Depression across menopause: severity, symptoms, climacteric and hormonal background

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ABSTRACT

Menopausal depression is a common problem in menopausal women. In this paper we examine the symptoms of menopausal depression in relation to various stages of the menopausal transition, defined according to the STRAW + 10 classification. The present study included 201 women aged 42-65 years admitted to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, because of climacteric symptoms. The intensity of climacteric symptoms in the studied women was evaluated using the Kupperman index, and depression symptoms were assessed using the Hamilton depression scale and the Beck Depression Inventory. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), 7ß-estradiol (E2), prolactin (PRL), total testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), thyrotropin (TSH), free thyroxin (FT4), progesterone and cortisol 8:00 and 16:00 levels were evaluated in all the studied women. We concluded that depression is most frequent in late menopausal transition, and that depressive symptoms are related to hormones during menopausal transition but not during postmenopause.

KEYWORDS

Depression, menopause.

Introduction

Menopausal women have a three-fold higher risk of depression than women in other periods of life [1]. It is estimated that clinically relevant depression may be diagnosed in about 50% of women seeking medical advice due to climacteric symptoms [2]. Menopausal depression usually has a mild course [2]. The etiology of depressive symptoms during menopausal transition remains unclear, although hormonal, neurotransmitter and neurosteroid changes [3, 4], cerebral blood flow changes [5], and genetic predisposition [6] are reported among etiological factors of climacteric depression. A history of depression and severe premenstrual syndrome as well as disturbed sleep, hot flashes and urinary and sexual dysfunction (thought to be connected with the incidence of depressive symptoms through a "domino effect"), are among the predictive factors of climacteric depression [7].

The Stages of Reproductive Aging Workshop (STRAW) [8] divides reproductive aging into two periods: menopausal transition and postmenopause. Menopausal transition comprises early menopausal transition and late menopausal transition. Early menopausal transition starts several years before the menopause and is characterized by menstrual cycle variability (cycle length > 7 days), increased FSH levels, and low anti-Mullerian hormone (AMH) and inhibin B levels. The late menopausal transition starts about 1-3 years before the menopause and is characterized by a cycle length longer than 60 days, low AMH and inhibin B levels, and a high FSH concentration (usually higher than 25IU/l) on days 2-5 of the cycle. The early postmenopausal period is the period between 1 yaer and 3 years after the menopause, when the main complaint is the presence of vasomotor symptoms. The late postmenopausal period starts later, when the main complaint is urogenital atrophy-related symptoms.

The aim of this study was to evaluate profiles of depression symptoms and their hormonal background in relation to the various stages of reproductive aging.

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Material and methods

The study included 201 women aged 42-65 years admitted to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, because of climacteric symptoms. The mean age of the studied women was 54.1 ± 4.8 years; 52 of them were still menstruating, or reported a time since last menses no longer than 12 months, whereas in 97 cases at least one year had elapsed since their last menstrual period. The women were divided into four study groups according to the STRAW classification categories:

- early menopausal transition group (EMT): 39 women with a cycle longer than 35 days and shorter than 60 days.
- late menopausal transition group (LMT): 34 women with a cycle longer than 60 days and shorter than 1 year.

Licens terms

- early postmenopause group (EP): 82 women between 1 year and 3 years after menopause.
- late postmenopause group (LP): 46 women at least 3 years after menopause.

The intensity of climacteric symptoms in the studied women was evaluated using the Kupperman index [9] and depression symptoms using the Hamilton depression scale [10] and Beck Depression Inventory [11]. Body mass index (BMI) was calculated using the BMI=body mass/height2 formula. Serum FSH, LH, E2, PRL, total testosterone, SHBG, DHEAS, TSH, fT4, progesterone and cortisol 8:00 and 16:00 levels were evaluated in all the studied women. In the still menstruating women, blood was drawn between the 8th and 12th day of the menstrual cycle. Serum FSH, LH, 17β-estradiol, total testosterone, SHBG, TSH, fT4, progesterone and cortisol concentrations were tested by immunoenzymatic methods (Roche Diagnostics, Mannheim, Germany). Intra- and interassay coefficient of variation (CV) ranges were 1.2-3.3% and 2.0-5.6%, respectively. DHEAS level was evaluated using the radioimmunological method (Diagnostic Products Corporation, Los Angeles, CA): intra-assay CV and interassay CV values were 5.1% and 11%, respectively.

