Effects of estradiol valerate associated with cyproterone acetate on some clinical and sexuality-related aspects in postmenopausal women

Efeitos do valerato de estradiol associado ao acetato de ciproterona em alguns parâmetros clínicos e da sexualidade em mulheres na pós-menopausa

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ABSTRACT

Objective: To evaluate the clinical effects of estrogen-progestin therapy in postmenopausal women, with particular emphasis on climacteric symptoms and sexuality. Methods: A prospective, blind, randomized, single-center, crossover, placebo-controlled study was carried out for 12 consecutive months in 40 postmenopausal women with a mean age of 52.2 years, with no contraindication to hormone therapy and with an intact uterus. The patients were divided into two groups: during the first six-month period of the study, one group received estradiol valerate 2 mg/day for 21 days/month associated with cyproterone acetate 1 mg/day in the last ten days of therapy (Climene™); the other group received one placebo tablet/day for 21 days/month. The treatments were then reversed, and the patients were followed-up for another six-month period. In the statistical analysis, the group receiving hormone therapy was denoted Group A, and the group receiving placebo Group B, regardless of the sequence in which the patient received the drug. Menopausal symptoms and sexuality were evaluated. Crossover analysis of variance and the McNemar test were used for statistical analysis. Results: A significant reduction was found in hot flashes and insomnia in the patients of Group A (the group that received hormone therapy). In this group, a significant improvement was also detected regarding sexual interest, communication with partner and ability to reach orgasm during penetration. Regarding the other issues, no statistically significant differences were detected. Conclusions: There was a significant improvement in menopausal symptoms and sexuality in the group of women that used hormone therapy.

Keywords: Hormone replacement therapy; Estrogen replacement therapy; Menopause; Sexuality; Valerates; Cyproterone acetate

RESUMO

Objetivo: Avaliar os efeitos clínicos da terapia estro-progestogênica em pacientes na pós–menopausa, com ênfase nos sintomas de climatério e sexualidade. Métodos: Estudo prospectivo, cego, randomizado, unicêntrico, cruzado e controlado com placebo, com duração de 12 meses consecutivos, feito com 40 mulheres na pós-menopausa (idade média de 52,2 anos) sem nenhuma contra-indicação para terapia hormonal e com útero íntegro, que foram divididas em dois grupos: nos primeiros seis meses de seguimento de estudo, um grupo recebeu valerato de estradiol 2 mg/dia por 21 dias/mês associado a acetato de ciproterona 1 mg/dia nos últimos dez dias (Climene™). O outro grupo recebeu um comprimido por dia, 21 dias/mês de placebo por seis meses. Os tratamentos foram então invertidos e as pacientes foram seguidas por mais seis meses. Para análise estatística o grupo que recebeu terapia hormonal foi referido como Grupo A e o grupo placebo como Grupo B. Avaliou-se a sintomatologia climatérica e a sexualidade. Aplicou-se a análise de variância (ANOVA, crossover) e o teste de McNemar.

Resultados: Nas pacientes do Grupo A, verificou-se redução significativa das ondas de calor e da insônia. No grupo que recebeu terapia hormonal, melhoria significativa foi também detectada com respeito ao interesse sexual, na comunicação com o parceiro e na capacidade de obter orgasmo durante a penetração. Para as

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INTRODUCTION

It is clearly defined that, for many women, reaching the climacteric and menopause often results in lack of motivation, low self-esteem and sensations of fear and emptiness. In addition to these emotional symptoms, women also undergo varying degrees of physical discomfort that are a result of the reduction in estrogen production. There are studies showing significant changes in sexual performance with the onset of the climacteric, mainly with regard to frequency of sexual intercourse and ability to reach orgasm\(^{(1)}\). The reduction in sexual desire is multifactorial and is correlated with psychosocial and organic factors resulting from the aging process itself, such as the arising of chronic and degenerative diseases and the lack of a sexually competent partner\(^{(2-4)}\). Hypoestrogenism is an additional factor that contributes to the occurrence of sexual changes in the postmenopausal woman, mainly in those cases in which climacteric symptomatology and genital atrophy are severe\(^{(5-6)}\).

Studies carried out by Rosen et al.\(^{(7)}\) showed that female sexual dysfunction affects more than 40% of women in the United States. These studies revealed that around one-third of American women have no sexual interest and 25% of them fail to reach orgasm. Approximately 20% of women report insufficient vaginal lubrication and 20% do not consider sexual activity enjoyable. These dysfunctions cause a serious impact on interpersonal relationships and on the quality of life of couples. However, they can be improved by the administration of specific hormone therapy\(^{(8)}\).

