Response of periodontal tissues to oral contraceptives

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Abstract

In postmenopausal women, osteoporosis has a negative outcome on teeth stability. Based on estrogen receptors ERa and ERβ found in periodontal tissues, the replacement hormonal therapy by oral contraceptives improves the density of alveolar bone and teeth stability, but without regaining the previous height of alveolus. Some possible adverse effects, such as gingival bleeding, epulis, oral mycosis and aphtosis that cease in 1-5 weeks after stopping the therapy, can be also observed. However, there is still no agreement regarding the incidence of bacterial plaque, gingivitis, gingival bleeding index, pocket probing depth and periodontal destruction between healthy control and postmenopausal women using oral contraceptives.

Keywords: *oral contraceptives, gingival inflammation, alveolar bone resorption*

Rezumat

La menopauză, osteoporoza afectează implantarea dinților. Grație existenței în țesuturile parodontale a doi receptori estrogeni, ERa și ERβ, tratamentul de substituție hormonală prin contraceptive orale ameliorează densitatea osului alveolar și stabilitatea dinților, dar nu asigură și refacerea înălțimii pereților alveolei. Pot apărea însă și efecte adverse, precum hemoragii gingivale, epulis, micoze orale sau afte care cedează însă la 1-5 săptămâni după încetarea tratamentului. Totuși, nu există încă un consens privind incidența plăcii bacteriene, gingivitei, indicelui de sângerare gingivală, adâncimii pungilor gingivale și a gradului de distrucție parodontală între femeile private de tratament hormonal și cele care folosesc contraceptivele orale.

Cuvinte-cheie: *contraceptive orale, inflamație gingivală, resorbție osoasă alveolară*

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Introduction

The periodontal ligament is a non-mineralized type of connective tissue consisting in a heterogeneous mesenchymal cell population, mainly fibroblastic and osteogenic or cementogenic, and attachment fibers with high content in collagen that links two distinct mineralized connective tissues, the root cementum and the alveolus bone[(1)].

The initial inflammation of periodontal tissues, termed plaque-induced gingivitis, begins at the gingival margin and modifies the local clinical appearance by changing the gingival contour and color, increasing gingival exudates and producing bleeding on probing the gingival sulcus[(2)].

Without on time and appropriate treatment, the periodontal tissues inflammation progresses, and its more advanced stage is represented by chronic periodontitis. Along with worsening of the initial signs and symptoms of the initial inflammation, loss of clinical attachment and alveolar bone, enlargement or recession of gingiva, tooth mobility and drifting are the chief added expressions of the disease[(3)]. Nevertheless, serum estradiol downregulates IL-1β release in gingival tissue, offering to menopausal and postmenopausal women a clinical improvement of gingival status[(4)].

Systemic bone in osteoporosis is also compromising the tooth stability, and the local alveolar bone loss might be a sign of advanced periodontal disease[(5)]. Unfortunately, though the estrogen replacement therapy decreases the alveolar bone porosity and strengthens the periodontal attachment, the bone socket height of affected teeth is not increased[(6)].

An extended study of postmenopausal osteoporotic women affected by chronic marginal periodontitis who followed an estrogen replacement therapy proved a lower incidence of deleterious effects of disease and lower costs of subsequent dental treatments than those hormonal untreated women[(7)]. Moreover, the periodontally involved postmenopausal women receiving estrogen replacement therapy preserved more teeth than men or non-estrogen treated women of the same age[(8)].

Oral contraceptives

Contraceptives are estrogen and progesterone gestational hormones synthesized to diminish the probability of ovulation[(9)]. In regard to periodontal tissues, commonly, the clinical outcomes of hormonal contraceptives intake, though lower in intensity, are similar to those found in pregnancy, such as enhanced gingival inflammation and higher rate of exudates secretion in gingival sulcus[(10)].

