

The Effect of Perimenopausal Estrogen Levels on Depression and Anxiety: A Pilot Study

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ABSTRACT

Objectives. Among women in the perimenopausal period, rapid hormonal changes can be seen. In the present study, we aimed to investigate the relationship between depression, anxiety and changing estrogen hormone levels at menopause. *Materials and Methods.* The research group was composed of 30 perimenopausal women who had FSH levels higher than 20 IU and irregular menses. Anxiety and depression status was assessed with the Hospital Anxiety and Depression Scale. Patients with or without depression or serious anxiety were compared in terms of age, body mass index (BMI), hot flushes, smoking, premenstrual syndrome (PMS) and estrogen levels. *Results.* There were no statistically significant differences in terms of hot flushes, BMI, smoking, age, and PMS in patients with or without depression/anxiety. Estrogen levels were statistically significantly lower in the group with depression compared to the group without depression ($p=0.026$). *Conclusion.* We believe that falling levels of estrogen in the perimenopausal period can be considered to be a risk factor for depression. The possible role of estrogen replacement in the treatment of depression and anxiety should be investigated in further studies.

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Keywords: Perimenopause, depression, anxiety, FSH, estrogen.

Introduction

The perimenopausal period usually begins in the late 40s. Menstrual irregularity is the most objective indicator used in the diagnosis of this period. Studies indicate that menopause can occur in one to two years with cycles exceeding 42 days.

The average age for perimenopause is 47.5, and 51 for menopause. It is reported that passage from regular menstruation cycles to amenorrhea can exceed eight years [1].

In the premenopausal period, an increase in

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follicular stimulating hormone level (FSH), a decrease in inhibition level, a slight increase in estradiol level, as well as a change in luteinizing hormone (LH) level are observed. In the last year before menopause, in the late perimenopausal period, reduction begins in estradiol levels to below 40 pg/mL. The perimenopausal years are the period in which FSH climbs to postmenopausal levels (above 20 IU/L) and LH stays within normal limits although menstruation continues [2]. 70% of peri- and postmenopausal patients show symptoms and indications related to estrogen deficiency. Apart from vasomotor symptoms, psychological symptoms and indications such as depression, anxiety, irritability, sleep disturbances, and decrease in libido are also prevalent [2]. It is reported that starting from the perimenopausal period there is an increase in risk of depression, including women without a past depression history [3]. It is stated that compared with the premenopausal period, there are persistent symptoms of mood in women in the perimenopausal period, a significant increase in depressive indications in the menopausal period through follow-up studies during this period, and that this risk minimizes significantly in the early postmenopausal period [4]. A five-year follow-up study states that there is a significant mood change in the perimenopausal period, and a 14 fold increase in risk of depression compared with the premenopausal period [5]. It is affirmed that psychological symptoms seen in the menopausal period may be related to changes in levels of estrogen, androgen or both, as well as to psychosocial and dynamic processes [6].

It is reported that changes in estrogen level in the perimenopausal period cause cognitive and mood changes by affecting acetylcholine and serotonin levels in the central nervous system [7]. Estrogen, as a steroid hormone, acts by increasing gene expression in the cell nucleus. There are two important estrogen receptors. The alpha-receptor is responsible for estrogen effects on cognitive functions, whereas the beta-receptor is responsible for the serotonergic system and emotional processes [8]. Mood, cognition and neuronal health are associated with the effect of estrogen on the central nervous system [9]. Estrogen increases

serotonin levels by reducing monoamine oxidase, which catabolizes serotonin, by separating tryptophan bound to albumin essential for serotonin synthesis, and by increasing serotonin transport [10].

While depression in women is more frequent starting from puberty, it is rather rare after the sixth and seventh decades of life. Depression peaks in women in the menarche to menopause period and premenstrual, postpartum and menopause periods, in which hormonal changes occur [11, 12]. It is believed that hormonal changes in the reproductive period may increase depression risk [13].

