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Short- and long-term impact by vasomotor symptoms in menopause and modern approaches to their correction

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The importance of management in women in menopause and postmenopause is not diminishing, but only gaining relevance. It is estimated that by 2050, more than 1.6 billion women worldwide will reach this age, compared to 1 billion in 2020.
Vasomotor symptoms (VMS) are the most common symptoms of menopause and affect more than 70% of women. They are diagnosed in 35-50% of women in perimenopause and 30-80% women in postmenopause. Most of these symptoms persist less than 7 years after the last menstrual period, but one in four women may experience them up to 10 years, and one in ten women may experience them after 10 years. They are based on complex endocrine, neuroendocrine and epigenetic mechanisms.
This article is a review of scientific literature publications aimed at determining the impact of VMSs on women's future life based on the analysis of published modern studies.
VMSs not only have a negative impact on a woman's quality of life, but also have potential importance for cardiovascular health. The increased risk of cardiovascular diseases (CVD) after menopause is attributed to a sharp decrease of endogenous estrogen levels, which indicates its potential cardioprotective effect in premenopausal women.
It has been established that VMSs are a risk factor for coronary heart disease and diabetes mellitus. The presence of non-alcoholic fatty liver disease is also significantly associated with an increased risk of early and severe forms of VMSs among perimenopausal women.
Taking into account that women spend a third of their lives in the postmenopausal period, it is important to analyze the experience of their management during this difficult period. It is based on focusing on a healthy lifestyle as part of primary prevention, including regular physical activity, calcium/vitamin D intake, maintaining an optimal body weight, avoiding stress, etc.
Menopausal hormone therapy (MHT) is considered as a first-line treatment for VMSs in menopause and perimenopause. Its use should be individualized, and initiation and discontinuation should not be based only on a woman's age. Assessment of baseline CVD risk, age and period since menopause are important. It is considered a priority for women with menopause before 10 years or under 60 years of age who have no contraindications to MHT.
Hormone therapy is not indicated only for the prevention of CVD. However, it has the potential to improve cardiovascular risk profile due to its beneficial effects on vascular function, lipid levels, glucose metabolism, and reduction of diabetes mellitus.
Non-hormonal VMS treatment has sufficient experience of use when there are medical contraindications to hormonal therapy or a woman's personal choice. However, MHT remains the most effective for VMS treatment.
Keywords: *menopause, postmenopause, period of menstrual transition, estrogens, vasomotor symptoms, hot flashes, night sweats, menopausal hormone therapy.*

Коротко- та довгострокові впливи вазомоторних симптомів у період клімактерію та сучасні підходи до їхньої корекції

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Значення питань менеджменту жінок у менопаузі та постменопаузі не зменшується, а тільки набуває актуальності. За оцінками фахівців, до 2050 р. понад 1,6 млрд жінок у всьому світі досягнуть цього віку порівняно з 1 млрд у 2020 р.
Вазомоторні симптоми (ВМС) є найбільш характерними для менопаузи та уражують понад 70% жінок. Їх діагностують у 35–50% жінок у перименопаузі та у 30–80% жінок – у постменопаузі. Більшість цих симптомів зберігається менше ніж через 7 років після останньої менструації, але у кожної четвертої жінки можуть спостерігатися до 10 років, а у кожної десятої – після 10 років. У їхній основі лежать складні ендокринні, нейроендокринні та епігенетичні механізми.
Ця стаття є оглядом наукових літературних публікацій, мета – визначення впливу ВМС на подальше життя жінок на підставі аналізу опублікованих сучасних досліджень.
ВМС не тільки негативно впливають на якість життя жінки, а й мають потенційну важливість для здоров'я серцево-судинної системи. Підвищення ризику серцево-судинних захворювань (ССЗ) після менопаузи пояснюють різким зниженням рівня ендогенного естрогену, що свідчить про його потенційний кардіопротекторний ефект у жінок до менопаузи.
Установлено, що ВМС є фактором ризику виникнення ішемічної хвороби серця, цукрового діабету. Наявність у жінки неалкогольної жирової хвороби печінки також значною мірою пов'язана з підвищеним ризиком поширених ранніх ВМС та їхніх тяжких форм серед жінок у період перименопаузи.