During pregnancy, there occur obvious clinical and histological changes in oral mucosa, particularly in gingival and periodontal tissues[(11)]. The local effects of using oral contraceptives, emerging from major systemic disadvantages of these drugs, are gingival inflammation

and loss of tooth attachment. The additional altered fibrinolytic activity is another deleterious outcome that has to be considered when surgical treatments are needed[12].

However, since the early 70s, in dental literature there have been mentioned numerous types of oral mucosa lesions provoked by oral contraceptives, such as hemorrhagic gingivitis, oral mycosis (*Candida albicans*), epulis, aphtosis, allergic erythema of the palate, and facial paralysis due to thrombosis of the facial artery that fortunately regressed in 1-5 weeks after stopping the medication[13].

As compared to formerly used oral contraceptives pills, which had a higher dosage of female sex hormones (20-50 mg estrogen/0.15-4 mg progesterone), the current formulations are delivered in lower daily amount of estrogen (0.05 mg) and progestins (1.5 mg)[14].

However, even in normal dose, progesterone-containing contraceptives may trigger a higher secretion of gingival exudates and volumetric augmentation of gingival papillae since the proinflammatory cytokines and local metabolic breakdown produces released from oral biofilms induce an exaggerated response of human body. When overdosing, the clinical appearance in pregnant women are dominated by gingival erithema, bleeding, gingival hyperplasia, and pregnancy epulis[14,15].

In women using oral contraceptives, the volume of salivary secretion of major salivary glands is increased, but it was noted a decrease of sialic acid, salivary proteins, hexosaminefucose and full amount of electrolytes[14].

Though the clinical studies confirm that the gingival inflammation becomes more intense in women when using oral contraceptives, by comparing with healthy control women, there is still no agreement concerning the differences in plaque, gingivitis, gingival bleeding indexes, periodontal destruction, and pocket probing depth. There are also under debate the outcomes of currently combined contraceptives, depending on total duration of their intake[14].

Effects of female sex hormones on periodontal tissues

Estrogens influence the periodontal tissues through various pathways:

- the involvement in gingival fibroblasts proliferation, synthesis and maturation of local connective tissue;
- increasing the degree of inflammation in gingival tissue, irrespective of bacterial biofilms presence;
- stimulation of neutrophils phagocytosis;
- slow down delivering of leukocytes from bone marrow;
- suppressing proinflammatory cytokines secretion in bone marrow cells and T-cell mediated inflammation;
- increasing the amount of acid mucopolysaccharide in oral mucosa;
- declining the defense capability of oral epithelium by dropping the keratinization and augmenting the glycogen content[14].

Modalities of progesterone influence on the periodontal tissues:

- suppressing the proliferation of gingival fibroblasts and subsequent collagen and non-collagenous protein synthesis resulting in a slow down of repair and maintenance potential of gingival collagen;
- enhancing the prostaglandins secretion, vasodilatation, vascular permeability simultaneously with slowing down the antiinflammatory effect of glucocorticoids;
- increasing the volume of gingival crevicular fluid and the amount of polymorphonuclear neutrophils and prostaglandin E2 coming out in gingival exudates[14].

Receptors of sex hormones in periodontal tissues

Periodontal tissues are chiefly perceptive to changes in hormonal balance of female sex hormones. While inflamed, the gingival tissue, due to its ability of metabolizing the steroid hormones, is increasing the release of active breakdown products of testosterone and estrogens, excepting the progesterone whose final metabolites are inactive[16].

The female sex hormones act as a ligand for estrogen receptors that are characterized by tissue specific distribution[1]. Estrogen (ER) and progesterone (PR) receptors were identified in human gingiva by biochemical technique, but their binding sites could not be located. No difference was observed regarding the number of binding sites between diseased gingival tissues and controls, though in phenytoin gingival hyperplasia their amount was higher compared to inflamed or healthy gingiva[17].

