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Original Article

A hidden reason for menopausal symptoms in premenopausal aged women: depression

Yasemin Cekmez[1], Fuat Torun[2], Ahmet Göçmen[1], Fatih Şanlıkan[1]

[1]Department of Obstetrics and Gynecology, Umraniye Medical and Research Hospital, İstanbul, Turkey; [2]Department of Psychiatry, Umraniye Medical and Research Hospital, İstanbul, Turkey

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Abstract: Background: The relationship between depression and reproductive hormone changes in menopausal women is well konown but recent animal studies showed that depression can also cause changes in reproductive hormone levels. According to this, we aimed to eveluate the impact of depression on circulating follicle-stimulating hormone and estradiol levels in premenopausal women in terms of menopausal symptoms. Material-method: A total of 120 premenoupausal women (age ranges 41-45) were divided into two groups as: study group consisted of patients (n = 60) with depression and the control group (n = 60) involved healthy women. Psychometric assessment of study group was done by the Turkish version of Structured Clinical Interview for DSM-IV Diagnosis.The presence of menopausal symptoms of all subjects was assessed by the Turkish version of Menopause Rating Scale and hormonal activity by estimating estradiol and follicle-stimulating hormone levels. Results: Study group had significantly lower mean concentration of estradiol and higher intensity of menopausal symptoms than control group. Presence and severity of menopausal symptoms were not associated with follicle-stimulating hormone concentrations. Conclusion: The results of this study confirm the connection between menopausal symptoms and depression both on clinical and physiological level.The current study is unique in its ability to assess the effects of depression on menopausal symptoms in women as they are still reproductive.

Keywords: Menopause, FSH, estradiol, MRS, SCID-I

Introduction

Depression is a common and costly disorder [1] which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality [2]. It is one of the most important causes of disability worldwide [3]. Due to the clinical and etiological heterogeneity of depression, it has been difficult to elucidate its pathophysiology.

Accumulating biological and epidemiological evidence supports a role for estradiol (E2) in depression. Estrogen receptors are present in the brain and estrogen has been shown to modulate neurotransmitter turn-over and stimulates serotonergic activity through the regulation of receptor number and function [4], all of which strongly suggest that estrogen can influence mood and well-being [5]. It is reported that women are most likely to develop mood symptoms (i.e., depressed mood, apathy) during the mid to late-luteal phase of their menstrual cycle, a period during which progesterone levels are peaking while E2 levels are declining [6].

In the literature, there are many studies that investigate the relationship between depression and reproductive hormone changes in menopausal women but recent animal studies showed that depression can also cause changes in reproductive hormone levels by itself [7]. According to this, we aimed to investigate the correlation between depression and circulating follicle-stimulating hormone (FSH) and E2 levels in premenopausal women in terms of menopausal symptoms scored with Menopause Rating Scale (MRS).

Materials and methods

This prospective study was conducted between January-April 2014 at the Obstetrics & Gynecology and Psychiatry Department of Ümraniye Medical and Research Hospital. Scientific and ethical approvals were received from the Institutional Review Board of Ümraniye

Table 1. Descriptive statistics at healthy group and patient with depression

Variables	Healthy (n = 60)	With depression (n = 60)	*P*
	Mean ± SD	Mean ± SD	
Age (year)	42.00 ± 1.97	41.73 ± 1.96	0.601
FSH (mIU/mL)	11.86 ± 7.00	16.01 ± 10.91	0.085
Estradiol (pg/mL)	91.90 ± 31.29	74.37 ± 22.35	0.015
Menopausal rating scale			
Total score	15.27 ± 2.15	24.10 ± 2.80	0.001
Somato-vegetative symptoms	6.63 ± 2.11	9.50 ± 1.78	0.001
Psychological symptoms	4.27 ± 1.01	8.63 ± 1.16	0.001
Urogenital symptoms	4.33 ± 1.15	5.90 ± 1.16	0.001
Depression duration (month)		11.60 ± 2.29	

Table 2. Correlations between MRS and age, estradiol, FSH at healthy group

MRS	Estradiol		FSH	
	r	*P*	r	*P*
Total score	-0.176	0.354	0.242	0.198
Somato-vegetative symptoms	-0.088	0.642	-0.016	0.934
Psychological symptoms	-0.164	0.386	0.462	0.010
Urogenital symptoms	0.010	0.956	-0.021	0.911

Medical and Research Hospital. All participants gave written informed consent.