Ураховуючи те, що третину свого життя жінки перебувають у постменопаузі, важливим є аналіз досвіду їхнього менеджменту у цей складний період. Його основою є зосередження на здоровому способі життя як частині первинної профілактики, включаючи регулярне фізичне навантаження, вживання кальцію/вітаміну D, підтримання оптимальної маси тіла, уникання стресу тощо.
Менопаузальна гормональна терапія (МГТ) розглядається як лікування ВМС першої лінії у менопаузі та перименопаузі. Її застосування має бути індивідуалізованим, а початок і припинення не повинні базуватися виключно на віці жінки. Важливим є оцінювання базового ризику ССЗ, віку і часу після настання менопаузи. Воно вважається пріоритетним для жінок з менопаузою до 10 років або віком до 60 років, що не мають протипоказань до МГТ.
Гормонотерапія не показана виключно для профілактики ССЗ. Але вона має потенціал для поліпшення профілю серцево-судинного ризику завдяки своєму сприятливому впливу на судинну функцію, рівень ліпідів, метаболізм глюкози, зниження захворюваності на цукровий діабет.
Негормональне лікування ВМС має достатній досвід застосування, коли існують медичні протипоказання до гормональної терапії або особистий вибір жінки. Однак саме МГТ залишається найефективнішим засобом лікування ВМС.
Ключові слова: *менопауза, постменопауза, період менструального переходу, естрогени, вазомоторні симптоми, припливи, нічна пітливість, менопаузальна гормональна терапія.*

Over the past 70 years, the history of women has changed. Thus, their life expectancy has increased by about 18 years compared to the last century, thus significantly extending life after the last menstrual period. Menopause often causes vasomotor symptoms (VMS) and genitourinary syndrome symptoms, which can be very unpleasant and significantly affect private and social life [1].

According to the criteria of STRAW+10 (Stages of Reproductive Aging Workshop), 4 periods of menopause are distinguished: the menopausal transition, menopause, perimenopause and postmenopause. It is the menopausal transition that is characterized by the variability of menstrual cycles, against the background of which VMS and psychoemotional symptoms of estrogen deficiency appear [2].

A physiological decrease in the level of endogenous estrogen can lead to VMS, sleep disturbances and mood disorders. Long-term effects of estrogen loss include menopausal genitourinary syndrome and osteoporosis [3, 4]. Estrogen plays an important role in the regulation and coordination of energy homeostasis during female growth, development, reproduction, and aging. Estrogen receptors (ER) are widely exposed in the brain and in almost all tissues of the body. In the brain, estrogen via the ER regulates appetite, energy expenditure and supports cellular glucose metabolism, including glucose transport, aerobic glycolysis, and mitochondrial function.

Thus, estrogen is a fundamental regulator of the metabolic system of the female brain and body [5, 6]. Estrogens are known to make a significant contribution to the regulation of vasomotor tone, meanwhile receptor- and ligand-specific signaling pathways still require further investigation. The most well-known vascular effect of estradiol is the production of nitric oxide (NO), which occurs through both genomic and non-genomic mechanisms [7].

VMSs are characteristic symptoms of menopause, affecting more than 70% of women [8–10]. Hot flashes are one of the well-known classic symptoms of the menopausal transition [11]. They are based on complex endocrine, neuroendocrine and epigenetic mechanisms [10]. Menopausal symptoms most commonly to start out moderate grade and then increase in the menopausal transition as prolonged amenorrhea and hypestrogenism predominate.

VMSs can significantly impair the quality of life. Hot flashes last several minutes, starting with a feeling of redness that spreads over the upper part of the body. These symptoms are caused by a rapid increase in body temperature, which is accompanied by dilation of blood vessels [1, 11, 12]. Hot flashes are described as temporary episodes of feeling warm, flushed, and profuse sweating of the face and breast [11].

The occurrence of VMSs increases during the menopausal transition and peaks approximately 1 year after the last menstrual period [13]. Thus, VMSs occur in 35-50% of perimenopausal women and from 30 to 80% of postmenopausal women. Hot flashes that occur at night, as usual, during sleep, are often accompanied by sweating [14]. Most of them persist for less than 7 years after the last menstrual period, but in 25% of women, hot flashes can continue for up to 10 years, and in 10% – after 10 years [9, 15].

VMSs include a range of symptoms, such as sweating, palpitations and anxiety, which contribute to a woman's sleep disturbance, discomfort and distress. They can be associated with other diseases, such as hyperthyroidism, hypoglycemia, carcinoid syndrome, pheochromocytoma, and malignant tumors, so differential diagnosis is extremely important [10].

