



## Serum levels of progesterone and estradiol in menopausal women and users of hormonal contraceptives undergoing dental treatment

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### Abstract

**Objectives:** to assess whether women who are using hormonal contraceptives are at similar risk to menopause for oral problems related to falling levels of sexual hormones. **Methods:** serum estradiol and progesterone were measured to compare levels among women of childbearing age who use oral contraceptives or intrauterine devices with menopausal or hysterectomized women. The Mann-Whitney test was used to compare the plasma concentration of progesterone and estradiol between the groups and statistical significance was set

at  $p < 0.05$ . **Results:** fifty-two (52) women divided into two groups, 27 women aged 16 to 47 years, which used oral contraceptive methods or hormonal intrauterine device and 25 menopausal or hysterectomized women aged 45 to 76 years. Progesterone serum concentration ( $0.36 \pm 0.13$  ng / mL vs.  $0.21 \pm 0.03$  ng / mL,  $p = 0.001$ ) was significantly higher in the contraceptive group. The concentration of estradiol ( $19.8 \pm 12.5$  ng / mL vs.  $15.2 \pm 4.6$  ng / mL,  $p = 0.263$ ) was similar between the groups. **Conclusions:** women of childbearing age using hormonal contraceptives had similar estradiol levels to those of menopausal women. Low levels of this hormone may predispose to oral pathologies, so women should receive special attention at the dental care level.

## Introduction

Oral health involves complex multifactorial relationships in which the endocrine system plays an important role.<sup>1</sup> Sexual hormones (SH) play a role in the proliferation, differentiation

and growth of target cells in areas such as the alveolar bone, gingiva, ligament periodontal and root cementum. The modulation in SH levels during puberty, menstruation, pregnancy and menopause can influence the sensitivity to periodontal disease.<sup>2</sup>

The number of oral hormonal contraceptives (OHC) is increasing worldwide because of their use as a method of birth control and regulation of the menstrual cycle and ovulation.<sup>3</sup> Studies have shown that OHC may predispose to gingival insertion and inflammation in the subgingival environment, culminating in periodontal disease<sup>4</sup>, which manifests as bleeding and greater depth of the periodontal pocket due to increased cellularity and increased gingival size.<sup>5</sup>

Menopause is the period in the lifetime of a woman where hormonal production of progesterone and estradiol decrease at the end of the fertile age. The decrease of hormonal levels directly affects the oral cavity, which is where the receptors for the hormones are present. Oral xerostomia, hyposalivation, ha-

litis, bone postmortem, and periodontitis are signs and symptoms frequently associated with menopause.<sup>6</sup> Reactions to OHC or the use of intrauterine devices (IUD), which include gingivitis and periodontal diseases, are very similar to those that occur in menopausal women.<sup>3</sup>

Dental problems usually appear at times, such as pregnancy, puberty, and menopause, suggesting that hormonal changes may trigger these problems<sup>7</sup>. The most frequently encountered problems are those found in menopause, which may be related to the fall in hormonal levels, especially estradiol.<sup>8</sup>

The main objective of this study was to compare progesterone and estradiol serum levels among women of childbearing age who use oral contraceptive methods or hormonal IUD, with menopausal or hysterectomized women to assess whether women using contraceptive agents are at similar risk to menopausal women for oral pathologies.

## Methods

This is a cross-sectional study involving 52 women (n = 52) who were treated in a private dental office between January 2016 and December 2017, and who underwent an initial dental evaluation which included a request for serum levels of estradiol and progesterone. The inclusion criteria for participation in the study were female, at a fertile age of over 16 years, using OHC or IUD with progesterone, and menopausal or hysterectomized women who had never had any hormone replacement therapy (HRT). Participants were separated into two groups. Group I: 27 participants (n = 27) of childbearing age using OHC or IUD and Group II: 25 (n = 25) women who were menopausal and hysterectomized for more than five years who had never had any HRT. There were no sample calculations in this study, including all the women who had submitted the dosage of estrogen and progesterone in a private laboratory of clinical analyzes.

