Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 13 (62) No. 2 – 2020
https://doi.org/10.31926/but.ms.2020.62.13.2.1

HORMONAL FLUCTUATIONS RELATED TO DEPRESSIVE SYMPTOMS IN MENOPAUSE

A. BĂLAN[1] P. DVORNIC[2] C. NISIOI[2]
C. MARTINESCU[1] D.PANAIT[1] M.A. MOGA[1]

Abstract: *Depression has a high incidence among perimenopausal women. This systematic review focuses on the connection between hormonal fluctuations and depressive symptoms. The 5% chances of depression are correlated with increasing additional years between menarche and the menopausal transition (MT) onset. The higher rates of depressive symptoms were associated with more substantial variation in serum estradiol. Progesterone values higher than 6 ng / dL has been linked with lower rates of depressive symptoms. These results may also indicate an interaction between the ovarian hormones, serotonin deficiency and cortisol levels after menopause.*

Key words: *hormonal fluctuations, depression, perimenopause*

1. Introduction

The perimenopause begins typically at a median age of 45.5-47.5 years old [15]. It has an average of 4 years duration until menopause installs [40]. One of the symptoms of menopause change is prolonged menstrual intervals, with shorter cycles or amenorrhea owing to the significant hormonal variations. Besides these, the hypothalamic-pituitary-adrenal axis is deregulated. Some of the signs of menopause are common and are categorized into syndromes and symptomatology: hot sweats, urinary incontinence, genital atrophy, reduced sexual activity, depression.

Depression is a frequent symptom in perimenopausal women [13]. Depression diagnosis requires a minimum of five depressive symptoms that occur for at least two weeks almost daily for more than half the day and result in impairment of function [44]. Approximately 27% of persons with depression reported severe job and family problems, and 80% of persons described some degree of functional impairment. Using the survey, the authors observed that

[1] Faculty of Medicine, Transilvania University of Brasov
[2] Clinical Hospital of Obstetrics and Gynecology "Dr. I. A. Sbarcea" Brasov.
* Corresponding author: dr.andreeabalan@gmail.com

depression rates were higher in the 40-59 years old group [32].

The estimation of significant depression symptoms during one month was 5% for women aged 45-54 and on lifetime was 21,8% [2]. The rate of chronic depression in the 45-54 years-old population was higher than in older people, with the risk of recurrence after the first episode of 50% and after three events of 90 % [12]. More current midlife female findings have found that women aged 40-55 years are more prone to experience depressive symptoms.

In this age group, 40.5% described depressive symptoms in the past two weeks, in the Study of Women's Health Across the Nation (SWAN) [4]. Researchers found that depressive symptoms were found in 38% of the late perimenopausal woman, 26% of premenopausal women, and 28% of postmenopausal women [18]. Soares et al. estimated that a quarter of women aged 40-58 years old had symptoms of depressive disorders [39]. However, Bosworth et al. concluded that around 29% of women ages 45 and 54 had elevated rates of symptoms of depression. Their study was based on an updated Depression Scale (CES-D), but did not identify an association between menopause and depressive symptoms [2]. Such findings suggest a high prevalence of these symptoms in the period to menopause, with an elevated risk of depressive illness.

2. Menopause

Menopause is the eventual termination of menstruation triggered by a lack of ovarian activity. After 12 months of amenorrhea, it is clinically diagnosed. Before menopause, it exists a transition phase called perimenopause [38]. The menopause is characterized by a variety of modifications, some of them specific, some unspecific, divided into syndromes and symptoms.

2.1. Syndromes

The connection between menopause and coronary heart disease is based on estrogen withdrawal. Menopause affects many factors such as body fat distribution, blood pressure, sympathetic tone, endothelial function, glucose tolerance. [36] A malfunction of these factors could lead to coronary heart disease. Osteoporosis is another syndrome present in menopause, characterized by decreased skeletal mass accompanied by an increased skeletal fragility [25]. Estrogens deficiency causes skeletal remodeling. Other conditions that favor this are lack of physical activity, calcium and vitamin D insufficiency, substance misuse, nicotine, caffeine, and glucocorticoid usage [27].

2.2. Symptoms

Hot flashes are one of the most common signs often correlated with perspiration and flushing. They can last seconds to an hour, can be frequent or occasional, some women tolerate it, but for other women, work, sleep or daily activities are affected.