A total of 120 reproductive aged women (ages range between 41-45) were included in the study. The subjects divided into two groups: The study group involved patients (n = 60) with depression diagnosed by using MDRS ,whereas the control group involved women who never had depression and were regularly menstruating for at least 1 year (n = 60). Women who had any other psychiatric disorders, a history of Diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, insulin resistance, had a Body mass index > 30 kg/m^2, were below the age of 41 and above the age of 45 were excluded from the study. All depressive women had the onset of illness after 40 years of age and all were menstruating regularly before the disease onset. The duration of depressive episode ranged between 3-24 months. All patients were drug-free for at least 7 days before the study performed.

Assessment of depression

Psychometric assessment was done by a psychiatrist in our psychiatry department by means of SCID-I is a semi-structured interview for DSM-IV axis I diagnosis,which is administered by trained interviewers.It consists of 6 modules and usually administered within 25 to 50 minutes [8].

Serum hormone measurements

A fasting morning blood sample was taken from all women at the third day of their menstruation (during follicular phase) before any medication given. The double antibody radioimmunoassay (RIA) kit from Diagnostic Products Corporation (Los Angeles, USA) was used to measure total serum E2. FSH was measured using the TOSOH AIA1200 automated enzyme immunoassay (Abbott Laboratories).

Assessment of menopausal symptoms

All subjects were interviewed by a gynecologist in our gynecology department by means of MRS which measures a total of 11 symptoms. Each symptom was rated by the woman herself according to its severity using a 5-point rating scale from not at all (0) to extremely (4). Symptoms were divided as psychological symptoms: 0 to 16 scoring points (4 symptoms: depressed, irritable, anxious, exhausted), somato-vegetative symptoms: 0 to 16 points (4 symptoms: sweating/flush, cardiac complaints, sleeping disorders, joint & muscle complaints), urogenital symptoms: 0 to 12 points (3 symptoms: sexual problems, urinary complaints, vaginal dryness) [9]. Women indicated whether they were bothered by this list of 11 common symptoms in the last 2-weeks.

Statistical assesment

The data were analyzed using the SPSS software version 11.5. The intra-group categorical variables were compared using t test (two tail). The values were expressed as the mean and standard deviation. For parametric values, Pearson's correlation analysis was usedand covariate adjustment was applied for the study group to purify the impact of duration of depres-

Table 3. Correlations between MRS and age, estradiol, FSH at patient with depression

MRS	Estradiol		FSH		Depression Duration	
	r	*P*	r	*P*	r	*P*
Total score	0.440	0.014	0.024	0.901	0.151	0.425
Somato-vegetative symptoms	0.128	0.500	-0.029	0.878	0.118	0.534
Psychological symptoms	0.463	0.023	0.185	0.329	0.223	0.236
Urogenital symptoms	0.212	0.260	-0.140	0.461	-0.81	0.672

Table 4. Correlations between MRS and estradiol, FSH with depression score adjustment in patient with depression

MRS	Estradiol		FSH	
	r	*P*	r	*P*
Total score	0.346	0.061	-0.218	0.247
Somato-vegetative symptoms	0.210	0.266	-0.267	0.153
Psychological symptoms	0.218	0.247	-0.019	0.920
Urogenital symptoms	0.198	0.294	-0.142	0.455

sion on E2 and FSH levels. P < 0.05 was considered statistically significant.

Results

Descriptive statistics at healthy group and patient with depression are listed in **Table 1**.

Correlation between E2-FSH levels and depression

In study group E2 levels were statistically lower than control group (74.37 ± 22,35 vs 91.90 ± 31.29, respectively) (*P* = 0.015) (**Table 1**). There were no statistically significant differences detected for FSH levels between groups (*P* = 0.085).

Correlation between E2-FSH levels and MRS subscores

A positive correlation was detected between FSH levels and psychological symptoms in control group (r = 0.462, *P* = 0.010) (**Table 2**). There was a negative correlation between E2 levels and MRS total scores (r = 0.440, *P* = 0.014) and psychological symptoms subscores in study group (r = 0.463, *P* = 0.023) (**Table 3**).