The estrogen receptors are transcription factors broadly expressed in different tissues as two subtypes, ERα and ERβ[18]. The cells of periodontal ligament have binding sites for endogenous 17β-oestradiol, which binds to both aforementioned receptors, based on its high affinity for ERα and ERβ proteins[19].

In addition to bone and lipid metabolism, the endothelial nitric oxide synthase activity is kept up by ERα expression. However, the data from literature regarding the ability of human periodontal cells to express specific mRNA for ERα receptors are still controversial[3], and the reason for their non-detection seems to be rather methodological[16].

The first report proving the ERβ existence in periodontal ligament cells suggested that the gene expression relies mostly through ERβ, as no obvious immunoreactivity for ERα was identified in cellular nuclei. Nevertheless, no difference was noticed between males and females[18]. Though earlier there were demonstrated both receptors ERα and ERβ in the periodontal ligament cells by polymerase chain reaction, it seems that ERβ is of major importance in mediating the gene transcription[18,20].

Periodontal ligament cells are stimulated by estrogens in osteogenic activity through ERβ, resulting in proliferation, osteoblastic differentiation, collagen synthesis, and configuration of mineralized nodules. Not

of less importance is the upregulation of key molecules such as alkaline phosphatase and osteocalcin or the ERβ contribution in expressing the periostin, which is highly involved in preserving the anatomic integrity of periodontal tissue when the tooth is exposed during chewing to occlusal overload[1].

In addition to classically accepted ERα and ERβ signaling[21], later on it was also reported a mitochondrial ERβ, which induces in human periodontal ligament cells the slowdown of cytochrome c oxidase subunit I expression, a mitochondrial enzyme engaged in oxidative phosphorylation[19]. The mitochondrial gene transcription may be regulated by estrogen because the mitochondrial genome proved to be equipped with base-pair sequences belonging to the estrogen response elements which bind both receptors ERα and ERβ[1,22].

Though accepted that estrogens regulate ATP production in mitochondria, the ERs subtype receptors in periodontal ligament cells are still not accurately proved. Moreover, unlike the periodontal tissue, in blood vessels estrogens enhance cytochrome c oxidase subunit I expression. An explanation might be the different cell types, such as endothelial and vascular smooth muscle which express both ERs receptors, ERα and ERβ, as compared to periodontal ligament cells, expressing chiefly ERβ[19].

The reduced energy release in periodontal ligament cells due to estrogen effect on cytochrome c oxidase subunit I expression downgrades the normal activity of cells, resulting in lower cell proliferation and collagen synthesis until another compensatory metabolic pathway under hypoxic conditions would be triggered[19].

There is a buildup of data advocating the presence of estrogen receptors in gingival tissue and fibroblasts, which are either spread out in *lamina propria*, or located in periodontal ligament. Moreover, these receptors were also found in periosteal fibroblasts and osteoblasts[14].

Looking for the presence of mRNAs corresponding to estrogen and androgen receptor expression by using the reverse-transcribed polymerase chain reaction, the androgen expression in human gingival and periodontal tissue and in corresponding fibroblasts was readily detected, unlike the transcripts for estrogen receptors that were not identified[23].

As DES (diethylstilbesterol) and DHT (dihydrotestosterone) do not modify the activity of the androgen receptor gene and do not induce the expression of the mRNA estrogen receptor in fibroblast, it was thought that the gingival tissue cannot respond directly to female sex hormones, but are sensitive to anabolic effects of androgens[23].

In postmenopausal women and in a 19-year-old woman, estrogen receptor mRNA were detected in oral mucosa, major salivary glands (parotid and submandibular glands) and minor salivary glands (labial glands), proving the biological role of estrogens in oral cavity tissues[24].

Oral microflora – contraceptives interplay

Depending on microorganisms density inside the biofilms, the crosstalk between bacterial cells relies on a molecular signaling pathway, termed quorum sensing, which is in charge with gene expression of biofilm population. Moreover, these quorum sensing molecules proved to regulate the immune response of the host[25].

