ORIGINAL PAPER

Submitted: 19.09.2021
Accepted: 07.08.2022
Early publication date: 09.12.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0094
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 6/2022

Hormones and depression in advanced age

Katarzyna Winczyk[1], Tomasz Kostka[2], Hanna Pisarek[1], Agnieszka Guligowska[2], Edyta Piechocka-Wochniak[2], Jacek Świętosławski[1], Marek Pawlikowski[1]

[1]*Department of Neuroendocrinology, Chair of Laboratory and Molecular Diagnostics, Medical University of Lodz, Poland*
[2]*Department of Geriatrics, Healthy Ageing Research Centre, Medical University of Lodz, Poland*

Abstract

Introduction: In older people, depression and mental disability are more frequently present than in younger subjects. It is found that depression is a risk factor for dementia, just as dementia is a risk factor for depression. In turn, both disturbances are known to be influenced by hormones. The present study aimed to see whether the hormonal changes in subjects over 75 years old correlate with the symptoms of depression measured using the Geriatric Depression Scale (GDS).

Material and methods: In a group of patients aged over 75 years, concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, testosterone, dehydroepiandrosterone sulphate (DHEAs), and cortisol were measured in serum with the use of chemiluminescence. The symptoms of depression were estimated by GDS, and the mental functions were assessed by the Mini-Mental State Examination (MMSE). The correlations between the obtained results were estimated by Spearman's test.

Results and Conclusions: A significant correlation between GDS and MMSE scores was observed in the investigated patients. Some statistically significant correlations concerning cortisol and testosterone with GDS were observed in women, but not in men. On the other hand, no significant correlations between concentrations of FSH, LH, DHEAs, and oestradiol with GDS were noticed. Our data support the role of cortisol (possibly secreted during chronic stress) in the risk of depression. The gender difference in the mechanism of depression and stress in older age could be also hypothesized. **(Endokrynol Pol 2022; 73 (6): 917–921)**

Key words: *depression; hormones; aging; GDS; MMSE*

Introduction

The World Health Organization (WHO) points out that the most common mental and neurological disorders in the older population (over 60 years) are dementia and depression, which affect approximately 5% and 7% of the subjects, respectively. Moreover, up to 15% of older people exhibit clinical symptoms of depression [1]. Depression is both underdiagnosed and undertreated in primary care settings. The symptoms are often overlooked and untreated because they co-occur with other problems encountered by older adults. The characteristic features in advanced age include a large variety of symptoms including an increase in the incidence of mild depression, the coexistence of depression and dementia, the frequent comorbidity of depression and somatic diseases, as well as increased severity of somatic complaints [2]. Depression is a leading cause of lack of independence and disability around the world, and it diminishes the quality of life, especially among older people [3, 4], which contributes significantly to the overall global burden of the disease [1, 5]. This mental disorder also increases the perception of poor health, the utilization of health care services, and costs [5].

Understanding the causes of this mood disturbance in the elderly is a widely discussed topic, both in the context of diagnostics and potential therapeutic targets. Scientific studies indicate the potential relationship of depression of older people with dementia as well as with hormonal changes. Depression is likely to be a risk factor for dementia, just as dementia is a risk factor for depression, and in the group of people with dementia, at least 20% of subjects develop a depressive syndrome [6]. Up to 40–50% of patients with Alzheimer's disease show depressive symptoms. Depression can sometimes overtake the appearance of dementia and is more common in the early stages of the disease [7–9]. The disturbed levels of hormones such as dehydroepiandrosterone (DHEA) cortisol, testosterone, oestradiol, luteinizing hormone, and follicle-stimulating hormone may also be associated with the onset of mood disorders and depression. An important role is linked to the alterations of hypothalamic-pituitary-adrenal axis functions [10]. Frequent mood swings, irritability, anxiety, a tendency to depression,

Katarzyna Winczyk, Department of Neuroendocrinology, Chair of Laboratory and Molecular Diagnostics, Medical University of Lodz, Poland; e-mail: katarzyna.winczyk@umed.lodz.pl

and memory impairment are quite typical menopausal and andropausal symptoms (for reviews see: [11, 12]). Testosterone affects the processes that take place in the hippocampus: the brain structure that plays a central role in regulating memory processes, emotions, and mood and the development of depression. Men with hypogonadism — a defect that makes the testicles not produce or produce too little testosterone — more often suffer from depression and anxiety disorders [13]. A deficiency of oestradiol can also lead to irritability as well as depressed mood and depression [14, 15]. A better understanding of the relationship between depression and hormone management in elderly people will allow the development of therapeutic indications, as in the case of vasomotor symptoms.

