Psychiatr. Pol. 2015; 49(3): 615–623
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/33442

Disturbances of sleep continuity in women during the menopausal transition

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Summary

Aim. The objective of the study was to evaluate the prevalence of sleep continuity disorders in women during menopausal transition, to evaluate the relationship between disturbances of sleep continuity and the severity of menopausal syndrome and the occurrence of various symptoms of this syndrome, as well as to evaluate the association between the presence of sleep disturbances and serum concentrations of gonadotropins, prolactin and sex hormones.

Methods. Consecutive 140 women (mean age 54.4 ± 4.7 years) searching for the treatment in the Clinic for Gynaecological Endocrinology who reported symptoms of menopausal syndrome were investigated. The type and severity of disturbances of sleep continuity were evaluated using a survey based on the sleep related questions from Hamilton Depression Rating Scale. The severity of symptoms of menopausal syndrome was assessed using the Kupperman Index. The concentration of the following hormones in blood serum was tested: FSH, LH, 17β-estradiol, PRL, total testosterone, DHEAS and SHBG.

Results. Disturbances of sleep continuity were a prevalent complaint in the studied group of women. Difficulties in falling asleep were found in 57.8% of women, difficulties in maintaining sleep in 70%, waking up too early in 60.7%. The severity of all three types of sleep continuity disturbances was related to the severity of menopausal syndrome as measured with Kupperman Index (Spearman correlation coefficient $r = 0.63$, $r = 0.61$, $r = 0.52$, respectively; $p < 0.001$). Difficulties in maintaining sleep were negatively correlated with

The study was not sponsored.

the concentration of FSH ($r = -0.19$; $p < 0.05$), 17β-estradiol ($r = -0.19$; $p < 0.05$) and SHBG ($r = -0.18$; $p < 0.05$), difficulties in falling asleep negatively correlated with the concentration of 17β-estradiol in the blood serum ($r = -0.19$; $p < 0.05$).

Conclusions. Sleep continuity disturbances are frequently reported by women during the menopausal transition. Interventions aimed at reducing the symptoms of menopausal syndrome should be considered as important action to improve sleep quality in this population of patients.

Key words: menopause, climacteric syndrome, disturbances of sleep continuity

Introduction

Insomnia is a common health problem in women during menopause [1–4]. Its occurrence significantly impairs the quality of life [5], is associated with the presence of climacteric symptoms (hot flashes, night sweats), mood disorders and anxiety. It increases the risk of coronary heart disease, metabolic disorders and obesity, and thereby significantly increases the cost of health care.

Frequent occurrence of insomnia during menopause is related to typical for this period of life hormonal changes, which are also the major cause of climacteric symptoms. In women during menopausal transition the presence of menopausal syndrome is an indication for assessment of hormonal levels and hormone replacement therapy. Such approach, combined with cognitive-behavioural therapy and pharmacotherapy, allows for effective treatment of sleep disturbances in menopausal women [6–8].

Aim

The objective of the study was to evaluate the following: the frequency of the occurrence of disturbances of sleep continuity in women during the menopausal transition, the relationships between disturbances of sleep continuity and the symptoms of menopausal syndrome, and the link between disturbances of sleep continuity and the woman's hormonal status.

Material

Consecutive 140 women seeking treatment for symptoms of menopausal syndrome in the Department of Gynecological Endocrinology were investigated. The mean age of the examined women was 54.4 ± 4.7 years (range 42–65 years). 45 of the examined women still menstruated and 95 reported that it has been at least one year since their last menstrual period. The mean BMI value of the participants was found to be 26.7 ± 4.5 kg/m^2. Two of the studied women were diagnosed as being underweight (BMI: < 19 kg/m^2), 52 were diagnosed as having the proper BMI (BMI: 19–25 kg/m^2), 58 were overweight (BMI: 25–30 kg/m^2) and 28 were obese (BMI > 30 kg/m^2).

The inclusion criteria was to exclude the presence of conditions that influence the concentrations of the tested hormones, such as hypertension, neurological and mental diseases, gastrointestinal and endocrine diseases, ischemic heart disease, history

of ischemic attacks on the CNS, peripheral vascular lesions, alcohol abuse, smoking, use of drugs that affect the serotonergic, and the use of hormone replacement therapy within 6 weeks before the start of the study.

Method

The severity of the symptoms of menopausal syndrome was evaluated using the Kupperman Index (Table 1).