Ehrenthal et al. reported that 58% of women [9] in their study had hot flashes around their final menses in the two years. While there is some proof that hot flashes are linked to hypertriglyceridemia, [30] further research is needed on this relationship. There are also some postmenopausal modifications in the urinary tract, including thinning of urethral mucosa, reduced responsiveness of alpha-adrenergic receptors, and bladder trigone atrophy, which causes bladder incontinence and irritative urinary

symptoms. [7] We cannot conclude the connection between menopause and urinary tract infections. Still, during menopause, certain physiological modifications arise, such as elevated vaginal pH and a vaginal flora modification that may contribute to increased infection risk. Dyspareunia, itching, and irritation are the most common symptoms of vaginal atrophy, and some of the clinical findings are friability, epithelial pallor, absence of rugae, and petechiae. The signs can be found in the absence of symptoms [21]. A cause of morbidity and disability in middle-aged women are mood disorders. Menopausal depression includes also uncommon symptoms, with a more subtle setting, and a multifactorial etiology [8], [33]. All of these may represent obstacles in diagnosis and treatment based on etiological aspects. What is still a matter of debate is the relation between menopause and depressive symptoms. A big discussion is to establish that depression is triggered by hormonal shifts or psychological/ environmental causes linked to women's life-cycle and aging. Recent findings have found that there is a correlation between the decreased level of hormones and increased susceptibility to mood disorders in perimenopause. They suggest that loss in estrogen is triggering significant depression [14].

The symptoms intensify in the transition to menopause, and some women experience menopausal symptomatology in the perimenopause stage. The transition to menopause is triggered by reducing the function of the ovarian function. The premenopausal stage is associated with increased levels of inhibin B, a protein complex that inhibits follicle-stimulating hormone release. [28],[34] Most women begin with changes in menstrual cycle length that become longer, luteal progesterone levels decrease, and the third phase is characterized by high levels of estradiol [15]. The perimenopause is a discrete stage and usually, it ends 12 months after the last period [19].

GRH (gonadotropin-releasing hormone) is released in a pulsatile manner during a woman's fertile life, with a role in the cyclic release of gonadotropins– FSH and LH. All of these hormones play a role in producing ovarian sex steroids, estrogen, progesterone, peptide hormones like inhibin. [43] Increased exposure to ovarian hormone fluctuations, as well as deregulation of HPA, occur during the menopause transition. The neuroendocrine pathways by which the menopause transformation hormonal system complex may cause depressive symptoms are not understood. However, several mechanisms are being investigated (anti-inflammatory and neuroprotective effects of estradiol, modulation of limbic processing, memory and emotions) [1], [3], [10], [42]. One trigger for menopausal transition could be ovarian hormone fluctuations, especially estradiol fluctuations that can have a negative impact on serotonergic and noradrenergic systems [17]. The changes in estrogen level are seen through and after menopause. Estrogens are responsible for multiple functions in the brain, such as homeostasis control, neuronal protection and synaptic plasticity [26]. They exert their influence by a slower genomic mode of action, including binding of estrogen to nuclear estrogen receptors and subsequent transcription control and subsequent calcium, ion and kinase signaling modulation of non-genomic membrane pathways [20].

The fluctuations of neurosteroid derived from progesterone have a significant impact on health. The most studied neurosteroid derived from progesterone in humans is allopregnanolone (ALLO), a metabolite with a reduced A-ring of progesterone. ALLO is a stress-responsive metabolite being an allosteric modulator of gamma aminobutyric acid receptors by a dose-dependent increased of chlorine ion channels, caused by GABA [1], [35].

GABA's function in controlling the HPA axis is to limit the magnitude and length of the stress response [6]. Through modulating GABAergic signaling, ALLO not only accentuates the HPA axis adversely to return it to homeostasis after the tension, but also exerts significant antidepressant effects [35], [37].

In women of reproductive age, the main origins of ALLO are the adrenal glands and the luteal body. In premenopausal women, concentrations of ALLO are increased in the luteal phase and decreased in the follicular period. It is important to note that the peripherally derived ALLO freely crosses the blood-brain barrier and contributes significantly to the central nervous system concentrations [29]. Increased anovulatory cycle rates contribute to less regular luteal phases. Although the presence of progesterone is an essential determinant of ALLO, estradiol has a beneficial impact on ALLO development by modulating the enzymes involved in transforming progesterone into ALLO [31]. The GABAA receptor's inability to show adaptive homeostatic plasticity in the sense of steroid hormone variability is believed to be involved in PMDD production and postpartum depression [22-24]. Insufficient plasticity of the GABAA receptor in the menopausal transition or maladaptive changes in the GABAA receptor may contribute to mood disorders during the menopausal transition when the concentrations of estradiol and progesterone become irregular and unpredictable. As far as GABA-ergic disorders are involved in perimenopausal depression, the genes that express GABAA receptor subunits could be involved in predisposing individuals to react inappropriately to ALLO variations, and therefore have an increased risk of perimenopausal depression. The GABAA receptor subunit's gene polymorphisms are individually correlated with the likelihood of certain psychiatric illnesses, drug dependency, major depressive disorder, bipolar illness, and schizophrenia [40, 41].