For the statistical analysis, the Kruskal-Wallis test and a two-tailed test were used to assess the differences between the studied groups and Spearman's test was used to assess correlations between variables. The study was approved by the Poznań University of Medical Sciences ethics committee, and financed by the State Committee for Scientific Research (project no: 50305-01109136-12261-08039). The authors declare no conflict of interest.

Results

Correlations were found between the Hamilton depression scale and Beck Depression Inventory in all the studied groups (EMT: Spearman R=0.83 p<0.05; LMT: Spearman R=0.79 p<0.05; EP: Spearman R=0.67 p<0.05; LP: Spearman R=0.87 p<0.05).

There were also correlations, in all the studied groups, between the Hamilton depression scale and the Kupperman index (EMT: Spearman R=0.66 p<0.05; LMT: Spearman R=0.55 p<0.05; EP: Spearman R=0.71 p<0.05; LP: Spearman R=0.61 p<0.05), and between the Beck Depression Inventory and the

Table 1 Clinical and hormonal characteristics of the studied groups.

Parameter	EMT	LMT	EP	LP	Kruskal-Wallis test
Number of women	39	34	82	46	-
Age (years)	50.0±3.8	52.1±2.9	53.9±6.5	58.6±5.5	(1)
Time since last menstruation/ menopause (m=months, y=years)	1.3m±0.4	5.7m±2.3	3.3y±1.6	10.9y±4.3	-
BMI (kg/m^2)	26.2±4.7	26.9±4.0	26.3±6.2	27.2±4.4	NS
Kuperman index	23.9±12.8	30.6±13.6	25.8±13.2	24.4±12.3	NS
FSH (IU/l)	38.7±37.8	68.2±38.8	76.9±33.5	72.1±20.9	(2)
LH (IU/l)	23.8±18.9	42.3±21.2	37.3±14.8	33.5±12.4	(3)
E2 (pg/ml)	101.9±135.9	64.7±114.5	33.0±82.6	17.1±9.7	(4)
PRL (ng/ml)	16.7±15.1	15.1±9.5	12.6±8.6	12.5±7.4	NS
Testosterone (ng/ml)	0.31±0.2	0.29±0.16	0.27±0.17	0.27±0.26	NS
Progesterone (ng/ml)	2.44±4.7	0.44±0.42	0.39±0.23	0.30±0.2	(5)
SHBG (nmol/l)	59.7±34.8	54.5±27.6	57.8±31.3	65.7±53.4	NS
DHEAS (ng/ml)	1.65±1,05	1.36±0.75	1.36±0.69	1.1±0.81	(6)
TSH (mIU/l)	2.9±3.7	2.24±1.6	2.5±3.0	2.06±1,1	NS
Ft4 (pmol/l)	1.09±0.28	1.13±0.18	1.25±0.48	1.23±0.26	NS
Cortisol 8:00 (nmol/l)	110.2±55.1	97.6±53	114.9±51.1	115.2±55.5	NS
Cortisol 16:00 (nmol/l)	67.9±30.5	58.6±31.9	68.5±35.9	67.9±35.7	NS

(1) EMT vs LMT: NS; EMT vs EP: p=0.000002; EMT vs LP: p=0.000001; LMT vs EP: p=0.01; LMT vs LP: p=0.000001; EP vs LP: 0.002.
(2) EMT vs LMT: p=0.01; EMT vs EP: p=0.000001; EMT vs LP: p=0.0002; LMT vs EP: NS; LMT vs LP: NS; EP vs LP: NS.
(3) EMT vs LMT: 0.0001; EMT vs EP: p=0.0003; EMT vs LP: NS; LMT vs EP: NS; LMT vs LP: NS; EP vs LP: NS.
(4) EMT vs LMT: NS; EMT vs EP: p=0.00008; EMT vs LP: 0.0005; LMT vs EP: NS; LMT vs LP: NS; EP vs LP: NS.
(5) EMT vs LMT: NS; EMT vs EP: NS; EMT vs LP: 0.0008; LMT vs EP: NS; LMT vs LP: NS; EP vs LP: NS.
(6) EMT vs LMT: NS; EMT vs EP: NS; EMT vs LP: 0.03; LMT vs EP: NS; LMT vs LP: NS; EP vs LP: NS.

Kupperman index (EMT: Spearman R=0.63 p<0.05; LMT: Spearman R=0.43 p<0.05; EP: Spearman R=0.45 p<0.05; LP: Spearman R=0.53 p<0.05). With regard to the hormonal background to depression, correlations were found, in the EMT group, between the Hamilton depression scale and serum levels of testosterone (Spearman R=0.47 p<0.05), progesterone (Spearman R=0.45 p<0.05) and DHEAS (Spearman R=0.35 p<0.05), while in the LMT group there was a correlation between the Beck Depression Inventory and progesterone (Spearman R=-0.41 p<0.05).

