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Evaluation of the quality of life of postmenopausal women using an estradiol and drospirenone combined oral hormone replacement therapy

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Abstract

Introduction: The aim of this study was to estimate the beneficial effects of drospirenone/estradiol combination in postmenopausal women, concerning the improvement of quality of life.

Materials and Methods: Sixty one women took part in a non-comparative follow - up study after consent. They were up to one year menopausal, presented climasteric symptoms, had intact uterus and no contraindications. A drospirenone (2mg) and estradiol (1mg) combination (hormone replacement therapy, HRT) was given to all of them. Women had a follow up at 3 and 6 months after inclusion. The main outcome of the study was quality of life, assessed by means of women's health questionnaire (WHQ). WHQ's factors were compared through different time points using non - parametric Friedman's test for paired samples. Categorical data were compared using McNemar's test.

Results: Response rate for the WHQ was 100% at baseline and 3 months and 97% at the 6 months visit. According to patients and physicians, tolerability and therapeutic success of HRT was excellent for all (n=61) and almost all (n=60) women, respectively. Most common symptoms were headache, breast tenderness and vertigo in either mild or moderate form. All symptoms were reduced at the 2nd and disappeared completely at the 3rd visit. All WHQ factors scores, but not attractiveness, showed a statistically significant reduction (better QoL) between baseline and 3 and 6 months after. Anxiety symptoms and vasomotor symptoms scores were constant and equal to zero after 6 months.

Conclusions: The intake of the HRT containing drospirenone/estradiol combination is associated with a significant improvement of general quality of life.

Key words: menopause; drospirenone/estradiol; hormone replacement therapy; quality of life

The menopause is a natural life process which usually occurs between the ages of 45 - 55, although it can happen earlier or later. This period of a woman's life is associated with psychological

changes resulting from decreased estrogen production. The most common symptoms resulting from this hormonal disturbance are loss of confidence, depressed mood states, irritability, difficulty in concentrating and physical symptoms[1]. Researchers consider that the relief of climacteric symptoms is a significant point in public and medical society [2].The primary aim of hormone replacement therapy (HRT) is to improve the physical and psychological well - being of women who suffer from climacteric disorders, i.e to improve the quality of life (QoL). Vasomotor symptoms are the most frequent indication for HRT as well as the improvement of urogenital problems[3,4]. The role of HRT in the treatment and prevention of severe, long - term disorders such as osteoporosis and cardiovascular diseases, was studied and shown a beneficial effect on these disorders[5].

During the climacteric period, the serum levels of both steroidal sex hormones decrease, but the withdrawal of estrogens leads to climacteric symptoms and long - term diseases. So when hormone replacement became popular in '50s and '60s, estrogen replacement (ERT) was used as HRT[6,7]. Randomized clinical trials have demonstrated that estrogen replacement is beneficial on prevention of osteoporosis reducing significantly fractures among osteoporotic postmenopausal women[8,9]. However, a large meta - analysis has shown that therapies for postmenopausal osteoporosis have a trend toward a reduced incidence in vertebral and nonvertebral fractures that was not significant[10]. Women's health initiative (WHI) study showed that the long - term use of estrogen replacement therapy was eliminated because of the augmented incidents of breast cancer [11].When it was determined that the lack of an opposing progestogen increased the risk of endometrial cancer, the use of the combination estrogen - progestogen was recommended[12].The combined therapy including ERT with synthetic progestins has presented severe adverse side effects such as breast cancer and undesirable influence on metabolism and cardiovascular diseases[13,14].

Drospirenone (DRSP) is a progestin derived from 17a - spironolactone that has been found to have a pharmacological profile that resembles natural progesterone[15]. Its unique property, compared to other progestogens, is that the drospirenone combines potent progestational, antiandrogenic and antimineralocorticoid activity[16]. The natural estrogen 17β - estradiol (E2) and DRSP composed a new model of continuous HRT that has recently been released [17]. The use of an E2/DRSP combination may have a positive effect on women who suffer from postmenopausal symptoms[17]. Although this new continuous combined HRT has shown a good clinical profile, the number of studies available regarding effect on QoL is limited. This study was designed to estimate the beneficial effects of drospirenone/estradiol combination, in postmenopausal women, concerning the improvement of QoL.