In the literature there is no analysis that comprehensively assesses the effect of hormone levels on the occurrence of depression and mood disorders in the elderly population. Therefore, the present study aimed to see whether the hormonal changes in adults over 75 years old correlate with the symptoms of depression measured using the Geriatric Depression Scale (GDS) scores.

Material and methods

Patients

The project was approved by the Bioethics Committee of the Medical University of Lodz, decision number RNN/363/17/KE. The study material comprised 100 volunteer outpatients of the Geriatric University Clinic, Central Veterans' Hospital in Lodz (Poland): 61 women (aged in the time of investigation 76–90 years; mean age: 80.6 years) and 39 men (aged 76–88 years; mean age: 79.6 years). The anthropometric data (body mass index [BMI], waist-to-hip ratio [WHR]) are presented and discussed elsewhere [18]. The patients who had thyroid or adrenal disorders, diabetes, or severe hypertension were excluded at the recruitment phase. Similarly, the patients who took the hormonal preparations (e.g. thyroxine, corticoids, oestradiol, testosterone, DHEA) for the 12 months preceding the study were also excluded.

Laboratory measurements

The quantitative determinations of the levels of the following hormones in blood serum were performed: follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2), testosterone, dehydroepiandrosterone sulphate (DHEAs), and cortisol. The blood samples were taken from the cubital vein in the morning. For the determinations, we used technology based on competitive or sandwich chemiluminescence immunoassays (CLIA). The measurements were performed on the LIAISON XL analyser from DiaSorin Inc. (Saluggia, VC, Italy or Stillwater, MN, United States) using the kits produced by this company and dedicated to this analyser.

Measurement of mental functions and depression

The symptoms of depression were assessed with the 15-item Geriatric Depression Scale (GDS), characterizing the emotional status of the participants in the previous 2 weeks. The GDS contains 15 "yes" or "no" questions characterizing the depressive status of the respondent. The raw scores range from 0 to 15, where a higher score indicates deeper depression. A cut-off value of 0–5 was defined as the absence of depression, 6–9 as "probable depression", and 10–15 as "definite depression" [16].

Mental functions were assessed by the Mini-Mental State Examination (MMSE), a 30-point questionnaire used extensively in clinical and research settings to measure cognitive impairment. A score of 24 or more (out of 30) indicates a normal cognition, and scores below can indicate severe (≤ 9 points), moderate (10–18 points), or mild (19–23 points) cognitive impairment [17].

Statistical analysis

The correlations (r_s) of the numerical data with the use of Spearman's test were evaluated. Statistical significance was set at $p \leq 0.05$

Results

The results of hormone measurements are shown in Table 1. Their mutual correlations were described in our previous paper, as were the results of BMI and WHR measurements [18]. It was found that LH and FSH concentrations are negatively correlated with body mass, BMI, and WHR. In the present study we confronted the hormone levels with the GDS scores. The majority of the examined subjects presented "normal" values of GDS scores (women 90.2%, men 87.2%). A significant negative correlation between GDS and MMSE scores was observed in the women ($r_s = –0.3151$) and in the men ($r_s = –0.3157$), which means that depression is correlated positively with mental disability. No significant correlations between concentrations of FSH, LH, DHEAs, and oestradiol with GDS were noticed. On the other hand, some statistically significant correlations concerning cortisol and testosterone with GDS were observed. A positive correlation between cortisol levels and GDS values was found in the women ($r_s = +0.4040$; Fig. 1). Such a correlation was not observed in the men. Finally, testosterone levels are positively correlated with GDS in the women ($r_s = +0.2816$;