This research was submitted and approved by the Potiguar

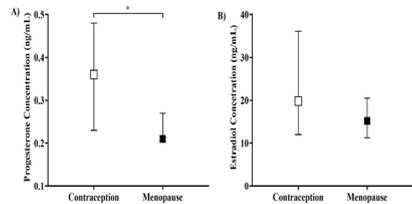
University institutional board, CAAE-88487618.0.0000.5296.

### Statistical analysis

The Shapiro-Wilk test verified the normal distribution of the data. The age variable presented normal distribution and is presented in mean and standard deviation. Serum levels of progesterone and estradiol were not normally distributed, and the descriptive data were presented in a median and semi-interquartile range. Student's t-test for an independent sample was used to compare the age of women between the contraceptive and menopausal groups. The Mann-Whitney test was used to compare the concentration of progesterone and estradiol between contraceptive and menopausal groups. Besides, this test was used to compare the age, progesterone, and estradiol concentrations among women using OHC or IUD. A statistical significance level of 5% was considered for all analyzes. All analyses were performed using the statistical package SPSS version 25.0 (IBM®, Chicago, IL, USA).

### Results

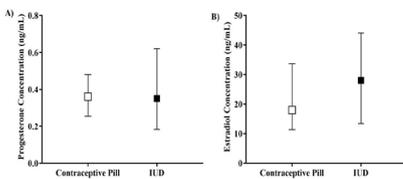
Fifty-two (52) women were included in the study, 27 were allocated to the contraceptive group and 25 were in the menopausal group. Women in the contraceptive group were between 16 and 47 years of age, while in the menopausal group the ages ranged from 45 to 76 years, with mean and standard deviation ( $33.4 \pm 8.0$  vs.  $61.9 \pm 8.7$  years,  $t(50) = -12.3$ ,  $p < 0.001$ ), respectively. The concentration of progesterone ( $0.36 \pm 0.13$  ng / mL vs.  $0.21 \pm 0.03$  ng / mL,  $U = 165$ ,  $z = -3,199$ ,  $p = 0.001$ ) was significantly higher in the contraceptive group (Figure 1A). The concentration of estradiol ( $19.8 \pm 12.5$  ng / mL vs.  $15.2 \pm 4.6$  ng / mL,  $U = 276.5$ ,  $z = -1,199$ ,  $p = 0.263$ ) was similar between the groups (Figure 1B).



**Figure 1.** Progesterone and estradiol concentrations among users of contra-

ceptive agents and menopausal women. **Figure 1A.** Progesterone concentration. **Figure 1B.** Estradiol concentration. Data expressed in median and quartiles 25 and 75. \* = statistically significant.

Among the 27 women who used contraceptive agents, 21 used oral contraceptives and six used IUD with progesterone. Among these women, the age was similar ( $32.0 \pm 5.8$  vs.  $37.5 \pm 7.0$  years,  $U = 33$ ,  $z = -1.753$ ,  $p = 0.085$ ), respectively. In addition, the concentration of progesterone ( $0.36 \pm 11.5$  vs.  $0.35 \pm 0.22$  ng / mL,  $U = 66$ ,  $z = 0.175$ ,  $p = 0.877$ ) and estradiol ( $18, 0 \pm 11, 1$  vs.  $28, 1 \pm 15, 3$  ng/mL;  $U = 43,5$ ;  $z = -1,139$ ;  $p = 0,263$ ) was not different (Figure 2).



**Figure 2.** Progesterone and estradiol concentrations among users of oral contraceptives and hormonal intrauterine devices (IUD). **Figure 2A.** Progesterone concentration. **Figure 2B.** Estradiol Concentration. Data expressed in median and quartiles 25 and 75.