In another research, Joffe et al. found 50 women between 35-50 years old with perimenopausal symptoms and reported that the absence of progesterone at rates suggesting recent ovulation and estradiol variation is correlated with depression symptomatology throughout the menopause process. They discovered that for an increase of 10% of estradiol variability, there is an increase of 1.1 on the Montgomery-Asberg Depression Rating Scale of depression score and a decrease of 2.7 for those with progesterone level [20].

Cohen L.S. et al. observed in the Havard Study of Moods and Cycles that an increased risk of developing depressive symptomatol-ogy is correlated with vasomotor symptoms. There is a hypothesis that estrogen and serotonin may modulate hypothalamic thermoregulatory activity, and sudden shifts in hormone levels and neuromodulatory activity led to the onset of depression and vasomotor symptoms [5].

Gordon et al. conducted a research in 2015 to discover that estradiol fluctuations predict the appearance of depressive symptoms 14 months before

the beginning of the menopausal transition/early perimenopause [16]. Rajewska et al. [33] observed that between menopausal and depressive symptoms is a relation between both clinical and psychological and it may be due to ovarian hormones, cortisol and serotonin deficiency.

Table 1 summarizes all the studies included in this review.

Summarizes studies included in the review Table 1

Ref.	Year	No. cases	Age	Outcome	Results
[17]	2020	101	45-55	• E1G; • PdG; • cortisol • awakening response (CAR); • CES-D; • vasomotor symptoms (VMS); • Major Depressive Disorder	• PdG-CES-D: − 0.70 to +0.88 • absPdG-CES-D: − 0.73 to 0.86 • PdG mood sensitivity strength: 0.0 to 0.88 • -E1G-CES-D: − 0.87 to +0.68 • absE1G-CES-D: −0.74 to +0.80 • E1G sensitivity strength: 0.0 to +0.87 (median=0.20).
[26]	2017	1306	42-52	• age, years • (BMI) • Age at onset menopausal transition • Menarche age; • CES-D;	• a 5% lower chances of depression are correlated with each additional year between menarche and MT initiation
[20]	2019	50	35-56	• Age, • BMI • History of depression • Estradiol, Progesterone • VMS, MADRS	• higher serum estradiol variability is associated with higher depressive symptom levels • the amount of progesterone > 6 ng / dL was correlated with lower rates of depressive symptoms
[5]	2006	460	36-45	• Age; Education; Parity • Prior use of contraceptives • Vasomotor symptoms	• increased risk for depression appears to be highlighted by the presence of vasomotor symptoms
[16]	2015	52	45-60	• Age; Race • Mean Greene Climacteric Scale (GCS) • Vasomotor Subscale score • History of major depressive disorder • Mean CES-D score change • Estradiol, Progesterone • Menopausal status at baseline • Menopausal status at month 14	• the volatility of estradiol was not related to CES-D performance (p<0,01) • estradiol variability was associated with greater anger/hostility • feelings of rejection but not anxiety (p=0,23) or fear (p<0,08)
[33]	2003	90	38-46	• Age • Kupperman-Blatt Menopausal Index (KMI) • Estradiol, FSH • Prolactin concentration • Cortisol concentration	• there was a relation between the severity of depressive symptoms with FSH, but not one with estrogen. • cortisol level was higher versus prolactin which decreased in depressive women.

4. Conclusions

The occurrence of depressive symptoms in perimenopause is associated with a variety of factors, both on the clinical and psychological levels. The results may also indicate an interaction of ovarian hormones, cortisol, and serotonin

deficiency in this process. The literature review suggests a connection between the perimenopause and the signs of depression. The variations in rates of FSH and E2 affect the recurrence of new-onset depression rather than the total decrease in the development of estrogen is uncertain. There are no compatible findings of a connection between the severity or presence of mood symptoms and any serum hormone level. Neurobiological studies show encouraging effects of estradiol on dopaminergic, cholinergic, noradrenergic, and serotonergic and GABAergic functions and progestogens seem to oppose some of these effects. Association of antidepressant and hormone therapy appears to be the best treatment choice for severe postmenopausal depression in terms of efficacy, level of recovery, and duration of relapse throughout the follow-up relative to hormonal therapy alone.