Table 1. **Kupperman Index**

Menopause symptoms	Scores*
Hot flashes	4
Sweating	2
Sleep disorders	2
Irritability	2
Depressed mood	1
Dizziness	1
General weakness	1
Joint pains	1
Headaches	1
Heart pounding or palpitations	1
Paraesthesia	1

*Kupperman Index is calculated by adding up the scores for the individual symptoms after multiplying it by the multiplier, the value of which depends on the degree of the severity of a given symptom (Lack of a symptom: multiplier 0, low severity of a symptom: multiplier 1, average severity of a symptom: multiplier 2, high severity of a symptom: multiplier 3). A value of Kupperman Index between 15 and 20 is interpreted as mild climacteric syndrome, between 21 and 35 as climacteric syndrome of average severity, and more than 35 as severe menopausal syndrome

The degree of severity of disturbances of sleep continuity was evaluated using a survey based on the following sleep related questions from the Hamilton Depression Rating Scale (HDRS):

- difficulties in falling asleep:

0 no difficulty in falling asleep;
1 sporadic difficulty in falling asleep (more than 30 minutes before falling asleep);
2 frequent, significant difficulties in falling asleep;

- difficulties in maintaining sleep (light, interrupted sleep):

0 no difficulty;
1 anxiety, light, fitful sleep;
2 waking up at night, getting out of bed (other than due to physiological needs);

- waking up too early in the morning:

0 no difficulty;

1 waking up and going back to sleep at dawn;
2 inability to fall asleep again after waking up too early.

The concentration of the following hormones in blood serum was tested in all women undergoing the research: follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17β-estradiol, prolactin (PRL), total testosterone, dehydroepiandrosteron (DHEAS) and sex hormone binding globulin (SHBG). In all patients, blood sample was taken in the morning on an empty stomach, in case of menstruating women between 8th and 12th day of menstrual cycle. The blood was centrifuged for 10 minutes at 3 500 revolutions per minute and then the test for concentrations of the hormones in serum were performed. Tests of the blood serum concentration of the hormones PRL, FSH, LH, 17β-estradiol, total testosterone and SHBG were carried out using the immuno-enzymatic method (Roche Diagnostics, Mannheim, Germany). The ranges of the intra- and inter-assay coefficient of variation (CV) were: PRL: 1.8–4% and 0.8–1.7%; FSH: 1.4–2.0% and 1.3–2.8%; LH: 0.8–1.8% and 0.6–1.2%; 17β-estradiol: 1.6–5.7% and 1.4–3.3%; total testosterone: 1.2–4.7% and 2.1–14.8%; SHBG: 2.1–2.7% and 1.1–1.7%. The concentration of DHEAS was determined using the radio-immunological method (Diagnostic Products Corporation, Los Angeles, CA). The range of the intraassay was 5.1%, and the interassay was 11%.

The statistical analysis included: the assessment of the frequency of occurrence of the three studied types of disturbances of sleep continuity, the assessment of the relationships between the three investigated types of disturbances of sleep continuity and the severity of climacteric syndrome, as well the occurrence of symptoms of climacteric syndrome, and the assessment of the relationships between the three types of disturbances of sleep continuity and the concentration of the tested hormones in the blood serum. The strength of the investigated relationships were measured by calculation of the Spearman's correlation coefficients. The level of significance was defined as $p < 0.05$.

Results

Disturbances of sleep continuity were a prevalent complaint in the study group. The frequency of occurrence of all three investigated types of sleep continuity disturbances is shown in Table 2.

Table 2. **Frequency of occurrence of three types of sleep continuity disturbances in the examined group**

Type of sleep continuity disturbances	Number of subjects (%)
Difficulties in falling asleep:	81 (57.8%)
– sporadic difficulty in falling asleep (more than 30 minutes before falling asleep)	30(21.4%)
– frequent, significant difficulties in falling asleep	51(36.4%)
Difficulties maintaining asleep (Light, interrupted sleep):	98 (70%)
– anxiety, light, fitful sleep	38 (27.1%)
– waking up at night, getting out of bed (other than due to physiological needs)	60 (42.9%)

table continued on the next page

Waking up too early:	85 (60.7%)
– waking up and going back to sleep at dawn	31 (22.1%)
– inability to fall asleep again after waking up too early.	54 (38.6%)

The results of the Kupperman Index and the results of hormone tests carried out in the examined group are presented in Table 3.