The basic task of this pathway is to coordinate bacterial functions such as virulence, motility and ability for biofilm formation, and its efficiency is based upon three major classes of signaling molecules, known as autoinducers, as follows: Al-1, corresponding to Gram-negative bacteria; Al-2, for both Gram-positive and Gram-negative bacteria; and Al-3, which is specific to *E. coli* and *Salmonella*[25].

The autoinducers are involved in cell migration, apoptosis and epithelial homeostasis, including the adhesion between gingival keratinocytes. It was also observed that Al-1 inducers may disrupt the epithelial barrier of the gingiva[25].

Some *Prevotella* species – such as *P. intermedia*, *P. nigrescens*, *P. aurantiaca* and *P. pallens* – proved to utilize estrogen and progesterone during pregnancy. Mainly *P. intermedia* and *P. nigrescens* are found in gingival inflammation and pregnancy gingivitis, as compared to *P. pallens*, which is mirroring the status of periodontal health[25].

P. intermedia and *P. nigrescens* augment the gingival keratinocytes production of IL-6 and IL-8 cytokines. Some *Prevotella* species are also in charge with cytokines IL-1 and IL-23 expression by activating TLR-2. However, *Prevotella* species may trigger the IL-6, IL-8 and CCL20 chemokine release from gingival epithelium, promoting the defensive immune response, as well as the PMN migration to the inflamed periodontal tissues[25].

Particularly *P. intermedia* is a recognized periodontopathogen positively correlated with increased amounts of estradiol and progesterone. However, 17β-estradiol slows down the TNF-α and IL-1β expression in gingival keratinocytes, as well as the release of TNF-α and IL-8 by ERβ receptor[25].

Periodontopathogenic species of *Prevotella intermedia* were found in plaque samples of 22 out of 29 healthy women aged between 20 and 32 years old, before starting the medication with contraceptives containing 0.02 mg ethinyl estradiol and 0.15 mg desogestrel, respectively 0.03 mg ethinyl estradiol and 2 mg dienogest. After 10 day of contraceptive treatment, only a small variation of microbial content was found related to pretreatment status[26].

Some years ago, a novel procedure termed biotransformation was introduced in the pharmaceutical field to obtain drugs and chemicals. According to this technique, it was found that *Cephalosporium aphidicola* and *Cunningshamella elegans* fungi could metabolize oral contraceptives such as ethisterone (17α-ethynyl-17β-hydrozyandrost-4-en-3-one), a widely used synthetic steroid, having androgenic activity[27].

The biotransformation of ethisterone with *Cunningshamella blackesleeana* ATCC 8688a resulted into two

metabolites, 17α-ethynyl-6β,15β-trihydrozyandrost-4-en-3-one and 17α-ethynyl-7β,15β,17β-trihydrozyandrost-4-en-3-one. Used in a biotransformation study, another fungus, *Aspergillus niger* ATCC 1015, resulted in obtaining both a known metabolite, 17α-ethynyl-11α,17β-dihydrozyandrost-4-en-3-one, and a new metabolite, 17α-ethynyl-6α,15β,17β-dihydrozyandrost-4-en-3-one. However, all these four metabolites must be assessed for their contraceptive activity[28].

Conclusions

The periodontally involved postmenopausal women receiving estrogen replacement therapy seem to preserve more teeth than men or non-estrogen treated women of the same age, by proving a lower incidence of deleterious effects of periodontal disease, decreased severity of periodontal disease, and lower costs of subsequent dental treatments[29-31]. Though the oral contraceptives increase alveolar bone density and strengthen the periodontal attachment, they have no proved outcome on reconstructing the previous height of tooth alveolus. Also, the side effects of oral contraceptives in postmenopausal women must be carefully monitored, knowing the risks associated with this therapy: coronary heart disease, thromboembolic stroke, breast and endometrial cancer[32]. ■

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