## Discussion

This study evaluated the hormonal levels of women using contraceptive agents to verify the possible hormonal changes that occurred when using these contraceptive methods and found that there is no statistically significant difference among menopausal or hysterectomized women and users of contraceptives containing estrogen and progesterone, concerning serum estradiol levels.

Estrogen has significant actions in the oral cavity. Receptors for estrogen are in the gingiva, fibroblasts, osteoblasts, and periodontal ligaments. Women with low levels of estrogen tend to present more dental pain, greater gingival recession, dental mobility, and bone loss.<sup>9</sup> The findings of this study demonstrate that women who use hormonal contraceptives had similar levels of estradiol to that of menopausal women.

There is a natural decline in steroid hormones that may lead to increased inflammatory processes, loss of bone matrix deposition, decreased protein activity and decreased tissue lubrication during me-

nopause.<sup>10,11</sup> These hormones also play a significant role in maintaining bone mass, influencing bone mineral metabolism, inducing proliferation of fibroblasts and keratinocytes and increasing the synthesis of fibrous collagen.<sup>12,13</sup>

A study with estrogen-deficient female mice demonstrated that hormone deficiency leads to loss of mandibular bone.<sup>13</sup> Osteoblasts exhibit estrogen receptors that could explain the direct action of this hormone on the bone.<sup>14</sup>

Systemic bone loss is an essential effect of decreasing levels of estradiol. The deficiency of this hormone leads to the positive regulation of immune cells (macrophages and monocytes) and osteoclasts, responsible for higher production of cytokines of bone resorption.<sup>6</sup>

The sub-products released by lipopolysaccharides related to periodontal tissues and bacterial plaque biofilms stimulate the production of inflammatory cytokines, which further activate osteoclasts that reabsorb the bone.<sup>6</sup> Interleukins and Tumor Necrosis Factor (TNF) promote osteoclas-

tic stimulation.<sup>15</sup> In this study, women of childbearing age using OHC had similar serum levels of estradiol to that of menopausal women, and this may predispose them to the appearance of dental disorders.

Progesterone is active in bone metabolism and has a significant effect on bone formation through direct involvement of osteoblast receptors. This hormone promotes the increase of vascular dilatation on periodontal tissues, increasing prostaglandin E2 in the gingival fluid. In addition, it can produce reduction of glucocorticoid anti-inflammatory effect, inhibition of collagen synthesis in periodontal ligament fibroblasts, alteration of the rate and pattern of collagen production in the gingiva, resulting in increased metabolic degradation of folate, necessary for the maintenance and repair of the tissues.<sup>16</sup>

The systemic response of an organism to periodontal infections varies individually and depends on the individual's lipid composition.<sup>17</sup> Progestin, for example, decreases HDL when compared to natural progesterone,

which does not affect levels of this lipoprotein whereas estradiol can inhibit LDL oxidation, which can interfere with osseointegration of dental implants<sup>18,19</sup>

According to Krysiaka *et al.*<sup>20</sup>, the use of OHC is a risk factor for numerous oral and systemic complications. Patients using OHC present more gingival inflammation with greater bleeding in periodontal probing regardless of the amount of bacterial plaque<sup>5</sup>. This fact places these women at risk of contracting oral pathologies triggered by the drop-in levels of estradiol.

This study has some limitations: the small sample, the cross-sectional character of the study and the impossibility of associating oral pathologies with the hormonal levels.

Future research on oral pathologies related to the fall in hormone levels should prospectively assess, in a larger sample and with strict control of confounding bias, the association of reduced serum levels of estradiol and progesterone with disorders in the oral cavity.

Women of childbearing age

who use OHC or IUD with progesterone have serum estradiol levels like those in menopausal or hysterectomized women. The numerous oral pathologies that can occur due to changes in hormonal levels, such as the drop-in estradiol serum concentration, place patients who use contraceptive agents at risk of complications in teeth, gums and other places in the oral cavity.

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### **Conflicts of interest**

None declared

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