Table 3. **The results of the Kupperman Index and hormone tests in the examined group**

Tested parameter	Mean ± standard deviation
Kupperman Index	26 ± 13
BMI (kg/m^2)	26.7 ± 4.5
FSH (IU/l)	71.2 ± 35.6
LH (IU/l)	36.2 ± 17.8
17β-estradiol (pg/ml)	36.7 ± 65.2
PRL (ng/ml)	11.3 ± 4.7
Total testosterone (ng/ml)	0.27 ± 0.16
DHEAS (µg/dl)	1.34 ± 0.71
SHBG (nmol/l)	61.2 ± 38.6

Significant correlations were found between the degree of severity of all studied types of sleep continuity disturbances and the score of the Kupperman Index, as well as between each of the studied insomnia types and each symptom included in the calculation of the Kupperman Index (Table 4).

Table 4. **The correlations between the severity of sleep continuity disturbances, the severity of the menopausal syndrome (Kupperman Index) and the symptoms of the menopausal syndrome (Person Correlation Test)**

Type of sleep continuity disturbances	Hot flashes	Sweating	Sleep disorders	Irritability	Depressed mood	Dizziness	General weakness	Joint pains	Headaches	Heart pounding or palpitations	Paraesthesia	Kupperman Index
Difficulties in falling asleep	r=0.33 ***	r=0.27 **	r=0.75 ***	r=0.32 ***	r=0.50 ***	r=0.39 ***	r=0.33 ***	r=0.41 ***	r=0.28 **	r=0.44 ***	r=0.46 ***	r=0.63 ***
Difficulties in maintaining sleep	r=0.38 ***	r=0.29 ***	r=0.76 ***	r=0.47 ***	r=0.34 ***	r=0.29 ***	r=0.30 ***	r=0.26 **	r=0.26 **	r=0.28 **	r=0.37 ***	r=0.61 ***
Waking up too early	r=0.34 ***	r=0.33 ***	r=0.57 ***	r=0.45 ***	r=0.29 ***	r=0.24 **	r=0.23 **	r=0.22 **	r=0.28 **	r=0.19 *	r=0.26 **	r=0.52 ***

Spearman's test: *p < 0.05, **p < 0.01, ***p < 0.001

The severity of the studied types of sleep continuity disturbances was not related to age, the time since the last period or the BMI. Regarding the relationship between the severity of types of sleep continuity disturbances and the concentration of hormones in blood serum, a negative correlation was found between the severity of difficulties in maintaining sleep and the serum concentration of FSH ($r = –0.19$, $p < 0.05$). There were also negative correlations between the severity of difficulties in falling asleep ($r = –0.19$, $p < 0.05$), difficulties in maintaining sleep ($r = –0.17$, $p < 0.05$) and the serum concentration of 17β-estradiol. Finally, there was a negative correlation between the severity of difficulties in maintaining sleep and the serum concentration of SHBG ($r = –0.18$, $p < 0.05$).

Discussion

The frequency of occurrence of sleep continuity disturbances in the examined group of women during the menopausal transition was high (57.8%–70%). Other authors have reported a high frequency of occurrence of sleep continuity disturbances in women in this period of life as well. In the analysis by the National Institutes of Health, the frequency of the occurrence of insomnia during menopause was higher than it was in younger women (39%–47% vs. 16%–42%) [1]. In the Penn Ovarian Aging Study, the frequency of the occurrence of sleep disorders in women during the menopausal transition was 43–53% [2], while in the Study of Women's Health Across the Nation (SWAN), the frequency of the occurrence of insomnia in women aged 40–55 amounted to 37.3% [3]. Kravitz et al. found that menopausal women experienced problems with sleep 29% more often than did pre-menopausal women [4].

The frequency of occurrence of sleep continuity disturbances in the current study was higher than reported before [1–4]. It can be explained by at least two important factors. Firstly, in the current study, assessment of sleep using questions taken from the HDRS scale were related only to selected parameters of sleep continuity (falling asleep, sleep maintenance, waking up in the morning), while in previous studies other symptoms of insomnia were also evaluated. For this reason, we believe that the use of scale that will allow for more specific assessment of insomnia would lead to obtain lower results. Such a scale is, for example, Athens Insomnia Scale, which is also available in Polish [9]. Secondly, sleep continuity disturbance in surveyed women could be a predictor of depression. It was shown that more than 19% of perimenopausal women attending their gynaecologists suffer from depressive disorders [10]. For both these reasons the high prevalence of sleep continuity disturbances found in the current study should be regarded as a high prevalence of sleep related problems among women in menopausal transition and not as a diagnosis of insomnia or other sleep disorders. To diagnose nonorganic insomnia it is necessary to assess whether a reported disturbances of sleep continuity and sleep quality cause significant distress or impairment in functioning during the day (Athens Insomnia Scale includes such questions), and to exclude that sleep disturbances occur in the context of a mental disorder, somatic or neurologic disease, substance use, or use of medication.