Investigation of the hormonal background to climacteric symptoms revealed, in the EMT group, correlations between the Kupperman index and serum levels of 17β-estradiol (Spearman R=-0.33 p<0.05) and testostosterone (Spearman R=0.38 p<0.05). In the LMT group, there emerged a correlation between the Kupperman index and serum 17β-estradiol level (Spearman R=-0.38 p<0.05). In the LP group there was a correlation between the Kupperman index and serum cortisol 16:00 level (Spearman R=-0.39 p<0.05).

Discussion

The four studied groups (early menopausal transition, late menopausal transition, early postmenopause and late postmenopause) differed in frequency of depression as assessed using the Hamilton depression scale. Depression was found to be most frequent in the late menopausal transition group and least common in the late postmenopause group. Similar data were presented by Maki et al., who reported that the early and late menopausal transition stages as well as the early postmenopause stage are a window of vulnerability for the development of both depressive symptoms and major depressive episodes [12]. The frequency of depression was high in all the groups considered in our study (69.2%, 82.3%, 70.7%, 56.5%), a finding in line with other studies which reveal a high frequency of depression in menopausal women [2, 13, 14]. The most frequent symptoms of depression in all the studied groups were general somatic symptoms, loss of interest in activities, shallow sleep, psychological symptoms of anxiety and fear, and so-

Table 2 Depression and depression symptoms in the studied groups according to the Hamilton scale.

Parameter	EMT	LMT	EP	LP	Kruskal-Wallis test
Hamilton scale score	10.6±6.6	12.1±6.7	11.6±6.7	9.5±6.6	NS
Beck Depression Inventory score	12.4±8.2	13.6±9.3	13.7±9.6	11.7±8.6	NS
Depression on Hamilton scale (≥8 points)	27 (69.2%)	28 (82.3%)	58 (70.7%)	26 (56.5%)	(1)
Depressive mood	13 (33.3%)	15 (43.5%)	35 (42%)	14 (30.8%)	NS
Feelings of guilt	17 (44.2%)	14 (40.6%)	34 (40.8%)	14 (30.8%)	NS
Suicidal thoughts and tendencies	8 (20.8%)	7 (20.3%)	19 (22.8%)	11 (24.2%)	NS
Sleep disorders	22 (57.2%)	21 (60.9%)	45 (54%)	20 (44%)	NS
Shallow sleep	23 (59.8%)	25 (72.5%)	56 (67.2%)	24 (52.8%)	NS
Waking early	20 (52%)	22 (63.8%)	50 (60%)	21 (46.2%)	NS
Loss of interest in activities	24 (62.4%)	20 (58%)	49 (58.8%)	19 (41.8%)	NS
Slowness of movement	10 (26%)	8 (23.2%)	19 (22.8%)	8 (17.6%)	NS
Sensorimotor anxiety	5 (13%)	8 (23.2%)	13 (15.6%)	7 (15.4%)	NS
Psychological symptoms of anxiety and fear	23 (59.8%)	25 (72.5%)	51 (61.2%)	25 (55%)	NS
Somatic symptoms of anxiety and fear	23 (59.8%)	28 (81.2%)	57 (68.4%)	25 (55%)	(2)
Gastrointestinal symptoms	10 (26%)	6 (17.4%)	16 (19.2%)	4 (8.8%)	NS
General somatic symptoms	25 (65%)	27 (78.3%)	53 (63.6%)	26 (57.2%)	NS
Symptoms of the genitourinary system	22 (57.2%)	20 (58%)	46 (55.2%)	23 (50.6%)	NS
Hypochondria	7 (18.2%)	11 (31.9%)	10 (12%)	4 (8.8%)	(3)
Weight loss	1 (2.6%)	1 (2.9%)	4 (4.8%)	1 (2.2%)	NS
Self-criticism	4 (10.4%)	1 (2.9%)	5 (6%)	2 (4.4%)	NS

(1) LMT vs LP p=0.014897.
(2) EMT vs LMT p=0.033092; LMT vs LP p=0.046539.
(3) LMT vs EP p=0.015551; LMT vs LP p=0.016320.