Table 1. *Hormone concentrations measured in women (W) and in men (M)*

	FSH [mIU/mL]	LH [mIU/mL]	Oestradiol [pmol/L]	Testosterone [nmol/L]	DHEAs [μg/dL]	Cortisol [μg/dL]
W	87.9 ± 27.17	21.2 ± 7.53	56.5 ± 18.88	0.79 ± 0.43	42.5 ± 28.84	14.9 ± 7.35
M	23.3 ± 24.40	8.3 ± 7.01	113.6 ± 36.79	12.1 ± 5.41	58.2 ± 36.27	17.3 ± 5.76

FSH — follicle-stimulating hormone; LH — luteinizing hormone; DHEAs — dehydroepiandrosterone sulphate

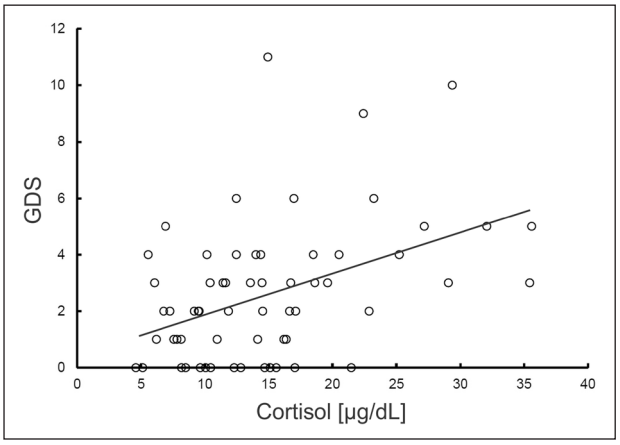

Figure 1. *The significant positive correlation of Geriatric Depression Scale (GDS) scores and cortisol concentrations in older women (r_s = +0.4040)*

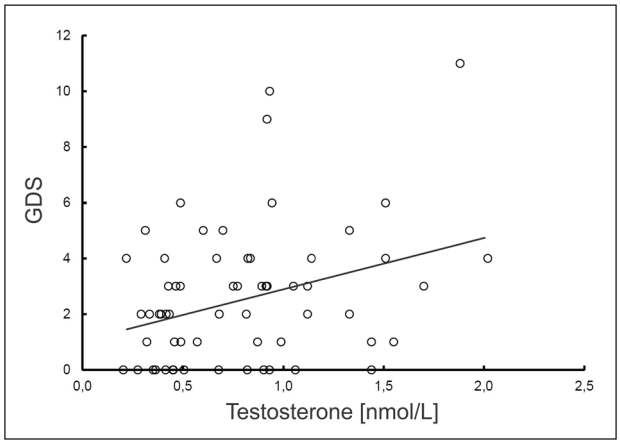

Figure 2. *The significant positive correlation of Geriatric Depression Scale (GDS) scores and testosterone concentrations in older women (r_s = +0.2816)*

Fig. 2). Conversely, in the men this relation was negative although not significant (r_s = –0.2938, p = 0.07).

Discussion and Conclusions

This is the first study assessing the relationship of FSH and LH to the symptoms of depression in both men and women of advanced age. We were not able to demonstrate any association of depression symptoms with circulating gonadotropins, but we did show some associations of depression symptoms with cortisol and testosterone levels that have previously been shown in younger populations. The observed correlations of GDS and MMSE are compatible with the previously reported causal relationship between depression and dementia in older age [6]. The important finding in this study was the observation of a positive correlation of serum cortisol concentrations and GDS scores in older women. This observation is compatible with many studies, showing the higher levels of cortisol measured in different biological materials (plasma, saliva, urine, hair) from depressed patients of various age and sex [19–24]. Our observation, taken together with the previous data, indicates that stress is an important causal factor of depression. However, we cannot exclude a reciprocal role of depression in evoking stress. Oldehinkel et al. denied the link between depression and stress manifested by enhancement of cortisol secretion [25]. They found no difference in urinary free cortisol excretion between depressed elderly persons and non-depressed control subjects. Moreover, they observed several cases of the cortisol hyposecretion in chronic depression, especially in males. The latter statement is interesting in confrontation with our observation of the lack of correlation between cortisol levels and GDS in the men. However, the lack of statistically significant correlation between the GDS scale and cortisol secretion in men could be a result of the lack of material in this sex. Barca et al., who investigated the relationship of cortisol levels with depression and cognitive function in older patients, found elevated hormone levels in subjects with dementia accompanied by depression in comparison to those with either depression or dementia [26]. The quoted authors also found a relationship between cortisol levels and MMSE scores. The higher levels of this hormone are also considered as a risk factor of dementia and Alzheimer's disease by other authors (for review see: [27]).

