ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 1, 63–67
ISSN 1899–5276

Emel Kiyak Caglayan[1, A, D], Mustafa Kara[1, B], Sema Etiz[2, B, F], Pinar Kumru[3, C, D], Nurettin Aka[2, F], Gultekin Kose[2]

The Effects of Progesterone Selection on Psychological Symptoms in Hormone Replacement Therapy

[1] Department of Obstetrics and Gynecology, Bozok University Faculty of Medicine, Yozgat, Turkey
[2] Department of Obstetrics and Gynecology, Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey
[3] Department of Obstetrics and Gynecology, Zeynep Kamil Research and Training Hospital, Istanbul, Turkey

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Objectives. The aim of this study is to evaluate the effects of hormone replacement therapy using dienogest and medroxyprogesterone acetate on psychological symptoms in perimenopausal and postmenopausal women.
Material and Methods. A total of 73 patients who sought treatment at the menopause units of the authors' gynecology and obstetrics clinics between of November 2003 and October 2004 complaining of vasomotor symptoms were included in the study prospectively. The cases were divided into two groups: Group I (37 patients) was given 2 mg estradiol valerate and 2 mg dienogest, and Group II (36 patients) was given 2 mg estradiol valerate and 10 mg medroxyprogesterone acetate. The groups' results in months 0 and 6 were compared through the evaluation of vasomotor and psychological symptom levels.
Results. No significant difference was found between the groups when the initial levels of vasomotor and psychological symptom subtypes were compared ($p = 0.16$). It was observed that all the psychological symptoms decreased in the 6th month in the group using dienogest in comparison with the initial situation, and that psychological symptoms increased in the group using medroxyprogesterone acetate in the evaluation performed in the 6th month compared with the initial levels. It was also found out that there was a statistically significant difference between the two groups when compared in terms of these symptoms ($p < 0.0001$).
Conclusions. While the use of dienogest normalizes the general psychological situation and sleep, it was observed that the use of medroxyprogesterone acetate (MPA) worsens the general psychological situation (**Adv Clin Exp Med 2014, 23, 1, 63–67**).

Key words: menopause, dienogest, medroxyprogesterone acetate, psychological symptoms.

Menopause is generally defined as the ending of menstruation. Psychological, social and cultural factors should be evaluated together in menopausal period. Although menopause is accepted as an endocrinopathy, its symptoms play an important role in a woman's life. It is controversial whether this period is clinically a psychological disorder or a period that causes psychological symptoms to emerge more [1]. While some patients go through this period with mild complaints, the others can have a series of symptoms of physiological changes such as feeling hot, vasomotor symptoms, changes in mood, sleep disorders and somatic complaints. The effects on cognitive functions can reduce the quality of life and social relationships. The aim of post-menopausal hormone therapy is to improve the quality of the patient's life and prevent the negative changes affecting the patient's life. Acute menopausal symptoms are an effect of a decrease in estrogen levels [2, 3].

The influence of hormone replacement therapy (HRT) was assessed in a recent study that investigated the symptoms arising in the menopausal period of women treated with some of the

current HRT preparations [4]. HRT improved negative menopausal symptoms by affecting the central nervous system (CNS). However, some of the HRT preparations used for treatment are thought to worsen the woman's current psychological situation. Among the explanations proposed for the fact that psychological symptoms deteriorate with HRT are a premorbid personality structure reacting to different progesterone types, or the structural sensitivity of women with individual predispositions [5].

The aim of the current study is to investigate the effects of 2 different HRT preparations used in menopause, particularly their effects on patients' vasomotor symptoms and current psychological situations, and their psychological interactions after 6 months of treatment.

Material and Methods

This was a prospective randomized controlled study. Seventy-three women who sought treatment at the menopause units of the authors' gynecology and obstetrics clinics between November 2003 and October 2004 were included in the study. The study was reviewed and approved by local ethical committee. Informed consent was obtained from all the participants. They were randomly divided into 2 groups: the first group constituted 37 patients, and the second one was made up of 36 patients. No patient was excluded from the study for any reason. The general characteristics of the patients noted in the follow-up included in the study were: the date of the last menstrual period, educational and occupational situations, marital status, number of children, daily smoking and body mass index (BMI). The participants in Group I were given 2 mg estradiol valerate and 2 mg dienogest once a day, while the participants in Group II were given 2 mg estradiol valerate and 10 mg medroxyprogesterone acetate per day.