Premenstrual dysphoric syndrome, postpartum depression and perimenopausal depression triad are designated as the hormone-related depressive disorders [14]. While 20-40% of women have premenstrual syndrome (PMS), 3-5% of them show severe symptoms that can be diagnosed as premenstrual dysphoric disorder [15]. It is observed that although there is no menstruation after hysterectomy protecting the ovaries, PMS symptoms continue. This situation is called 'ovarian cycles syndrome' [16]. In this case, suppression of ovarian activity causes regression in PMS complaints [14]. Depressive symptoms decline following estrogen application in premenstrual syndrome [17]. By applying estrogen or estrogen and androgen together for women with surgical menopause a recovery in mood is reported. A significant decrease in the severity of depression and anxiety and in vasomotor symptoms has been shown in menopausal women who were given tibolone with estrogenic effects and transdermal estrogen [18].

There are rapid hormonal changes in women who are in the premenopausal period. In this study, we aimed to investigate if there was a relationship of estrogen levels, as one of these hormones with changing levels, with depression and anxiety.

Materials and Methods

This study was carried out over two months. In this period, thirty perimenopausal women were included in the study following their written approval, who were admitted to the Sevket Yilmaz

Table 1. Comparison of groups with and without depression in terms of sociodemographic data, clinical variables and estrogen levels.

	With depression min-max (n=15)	Without depression min-max (n=15)	P
Age	45.6-50	46-50.5	0.367*
BMI	22.9-30.2	22.6± 30.1	0.512*
Hot flushes +/-	11/4	11/4	1.00**
Smoking +/-	6/9	5/10	0.705**
PMS +/-	2/13	1/14	0.543**
Estrogen	19.7-32.3	72.4-74	0.026*

SD : Standard Deviation, *Mann Whitney U, **chi-square

Training and Research Hospital Obstetrics and Gynecology Clinic with menstrual irregularity and with a level of FSH higher than 20 IU. Those having a psychiatric disorder apart from anxiety and depression in their past psychiatric history and those already receiving hormonal replacement treatment were excluded from the study. Data was obtained from the patients for age, body mass index (BMI), hot flushes, smoking, and premenstrual syndrome (PMS). Anxiety and depression were assessed with the Hospital

Anxiety and Depression Scale [19]. This is a self-report scale with 14 articles, composed of 7 symptoms of anxiety and 7 of depression. As a result of a study executed in Turkey, the cut-off point for the anxiety subscale was 10/11 and for the depression subscale was 7/8 [20]. In statistical assessment of age and estrogen levels, which are continuous variables in the groups with/without depression and with/without evident anxiety, we compared the results by Mann Whitney U test. Qualitative variables were compared by chi-square test. Ethical approval was obtained from The Ethical Committee of the Hospital.

Results

When the 15 patients with depression were compared with the 15 without depression, there was no significant statistical difference between

the groups in terms of age, BMI, smoking, PMS, and hot flushes. Estrogen level in the group with depression was significantly lower than that in the group without depression ($p=0.026$) (Table 1). The same patient group was divided according to the presence of an evident anxiety or not, and when 11 patients with an evident anxiety were compared with 19 patients without anxiety, it was found that there was no statistically significant difference between them in terms of age, BMI, smoking, PMS, hot flushes and estrogen levels (Table 2). PMS was more frequent in smoking patients than non-smoking patients. All of the patients with PMS were smokers and only 29.6% of patients without PMS were smokers ($p=0.016$).

Discussion

Although the perimenopausal period was found to be associated with depression, no relationship between hormone levels and intensity of mood disorder has been shown [21]. In our study investigating the relationship between estrogen levels and depression and anxiety in women in the perimenopausal period, we found that there was no significant relation between estrogen level and anxiety, while on the other hand the estrogen level of the group with depression was significantly lower than those without depression. In a previous

Table 2. Comparison of groups with and without evident anxiety in terms of socio-demographic data, clinical variables and estrogen levels.