Unexpectedly, we did not find any significant relation between GDS and DHEAs. The low DHEA is considered to be linked with depression, and attempts of depression treatment with this hormone have been performed [28]. Higher serum DHEAs level was shown to protect against the onset of depression in elderly subjects [29]. Higher serum DHEAs levels are also protectively associated with depression symptoms in old Japanese men, but not in women [30]. The declines of DHEA (estimated as DHEAs) are also connected with the impairment of cognitive functions [31], including Alzheimer's disease [32]. In light of the data quoted above, we expected a negative correlation between this hormone and depression symptoms in our patients. A sharp decrease of DHEA and DHEAs secretions in older persons are a result of age-related adrenal zona reticularis atrophy (for review see: [33]). Secretions of cortisol and DHEA are stimulated by adrenocorticotropic hormone (ACTH), and both adrenal hormones are oversecreted during stress. Thus, the alterations of their secretion may go in the same direction, but their biological actions remain opposite. The lack of more evident relations between DHEAs concentrations and depression may be explained in our patients by

the absence of a DHEAs response to the activation of the pituitary-adrenal axis in very old age (over 75 years). Gender-dependence occurs in the relationship between testosterone levels and GDS results. Higher testosterone levels accompany higher depression scores in women, but not in men. A similar observation has been reported in women during the menopausal transition [34]. The explication of this result is probably a psychological one; the eventual symptoms of androgenization are psychologically undesired in the case of women, but not in men. As has been summarized in a recent systematic review, the data on the relationship between endogenous sex hormones and depressive symptoms are inconclusive [35]. Available information is even more scarce on the potential link between circulating gonadotropins and depression. In one available study depressive symptoms were not associated with circulating gonadotropins in regularly menstruating women [36]. On the other hand, women aged 36 to 45 years with a history of lifetime depression had higher levels of serum LH and FSH and lower levels of oestradiol [37]. Postmenopausal women with a decline in total serum oestradiol and a large increase in FSH levels over the 2-year period had increased risk of depressive symptoms [38]. In the present study we did not find any relationship between FSH, LH, and oestradiol and depressive symptoms. We did not find any relationship between the remaining examined hormones and depressive symptoms evaluated by GDS, but we cannot exclude their existence. Our negative results may depend on lack of material as well as on the much older age of our patients in comparison to those investigated by other authors.

To summarize, cortisol is a hormone strongly related to depression in older women. This observation suggests the possible involvement of stress in the pathogenesis of mood disturbances, at least in this gender. Further studies on larger material are needed to confirm and explain the gender-dependent role of stress in the aging.