The Symptom Checklist-90-R (SCL-90-R) and Kupperman index were given to the subjects upon their initial hospital admission and after 6 months, and the results obtained from the patients were evaluated by psychologists in single-blind study style [6–8]. The level of stress and the response of these symptoms to the treatment were assessed at the beginning of the treatment and in the 6th month. While the findings obtained in the study were being evaluated, Statistical Package for Social Sciences for Windows (SPSS) software (version 11.0) was used for the statistical analysis. Frequency counting, average and standard deviation, which are descriptive statistical methods, were used. The Kolmogorov-Smirnov test and graphical representation were utilized for the normality distribution of the data. To compare the quantitative data, the Mann-Whitney *U* test was performed; and to compare the qualitative data, the chi-square test was carried out. The results were in the 95% confidence interval, the level of significance was $p < 0.05$ and the highest level of significance was $p < 0.01$.

Results

There was no statistically significant difference between the 2 groups according to the Kupperman index ($p = 0.16$). Temporal changes in both Group I and Group II were significantly higher in the 6th month than at the start of the treatment ($p < 0.0001$) (Table 1). The difference between the initial somatization scores in the 2 groups was not statistically significant ($p = 0.25$). Group I's symptoms were significantly improved in Month 6th as compared to the 1st month ($p < 0.0001$). In Group II, the symptoms were worse in the 6th month than in the 1st month and this difference was also statistically significant ($p < 0.0001$).

While in Group I social anxiety scores were found to be significantly lower in the 6th month than 1st month, in Group II the symptoms were stronger in the 6th month than at the beginning ($p < 0.0001$).

Depression scores in the 6th month were found to be significantly higher in Group II than in Group I ($p < 0.0001$). Anxiety scores in the 6th month were found to be significantly higher in Group II than Group I ($p < 0.0001$). At the beginning, the scores for anger and hostility were not significantly different between the 2 groups ($p = 0.57$). However, 6 months later, those scores

Table 1. Kupperman index distribution in the groups

Kupperman Index	Group I ($x \pm_{Sx}$)	Group II ($x \pm_{Sx}$)	Total	p value
Beginning	25.4 ± 5.7	23.2 ± 7.02	24.3 ± 6.5	0.16
6th Month	7.8 ± 4.6	8.6 ± 4.5	8.2 ± 4.5	0.38
Temporal Change (p)	0.00001	0.00001	0.00001	

$X \pm_{Sx}$ – average ± standard deviation.

Table 2. The results of the analysis of the psychiatric symptom and complaint screening test (SCL-90-R) for 9 different symptoms and an additional scale at the start and in the 6th month

	Scoring time	Group I ($x \pm_{Sx}$)	Group II ($x \pm_{Sx}$)	p value/temporal change
Somatization	Month 0	2.3 ± 0.5	2.1 ± 0.6	0.25
	Month 6	1.01 ± 0.3	3.2 ± 0.3	< 0.0001
Obsessive-compulsive scale	Month 0	2.1 ± 0.5	2.2 ± 0.6	0.39
	Month 6	0.9 ± 0.4	3.7 ± 0.3	< 0.0001
Social anxiety	Month 0	2.4 ± 0.5	2.2 ± 0.6	0.17
	Month 6	0.9 ± 0.4	3.6 ± 0.3	< 0.0001
Depression	Month 0	2.3 ± 0.7	2.1 ± 0.8	0.36–41
	Month 6	0.5 ± 0.4	3.6 ± 0.4	< 0.0001
Anxiety	Month 0	2.4 ± 0.6	2.2 ± 0.6	0.20
	Month 6	0.9 ± 0.5	3.6 ± 0.3	< 0.0001
Anger/Hostility	Month 0	2.5 ± 0.5	2.3 ± 0.7	0.57
	Month 6	0.8 ± 0.5	3.5 ± 0.3	< 0.0001
Phobic anxiety	Month 0	2.1 ± 0.6	2.2 ± 0.6	0.53
	Month 6	0.9 ± 0.5	3.6 ± 0.3	< 0.0001
Paranoid ideation	Month 0	2.2 ± 0.4	2.1 ± 0.3	0.99
	Month 6	0.6 ± 0.5	3.4 ± 0.3	< 0.0001
Psychoticism	Month 0	2.04 ± 0.4	2.06 ± 0.4	0.54
	Month 6	0.4 ± 0.4	3.5 ± 0.3	< 0.0001
Additional Scale	Month 0	2.3 ± 0.7	2.3 ± 0.6	0.9
	Month 6	0.8 ± 0.4	3.6 ± 0.3	< 0.0001

$X \pm_{Sx}$ – average ± standard deviation.
**p* value of the temporal change of the evaluation for all 9 symptoms and additional scale at initial and in the 6th month was determined as < 0.0001 among the groups.

were significantly lower in Group I than Group II ($p < 0.0001$).

