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REVIEW ARTICLE

INFLUENCE OF FEMALE SEX HORMONES ON PERIODONTIUM - A REVIEW

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ABSTRACT

Hormones are specific regulatory molecules that have potent effects on the major determinants of the development and the integrity of the skeleton and oral cavity including periodontal tissues. It is clear that periodontal manifestations occur when an imbalance of these steroid hormones take place. This review article focuses on how these hormones influence the periodontium at different life stages such as puberty, menstruation, pregnancy, menopause and postmenopause. Hormonal influences may appear in oral tissues before other systemic manifestations are apparent. Therefore, it is the clinician's responsibility to recognize, customize and vary periodontal therapy based on the individual female and the stage of her life cycle.

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INTRODUCTION

Hormones are specific regulatory molecules that modulate reproduction, growth and development and the maintenance of internal environments as well as energy production, utilization and storage (Mariotti, 1994). Sex steroid hormones, in addition to its role in reproductive function have potent effects on the nervous and cardiovascular system, and on major determinants of the development and integrity of the skeleton and oral cavity including periodontal tissues (McCauley *et al.,* 2002). Currently accepted periodontal disease classification recognizes the influence of endogenously produced sex hormones on the periodontium (Armitage, 1999). A better understanding of the periodontal changes to varying hormonal levels throughout life can help the dental practitioner in diagnosis and treatment.

Estrogen and progesterone

Estrogens play a crucial role in many vital activities, including the development and maintenance of secondary sex characteristics, uterine growth, pulsatile release of luteinizing hormone from the anterior pituitary gland and the development of peripheral and axial skeleton (Mariotti, 1994; McCauley *et al.,* 2002). Another hormone critical for females is progesterone secreted by the corpus luteum, placenta, and the adrenal cortex, and it is active in bone metabolism and has significant effect in the coupling of bone resorption and bone formation by engaging osteoblast receptors directly (Gallagher *et al.,* 1991). Estrogen and progesterone have significant biological actions that can affect other organ systems including the oral cavity (Pack and Thomson, 1980). Receptors for estrogen and progesterone have been demonstrated in the gingiva, in which the gingiva can be thought of as a target organ for progesterone and estrogen (Vittek *et al.,* 1982). Estrogen receptors are also found on periosteal fibroblasts, scattered fibroblasts of the lamina propria, and also periodontal ligament fibroblasts and osteoblasts (Eriksen *et al.,* 1988). Table 1 and 2 depicts the effect of estrogen and progesterone on periodontal tissues.

Table 1. Effects of estrogen on periodontal tissues

- Decreases keratinization while increasing epithelial glycogen that results in the diminution in the effectiveness of the epithelial barrier (Manson *et al.,* 2004).
- Increases cellular proliferation in blood vessels (Lindhe and Branemark, 1967).
- Stimulates PMN phagocytosis (Hofmann *et al.,* 1986).

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- Inhibits PMN chemotaxis (Ito *et al.,* 1995)
- Suppress leukocyte production from the bone marrow (Josefsson *et al.,* 1992)
- Inhibits proinflammatory cytokines released by marrow cells (Gordon *et al.,* 2001)
- Reduces T-cell mediated inflammation (Josefsson *et al.,* 1992)
- Stimulates the proliferation of the gingival fibroblasts (Beagrie, 1996)
- Stimulates the synthesis and maturation of gingival connective tissues (Beagrie)
- Increases the amount of gingival inflammation with no increase of plaque (Reinhardt *et al.,* 1999)

Table 2. Effects of progesterone on periodontal tissues

- Increases vascular dilatation, thus increases permeability (Mascarenhas *et al.,* 2003)
- Increases the production of prostaglandins (ElAttar, 1976)
- Increases PMNL and prostaglandin E2 in the gingival crevicular fluid (GCF) (ElAttar, 1976)
- Reduces glucocorticoid anti-inflammatory effect (Chen *et al.,* 1977)
- Inhibits collagen and noncollagen synthesis in PDL fibroblast (Tilakaratne and Soory, 1999)
- Inhibits proliferation of human gingival fibroblast proliferation (Mealey and Moritz, 2000)
- Alters rate and pattern of collagen production in gingiva resulting in reduced repair and maintenance potential (Pack and Thomson, 1980)
- Increases the metabolic breakdown of folate which is necessary for tissue maintenance and repair (Pack and Thomson, 1980)

