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MENOPAUSAL TRANSITION AS A CRITICAL STAGE OF REPRODUCTIVE AGING: NEUROENDOCRINE AND CARDIOMETABOLIC IMPLICATIONS

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Abstract:

The menopausal transition is a critical stage of reproductive aging characterized by declining ovarian function, hormonal fluctuations, and systemic neuroendocrine remodeling. Alterations in central neurotransmitter systems, including serotonergic, noradrenergic, dopaminergic, and KNDy pathways, contribute to vasomotor symptoms, which reflect underlying autonomic and vascular dysregulation. Estrogen deficiency is associated with increased sympathetic activity, activation of the hypothalamic–pituitary–adrenal axis, insulin resistance, dyslipidemia, abdominal obesity, and low-grade inflammation, leading to elevated cardiometabolic risk. Psychoemotional disturbances and sleep disorders further exacerbate these processes through stress-related mechanisms. The menopausal transition should therefore be considered a systemic condition with potential long-term health implications, while vasomotor symptoms may serve as clinical markers of adverse cardiometabolic changes.

Keywords: Menopausal transition, estrogen deficiency, vasomotor symptoms, neuroendocrine regulation, cardiometabolic risk.

INTRODUCTION. The menopausal transition represents a physiological stage of reproductive aging characterized by a gradual decline in ovarian function, reduced estrogen production, and reorganization of neuroendocrine regulation (STRAW+10) [8,13]. This period is associated with menstrual cycle variability, fluctuations in follicle-stimulating hormone (FSH) and estradiol levels, and the development of menopausal symptoms of varying severity [26].

According to the international STRAW+10 classification, the menopausal transition is divided into early and late stages, differing in menstrual patterns and hormonal changes [13,21]. A key biochemical marker is an elevation in FSH levels against a background of declining ovarian reserve, reflecting impaired feedback within the hypothalamic–pituitary–ovarian (HPO) axis [22].

Local studies also emphasize the systemic nature of the menopausal transition. According to Nabieva D.Yu. (2024), premature and early menopause are associated with pronounced hormonal, metabolic, and psychoemotional disturbances, highlighting the multifactorial nature of this condition. Estrogen deficiency has been shown to initiate not only neurovegetative symptoms but also metabolic alterations that contribute to cardiovascular risk [4]. Umarhodzhaeva Z.A. (2022) notes that the course of menopause is largely determined by phenotypic characteristics, including fat distribution patterns and endocrine regulation, reflecting individual variability in adaptive mechanisms during reproductive aging [7]. Mukhamedova N.Kh. (2017) demonstrated that even in the premenopausal period, conditions predisposing to metabolic syndrome—such as abdominal obesity, insulin resistance, and dyslipidemia—begin to develop and intensify with progressive estrogen deficiency [3].

Recent international data indicate that the menopausal transition is accompanied not only by hormonal changes but also by activation of systemic inflammation, oxidative stress, and endothelial dysfunction [23,38]. These processes are considered key pathogenic mechanisms underlying increased cardiometabolic risk during perimenopause [5,6,9].

Thus, the menopausal transition should be regarded not only as a stage of physiological reproductive decline but also as a period of systemic neuroendocrine and metabolic remodeling, necessitating a comprehensive clinical and laboratory approach to the assessment of women during this life stage [24].

METHODS. This review was designed to synthesize current evidence on the neuroendocrine, metabolic, and clinical aspects of the menopausal transition. A structured literature search was conducted using

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PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar to identify relevant publications.

The search strategy incorporated combinations of predefined keywords, including "menopausal transition", "perimenopause", "estrogen deficiency", "hypothalamic–pituitary–ovarian axis", "vasomotor symptoms", "KNDy neurons", "neurotransmitters", "cardiometabolic risk", "insulin resistance", "metabolic syndrome", "psychological symptoms", and "sleep disturbances". The search was limited to studies published between 2000 and 2025, with priority given to more recent evidence. Reference lists of selected articles were also screened to identify additional relevant publications.