At the onset of the treatment, phobic anxiety scores were not significantly different between the two groups ($p = 0.53$), but at the end of the 6th month, they were found to be higher in Group II than in Group I. This difference was statistically significant ($p < 0.0001$).

Paranoid ideation was assessed and there was no statistically significant difference between the two groups at the beginning ($p = 0.99$) When the scores were reassessed after 6 months, the measurement was significantly lower in Group I than in Group II ($p < 0.0001$) At the beginning, the scores for psychoticism did not significantly differ between the 2 groups ($p = 0.54$). Months later, these scores were found to be significantly higher in Group II than in Group I ($p < 0.0001$) (Table 2).

Discussion

A considerable degree of recovery was noted in the group using dienogest. In all the subgroups of psychological parameters – including somatization, obsessive-compulsive disorder, phobic anxiety, depression, anger and hostility, paranoid ideation and psychoticism – the differences were found to be statistically significant when comparing the initial month and the 6th month. Among the psychological subgroups whose symptoms improved to a more notable degree, somatization came first, while obsessive-compulsive disorder and social anxiety ranked number two. Comparing all the parameters in the 6th month between the Group I and Group II, the improvement of Group I, using dienogest, was found to be higher than in Group II, using MPA. This psychological improvement provided by dienogest

is statistically significant ($p < 0.0001$). With regard to the group using MPA, it was determined that the participants' psychological situation became worse in the 6th month in comparison with the initial status, and this decline was statistically significant ($p < 0.0001$). Although the curative effects of MPA on vasomotor symptoms is the same as the effects of dienogest, the authors note that MPA affects the patient's mood, sleep, depression and other psychological subparameters negatively.

Similar results were found in Schneider's neurophysiological study: that dienogest provided complete recovery in vasomotor and neurovegetative symptoms, and great improvement in postmenopausal women with cognitive functions and sleep disorders. The authors concluded that the use of dienogest in continuous combined hormone replacement treatment was specifically indicated for postmenopausal women with disorders of alertness and mood [8, 9]. Graser et al. compared 2 mg estradiol valerate and different dose combinations of dienogest (0.5, 1, 2, 3 and 4 mg). They stated that all of the dienogest doses provided significant recovery in vasomotor and psychoneurotic symptoms [10]. Oettel et al. stated that 2 mg estradiol and 2 mg dienogest affected postmenopausal symptoms related to insomnia, sleep patterns and the patient's general well-being [11].

Saletu et al. carried out an evaluation of the alertness of patients with postmenopausal syndrome suffering from insomnia, using EEG mapping in a double-blind placebo-controlled study. They compared a continuous 2 mg estradiol valerate + 2 mg dienogest treatment with single estrogen therapy, and determined that 2 mg of estradiol valerate improved alertness slightly. The addition of dienogest did not minimize the effect of estrogen, but rather increased it. This made the combination superior to both a placebo and to estradiol [12]. Saletu et al. also evaluated the quality of sleeping and awakening in 55 patients with insomnia in a double-blind, trifurcate and placebo-controlled study. They stated that estrogen/progesterone combinations with dienogest significantly improved subjective sleep quality and sleep-related disorders, and marginally improved the objective quality of sleep and awakening [13].

A multi-center double-blind study compared the use of estradiol valerate 2 mg + dienogest 2 mg, estradiol valerate 2 mg + dienogest 3 mg and estradiol valerate 2 mg + norethisteroneacetate (NETA) 1 mg daily throughout a year in 581 postmenopausal women. Their climacteric symptoms had been evaluated and Kupperman index scores were found to be 78.5%, 74.5% and 75% respectively [14–16]. Although a number of studies have reported physical side effects (constipation, bloating and breast pain) and psychological side effects (depression, fatigue, irritability) resulting from medroxyprogesterone acetate use, these were not observed in prospective randomized studies [17].

In a prospective study by Kirkham et al. it was observed that there was no significant difference in terms of depression and psychological symptoms in patients using medroxyprogesterone acetate treatment and those using a placebo [17]. In another *in vitro* study, it was demonstrated that medroxyprogesterone acetate and metabolites influenced memory, learning and other cognitive functions unfavorably through the GABA-ergic system, and could cause neuronal toxicity, this effect was not clearly revealed in *in vivo* clinical and preclinical studies [18].

In spite of the fact different ideas about the effect of medroxyprogesterone acetate on psychological symptoms can be found in the literature, the authors of the current article observed that in the group taking MPA (Group II) all the psychological symptoms worsened in the 6th month compared to the start of the treatment. When patients were categorized according to their worst psychological symptoms, anger and hostility were more common, followed by eating and sleeping disorders.