OBJECTIVE

To evaluate the effects of estradiol valerate associated with an anti-androgenic progestogen on some clinical aspects and sexuality in postmenopausal women who had a partner capable of performing coitus.

METHODS

Forty postmenopausal women (amenorrhea and increased follicle-stimulating hormone (FSH) plasma levels) with no contraindication for hormone therapy and an intact uterus were enrolled in a prospective, blind, randomized, single-center, crossover, placebo-controlled study, carried out over a period of 12 consecutive months. The women in the study sample were receiving care at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). Women with systemic, endocrine or psychiatric diseases, smokers of more than ten cigarettes/day, and users of hormone therapy or any medication that could interfere with menopausal symptoms and/or sexuality were excluded from the study. The study was approved by the Internal Ethics Committee of the Institution prior to its initiation.

Among the 40 patients enrolled in the study, two failed to return for follow-up visits and two withdrew their consent. Thus, 36 patients were included in the efficacy analysis. The women were divided into two groups: in the first six-month period of the study, one group of 17 women received estradiol valerate 2 mg/day for 21 days/month associated with cyproterone acetate 1 mg/day in the last ten days of therapy (Climene™, Schering, Brazil), and the other group (n = 19) received one placebo tablet/day for 21 days/month. The treatments were then reversed and the patients were followed-up for another six-month period.

The mean age of the women studied was 52.2 ± 4.2 years. Thirty-one (86.1%) women were white (Caucasian?), three (8.3%) were black, and two (5.6%) were of Asian descent. Their body mass index (BMI) ranged from 20.06 to 38.62 (mean 26.99 ± 4.8, Table 1).

General physical and gynecological examinations were normal in all patients. The following parameters were evaluated, in the first, third and sixth cycles:

- climacteric symptomatology according to the Kupperman’s Index\(^{(9)}\);
- sexuality according to the Golombok-Rust Inventory of Sexual Satisfaction (GRISS)\(^{(10)}\), consisting of 28 questions (Appendix 1) designed to evaluate the way in which each woman relates to her own body and to that of her partner, her level of interest in sexual activity, quality of communication with her partner, as well as frequency of sexual intercourse and capacity to reach orgasm. Answers vary according to intensity, ranging from none to the highest degree of intensity observed by the woman. There are five options of answers: always, generally, occasionally, hardly ever or never. Additional analyses were carried out, in which “always” and “generally” were considered to be affirmative answers and “never”, “hardly ever” and “occasionally” were considered negative answers.

Statistical analysis

For the purposes of statistical analysis, the group receiving hormone therapy was named Group A and the placebo group was designated Group B, regardless of the sequence
in which the patient received the drug. An exception was made for the ANOVA test, applied to the sums of the indices observed in the first, third and sixth cycles for each sub-item, in which the crossover model was used and the sequence in which medication was received was taken into account; and for the dichotomous McNemar’s test, for which the level of significance had to be adjusted from 5 to 1.7%. This adjustment was necessary because three tests were applied to the same variable, comparing each time-point with the basal evaluation.

**RESULTS**

According to the Kupperman’s index, a significantly lower number of hot flashes were recorded in patients of Group A (F = 15.72; p < 0.001), and there was no inter or intra-patient difference in the sequence of medication received. Frequency of insomnia was also significantly lower in Group A (F = 6.59; p < 0.05). Scores for paresthesia, melancholia and arthralgia/myalgia were significantly lower during the use of the second medication received, regardless of whether it was hormone therapy or placebo. No difference was noticed between treatments with respect to the other items comprised by the Kupperman’s index.

Regarding the analysis of the 28 questions comprised by the Golombok Rust Inventory of Sexual Satisfaction (GRISS), only those answers for which statistical significance was found, either between study groups or between the two sequences of treatment, are discussed (Table 2 and Appendix 1).

With respect to question 1, “Are you uninterested in sex?”, there was a statistically significant difference both between the groups (F = 6.25; p < 0.05) and between the two sequences of treatment (F = 5.43; p < 0.05). However, when the changes between baseline values and the values obtained during treatment were analyzed for each patient individually, no statistically significant differences were found between placebo and hormone treatment (McNemar’s test, Table 3).

With regard to questions 3 and 11, “Are there weeks in which you do not have sexual intercourse?” and “Can you place your finger in your vagina without feeling any discomfort?”, the intra-patient analysis of variation showed that the sequence in which the medication was received resulted in a statistically significant difference (F = 6.95; p < 0.05; and F = 10.36; p < 0.01, respectively).