	With evident anxiety min-max (n=11)	Without evident anxiety min-max (n=19)	Correlation (9 value)
Age	45.6-50.1	45.4-49.5	0.611*
BMI	25.8-30.4	21.5-28.4	0.372*
Hot flushes +/-	9/2	13/6	0.672**
Smoking +/-	6/5	5/14	0.238**
PMS +/-	2/9	1/18	0.256**
Estrogen	34-39.3	67.8-69.2	0.250*

SD: Standard Deviation, *Mann Whitney U, **chi-square

study analyzing this relation in postmenopausal patients, high anxiety and depression ratios were found with low estradiol levels [22]. In a study performed in Turkey, depression was more common among menopausal women with low E2 levels, and on the other hand anxiety was more common among women with both low E2 and FSH [23]. In our study, lower estradiol levels were observed in the group with anxiety, although this was not statistically significant. We think that the limited number of patients was not sufficient to show this relation. Nonetheless, the relation between high estrogen levels and reduction in depression ratio that was identified in our study was also seen in other research [24]. In contrast to the results of our study, there are also some studies indicating that there is no relation between estrogen level and depression in the perimenopausal period [25].

According to our study, there is no important relation between body mass index (BMI) and depression. In a study analyzing depression and estrogen in postmenopausal patients, it was affirmed that BMI may be an independent factor with a relation between depression and BMI [22]. We have also not found a significant relation between hot flushes and depression and anxiety in our study. Hot flushes occur due to a disorder of hypothalamus regulation, which is the thermoregulatory center, as a result of estrogen deficiency [26]. Hot flushes are usually seen in advanced stages of menopause and in the early years of the postmenopausal period [27]. A study investigating the relationship between

hot flushes and depression states that there is a strong relation between these two, and both depression and hot flushes occur due to sensitivity to changes in estrogen [28]. It is also reported that women with depression in the perimenopausal period complain more frequently about hot flushes with high severity and so are admitted more frequently for treatment [29]. In a study in which women who did not receive premenopausal psychiatric treatment or hormonal replacement treatment (HRT) were followed for six years, a strong relation between anxiety and hot flush symptoms was found [30].

In our study, we did not find a significant relation between PMS history and depression and anxiety. Depression risk increases in women with premenstrual dysphoric disorder diagnosis, and it is reported that 40-78% of these individuals have a mood and anxiety disorder history [31]. It is stated that the existence of PMS history is predictive for depression in the menopausal period [4].

In our study, we did not find a significant relation between smoking and perimenopausal depression and hot flushes. Smoking is more related to early menopause; this situation is associated with the anti-estrogenic effect of cigarettes [32]. In addition, more hot flush complaints are reported with depressive symptoms with smoking in the reproductive period before menopause [33] and smoking patients with depression in the perimenopausal period [34].

The small number of cases is one of the

limitations of this study. The fact that we have not determined a significant relation between perimenopausal depression and BMI, PMS, hot flushes, and smoking and the incompatibility of this finding with the literature may be because the number of patients was not sufficient to show this relation.

Giving transdermal estradiol to perimenopausal women has an antidepressant effect [35]. Although estrogen treatment was not effective in postmenopausal women, its effectiveness was proven for patients with perimenopausal depression [36]. After perimenopausal women with major depression diagnosis were given 17 β estradiol, it was found that the antidepressant effect of hormone treatment was independent from physical effects [37]. In a meta-analysis in which thirty-eight studies were evaluated, it was seen that hormone therapy provides a reduction in the depressive mood [38]. Following depressive disorder diagnosis, the first treatment option in the menopausal period is with selective serotonin reuptake inhibitors. If estrogen deficiency in the perimenopausal period is treated as an independent risk factor, it can be assumed that estrogen can

have a place in the treatment of depression and anxiety disorders during the perimenopausal period [39]. Estrogen treatment has a wide range of uses in menopausal complaints; it is especially effective for hot flushes. It may be a treatment option for women with depression in the perimenopausal period who do not have breast cancer, thromboembolism risk or any other contraindications. It is also assumed that use of estrogen in women with depression in the perimenopausal period may provide additional benefit in terms of disease with increasing risk. Short-term estrogen treatment is reported to have positive effects on mood by reducing vasomotor symptoms and sleeping problems [39]. In a randomized controlled study it was found that an application of estrogen over 3-6 weeks is effective for perimenopausal depressive patients [40].

In conclusion, we believe that decreasing estrogen in the perimenopausal period can be evaluated as an independent risk factor for depression and anxiety. The probable role of estrogen in depression and anxiety treatment in the perimenopausal period should be examined in further studies.

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