Periodontal manifestations related to endogenous sex hormones

Puberty

Puberty is associated with a major increase in the secretions of the sex steroid hormones: testosterone in males and estradiol in females (Mascarenhas *et al.,* 2000). Several cross-sectional and longitudinal studies have demonstrated an increase in gingival inflammation without accompanying an increase in plaque levels during puberty (Mariotti, 1994). 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. Especially, there is an increased prevalence of certain bacterial species such as *Prevotellaintermedia* and *Capnocytophaga* species. Both estradiol and progesterone have been shown to selectively accumulate by *P.intermedia* as a substitute for vitamin K, and thus postulated to be acting as a growth factor for this microorganism. *Capnocytophaga* species have also been noted to increase in number as well as proportion in the subgingival milieu during puberty, and have been shown to correlate with an increased bleeding tendency.[21] A brief summary is given in table 3 and fig 1 and 2 depicts gingival inflammation seen in puberty.

Table 3. Clinical and microbial changes in periodontal tissues during puberty

- Increased gingival inflammation without accompanying an increase in plaque levels (Mariotti, 1994).
- Increased prevalence of certain bacterial species such as P. intermedia and Capnocytophaga species (Kasperk *et al.,* 1997).

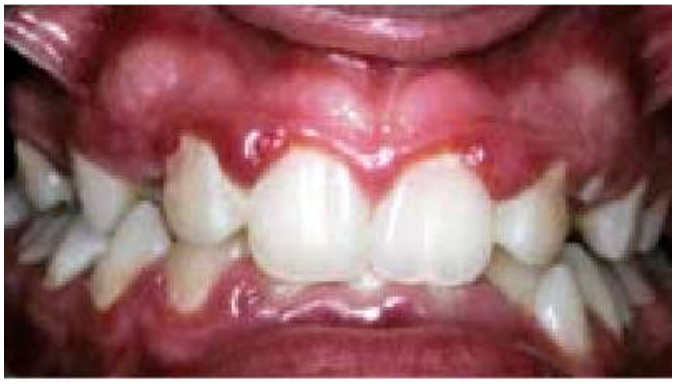

Fig. 1.

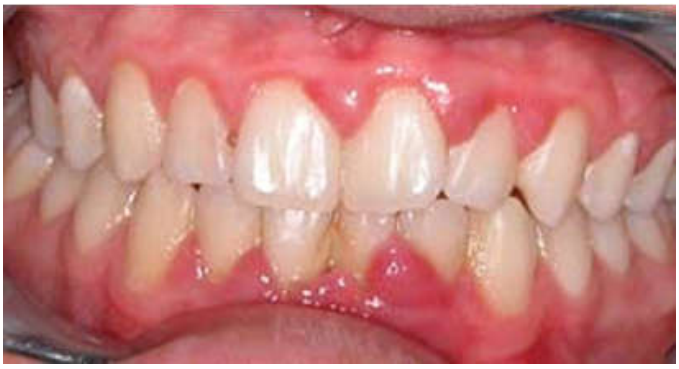

Fig. 2.

Fig 1 and 2. Gingival inflammation noted at interproximal sites at puberty

Menstruation

The onset of 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 (Mealey and Moritz, 2000). The first phase is the follicular or proliferative phase where the levels of follicle stimulating hormone and estrogen are elevated, and estrogen peaks approximately two days before ovulation. After ovulation the secretory or luteal phase begins at approximately day 14 of the cycle. This phase is characterized by the synthesis and release of estrogen and progesterone by the follicular cells (Mealey and Moritz, 2000). As a result of changes that are seen by increase in level of estrogen and progesterone as described earlier there is significant gingival inflammatory changes (Pack and Thomson, 1980). Bleeding and a swollen gingiva, an increase in gingival exudates, (Gusberti *et al.,* 1990) and a minor increase in tooth mobility have all been demonstrated during menses.

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 (Lindhe and Attström, 1971). 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 (Lindhe and Attström, 1971). Table 4 depicts clinical changes seen in periodontal tissues during menstruation.