Materials and methods

A non - comparative follow - up study was conducted from October 2007 to September 2008. Women were recruited from the department of obstetrics and gynecology of the Medical school of Democritus university of Thrace. Women were eligible to participate if they were postmenopausal for more than one year, with estrogen deficiency symptoms, but healthy otherwise and they had newly decided to be treated with HRT. Other inclusion criteria were intact uterus, normal cervical or vaginal smear and mammography and absence of contraindications[13,14]. Written informed consent was obtained from every patient and the study was approved by the institutional ethical committe.

A continuous combined regiment (E2/DRSP) containing 1mgr E2 and 2mgr DRSP for daily intake was subscribed to all of them. Women completed a confirmation of participation form, containing demographic and symptoms' characteristics. Women's health questionnaire (WHQ) was also completed, measuring QoL, and women had to complete symptoms and WHQ at baseline, at 3 months and at 6 months after inclusion. A form with adverse events and concomitant medication was completed by the physicians throughout the study. The main outcome of the study was QoL.

Table 1. Description of symptoms

Symptoms/ intensity	Number of women (%)			p*
	Baseline	3 months	6 months	
Headache	47 (77)	8 (13.1)	0	<0.001
Mild	15 (31.9)	7 (87.5)	-	
Moderate	25 (53.2)	1 (12.5)	-	
Severe	7 (14.9)	0	-	
Vertigo	35 (57.4)	1 (1.6)	0	-
Mild	16 (45.7)	1 (100)	-	
Moderate	17 (48.6)	0	-	
Severe	2 (5.7)	0	-	
Nausea	26 (42.6)	0	0	-
Mild	13 (52)	-	-	
Moderate	12 (48)	-	-	
Severe	0	-	-	
Emesis	13 (21.3)	2 (3.3)	0	0.003
Mild	7 (53.8)	1 (50)	-	
Moderate	6 (46.2)	1 (50)	-	
Severe	0	0	-	
Breast tenderness	34 (55.7)	2 (3.3)	0	<0.001
Mild	10 (29.4)	1 (50)	-	
Moderate	19 (55.9)	1 (50)	-	
Severe	5 (14.7)	0	-	
Swollen extremities	26 (42.6)	1 (1.6)	0	<0.001
Mild	13 (50)	0	-	
Moderate	12 (46.2)	0	-	
Severe	1 (3.8)	1 (100)	-	
Abdominal bloating	17 (27.9)	0	0	-
Mild	12 (70.6)	-	-	
Moderate	4 (23.5)	-	-	
Severe	1 (5.9)	-	-	

*Mc Nemar's test between baseline and 3 months symptoms

The WHQ was composed of 37 items investigating 9 dimensions: depressed mood, somatic symptoms, memory/concentration, vasomotor symptoms, anxiety/fears, sexual behavior, sleep problems, menstrual symptoms and attractiveness. Answers to the questions were: yes definitely, yes sometimes, no - not much, no - not at all. Answers were reduced to a binary scale with answers "yes definitely" and "yes sometimes" recoded as 0 and representing good QoL and answers "no - not much" and "no - not at all" recoded as 1 and representing bad QoL. 5 items (items 7, 10, 21, 25, 31 and 32) were reversed coded. The score for each factor was the mean of the non-missing items of the dimension[18,19].

Descriptive analysis of categorical and continuous variables was done by means of percentages and means, standard deviations, medians, quartiles respectively. Reliability of WHQ's factors was tested