Studies were considered eligible if they addressed hormonal, neuroendocrine, metabolic, or clinical changes during the menopausal transition and were conducted in human populations. Both original research articles and review papers, including systematic reviews and meta-analyses, were included. Only studies published in peer-reviewed journals in English or Russian were considered.

Studies focusing exclusively on postmenopause without relevance to the transitional period, publications lacking sufficient methodological rigor or clinical relevance, and conference abstracts without full-text availability were excluded.

Study selection was performed based on relevance to the objectives of the review. A qualitative synthesis approach was applied to integrate findings across studies, with emphasis on consistency of reported mechanisms and clinical associations. Particular attention was given to neuroendocrine regulation, the pathophysiology of vasomotor symptoms, and the relationship between estrogen deficiency and cardiometabolic risk.

This approach allowed identification of converging evidence regarding the systemic nature of the menopausal transition and its role in shaping long-term cardiometabolic outcomes.

Pathophysiology. The menopausal transition is characterized by complex restructuring of the hypothalamic–pituitary–ovarian axis. A decline in the number of antral follicles leads to reduced production of inhibin B and estradiol, disrupting negative feedback mechanisms and resulting in compensatory elevation of FSH secretion [16,19]. Elevated FSH levels are considered one of the earliest biochemical markers of declining ovarian function [9–11].

Estradiol levels during perimenopause exhibit pronounced fluctuations, distinguishing this stage from the stable hypoestrogenic state of postmenopause [12,13]. Importantly, hormonal instability—rather than absolute estrogen deficiency—plays a central role in the development of menopausal symptoms in early stages [26].

Against the background of progressive estrogen deficiency, central regulatory mechanisms undergo significant alterations. Estrogens modulate hypothalamic neurotransmitter systems, including serotonergic, noradrenergic, and dopaminergic pathways [10,11]. Their decline leads to changes in thermoregulatory thresholds, autonomic imbalance, and the development of neurovegetative symptoms [23,24].

Contemporary concepts associate vasomotor symptoms with a narrowing of the so-called "thermoneutral zone" in the hypothalamus. Reduced estrogen stimulation alters the activity of KNDy neurons (kisspeptin, neurokinin B, and dynorphin-producing neurons), resulting in dysregulation of the thermoregulatory center [28].

Vasomotor symptoms (hot flashes, night sweats) are considered clinical manifestations of transient vasodilation accompanied by activation of the sympathetic nervous system. These episodes are associated with increased skin temperature, elevated heart rate, and changes in vascular tone, indicating involvement of the cardiovascular system [36,38]. This suggests that vasomotor symptoms are not merely subjective discomfort but reflect deeper neurovegetative and vascular mechanisms.

Metabolic and Cardiovascular Changes. Estrogens play a key role in regulating lipid metabolism, insulin sensitivity, and fat distribution. Their decline is associated with increased abdominal adiposity, reduced insulin receptor sensitivity, elevated low-density lipoprotein (LDL) levels, decreased high-density lipoprotein (HDL), and activation of pro-inflammatory cytokines [12,17].

Mukhamedova N.Kh. reported a significant increase in the prevalence of metabolic syndrome in pre- and postmenopausal women, with insulin resistance and abdominal obesity identified as key pathogenic components [3]. Kayumova D.T. emphasizes that perimenopause is associated with increased comorbidity, including metabolic and cardiovascular disorders, necessitating optimization of preventive strategies [1,2]. Nabieva D.Yu. (2024) further highlights that premature menopause is associated with more pronounced metabolic disturbances, confirming the systemic impact of estrogen deficiency [4].

The concept of a "therapeutic window" is discussed in international literature, referring to a period during which early intervention may influence long-term cardiometabolic outcomes [24]. Domestic studies also

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stress the importance of early risk stratification and individualized management approaches in perimenopausal women [1–4].