matic symptoms of anxiety and fear. The groups also differed in frequency of somatic symptoms of anxiety and fear and frequency of hypochondria. Both hypochondria and somatic symptoms of anxiety and fear were most frequent in the late menopausal transition group and less frequent in the early menopausal transition, early postmenopause and late postmenopause groups. Our data are similar to the observations of other authors, who report a characteristic pattern of menopausal depression, which includes several physical and psychological symptoms, such as muscle pain, weight gain, low energy levels, decreased self-esteem, feelings of isolation, cognitive impairment and decreased libido [3, 5, 15]. Typical signs of perimenopausal depression are: a milder mood presentation, anger, irritability and paranoia, manifesting as verbal outbursts over minor stressors [16]. Mood changes in perimenopausal depression may last minutes to hours and spontaneously resolve [7]. Perimenopausal depression is associated with increased fatigue and decreased energy levels [15, 17-18]. It is related to psychosocial factors, among which perception of aging and childbearing status, habits, and stressful family/life roles are reported [15]. With regard to the perception of aging, a tendency to value young people more than the elderly can increase the likelihood of depression during menopause [15]. Communities that place more value on young people have higher rates of menopausal depression. Smoking and limited physical activity may also increase the frequency of menopausal depression [19]. The stress of disharmonious family relationships has been linked to higher rates of depressive symptoms during perimenopause [15, 20]. Menopausal depression is a subtype of depression with a unique etiology and specific symptom characteristics. Women with menopausal depression respond differently to antidepressant medications in comparison to other patients with depression [21].

The etiology of perimenopausal depression is related to hormonal changes, which in turn lead to changes in neurotransmitter systems regulating mood modulation [22]. Estrogens and progesterone influence neurogenenesis, neurotransmission and neuronal regeneration and have anti-inflammatory effects at the level of CNS [23]. Correlations between depressive symptoms and hormones in our study were present in early menopausal transition and late menopausal transition groups. Hormones were not found to be related to severity of depressive symptoms in postmenopausal women. As regards single hormones, there emerged a negative correlation between the severity of depressive symptoms and progesterone, and positive correlations between depressive symptoms and androgens (testosterone and DHEAS).

Most studies on the relationship between progesterone and depression report a negative effect of progesterone on mood. Progesterone increases the activity of serotonin-degrading enzymes: monoaminooxydase and catechol metylotransferase. A mood-impairing effect of progesterone has also been observed in studies exploring the etiology of premenstrual syndrome. In depressive patients a correlation between Montgomery-Asberg Depression Rating Scale score and serum progesterone concentration was reported [24]. The negative correlation between depressive symptoms and progesterone observed in our study may be explained by the positive influence of estrogen on mood. The patients in our sample with higher progesterone levels may ovulated and had higher estrogen levels.

With regard to the effects of androgens on menopausal depression, studies give various results. Testosterone supplementation in women with major depressive disorder significantly improved the clinical state [3], and testosterone treatment reversed mood disturbances and depression in women after surgical removal of the ovaries [25]. A single dose of testosterone reduced anxiety in the fear-potentiated startle response [26]. Transdermal testosterone in women experiencing age-related declines in androgens resulted in improved mood and psychological well-being [27]. On the other hand, Rohr reported that testosterone can negatively impact mood in women, and can even contribute to the onset of major depressive disorder [28]. Androgens may influence the clinical picture of depression, but there is still no clearly reliable method of androgen level evaluation.

Our groups did not differ in relation to the severity of climacteric symptoms measured using the Kupperman index. Climacteric symptoms were found to be dependent on hormone levels only during menopausal transition. Specifically, climacteric symptoms were dependent on E2 (negative correlation) and testosterone (positive correlation). It is worth stressing that the climacteric symptoms were estrogen dependent, whereas the depression symptoms were not. In late postmenopause climacteric symptoms were not dependent on sex steroids but on cortisol (negative correlation).

The groups differed in age and this may have influenced the severity and frequency of the studied symptoms. Older age is related to a higher risk of depression. The prevalence of depression after the age of 60 is estimated to be 13.3% [29]. An older age at menopause was associated with a lower risk of menopausal depression [30].

There were no differences in BMI between the studied groups; in all of them, the mean BMI was in the overweight range. Epidemiological data reveal that 2/3 of postmenopausal women in Poland have overweight or obesity status [31]. Weight gain during menopause is 0.5 kg per year [32]. This is due not only to hormonal changes but also environmental factors [33, 34]. Among these, urbanization, lower education level, higher parity, obesity in the family, lack of physical activity, marriage at a younger age, shift work, lack of sleep and depression are reported [35].

Conclusions

1. Depression is most frequent in late menopausal transition.
2. Depressive symptoms are related to hormones during menopausal transition, but not during the postmenopause phase.

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