Table 2. Women's health questionnaire (WHQ) factors at 3 time points

	Baseline	3 months	6 months	p*	p_1**	p_2***	p_3****
Depressed mood							
n	61	61	59				
Mean (SD)	0.62 (0.13)	0.3 (0.16)	0.24 (0.13)				
Median (Q1 - Q3)	0.57 (0.57 - 0.71)	0.29 (0.14 - 0.43)	0.14 (0.14 - 0.43)	<0.001	<0.001	<0.001	0.06
Somatic symptoms							
n	61	61	59				
Mean (SD)	0.71(0.27)	0.05 (0.11)	0.01 (0.04)				
Median (Q1 - Q3)	0.71 (0.57 - 1)	0 (0 - 0)	0 (0 - 0)	<0.001	<0.001	<0.001	0.37
Memory/concentration							
n	61	61	58				
Mean (SD)	0.68 (0.35)	0.07 (0.15)	0.01 (0.04)				
Median (Q1 - Q3)	0.67 (0.33 -1)	0 (0 - 0)	0 (0 - 0)	<0.001	<0.001	<0.001	0.18
Vasomotor symptoms							
n	61	61	58				
Mean (SD)	0.75 (0.34)	0.06 (0.16)	0				
Median (Q1 - Q3)	1 (0.5 - 1)	0 (0 - 0)	0 (0 - 0)	-	<0.001	-	-
Anxiety symptoms							
n	61	61	59				
Mean (SD)	0.87 (0.22)	0.07 (0.19)	0				
Median (Q1 - Q3)	1 (0.75 - 1)	0 (0 - 0)	0 (0 - 0)	-	<0.001	-	-
Sexual behaviour							
n	61	61	58				
Mean (SD)	0.59 (0.27)	0.26 (0.19)	0.2 (0.18)				
Median (Q1 - Q3)	0.67 (0.33 - 0.67)	0.33 (0 - 0.33)	0.33 (0 - 0.33)	<0.001	<0.001	<0.001	0.26
Sleeping problems							
n	61	61	59				
Mean (SD)	0.86 (0.21)	0.07 (0.15)	0.01 (0.06)				
Median (Q1 - Q3)	1 (0.67-1)	0 (0-0)	0 (0-0)	<0.001	<0.001	<0.001	0.33
Menstrual problems							
n	61	61	57				
Mean (SD)	0.58 (0.23)	0.04 (0.09)	0.02 (0.08)				
Median (Q1 - Q3)	0.5 (0.5 - 0.75)	0 (0 - 0)	0 (0 - 0)	<0.001	<0.001	<0.001	1.00
Attractiveness							
n	61	61	58				
Mean (SD)	0.43 (0.42)	0.41 (0.39)	0.37 (0.40)				
Median (Q1-Q3)	0.5 (0 - 1)	0.5 (0 - 0.5)	0.5 (0 - 0.5)	0.58	-	-	-

*Friedman's test for paired samples
**Wilcoxon sign rank test with Bonferroni correction between baseline and 3 months
***Wilcoxon sign rank test with Bonferroni correction between baseline and 6 months
****Wilcoxon sign rank test with Bonferroni correction between 3 months and 6 months
– Tests not run due to constant variables

using Cronbach's alpha reliability coefficient. WHQ's factors scores were compared through different time points using non - parametric Friedman's test for paired samples. Wilcoxon's sign rank test with Bonferroni correction was used to test for differences between subgroups when a statistically significant result occurred in Friedman's test. Categorical data were compared using McNemar's test. Results were considered significant for $p < 0.05$.

Results

At the end of the study, 61 women, who met the inclusion criteria, completed their treatment and addressed the questionnaires. 60 (98%) were of Caucasian origin and 1 woman (2%) was black. Their ages ranged between 49 - 55 years with median 52 years. Only 1 out of 61 women had previous HRT, but she was out of any HRT treatment for more than 3 months prior to start the observational period. Response rate for the WHQ was 100% at baseline and 3 months later and 97% at the 3rd visit after 6 months. At the 1st visit (baseline), before HRT, most common symptoms were headache (77%, n=47), breast tenderness (55.7%, n=34) and vertigo (57.4%, n=35) in either mild or moderate form. According to patients and physicians, the treatment was well tolerated by all women (n=61) and no serious adverse effects were observed in any patient. Therapeutic success of HRT was excellent for almost all patients (n= 60). Table 1 gives symptoms of patients during the 3 visits in the hospital. There was a statistically significant improvement with all symptoms to be reduced at the second visit ($p \leq 0.003$),($p < 0.001$) and disappeared completely at 6 months.