References

1. Andréen, L., Sundström-Poromaa, I., Bixo, M., et al.: *Relationship between allopregnanolone and negative mood in postmenopausal women taking sequential hormone replacement therapy with vaginal progesterone*. In: Psychoneuro-endocrinology (2005), p.212–224.
2. Bosworth, H.B., Bastian, L.A., Kuchibhatla, M.N., et al.: *Depressive symptoms, menopausal status, and climacteric symptoms in women at midlife*. In: Psychosom Med. (2001) Vol.63, p.603-608.
3. Bredemann, T.M., McMahon, L.L.: *17b Estradiol increases resilience and improves hippocampal synaptic function in helpless ovariectomized rats*. In: Psychoneuroendocrinology (2014) Vol. 42, p.77–88.
4. Bromberger, J.T., Harlow, S., Avis, N., et al.: *Racial/ethnic differences in the prevalence of depressive symptoms among middle-aged women: the Study of Women's Health across the Nation (SWAN).* In: Am J Public Health (2004) Vol. 94, p.1378–1385.
5. Cohen, L.S., Claudio S.N., et al.: *Risk for New Onset of Depression during the Menopausal Transition*. In: Arch Gen Psychiatry (2006) Vol.63, p.385-390.
6. Cullinan, W.E., Ziegler, D.R., Herman, J.P.: *Functional role of local GABAergic influences on the HPA axis.* In: Brain Struct Funct (2008) Vol. 213, p.63–72.
7. Dennerstein, L.: *Sexuality, midlife, and menopause*. In: Menopause (2008) Vol. 15, p. 221–222.
8. Dennerstein, L., Guthrie, J.R., Clark, M., et al.: *A population-based study of depressed mood in middle-aged*. In: Menopause (2004) Vol.11, p.563–568.
9. Ehrenthal, D., Hoffman, M., Hillard, P.A.: *Menstrual Disorders.* In: American College of Physicians (2006), p. 125-141.
10. Epperson, C.N., Amin, Z., Ruparel, K., et al.: *Interactive effects of estrogen and serotonin on brain activation during working memory and affective processing in menopausal women*. In: Psychoneuroendocrinology (2012) Vol. 37, p.372–382.
11. Fatemi, S.H., Folsom, T.D., Rooney, R.J., et al.: *Expression of GABAA a2-, b1- and receptors are altered significantly in the lateral cerebellum of subjects with schizophrenia, major depression and bipolar disorder*. In: Transl Psychiatr. (2013) Vol.3, p.303.
12. Foster, C., Herring, J.: *Depression: Law and Ethics* (1st ed.). In: Oxford University Press (2017), p.58-75.

13. Freeman, E.W., Sammel, M.D., Lin, H., et al.: *Symptoms associated with menopausal transition and reproductive hormones in midlife women*. In: Obstetrics and Gynecology (2007) Vol. 110, p.230-240.
14. Freeman, E.W., Sammel, M.D., Lin, H., Nelson, D.B.: *Associations of hormones and menopausal status with depressed mood in women with no history of depression*. In: Arch Gen Psychiatry (2006) Vol.63, p.375–382.
15. Gordon, J.L., Girdler, S.S., Meltzer-Brody, S.E., et al.: *Ovarian Hormone Fluctuation, Neurosteroids, and HPA Axis Dysregulation in Perimenopausal Depression: A Novel Heuristic Model*. In: The American Journal of Psychiatry (2015). Vol. 172, p.227-236.
16. Gordon, J.L., Rubinow, D.R., et al.: *Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition*. *Menopause*. In: The Journal of the North American Menopause Society (2015) Vol. 23, p. 256-266.
17. Gordon, J.L., Sander, B., Eisenlohr-Moul, T.A., Sykes Tottenham, L.: *Mood sensitivity to estradiol predicts depressive symptoms in the menopause transition.* In: Psychological Medicine, p.1–9.
18. Guthier, J.R., Dennerstein, L., Taffe, J.R., et al.: *The Menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project.* In: Climacteric (2010), Vol.7, p.375-389.
19. Hillard, T., Abernethy, K., Hamoda, H., et al.: *Management of the menopause* (6th ed.). British Menopause Society (2017), p.2.
20. Joffe, H., de Wit, A., Coborn, J. et al.: *Impact of estradiol variability and progesterone on mood in perimenopausal women with depressive symptoms.* In: The Journal of Clinical Endocrinology & Metabolism (2020) Vol. 105, p. e642–e650.
21. Josimovich, J.B.: *Gynecologic Endocrinology,* (4th ed.). Springer US Plenum Press, New York, (2013), p. 374-387.
22. MacKenzie, G., Maguire, J.: *The role of ovarian hormone-derived neurosteroids on the regulation of GABAA receptors in affective disorders.* In: Psychopharmacology (2014) Vol. 231, p.3333–3342.
23. Maguire, J., Mody, I.: *GABA(A)R plasticity during pregnancy: relevance to postpartum depression.* In: Neuron (2008) Vol. 59, p.207–213.
24. Maguire, J., Mody, I.: *Steroid hormone fluctuations and GABA(A)R plasticity*. In: Psychoneuroendocrinology (2009) Vol. 34, p.S84–S90.
25. Marcus, R., Dempster, D.W., Cauley, J.A.: *Osteoporosis*. In: Medical (2013), p.1691-1699.
26. Marsh, W.K., Bromberg, J.T., Crawford, S.L., Leung, K.: *Lifelong estradiol exposure and risk of depressive symptoms during the transition to menopause and postmenopause. Menopause:* In: The Journal of the North American Menopause Society Vol. 24, p. 1351-1359.
27. Melmed, S., Polonsky, K.S., Larsen, P.R.: *Williams Textbook of Endocrinology* (12th ed.). Saunders Elsevier, Philadelphia, (2011), p. 579-817.
28. Milad, M.R., Zeidan, M.A., Contero, A, et al.: *The influence of gonadal hormones on conditioned fear extinction in healthy*