VMSs not only have a negative impact on quality of life, but also have potential importance for women's cardiovascular health [8, 16]. As of today, it has been established that increased blood pressure (BP) is associated with various manifestations of cardiovascular diseases (CVD). The risks associated with an increase in systolic blood pressure are realized starting from the age of 30 and spread over a wide age range [17]. It is known that BP increases with age in both sexes, but in women it exceeds the indicators of middle-aged and older men [18, 19].

The appearance of VMS predicts a higher level of blood pressure, and although the exact mechanism connecting them is not fully elucidated, there is evidence of greater activation of the sympathetic nervous system in this contingent of women [19]. Apparently that estradiol deficiency during menopause is associated with higher systolic BP, but this hypothesis has not been confirmed. No association between endogenous estradiol and systolic BP or risk of hypertension was found [19, 20].

A study published 20 years ago about artificial (surgical) menopause confirmed an increase in peripheral vascular resistance and BP in this age group of women , suggesting a role for ovarian hormones in modulating homeostatic pressure, and postmenopausal BP increases due to ovarian insufficiency and, above all, estrogen [21].

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As is known, the effects of endogenous estrogen are mediated through ER, and ER-dependent mechanisms that regulate vascular tone and include endothelium-independent vasodilation, increasing NO bioavailability, inhibition of vascular smooth muscle cell growth, vascular renin-angiotensin-aldosterone, endothelin, and sympathetic nervous systems [22].

Regarding the protective functions of progesterone, there is evidence that it lowers BP, suppresses coronary hyperactivity, and has potent vasodilator effects, etc. [23]. The beneficial effect of progesterone on the human cardiovascular system is realized through the induction of a rapid increase NO production in vascular endothelial cells [24]. Conducted research among a group of women aged 40–53 years, who do not smoke, established a connection between hot flashes and markers of endothelial dysfunction. However, such relationships were not observed in the group of women aged 54-60.

All associations were independent of CVD risk factors and endogenous estradiol concentrations. This indicates the potential value of considering the role of not only hormones, but also the endothelium in the physiology of early hot flashes [25].

CVD is the leading cause of death in adults and is more common in postmenopausal women than in men of the same age [26]. Mechanisms relating hot flashes to CVD risk are not fully elucidated, in part due to limited understanding of hot flashes physiology [27]. VMSs may represent a new female-specific CVD risk factor that generally persists after controlling for endogenous sex hormones and traditional CVD risk factors [8].

The increase in the risk of CVD after menopause is explained by a sharp decrease in the level of endogenous estrogen, which indicates its potential cardioprotective effect in premenopausal women [28, 29]. In postmenopausal women, when estrogen levels decline, the ovaries continues to produce testosterone, and this may be associated with an increase in atherosclerotic CVD at this age [30–32]. Women with VMSs (hot flashes and night sweats) have an increased risk of coronary heart disease [33].

The presence of hot flashes negatively affects the quality of sleep and is associated with chronic insomnia. A study analyzing the results of magnetic resonance imaging (MRI) confirmed that among menopausal symptoms, in addition to VMSs, insomnia increases the risk of coronary heart disease during the whole lifetime [34]. Regarding venous thrombosis, the relationship between VMSs and the risk of venous thrombosis is currently not established [35].

VMSs are also a risk factor for diabetes, especially for women who report night sweats (regardless of reported hot flashes). The presence of menopausal symptoms is associated with an increased risk of developing type 2 diabetes (18% increase) [14]. Menopause leads to an increased risk of accumulation of adipose tissue in the upper part of the body and an increase in the frequency of insulin resistance, accompanied by metabolic changes that contribute to the development of diabetes, especially type 2 [36–39].

Because type 2 diabetes depends on both chronological aging and ovarian aging, it is quite common in postmenopausal women [40]. Similarly, diabetes may affect ovarian aging, potentially causing women with type 1 diabetes and early-onset type 2 diabetes to experience early menopause compared with women without diabetes. And an earlier age of menopause is associated with a higher risk of type 2 diabetes later in life [37].

If we talk about body weight, it is known that the reproductive system modulates such regulation. Estradiol acts at the level of the cortex, hypothalamus, and brainstem and is crucial not only for reproductive function, but also for body weight regulation. The anorectic and thermogenic effects of estradiol can be direct, through genomic and non-genomic mechanisms, or indirect, through the activation of peripheral mediators such as insulin, leptin, and peptide-1 (GLP-1) [41, 42].