In brief, the present study showed that the use of dienogest provided significant improvement in all the psychological symptoms investigated, while the use of medroxyprogesterone acetate worsened psychiatric symptoms. However, because of a lack of consensus on this topic in the literature, large prospective randomized studies are required in order to research the effect of medroxyprogesterone acetate on psychological symptoms.

References

[1] **Zeyneloglu HB:** Ergeneli MTreatment of menopausal symptoms. J Drug Treat 1995, 8, 230–232.
[2] **Haines JC, Xinq SM, Park KH, Holinka CF, Ausmanas KM:** Prevalence of menopausal symptoms in different ethnic groups of Asian women and responsiveness to therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: The Pan-Asia menopause (PAM) study. Maturitas 2005, 52, 264–276.
[3] **Nelson HD:** Menopause. Lancet 2008, 371, 760–770.
[4] **Limouzin-Lamonthe MA, Mairon N, Joyce CR, Le Gal M:** Quality of life after the menapause: Influence of hormonal replacement therapy. Am J Obstet Gynecol 1994, 170, 618–624.

[5] **Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, and Shifren JL:** Short-term use of estradiol for depression in perimenopausal and postmenoupausal women: A preliminary report. Am J Psyhiatry 2003, 160, 1519–1522.
[6] **Dag I:** Validity and reliability of symptom checklist for university students (SCL-90-R). Turk Psikiyatri Derg 1991, 2, 5–12.
[7] **Aydemir O, Koroglu E:** Symptom checklist (SCL–90-R), clinical scales used in psychiatry. Eds.: Aydemir O, Koroglu E, Istanbul 2000, 33–41.
[8] **Schneider HP, Rosemeier HP, Schnitker J, Gerbsch S, Turck R:** Application and factor analysis of the menopause rating scale (MRS) in a post- marketing surveillance study of Climen. Maturitas 2000, 37, 113–124.
[9] **Schneider HP:** The role of antiandrogens in hormone replacement therapy. Climacteric 2000, 3, 21–27.
[10] **Graser TA, Müler A, Mellinger U, Mück AO, Lippert TH, Oettel M:** Continuous-combined treatment of the menopause with combinations of estradiol valerate and diogenest – a dose ranging study. Maturitas 2000, 35, 253–261.
[11] **Qettel M, Graser T, Hoffmann H:** The preclinical and clinical profile of diogenest A short overview. Drugs of Today 1999, 35, 3–12.
[12] **Saletu B, Anderer P, Gruber D, Metka M, Huber J:** Hormone replacement therapy and vigilance: double-blind, placebo-controlled EEG-mapping studies with an estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone in menopausal syndrome patients. Maturitas 2002, 43,165–181.
[13] **Saletu B:** Insomnia related to postmenopausal syndrome: Sleep laboratory studies on differences between patients and normal controls, and influence of an estrogen-progestogen combination with dienogest versus estrogen alone and placebo. Drugs of Today 2001, 37, 39–62.
[14] **Von Schoultz B:** Clinical efficacy and safety of combined estradiol valerate and dienogest: a new no-bleed treatment. Climacteric 2003, 6, 24–32.
[15] **Graser TA, Hoffmann H, Zimmermann, Oettel M:** New Oral Preparation for continuous combined hormone replacement therapy in postmenopausal women. Drugs of Today 2001, 37, 17–27.
[16] **Wellington K, Perry CM:** Estradiol valerate/dienogest. Drugs 2002, 62, 491–504.
[17] **Kirkham C, Hahn PM, Van Vugt DA, Carmichael JA, Reid RL:** A randomized, double-blind, placebo-controlled, cross-over trial to assess the side effects of medroxyprogesterone acetate in hormone replacement therapy. Obstet Gynecol 1991, 78, 93–97.
[18] **Braden BB, Talboom JS, Crain ID, Simard AR, Lukas RJ, Prokai L:** Medroxyprogesterone acetate impairs memory and alters the GABA'ergic system in aged surgically menopausal rats. Neurobiol Learn Mem 2010, 93, 444–453.

Address for correspondence:

Emel Kiyak Caglayan
Bozok University Faculty of Medicine
Adnan Menderes Bulvarı No. 190
66200 Yozgat
Turkey
Tel: + 90 354 212 70 01
E-mail**:** emelkiyak@hotmail.com

Conflict of interest: None declared

Received: 14.12.2012
Revised: 6.05.2013
Accepted: 20.02.2014