Correlation between MRS scores and depression

MRS total scores and subgroup scores (psychological symptoms, somato-vegetative symptoms, urogenital symptoms) were higher in study group than control group (**Table 1**).

Correlation between duration of depression and E2-FSH levels

There was negative correlation between duration of depression and E2 levels in study group (r = -0.476, *P* = 0.008). Duration of depression was found to be positive correlated with FSH levels (r = 0.869, *P* = 0.001). New E2 and FSH levels were found to be positive correlated with MRS total scores after covariate adjustment was applied for the study group to purify the impact of duration of depression on E2 and FSH levels (**Table 4**). But this result was not statistically significant (r = 0.346, *P* = 0.061).

Discussion

In the present study, we have evaluated the effect of depression on circulating FSH and E2 levels in premenopausal women in terms of menopausal symptoms. Our results show that in premenopausal aged women with depression E2 levels are lower than healthy women at the same age. MRS scores identified an increase in menopausal symptoms in women with depression at premenopausal period. As far as we know, this is the first study that examines the effects of depression on menopausal symptoms in premenopausal period with a valid symptom scale.

E2 is a well known hormone with its role in reproduction [10] and activation of sexual behavior [11]. In addition to this E2 also has anxiolytic properties [12], enhances spatial learning and memory, and improves the ability of females to respond appropriately to danger signals in their environment [13]. E2 modulates various pathways in the central nervous system [14] including the limbic hypothalamic-pituitary-adrenal axis [15] and has effects on mood and

cognition that are at least partly due to E2's modulation of the monoamine neurotransmitters like serotonin (5-HT) [16, 17]. 5-HT is implicated in the control of a number of behavioral and physiological functions. Decreased serotonergic neurotransmission has been proposed to play a key role in the etiology of depression [18]. We already know that the estrogen levels decrease physiologically in some life periods of women like postpartum, peri-post menopause and depression can occur in these periods.

Decrease of depressive symptoms by estrogen treatment in these periods of women life was reported in many studies [19] and this is another evidence for the effect of estrogen deficiency in the generation of depression [20]. Additionally, a meta-analysis on the effect of hormone replacement therapy on depressed mood during menopause suggested that E2 significantly reduced depressed mood [21]. A multisite longitudinal, epidemiologic study, SWAN (The study of women's health across midlife), designed to examine physical, psychological and social changes during menopausal transition also corrected the effect of E2 on women's mood at menopausal age [22].

In the present study, menopausal symptoms were investigated with MRS, which is a valid test for menopausal period. In a first look at our results; higher MRS scores of study group than control group can be related with more often psychological symptoms of MRS in patients with depression. But when MRS symptoms were investigated in different groups; urogenital and somato-vegetative symptoms were also higher in study group than the control. This can be counted as another evidence for increased menopausal symptoms due to decrease of estradiol in depression.

In recent years it has been discussing for giving E2 supplement in menopausal women with treatment resistant depression [23]. In animal studies; it was shown that using E2 with fluoxetine has a synergistic effect [24]. Our study also shows the low levels of E2 in premenopausal women with depression and this patient group can be used in further studies for investigating effect of E2 supplement on disease prognosis in selective patients. These studies can especially be useful in fluoxetine resistance patient group. Our study was performed with patients who had depressive complaints between 3-24 months. We determined that duration of depression is negatively correlated with E2 levels. This can be a new aim for a new study with larger numbers of patients diagnosed for a long time.

We were limited in our ability to examine racial/ethnic differences in this study because of the small size of the sample. However, in a future paper encompassing a larger patient group it can be focus on the characteristics and subgroups of premenopausal women that may be particularly vulnerable to depression and also can be focus on the synergistic effect of E2 supplementation to premenopausal aged depressive women's treatments.

In conclusion, we report a positive correlation between depression decreased E2 levels in premenopausal aged women. These hormonal changes affects patients and causes menopausal symptoms. Higher scores detected with MRS is another evidence for this relationship. However, new studies will be necessary to determine whether treatment with E2 has favorable effects for treating the women who has resistant depressive complaints to routine depression treatments in premenopausal age.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yasemin Cekmez, Department of Obstetrics and Gynecology, Umraniye Medical and Research Hospital, İstanbul, Turkey. Tel: 00 90 505 333 90 47; E-mail: yaseminkandicekmez@hotmail.com

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