Cirignotta et al. [11] suggested that the factor underlying the increased level of insomnia in women during the menopausal transition is not the advancement of meno-

pause, but age, given that around 45 years of age is a critical age for the occurrence of insomnia. In our study, there was no correlation between the severity of insomnia and age, which supports the findings in studies by other researchers [12].

With reference to the correlations between the occurrence of insomnia during the menopausal transition and the occurrence of other symptoms of the menopausal syndrome, this study, the SWAN study [3] and several other studies [13, 14] found that the occurrence of vasomotor symptoms is connected with the deterioration of the quality of sleep. Thurston et al. [5] concluded that there is a two-way correlation between hot flushes and insomnia. In the Penn Ovarian Aging Study [2], a more frequent occurrence of insomnia during the menopausal transition was found in women with depression symptoms.

In our study, a negative correlation between the degree of severity of difficulties in maintaining sleep and the concentration of FSH in blood serum was found. This study also found negative correlations between the severity of the difficulties in maintaining sleep and the concentration of 17β-estradiol in blood serum. We also found a negative correlation between the degree of severity of sleep maintenance disturbances and the concentration of SHBG in the blood serum.

A potential relationship between sleep continuity disturbances and female sex hormones is indicated by the more frequent occurrence of insomnia in women than in men across each age bracket [15]. The Penn Ovarian Aging Study [2] did not find a correlation between the occurrence of sleep disorders and the concentration of 17β-estradiol, while sleep disorders were observed more often in women that had a lower concentration of inhibin B. Kravitz et al. reported that not just the absolute concentration of 17β-estradiol and FSH, but the changes in those concentrations are related to sleep disturbances [14]. The decrease of the concentration of 17β-estradiol in blood serum was linked to difficulties in falling asleep and to frequent awakenings from sleep, while an increase of FSH correlated with more frequent awakenings at night [14]. In another study, the same authors found a correlation between the increase in the frequency of sleep disturbances and the increase of FSH in the blood serum of premenopausal women, as well as a correlation between the increase in the frequency of the sleep disturbances and the increase in the level of pregnanediol-3--glucuronide (progesterone metabolite) in perimenopausal women [4]. The impact of the changes in hormone levels on the occurrence of sleep disturbances was not dependent on the vasomotor symptoms and mood swings [4].

Sowers et al. [16] found that the greater increase of FSH concentration within the span of 5 to 7 years was connected with a longer duration of sleep, a higher percentage of delta waves (slow waves) in polysomnographic recordings, but a subjective quality of sleep was poorer. On the other hand, the sleep of women with a slower increase of FSH was much less efficient. The sleep parameters were not influenced by the rapidity of the estradiol concentration changes, even though a higher initial concentration of 17β-estradiol was connected with a slightly poorer sleep quality seven years later. In this period of time, the changes within the testosterone concentration were rather insignificant. However, the ratio of E2/T, which might reflect a growing androgenemia caused by menopause, gradually decreased throughout the menopau-

sal transition. A lower ratio of E2/T was connected with a shorter period of being awake after falling asleep (a sleep parameter referred to as "wake after sleep onset", or WASO), which would indicate decreased sleep fragmentation.

The menopausal status, as evaluated by changes in menstrual bleeding, did not indicate a connection with the occurrence of sleep continuity disorders in the analysis where hormones were also considered. This indicates that a better predictive factor for sleep disorders during the menopausal transition involves sex hormones as opposed to the menopausal status. Thus an assessment of hormonal status and, if needed, a hormonal therapy should be regarded as an important part of the treatment of insomnia it this life period of women.

Conclusions

1. The occurrence of insomnia symptoms during the menopausal transition is related to the degree of symptom severity of the climacteric syndrome. Therefore, interventions aimed at reducing the symptoms of climacteric syndrome should be considered as important action to improve sleep quality in this population of patients.
2. The occurrence of insomnia during the menopausal transition is not linked to age, time since last period, nor to the BMI.
3. The severity of the difficulties in maintaining sleep during the menopausal transition is negatively correlated with the concentration of FSH, 17β-estradiol and SHBG in the blood serum.
4. The severity of the difficulties in falling asleep negatively correlates with the concentration of 17β-estradiol in the blood serum.

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