References

1. WHO. Mental health of older adults 2017. https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults.
2. Fiske A, Wetherell JL, Gatz M. Depression in older adults. Annu Rev Clin Psychol. 2009; 5: 363–389, doi: 10.1146/annurev.clinpsy.032408.153621, indexed in Pubmed: 19327033.
3. Malhi GS, Das P, Outhred T, et al. Depression. Lancet. 2018; 392(10161): 2299–2312, doi: 10.1016/S0140-6736(18)31948-2, indexed in Pubmed: 30396512.
4. Guligowska A, Pigłowska M, Fife E, et al. Inappropriate nutrients intake is associated with lower functional status and inferior quality of life in older adults with depression. Clin Interv Aging. 2016; 11: 1505–1517, doi: 10.2147/CIA.S114669, indexed in Pubmed: 27822023.
5. WHO. Depression 2020. https://www.who.int/news-room/fact-sheets/detail/depression.
6. Rubin R. Exploring the Relationship Between Depression and Dementia. JAMA. 2018; 320(10): 961–962, doi: 10.1001/jama.2018.11154, indexed in Pubmed: 30140930.
7. Potter GG, Wagner HR, Burke JR, et al. Neuropsychological predictors of dementia in late-life major depressive disorder. Am J Geriatr Psychiatry. 2013; 21(3): 297–306, doi: 10.1016/j.jagp.2012.12.009, indexed in Pubmed: 23395197.
8. Crocco EA, Castro K, Loewenstein DA. How late-life depression affects cognition: neural mechanisms. Curr Psychiatry Rep. 2010; 12(1): 34–38, doi: 10.1007/s11920-009-0081-2, indexed in Pubmed: 20425308.
9. Valkanova V, Ebmeier KP, Allan CL. Depression is linked to dementia in older adults. Practitioner. 2017; 261(1800): 11–15, indexed in Pubmed: 29023080.
10. Juruena MF, Bocharova M, Agustini B, et al. Atypical depression and non-atypical depression: Is HPA axis function a biomarker? A systematic review. J Affect Disord. 2018; 233: 45–67, doi: 10.1016/j.jad.2017.09.052, indexed in Pubmed: 29150144.
11. Yeap BuB, Marriott RJ, Adams RJ, et al. Androgens In Men Study (AIMS): protocol for meta-analyses of individual participant data investigating associations of androgens with health outcomes in men. BMJ Open. 2020; 10(5): e034777, doi: 10.1136/bmjopen-2019-034777, indexed in Pubmed: 32398333.
12. Warren MP, Ng EPS. Menopause. In: Karasek K. ed. Aging and Age-related Diseases: The Basics. Nova Biomedical, Hauppauge 2006: 5–29.
13. Korenman SG, Grotts JF, Bell DS, et al. Depression in Nonclassical Hypogonadism in Young Men. J Endocr Soc. 2018; 2(11): 1306–1313, doi: 10.1210/js.2018-00137, indexed in Pubmed: 30430144.
14. Joffe H, de Wit A, Coborn J, et al. Impact of Estradiol Variability and Progesterone on Mood in Perimenopausal Women With Depressive Symptoms. J Clin Endocrinol Metab. 2020; 105(3), doi: 10.1210/clinem/dgz181, indexed in Pubmed: 31693131.
15. Gordon JL, Sander B, Eisenlohr-Moul TA, et al. Mood sensitivity to estradiol predicts depressive symptoms in the menopause transition. Psychol Med. 2021; 51(10): 1733–1741, doi: 10.1017/S0033291720000483, indexed in Pubmed: 32156321.
16. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982; 17(1): 37–49, doi: 10.1016/0022-3956(82)90033-4, indexed in Pubmed: 7183759.
17. Folstein M, Folstein S, McHugh P. "Mini-mental state". J Psychiatr Res. 1975; 12(3): 189–198, doi: 10.1016/0022-3956(75)90026-6.
18. Pawlikowski Łódź M, Kostka T, Pisarek H, et al. Gonadotropins and steroid hormones in older people: their mutual connections and relations to body mass indices. Endokrynol Pol. 2019; 70(6): 484–488, doi: 10.5603/EP.a2019.0037, indexed in Pubmed: 31529456.
19. Deuschle M, Weber B, Colla M, et al. Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: a re-evaluation study. Stress. 1998; 2(4): 281–287, doi: 10.3109/10253899809167292, indexed in Pubmed: 9876259.
20. Vogelzangs N, Suthers K, Ferrucci L, et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. Psychoneuroendocrinology. 2007; 32(2): 151–159, doi: 10.1016/j.psyneuen.2006.11.009, indexed in Pubmed: 17224244.
21. Vogelzangs N, Beekman ATF, Dik MG, et al. Late-life depression, cortisol, and the metabolic syndrome. Am J Geriatr Psychiatry. 2009; 17(8): 716–721, doi: 10.1097/JGP.0b013e3181aad5d7, indexed in Pubmed: 19625789.
22. Knorr U, Vinberg M, Kessing LV, et al. Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. Psychoneuroendocrinology. 2010; 35(9): 1275–1286, doi: 10.1016/j.psyneuen.2010.04.001, indexed in Pubmed: 20447770.
23. Mayer SE, Lopez-Duran NL, Sen S, et al. Chronic stress, hair cortisol and depression: A prospective and longitudinal study of medical internship. Psychoneuroendocrinology. 2018; 92: 57–65, doi: 10.1016/j.psyneuen.2018.03.020, indexed in Pubmed: 29627713.
24. Khan QU, Zaffar S, Rehan AM, et al. Relationship of Major Depression with Body Mass Index and Salivary Cortisol. Cureus. 2020; 12(1): e6577, doi: 10.7759/cureus.6577, indexed in Pubmed: 32047714.
25. Oldehinkel AJ, van den Berg MD, Flentge F, et al. Urinary free cortisol excretion in elderly persons with minor and major depression. Psychiatry Res. 2001; 104(1): 39–47, doi: 10.1016/s0165-1781(01)00300-6, indexed in Pubmed: 11600188.
26. Barca ML, Eldholm RS, Persson K, et al. Cortisol levels among older people with and without depression and dementia. Int Psychogeriatr. 2019; 31(4): 597–601, doi: 10.1017/S1041610218001199, indexed in Pubmed: 30556798.
27. Ouanes S, Popp J. High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. Front Aging Neurosci. 2019; 11: 43, doi: 10.3389/fnagi.2019.00043, indexed in Pubmed: 30881301.
28. Wolkowitz OM, Reus VI, Wolkowitz OM, et al. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry. 1997; 41(3): 311–318, doi: 10.1016/s0006-3223(96)00043-1, indexed in Pubmed: 9024954.
29. Souza-Teodoro LH, de Oliveira C, Walters K, et al. Higher serum dehydroepiandrosterone sulfate protects against the onset of depression in the elderly: Findings from the English Longitudinal Study of Aging