### Table 1. Demographic and baseline data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline data (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td></td>
<td>52.2 ± 4.2</td>
</tr>
<tr>
<td>Median</td>
<td>52.0</td>
</tr>
<tr>
<td>Range</td>
<td>42-61</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td></td>
<td>26.99 ± 4.8</td>
</tr>
<tr>
<td>Median</td>
<td>25.82</td>
</tr>
<tr>
<td>Range</td>
<td>20.06-38.62</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>119.5 ± 10.8</td>
</tr>
<tr>
<td>Median</td>
<td>120.0</td>
</tr>
<tr>
<td>Range</td>
<td>90-140</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>74.7 ± 7.1</td>
</tr>
<tr>
<td>Median</td>
<td>70.0</td>
</tr>
<tr>
<td>Range</td>
<td>58-90</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td></td>
<td>81.1 ± 5.7</td>
</tr>
<tr>
<td>Median</td>
<td>81.0</td>
</tr>
<tr>
<td>Range</td>
<td>60-92</td>
</tr>
<tr>
<td>Race [number (%)]</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>31 (86.1%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Asiatic</td>
<td>2 (5.6%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>29 (80.6%)</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (19.4%)</td>
</tr>
</tbody>
</table>

BMI = body mass index; sd = standard deviation

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**Table 2. Results of analysis of the questions in which statistically significant differences were found (ANOVA)**

<table>
<thead>
<tr>
<th></th>
<th>Questions</th>
<th>ANOVA</th>
<th>1</th>
<th>3</th>
<th>7</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inter-individual variance</td>
<td>Intra-individual variance</td>
<td></td>
<td>Effect of hormonal therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F = 5.43; p &lt; 0.05</td>
<td>F = 2.06 (ns)</td>
<td>F = 7.46; p = 0.05 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sequence effect</td>
<td>Intra-individual variance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
<td>F = 6.25; p &lt; 0.05</td>
<td>F = 6.95; p = 1.22 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
<td>F = 10.36; p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effect of hormonal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Table 3. Results of statistical analysis of the questions for which statistically significant differences were found (McNemar test)

<table>
<thead>
<tr>
<th>Questions</th>
<th>1st cycle</th>
<th>3rd cycle</th>
<th>6th cycle</th>
<th>1st cycle</th>
<th>3rd cycle</th>
<th>6th cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>χ²1 = 2.25 (ns)</td>
<td>χ²1 = 3.12 (ns)</td>
<td>χ²1 = 7.11; p &lt; 0.01</td>
<td>χ²1 = 3.20 (ns)</td>
<td>χ²1 = 3.20 (ns)</td>
<td>χ²1 = 3.20 (ns)</td>
</tr>
<tr>
<td>28</td>
<td>χ²1 = 0.12 (ns)</td>
<td>χ²1 = 1.07 (ns)</td>
<td>χ²1 = 7.69; p &lt; 0.01</td>
<td>χ²1 = 7.11; p &lt; 0.01</td>
<td>χ²1 = 6.12; p &lt; 0.02 (ns)</td>
<td>χ²1 = 3.28 (ns)</td>
</tr>
</tbody>
</table>

ns = not significant
Question 7, “Do you try to avoid sex with your partner?”, presented an intra-individual variation in patients that was statistically significant depending on the sequence in which the medication was received (hormone therapy/placebo, $F = 7.46; p < 0.05$).

ANOVA failed to detect any statistically significant differences in any of the other questions in the GRISS questionnaire.

With regard to question 2, “Do you ask your partner what he likes or does not like in your sexual life together?”, McNemar’s test detected a significant improvement during the sixth cycle of hormone therapy ($\chi^2 = 7.11; p < 0.01$) compared to baseline data.

Regarding question 28, “Do you sometimes fail to have an orgasm during penetration?”, statistically significant changes occurred in the sixth cycle when the patient was using hormone therapy ($\chi^2 = 7.69; p < 0.01$).

No alterations were found in breast, physical or gynecological examinations throughout the study, and there was very little change in body weight, systolic and diastolic blood pressure or heart rate during treatment.

Two patients (5.7%) reported bleeding during placebo use, and 32 (91.4%) reported withdrawal bleeding while in use of hormone therapy. Only one patient withdrew prematurely from the study because of adverse events (depression and suicidal ideation).