The description of the QoL factors used in the WHQ is shown in Table 2. Reliability of WHQ scale ranged from 0.9 to 0.8 at the 1st and 2nd visit respectively. Reliability of vasomotor symptoms, sexual behaviour, sleeping and menstrual problems was not satisfactory. Reliability for the remaining factors ranged from 0.25 (memory problems at visit 3) to 0.78 (somatic complains at visit 1). At the 1st visit (baseline), most women suffered from depressed mood (62%), somatic symptoms (71%), memory/concentration disorders (68%), vasomotor symptoms (75%), anxiety symptoms (87%), sexual behavior (59%) and sleeping (86%) problems, menstrual problems (58%) and feeling of reduced physical attractiveness (43%) (Table 2). After HRT administration, there was a statistically significant ($p < 0.001$) improvement in scores for eight out of the nine domains of the WHQ through time (Table 2). These eight WHQ domains were improved in scores between baseline and 3 months after and they were further amended 6 months after the beginning of the study. In contrast, significant differences were not found in attractiveness between none of the time points. There was no statistically significant difference between 3 and 6 months in any of the factors. Statistical difference of the improvement of anxiety symptoms and vasomotor symptoms scores is not shown in Table 2 as both factors were constant and equal to zero after 6 months treatment.

Discussion

In the present non - comparative follow - up study, we demonstrated that HRT containing E2/DRSP combination significantly improved the general QoL of menopausal women, who presented estrogen deficiency symptoms, but they were healthy otherwise and they had decided to be treated with HRT for first time. We found that their symptoms were reduced and disappeared after 3 and 6 months, respectively, and the factors that were associated with the QoL were significantly improved. This improvement was detected by using a symptoms questionnaire and the outcome specific WHQ, as previously described[18,19]. Similar results have been described in previous studies using combined HRT in early postmenopausal women. They demonstrated that continuous combined HRT was well tolerated and effective for the relief of climacteric symptoms and improved the QoL in early postmenopausal women[20,21].

QoL is an important end point in medical and health outcomes research. HRT has become an im-

portant factor that influences the QoL of postmenopausal women[22]. Chiu and colleagues found that HRT has a direct positive effect of on both the physical component summary score and mental component summary score of QoL in multiple regression analysis as well as in path analysis[23].Women take HRT in order to improve their QoL, suffering from symptoms such as depressed mood and anxiety, vasomotor and somatic symptoms, memory/concentration disorders, sexual behavior and sleeping problems, menstrual problems and feeling of reduced physical attractiveness[24,25]. These conditions might explain the reason for prescribing HRT despite the negative results of WHI trial for women who started treatment more than 10 year after menopause[26].

Moreover there are recent studies (WISDOM trial) focusing on health - related QoL measured at one year follow - up, which reported improved sleep and reduced vasomotor symptoms among women who started taking combined HRT many years after menopause[27]. On the contrary, there are studies with no differences between users and non users of HRT. This discrepancy might be found because these studies presented data from women who had been menopausal for up to 15 years[28].

In particular, the use in the HRT regiments containing DRSP which has a physiological profile closer to that of natural progesterone than any other synthetic progestin, represents a new potentially valuable therapeutic option for the effective management of menopause and its clinical sequelae[29]. The antialdosterone properties of DRSP effectively counteract sodium and water retention; therefore women receiving DRSP avoid estrogen - related water retention and weight gain[17].

In our study, the DRSP/E2 appears to enhance QoL with a short term positive effects on anxiety symptoms and vasomotor symptoms as well as and on headache, breast tenderness and vertigo. All symptoms were reduced at the second visit and disappeared completely at the 3rd visit. The tolerability of this regiment was also excellent. No serious adverse effects were observed in any patient. Our results are similar to those to other recent studies which found that E2/DRSP has favorable efficacy, safety profile and long term health benefits[17,30-32]. On the other hand, there are studies in which the use of E2/DRSP was not associated with a significant positive effect on QoL[17,33]. The limitation of our study is that the environment in which subjects were selected was a medical center. This study setting might result in selection bias because the climacteric symptoms of women who visit a medical center might be more severe than those of women who visit a private practice.

We may conclude that the combination of 1mgr E2 and 2mgr DRSP in a continuous regiment for daily intake is certainly a very important factor contributing to both the physical and mental components of QoL. Moreover our encouraging findings suggest that combined treatment with E2 and DRSP started recently after menopause is associated with significant reduction of menopausal symptoms and significant benefit in health - related QoL. Further research with appropriate measures is needed to assess more fully the impact of DRSP/E2 on all aspects of health - related QoL.

Conflict of interest

All authors declare no conflict of interest.

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