Table 4. Clinical changes in periodontal tissues during menstruation

- Bleeding and swollen gingival (Lindhe and Attström, 1971).
- An increase in gingival exudates (Gusberti *et al.,* 1990)
- Minor increase in tooth mobility (Lindhe and Attström, 1971).

Pregnancy

Some of the most remarkable endocrine related oral alterations occur during pregnancy due to increased plasma hormone levels (Gusberti *et al.,* 1990). Upon 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 100ng/ml and 6ng/ml respectively, by the end of the third trimester, and the potential biological impact of estrogen and progesterone take place in periodontal tissues during this period (Mariotti, 1994). Pregnancy gingivitis is extremely common occurring in a range between 30 and 100 per cent of all pregnant women. Pinard first described this situation in 1877 characterized with erythema, edema, hyperplasia and increased bleeding. Cases range from mild inflammation to severe hyperplasia, pain and bleeding. Increased gingival probing depths, increased gingival inflammation, increased gingival crevicular fluid flow, increased bleeding upon probing and increased tooth mobility are the clinical periodontal manifestations that have been described during pregnancy.

The anterior region of the mouth is more commonly affected and the interproximal sites tend to be the most involved areas (Hugoson, 1971). Gingival inflammatory changes in pregnancy usually begin during the second month and the severity of the disease increases through the eight month, after which there is an abrupt decrease related to a concomitant reduction in sex steroid hormone secretion. Moreover, it has been confirmed that during pregnancy the severity of gingival inflammation is correlated to elevations of sex steroid hormones and is reduced following parturition and the concomitant drop-off in hormone production (Hugoson, 1971). There is also an increased incidence of pyogenic granulomas during pregnancy at a prevalence of 0.2 to 9.6 per cent. The 'pregnancy tumour' or 'pregnancy associated pyogenic granuloma' appears most commonly during the second or the third month of pregnancy (Mealey and Moritz, 2003). Gingiva is the most common site involved (70 per cent) followed by tongue, lips, buccal mucosa and the palate. The pregnancy tumour develops as a result of an exaggerated inflammatory response to local irritations, then enlarges rapidly and bleeds easily, and becomes hyperplastic and nodular (Hugoson, 1971). Cinical and microbial changes in periodontal tissues during pregnancy is summarized in table 5 and figure 3 demonstrates the changes seen in pregnancy.

Table 5. Clinical and microbial changes in the periodontal tissues during pregnancy

- Increased gingival probing depths (Hugoson, 1971).
- Increased gingival inflammation (Hugoson, 1971).
- Increased gingival crevicular fluid flow (Hugoson, 1971).
- Increased bleeding upon probing (Hugoson, 1971).
- Increased tooth mobility (Hugoson, 1971).
- Increased incidences of pyogenic granulomas (ElAttar, 1976).
- Increased numbers of periodontopathogens especially P. gingivalis and P. Intermedia (Hugoson, 1971).