The decline in estradiol levels seen during menopause may lead to increased food intake (with loss of estradiol activity). Thus, postmenopausal decline in estradiol may contribute to the development of obesity and systemic and cerebral insulin resistance [42, 43]. Obesity is a well-known risk factor for chronic diseases. Numerous studies indicate a link between obesity and menopausal symptoms [44–46].

First of all, higher body mass index (BMI), waist size, and waist-to-hip ratio are associated with greater severity of menopausal symptoms [46]. Overweight and obesity increase the risk of vasomotor symptoms associated with early menarche [47]. A high BMI (≥25 kg/m^2) and smoking significantly increase the risk of frequent or severe VMSs in women. However, the opposite impact of BMI on the progress of VMSs was found out in postmenopausal women [48]. It should be noted that hormonal changes during menopause also affect the distribution of fat tissue in the body and, accordingly, increase the frequency of obesity. These body changes can have health consequences, including the development of cardiometabolic disease, osteoarthritis, cancer, cognitive decline, mental health, and menopausal symptoms [49].

The presence of nonalcoholic fatty liver disease (NAFLD) in a woman is also significantly associated with an increased risk of common early VMSs and their severe forms among perimenopausal women [50]. The prevalence of NAFLD in women is increasing worldwide. Women of reproductive age have a lower incidence of NAFLD compared to men, but this protection is lost after menopause, when the prevalence of NAFLD in postmenopausal women becomes similar to or exceeds that of age-matched men. Ongoing epidemiological, clinical, and experimental studies suggest a higher risk of NAFLD and higher rates of severe liver fibrosis in postmenopausal women [51]. NAFLD increases the incidence of postmenopausal women, the risk of type 2 diabetes and CVD [52].

More frequent hot flashes are associated with markers of carotid atherosclerosis among middle-aged women who reported daily hot flashes. In addition, a decrease in blood flow-mediated dilation (a marker of arterial endothelial dysfunction) and an increase in coronary artery calcium and aortic calcification were found in women with hot flashes [27, 53].

Multimodal MRI studies have shown that perimenopause is accompanied by changes in the cortex brain that are involved in many of its symptoms [54]. Thus, VMSs may be associated with markers of cerebrovascular health and, in particular, with brain volume and white matter hy-

perintensity (WMH). WMH is a marker of cerebral small vessel injury, which is thought to develop through small vessel disease and is associated with subsequent cognitive decline, dementia, and mortality. Because these changes can be detected decades before the onset of these brain disorders, they are considered an early marker [9, 54–56]. Therefore, the research findings challenge the perception of VMS as a benign symptom of middle age with limited clinical significance and highlight the potential link of VMSs to brain health [9].

The menopausal transition is a devastating process that can last more than a decade and cause symptoms in most women. It is important for clinicians to recognize the early signs and symptoms of the menopausal transition and be prepared to offer treatment to alleviate these symptoms [57].

The issues of managing women in menopause and postmenopause do not decrease, but only become more urgent. Experts estimate that by 2050, more than 1.6 billion women worldwide will reach this state, up from 1 billion in 2020 [58].

Management focuses on a healthy lifestyle as part of primary prevention, including regular exercise, calcium/vitamin D intake, maintaining an optimal weight, reducing stress, etc. [2].

Physical activity, weight loss, and quit up smoking are known to reduce the incidence of VMSs or their impact on quality of life, as well as reduce the risk of diabetes. Indeed, the psychosocial and physical benefits of these behavioral changes can motivate long-term lifestyle modification [59, 60]. Limited alcohol and sodium intake, smoking cessation have an additional positive effect on the health of the endothelium and bones [61].

International societies, including the Canadian Society of Obstetricians and Gynecologists and the North American Menopause Society (NAMS), recommend menopausal hormone therapy (MHT) as first-line treatment for VMSs of menopause and perimenopause [62–64]. The use of MHT should be individualized, its initiation and termination should not be based solely on the woman's age. Assessment of baseline CVD risk, age, and time since menopause is important [28].