(ELSA). Psychoneuroendocrinology. 2016; 64: 40–46, doi: 10.1016/j.psyneuen.2015.11.005, indexed in Pubmed: 26600009.
30. Michikawa T, Nishiwaki Y, Nakano M, et al. Higher serum dehydroepiandrosterone sulfate levels are protectively associated with depressive symptoms in men, but not in women: a community-based cohort study of older Japanese. Am J Geriatr Psychiatry. 2013; 21(11): 1154–1163, doi: 10.1016/j.jagp.2013.01.054, indexed in Pubmed: 23567366.
31. Moffat SD, Zonderman AB, Harman SM, et al. The relationship between longitudinal declines in dehydroepiandrosterone sulfate concentrations and cognitive performance in older men. Arch Intern Med. 2000; 160(14): 2193–2198, doi: 10.1001/archinte.160.14.2193, indexed in Pubmed: 10904463.
32. Sunderland T, Merril CR, Harrington MG, et al. Reduced plasma dehydroepiandrosterone concentrations in Alzheimer's disease. Lancet. 1989; 2(8662): 570, doi: 10.1016/s0140-6736(89)90700-9, indexed in Pubmed: 2570275.
33. Pawlikowski M, Karasek M. Dehydroeiandrosterone (DHEA) in aging. In: Karasek M. ed. Aging and age-related disease: the basics. Nova Biomedical, Hauppauge 2006: 65–81.
34. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: results from the Study of Women's Health Across the Nation (SWAN). Arch Gen Psychiatry. 2010; 67(6): 598–607, doi: 10.1001/archgenpsychiatry.2010.55, indexed in Pubmed: 20530009.
35. Morssinkhof MWL, van Wylick DW, Priester-Vink S, et al. Associations between sex hormones, sleep problems and depression: A systematic review. Neurosci Biobehav Rev. 2020; 118: 669–680, doi: 10.1016/j.neubiorev.2020.08.006, indexed in Pubmed: 32882313.
36. Prasad A, Schisterman EF, Schliep KC, et al. Depressive symptoms and their relationship with endogenous reproductive hormones and sporadic anovulation in premenopausal women. Ann Epidemiol. 2014; 24(12): 920–924, doi: 10.1016/j.annepidem.2014.10.005, indexed in Pubmed: 25453349.
37. Harlow BL, Wise LA, Otto MW, et al. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry. 2003; 60(1): 29–36, doi: 10.1001/archpsyc.60.1.29, indexed in Pubmed: 12511170.
38. Ryan J, Burger HG, Szoeke C, et al. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. Menopause. 2009; 16(3): 509–517, doi: 10.1097/gme.0b013e31818d635f, indexed in Pubmed: 19169164.