Neurotransmitter Mechanisms. Estrogens enhance the expression of serotonin receptors and the activity of tryptophan hydroxylase, a key enzyme in serotonin synthesis. Their decline leads to reduced serotonergic activity, resulting in decreased thermoregulatory thresholds, increased sensitivity to temperature changes, vasomotor symptoms, and anxiety-depressive disorders [19,20]. This mechanism is supported clinically by the effectiveness of selective serotonin reuptake inhibitors in managing vasomotor symptoms [28].

Estrogen deficiency is also associated with increased activity of hypothalamic noradrenergic neurons, leading to narrowing of the thermoneutral zone and heightened sympathetic activity. Even minor fluctuations in body temperature can trigger compensatory vasodilation and sweating [38]. Increased sympathetic reactivity is accompanied by tachycardia, altered heart rate variability, and blood pressure fluctuations [6,8].

Dopamine plays a role in mood regulation, motivation, and autonomic function. Estrogen-mediated modulation of dopaminergic pathways is reduced during menopause, contributing to emotional instability, sleep disturbances, and cognitive changes [31]. Dopaminergic dysregulation also affects energy balance and eating behavior, indirectly influencing body weight and fat distribution [32].

Psychoemotional and Sleep Disturbances. The menopausal transition is associated with significant psychoemotional changes. Epidemiological studies indicate that anxiety, depression, irritability, emotional lability, and sleep disturbances occur in 40–60% of perimenopausal women [11,26].

Estrogens modulate limbic system structures—including the hippocampus, amygdala, and prefrontal cortex—responsible for emotional regulation and stress response. Their decline is associated with reduced neuroprotection, impaired neuroplasticity, and imbalance between excitatory and inhibitory neurotransmitters [30,32].

Estrogen deficiency also activates the hypothalamic–pituitary–adrenal (HPA) axis, increasing cortisol levels. Chronic activation contributes to sympathetic overactivity, sleep disturbances, hyperglycemia, and insulin resistance [11,12]. Prolonged hypercortisolemia promotes abdominal fat redistribution, a key factor in metabolic syndrome development [33,34].

Sleep disturbances, often caused by nocturnal vasomotor symptoms, are associated with increased ghrelin, decreased leptin, increased appetite, insulin resistance, and elevated inflammatory markers such as hs-CRP [27]. The severity of vasomotor symptoms correlates with poor sleep quality and systemic inflammation [32].

CONCLUSION. Thus, the menopausal transition represents a complex stage of reproductive aging characterized not only by declining ovarian function but also by profound neuroendocrine, neurotransmitter, and metabolic remodeling. Fluctuating and declining estrogen levels lead to dysregulation of the hypothalamic–pituitary–ovarian axis, activation of the sympathetic nervous system, alterations in serotonergic, noradrenergic, and dopaminergic systems, and hyperactivation of the hypothalamic–pituitary–adrenal axis [22,26,37].

Vasomotor symptoms reflect disturbances in central thermoregulation but extend beyond neurovegetative manifestations. These episodes are associated with altered vascular reactivity, sympathetic activation, heart rate variability, and blood pressure fluctuations, indicating involvement of the cardiovascular system [38].

Simultaneously, estrogen deficiency contributes to insulin resistance, abdominal obesity, dyslipidemia, and low-grade systemic inflammation [10,12]. Psychoemotional disturbances and sleep disorders further exacerbate neurovegetative instability and metabolic dysregulation through stress-related mechanisms [31].

Overall, vasomotor, psychoemotional, and metabolic changes form an interconnected pathogenic complex. The menopausal transition should therefore be considered a critical period of integrated neuroendocrine and metabolic remodeling that may determine long-term cardiometabolic outcomes. In this context, particular attention should be paid to clinical phenotypes of menopausal syndrome, especially vasomotor symptoms, as potential indicators of adverse systemic changes.

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