Systemic estrogen alone or in combination with a progestogen reduces the frequency of VMSs by approximately 75%. Hormone therapy is not indicated exclusively for the prevention of CVD. But it has the potential to improve the cardiovascular risk profile due to its beneficial effects on vascular function, lipid levels, glucose metabolism, reducing the incidence of diabetes [65, 66]. MHT has a beneficial effect on glucose homeostasis as in women without diabetes as with type 2 diabetes [38, 40].

One reason estrogen has been thought to be cardioprotective is its beneficial effects on lipid and lipoprotein levels, namely lowering low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol. The feasibility of estrogen use is not in doubt, given that the menopause-related decline in circulating estrogen can cause metabolic signaling disturbances and a significant decrease in bioenergetics. All these biochemical changes can lead to an increased incidence of late-onset Alzheimer's disease, type 2 diabetes, hypertension and CVD in postmenopausal women [5].

There is now evidence to support an individualized approach to women based on cardiovascular risk, as some women with type 2 diabetes may be the best possible candidates for MHT. Treatment for type 2 diabetes in menopausal women involves lifestyle changes, including diet and exercise. However, most of these women will eventually need drug therapy [38, 67]. In a multidisciplinary approach to treatment, the choice of antidiabetic drugs should be based on the specific patient's characteristics and concomitant diseases, taking into account the metabolic, cardiovascular and bone effects of the drugs [67].

The prescribing of hormone therapy should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reassessment of the benefits and risks of continued therapy. MHT is considered a priority for women with menopause up to 10 years, or aged up to 60 years, who have no contraindications to MHT. The risks of hormone therapy vary depending on the type, dose, duration of use, route of administration, time of initiation, and whether a progestogen is used [63].

The risk of venous thromboembolism associated with transdermal MHT used in standard therapeutic doses does not exceed the baseline population risk [2]. The use of transdermal estrogen compared with oral estrogen medicaments is less likely to lead to thrombotic complications and possibly also to stroke and coronary heart disease, and therefore may be a better treatment option for women [28]. Transdermal 17β-estradiol has minimal effect on lipoprotein levels. These data suggest that hepatic first-pass metabolism of oral estrogens may be a major factor in changes in lipid and lipoprotein levels [68].

Progesterone in combination with estrogens reduces the average daily blood pressure rise e in postmenopausal women with both normal and high blood pressure. However, evidence has been accumulated that it has a protective effect on the cardiovascular system [69].

Therefore, the presence of cardiovascular risk factors is not a contraindication to MHT, if the optimal treatment of the underlying disease is selected. The use of MHT is not associated with an increase in blood pressure. Moreover, MHT is not contraindicated in women with arterial hypertension, they can be prescribed hormonal therapy if the blood pressure level is controlled by antihypertensive drugs [2].

Be noted that women in perimenopause may need contraception. The safest for perimenopausal women are combined hormonal contraceptives with natural estrogen in the dynamic dosage regime [2].

Despite the effectiveness of MHT, many menopausal women are not recommended to use it due to side effects and contraindications. All the benefits and risks of MHT must be considered. Therefore, other types of therapy may be prioritized [2, 10, 70]. Non-hormonal VMS treatment is an important alternative to MHT when hormone therapy is not an option due to medical contraindications or the woman's personal choice [2, 60].

Among the recommended non-hormonal treatment methods, special mention should go to cognitive-behavioral therapy, clinical hypnosis, the use of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, etc. Although hormone therapy and remains the most effective treatment for VMSs, it should

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be considered to use for women within 10 years of their last menstrual period [71]. That is why, in daily practice, gynecologists deal with issues of evaluating the benefit/risk ratio of MHT, including cardiovascular risk. When considering the issue of the use of MHT in categories of women with concomitant diseases, it is advisable to involve cardiologists, endocrinologists and doctors of other specialties for a comprehensive multidisciplinary assessment of the benefits and possible risks of MHT [72].

CONCLUSIONS

The issues of maintaining women's health in peri- and postmenopause are becoming more and more relevant in connection with the increase in life expectancy. VMSs are the most characteristic symptoms of menopause. They disrupt not only the quality of life, but have a potential impact on the health of the cardiovascular system, the development of diabetes, non-alcoholic fatty liver disease and cerebrovascular diseases.

It is important for clinicians of many specialties to be able to recognize the early signs and symptoms of the menopausal transition, to be ready to offer treatment to alleviate them and prevent long-term consequences. An important aspect of the management of patients with menopausal disorders is the awareness of medical professionals about the features of this women's age group, as well as the benefits of hormone therapy.

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