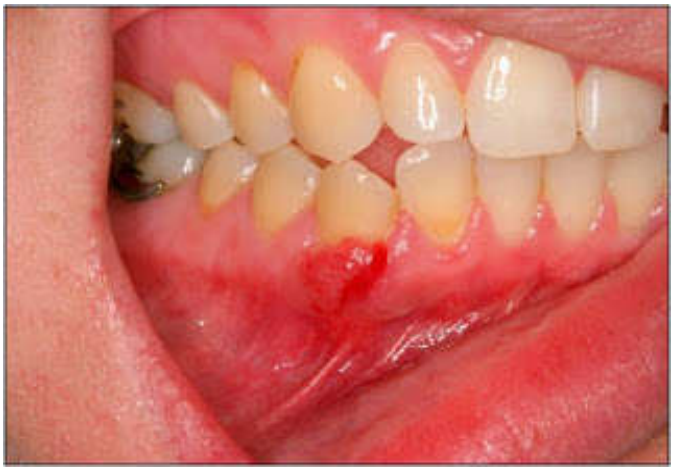

Fig. 3. Pregnancy tumor

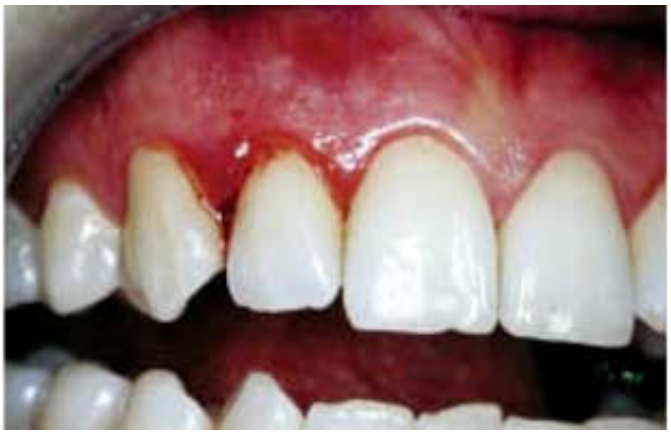

Fig. 4. Increased inflammation and hemorrhagic gingival site seen during use of oral contraceptives

Contraceptives

Hormonal contraceptives are agents based on the effects of gestational hormones that simulate a state of pregnancy to prevent ovulation (Mealey and Moritz, 2003). Current oral contraceptives consist of low doses of estrogens (0.05mg/day) and progestins (1.5mg/day). However, the initial formulations contained higher concentrations of sex hormones (20-50µg estrogen and 0.15-4mg progesterone). Gingival tissues may have an exaggerated response to local irritants. Inflammation ranges from mild edema and erythema to severe inflammation with hemorrhagic or hyperplastic gingival tissues (Fig 4). It has also been reported that there may be a spotty melanotic pigmentation of the skin with the use of oral contraceptives. This suggests a relationship between the use of oral contraceptives and the occurrence of gingival melanosis. Women taking oral contraceptives experience a twofold-increase 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 (Ferris, 1993). Impacts of contraceptives on clinical and microbial features of periodontal tissues are summarized in Table 6.

Table 6. Impact of contraceptives on clinical and microbial features of periodontal tissues

- Inflammation ranges from mild edema and erythema to severe inflammation with hemorrhagic or hyperplastic gingival tissues (Ferris, 1993).
- A 50 per cent increase in gingival fluid volume (Ferris, 1993).
- A 16-fold-increase in Bacteroides species (Ferris, 1993).

Menopause and postmenopause

Menopause usually begins between 45 and 55 years of age unless accelerated by hysterectomy and/or ovariectomy (Ferris, 1993). The levels of estrogen begin to drop mainly during the late follicular and luteal phase of the menstrual cycle when women approach menopause. The most significant problem that develops during menopause is osteoporosis (Ferris, 1993). Osteoporosis is a worldwide disease characterized by low bone mass and fragility and a consequent increase in fracture risk. Osteoporosis is also responsible for less crestal alveolar bone per unit volume, a condition that may promote quicker bone loss when encountered with infections such as periodontal infections. Moreover, osteoporotic/osteopenic women exhibited a higher frequency of alveolar bone height loss as well as crestal and subcrestal density loss compared to women with normal bone density. The incidence of periodontitis also correlates with signs of generalized osteoporosis (Ferris, 1993). The effects of reduced estrogen levels on epithelial keratinization along with decreased salivary gland flow, may have other significant effects on the periodontium. Women may demonstrate menopausal gingivostomatitis and the clinical signs of this disease are drying of the oral tissues, abnormal paleness of the gingival tissues, redness and bleeding on probing and brushing (Table 7). Oral discomfort is also commonly reported by postmenopausal women with burning sensation, xerostomia and bad taste (Mealey and Moritz, 2003).

Table 7. Clinical changes in the periodontal tissues during menopause and postmenopause

- Reduction in epithelial keratinisation (Friedlander, 2002).
- A reduction in salivary gland flow (Friedlander, 2002).
- Drying of the oral tissues (Friedlander, 2002).
- Redness and abnormal paleness of the gingival tissues (Friedlander, 2002).
- Bleeding on probing and brushing (Friedlander, 2002).

Peri or postmenopausal women take hormone replacement therapy (HRT) for relieving climacteric symptoms and increasing the quality of life. Effects of HRT on the periodontal tissues are summarized in Table 8.

Table 8. Effects of HRT on the periodontal tissues

- A protection takes place against tooth loss (Krall *et al.,* 1998).
- Reduction in gingival bleeding (Krall *et al.,* 1998).
- Reduction in the risk of edentulousim (Krall *et al.,* 1998).

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 life times 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.

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