**DISCUSSION**

The hormone therapy evaluated in this study consisted of estradiol valerate for 21 days/month associated with 1 mg cyproterone acetate during the last ten days of the 21-day therapy. This is the sequential hormone therapy regimen adopted by menopausal women who prefer to have cyclic bleeding patterns. The results of this study show significant improvement in hot flashes and insomnia with this therapy and this data is in agreement with other reports in the literature.$^{12-13}$

In this study, an increase of sexual interest was observed in the women during the period in which they were using the estrogen-progestin therapy compared to the phase in which they received placebo. Although many clinical trials have been carried out with the objective of evaluating the effects of estrogens on sexual function, there have been only few randomized, controlled studies. One such study was a trial carried out by Sherwin$^{14}$, in which conjugated equine estrogens were used by women who had undergone natural menopause. The author reported a significant increase in sexual desire in women during the 21-day period of hormone use compared to the 7-day period during which therapy was interrupted. No statistically significant differences were found in sexual desire between the groups of women who received higher or lower doses of conjugated equine estrogens, associated or not with medroxyprogesterone acetate. Dennerstein et al.$^{15}$ conducted during twelve months a double-blind, crossover study in women who had undergone surgical menopause, and compared estrogen-progestin therapy with estrogen therapy alone, progestin therapy alone and placebo. Estrogen therapy produced an increase in sexual desire compared to treatment with placebo or with progestins alone.

A study carried out by Fonseca et al.$^{16}$ to evaluate the clinical effects of the association of 2 mg 17β estradiol with 1 mg norethisterone acetate daily for six months showed a beneficial effect on sexuality, particularly with regard to sexual interest and satisfaction and also on climacteric symptoms.

Regarding the frequency of sexual intercourse, no increase was observed with the use of hormone therapy in the present study. A statistically significant improvement was found only when the woman received the placebo prior to hormone therapy (effective period). Nathorst-Boos et al.$^{17}$ studied the use of transdermal estrogen and reported a significant increase in the frequency of sexual intercourse with this therapy. The results of our study are in agreement with those published by Dennerstein et al.$^{15}$.

Estrogens enhance the action of vasoactive intestinal polypeptides which influence the endothelial and vascular change processes that occur during the sexual excitation phase, leading to transudation and vaginal lubrication$^{18}$.

An improvement in vaginal lubrication and the consequent reduction in discomfort during vaginal manipulation, as well as an improvement in communication and acceptance of sexual contact with the partner, achieved during hormone therapy, have also been reported by Nathorst-Boos et al.$^{17}$ and by Wiklund et al.$^{19}$, who compared transdermal estrogen therapy with placebo in women who had undergone natural menopause.

In the sixth cycle of this study, there was a significant improvement in the capacity of the women who received hormone therapy to reach orgasm during vaginal penetration. Dennerstein et al.$^{15}$ showed that orgasm frequency, from the highest to the lowest within the evaluated groups, occurred in the following sequence: group using estrogen therapy alone, estrogen-progestin therapy group, group using progestins alone, and, finally, the placebo group.

**CONCLUSION**

We concluded that this estrogen/progestogen association showed to be an effective hormonal treatment for postmenopausal women, improving climacteric symptoms and sexual function.
REFERENCES


Appendix 1 - Golombok-Rust Inventory of Sexual Satisfaction (GRISS)

1. Are you uninterested in sex?
2. Do you ask your partner what he likes or does not like in your sexual life together?
3. Are there weeks in which you do not have sexual intercourse?
4. Are you easily aroused?
5. Are you satisfied with the duration of foreplay prior to penetration?
6. Do you believe that your vagina is so tight that your partner’s penis will not be able to penetrate?
7. Do you try to avoid sex with your partner?
8. Do you achieve orgasm with your partner?
9. Do you like to hug and caress your partner’s body?
10. Do you consider your sex life with your partner satisfactory?
11. Can you place your finger in your vagina without feeling any discomfort?
12. Is it disagreeable to touch or caress your partner’s penis?
13. Do you become tense or anxious when your partner wants sex?
14. Do you consider it impossible to reach orgasm?
15. Do you have sexual intercourse more than twice a week?
16. Do you find it difficult to tell your partner what you like or do not like about your sexual life together?
17. Is your partner able to place his penis in your vagina without causing you any discomfort?
18. Do you feel a lack of love or affection in your sex life with your partner?
19. Do you enjoy having your partner touch and caress your genitals?
20. Do you refuse to have sex with your partner?
21. Are you able to reach orgasm when your partner stimulates your clitoris during foreplay?
22. Are you satisfied with the duration of penetration?
23. Do you feel aversion or repugnance with respect to what you and your partner do during sexual intercourse?
24. Do you believe that your vagina is so tight that your partner’s penis will be unable to penetrate deeply?
25. Is it disagreeable to be hugged or caressed by your partner?
26. Does your vagina become wet during sexual intercourse?
27. Do you enjoy intercourse with your partner?
28. Do you sometimes fail to have an orgasm during penetration?