humans. In: Neuroscience (2010) Vol. 168, p.652–658.
29. Mohler, H.: *Pharmacology of GABA and Glycine Neurotransmission*. In: Springer Science & Business Media Berlin, Heidelberg (2012), Vol. 150, p.134-141.
30. Paoletti, R., Crosignani, P.G., Kenemans, P.: *Women's Health and Menopause*: *Risk Reduction Strategies.* In: Springer Science & Business Media (2012), Vol. 11, p.137-142.
31. Pluchino, N., Cubeddu, A., Giannini, A., et al.: *Progestogens and brain: an update*. In: Maturitas (2009) Vol. 62 p. 349–355.
32. Pratt, L, A., Brody, D.J.: *Depression in the United States household population 2005-2006.* In NCHS Data Brief (2008) Vol. 7, p.1-8.
33. Rajewska, J., Rybakowsk,i J.K.: *Depression in premenopausal women: gonadal hormones, serotonergic system assessed by D-fenfluramine challenge test.* In: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2003) Vol. 27, p.705–709.
34. Raz, L., Khan, M.M., Mahesh, V.B., et al.: *Rapid estrogen signaling in the brain*. In: Neurosignals (2008) Vol.16, p. 140–53.
35. Rodrìguez-Landa, J.F., Contreras, C.M., Bernal-Morales, B., et al.: *Allopregnanolone reduces immobility in the forced swimming test and increases the firing rate of lateral septal neurons through actions on the GABAA receptor in the rat*. In: J Psychopharmacol. (2007) Vol. 21, p.76–84.
36. Rosano, G.M.C., Vitale, C., Marazzi, G., Volterrani, M.: *Menopause and cardiovascular disease: the evidence.* In: Climacteric (2007) Vol. 10 (Suppl 1), p. 19–24.
37. Sadeghipour, H.R., Ghasemi, M., Sadeghipour, H.: *Nitric oxide involvement in estrous cycle-dependent changes of the behavioural responses of female rats in the elevated plus-maze test*. In: Behavioural Brain Research (2007) Vol. 178, p. 10-17.
38. Singer, M.K., Wu, K., Kawanishi Y., et al.: *Comparison of the Menopause and Midlife Transition between Japanese American and European Women.* In: Medical Anthropology Quarterly (2002), Vol. 16, p. 64-91.
39. Soares, C.N.: *Menopausal transition and depression: who is at risk and how to treat it?* In: Expert Rev Neurother. (2007) Vol. 7, p.1285–1293.
40. Soares, N.C., Warren, M.: *The Menopausal Transition: Interface Between Gynecology and Psychiatry.* Karger Medical and Scientific Publishers (2009), Vol. 175, p. 1-18.
41. Soyka, M., Preuss, U.W., Hesselbrock, V., et al.: *GABA-A2 receptor subunit gene (GABRA2) polymorphisms and risk for alcohol de-pendence*. In: Journal of Psychiatric Research (2008) Vol. 42, p.184–191.
42. Vegeto, E., Benedusi, V., Maggi, A.: *Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neuro-degenerative diseases*. In: Frontiers in Neuroendocrinology (2008) Vol. 29, p. 507–519.
43. Vladareanu, R.: *Williams Ginecologie*, (2nd ed.). București. Ed. Hipocrate, (2015), p. 555-556.
44. *** American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, (5th ed.). American Psychiatric Association, Washington (2013).