puberty

Puberty marks the beginning of the sexual maturation of an individual into adulthood. It involves the reproductive changes occur between the average ages of 11 to 14 in most women. Most females who are systematically healthy with healthy gingiva will not develop significant periodontal changes due to puberty or menstruation; those who initially have gingivitis even with little accumulation of dental plaque will likely develop signs of puberty - or menstrual cycle associated gingivitis [21].

Gingival inflammation and enlargement associated with puberty are transitory and normalcy is usually restored in the post circumpubertal period. Higher proportions of P.intermedia in plaque samples of individuals during the stage of puberty is said to be the causative factor for puberty gingivitis.

Menstrual cycle

Two findings have been observed during menstrual cycle. They are:

- Gingival bleeding and increased production of gingival exudate sometimes associated with tooth mobility[22] and
- Ulceration of the oral mucosa (i.e. intraoral recurrentaphthous ulcers and vesicular herpes labialis).

The increase in levels of estrogen and progesterone is said to be responsible for the findings observed. Progesterone can cause reflux esophagitis which can be linked to apthous ulcers and increased permeability of vasculature is related to gingival bleeding.

Pregnancy

Gingival inflammatory changes in pregnancy usually begin during the second month and the severity of the disease increases through the eighth month, after which there is an abrupt decrease related to concomitant reduction in sex steroid hormone secretion. Moreover it has been confirmed that, during pregnancy, the severity of gingival inflammation is correlated to elevation of sex steroid hormones and is reduced following parturition and the concomitant drop off in hormone production [23].

Besides the steroid hormone factor, alterations in the immune system increased PGE2 synthesis when estradiol and progesterone are both in higher concentration, down regulation of IL-6 by progesterone, alteration of sub gingival microflora, and the increased prevalence of Pi bacterial species are all cited as cofactors [24]. The gingival inflammation observed in pregnant patients is termed as Pregnancy Gingivitis and few patients may progress from gingivitis to localized gingival overgrowth presenting it as Pregnancy Granuloma. Apart from these findings bleeding gums, increased tooth mobility is also observed in pregnant patients.

Menopause

The period during which the menstrual cycles cease and the female sex hormones diminish rapidly to almost none at all is called the menopause. Menopause usually begins between 45 and 55 years of age. Oral changes in menopause include thinning of the oral mucosa, oral discomfort (burning mouth), gingival recession, xerostomia, altered taste sensation, alveolar bone loss, and alveolar ridge resorption.

<div align="center">CONCLUSION</div>

Estrogens and Progesterone, being anabolic and catabolic respectively in independent action, together are related to periodontal status on the basis of a multifactorial impact that ultimately decides the internal environment of periodontium at a given time, or life stages like puberty, menstruation, pregnancy and menopause.

The studies reviewed have revealed that the two hormones are regulatory in protein metabolism and growth function and that they have potent effects on the major determinants of the development and integrity of the skeleton and oral cavity including periodontal tissues.

Establishing preventive periodontal measures will have beneficial effects on the oral health of the mother and child and help reduce the severity of periodontal conditions in future. Pregnant women in good health are unlikely to experience any significant gingival responses that would have serious implications. [25] To conclude, Periodontal homeostasis is a complex phenomenon involving the varied interactions of estrogens and progesterone within the physiologic concentration level or altered level as the case may be.

<div align="center">REFERENCES</div>

[1]   Voet D, Voet JG. Biochemistry. 2nd Ed. New York: John Wiley & Sons, Inc.; 1995: 493-507.
[2]   Samson-Wright. Applied Physiology, 5th Ed. London; 1956:200-210.

[3]   Ganong WF. Review of Medical Physiology, 19th Ed. New Delhi, Prentice Hall of India; 1999:450-460.
[4]   Lerner UH. Bone remodeling in postmenopausal osteoporosis. Journal of Dental Research, 2006; 85 (7): 584-595.
[5]   Lerner UH. J Dental Res 2006; 85 (7): 596 – 607.
[6]   Soory M. Dent Update 2000; 27: 380-383.
[7]   Hofbauer LC,Heufelder AE. J Mol Med 2001; 79: 243-253.
[8]   Mariotti A. Crit Rev Oral Biol Med 1994; 5:27-53.
[9]   Garcia Palacios V, Robinson LJ, Borysenko CW. J Biol Chem 2005; 280: 13720-13727.
[10]   Whitaker SB, Bouquot JE, Alimario AE, Whitaker TJ, Morgantown W & Cedarvill A. J Periodontol 1994; 65(3): 280-283.
[11]   Christiansen C, Riis BJ, Nilas L, Rodbrow P & Defton L. Lancet 1985; 2: 800-801.
[12]   Corgel JO. Carranza's Text Book of Periodontology; Periodontal therapy in the female patient,9th Ed;2003:610-616.
[13]   Nanba H, Nonura Y, Kinoshita M. Nippon Shishubyo Gakkai Kaishi 1989; 31:166-175.
[14]   Ojanotko-Harri A. J Steroid Biochem 1985; 23: 1031-1035.
[15]   Ojanotko A, Neinstedt W &Harri P. Arch Oral Biol 1980; 25: 481-484.
[16]   Tilakratne A &Soory M. J Clin Periodontol 1999; 26: 723-731.
[17]   Eriksen EF, Colvard DS, Berg NJ. Science 1988; 241: 84-86.
[18]   Tobias JH, Chow J, Colston KW. Endocrinol 1991; 128:408-412.
[19]   Horowitz J, Lorenzo JA. Local regulators of bone: IL-1, TNF, lymphotoxin, interferon-gamma, IL-8, IL-10, IL-4, the L1F/1L-6 family and additional cytokines, Principles of Bone Biology, 2nd Ed.,2002; San Diego, Academic Press: 961-978.
[20]   Elders PJ, Habets LL, Netelenbos IC, Van der Laiden LW, Van den Stelt PF. J Clin Periodontol 1992; 19: 492-496.
[21]   Weinberg Mea A. US Pharmacist 2002; 27 (9):1-6.
[22]   Kribbs PJ, Chesnut CH, Ott SM,Kilcoyne RF. J Prosthetic Dentistr 1990; 63: 86-89.
[23]   Ojanotko - Harri AO, Harri MP, Hurttia HM. J Clin Periodontol 1991; 118: 262-266.
[24]   Raber - Durbacher je, Van Steenbergen TJM, Van der Velden U, de Graff J. J Clin Periodontol 1994; 21: 549-558.
[25]   Raber-Durbacher JE, Leene W, Palmen - Bouva CC. J Periodontol 1993; 64: 211-218.