

Modern Aspects of Prevention and Treatment of Climacteric Course of Early and Premature Menopause

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Annotation: One of the most urgent problems in modern gynecology is the problem of premature or early menopause. Premature menopause (PM) refers to menopause that occurs before the age of 40, and early menopause (EM) refers to 45 years or earlier, both of which are below the median age of natural menopause (age 51). Since these conditions are fraught with multiple complications, the problem of treatment and prevention is a priority for modern medicine.

Keywords: early menopause, premature menopause, pathogenesis, hot flashes.

Introduction: The World Health Organization has developed a global strategy and action plan on ageing and health so that people live better and longer lives [1,4,5,9]. The average life expectancy of women has increased by almost 10 years over the past half century and is now approximately 78-86 years in most countries [2,3,8,11]. This leads to the fact that almost half of their lives they have to live during menopause with a constant risk of developing a number of symptoms and diseases of estrogen deficiency [9,10,14]. The extinction of the functions of organs and systems in perimenopause occurs due to a decrease in the intensity of synthesis and secretion of sex steroids, for which all organs and systems of the female body are "targets" [6,7,12,13]. Such physiological hypoestrogenism is explained, firstly, by the depletion of the reserves of the ovarian follicular apparatus, and secondly, by the apoptosis of germ cells with spontaneous genetic breakdowns accumulated over the years of life, that is, the menopausal period is normal physiological process.

Objective. By analyzing several studies conducted, to draw your own conclusions about the measures of treatment and prevention of this pathology.

Materials and methods of research. The materials for the data analysis were 12 studies from the database of sources PubMed, Research Gate, Cyberleninka regarding data on modern methods of treatment and prevention of early and premature menopause. In total, these studies analyzed the condition of 1407 patients, 7 of whom were excluded for various reasons. In all patients, the age of onset of premature and early menopause did not differ significantly from each other, which was the reason for combining the data that were analyzed during the comparison. Statistical analysis of the data was carried out using the Statistica package using the Fisher-Student's method.

Results of the study and their discussion. For almost 40 years, scientists around the world have been trying to find an adequate approach to the treatment and prevention of early and premature menopause. Since during early and premature menopause, estrogen deficiency is detected and many symptoms are associated with it, scientists decided, by replenishing the manifestations and complications of this pathology in the body. There is data clarifying the role of estradiol in disease prevention.

In 9 of the above studies, cemifuga extracts were used in the initial manifestations of premature and early menopause, then after the effect subsided for several months, women were offered MHT. At the same time, in patients, on average, the signs of menopausal syndrome in PM became almost insignificant in 78.3% of cases, while the remaining 21.7% of patients first needed MHT due to the insufficient effectiveness of phytoestrogens. It turned out that in this group of patients, the signs of menopause were severe, they had hot flashes at least 2 times a week, and there were signs of depression. And in three of the 12, the use of cemifuga extract and MHT were used together. In this category of women with signs of PM, it was milder, they were prescribed estrogen intake until the average age of natural menopause (approximately 51 years).

In these studies, there are very conflicting data regarding MHT in the treatment of genitourinary syndrome, while topical estrogens are more effective than oral estrogen. MHT reduces the frequency and severity of depressive disorders, improves memory and concentration, helps restore normal sleep, energy, emotionality, and increases skin elasticity in women with PM/RM. The effectiveness of MHT in the prevention of lesions of the musculoskeletal system has been proven. According to Russian researchers, 95.1% of women aged 35-50 are generally satisfied with hormonal therapy. MHT is prescribed in the following regimens: monotherapy with estrogens or progestogens, combined estrogen-progestogen therapy in a cyclic or continuous regimen. There are research results in which the above therapy, eliminating symptoms, reduces the likelihood of cervical cancer by 2 times, thereby reducing overall female mortality by more than 40%.

The WHI and ELITE study reported that MHT should be started as early as possible with the first onset of symptoms of premature menopause optimizing cardiovascular defense, a study of estrogen alone. Most of these studies show that the best cardiovascular outcomes were in women who had used it for 10 years or more. A selective modulator of estrogenic activity (tibolone) has an advantage in this therapy, it has estrogenic, progestogenic, and weak androgenic properties.

In modern society, women with PM/RM prefer herbal preparations can be an alternative to MHT. Extracts of red clover and cymifuga cohosh can neutralize the neurovegetative and psycho-emotional manifestations of menopausal syndrome in the early stages or in combination with other drugs. In addition, scientists are increasingly confronted with data regarding the efficacy of a plant peptide β -alanine – which has both central and peripheral effects (blocking mast cell degranulation). The possibility of stopping the incipient flush by sublingual use of 1200 mg of β -alanine has been described. But the only group of drugs for the treatment of menopausal syndrome with a level of evidence A (based on reliable and consistent scientific evidence) is MHT and its main component is estrogens, with mild and moderate severity of climacteric syndrome, it is possible to prescribe hormone-like compounds, phytopreparations, β -alanine (level of evidence B is based on insufficiently reliable or contradictory evidence). The herbal curcumin effectively inhibits d-galactose-induced oxidative stress, apoptosis, and ovarian damage through a mechanism involving the Nrf2/HO-1 and PI3K/Akt signaling pathways, suggesting that curcumin is a potential adjunct against PNUs.

V.A. Novikova et al. (2008) performed a clinical study involving 50 women with middle and late reproductive POVs. The mean age of women with POF was 30.0 ± 1.2 years. To compensate for the lack of female sex hormones, estrogen-containing drugs in the form of vaginal suppositories were used at a dose of 0.5 mg per vagina daily for 3 weeks. Then the patients were transferred to a maintenance dose of 0.5 mg twice a week for 2 months. As a result, 86% were found to have relief of RM symptoms. Recent evidence from extensive studies suggests possible differential effects depending on the type of estrogen, route of administration, or composition of MHT. The WHI study found minor trends in reduced rates of coronary heart disease, stroke, and cardiovascular mortality for transdermal estradiol compared to oral estrogens. Transdermal MHT also does not show an increase in the risk of venous thromboembolism, even in women with obesity or concomitant thrombophilia, probably avoiding the first-pass effect by not increasing levels of coagulation factors or hepato-binding globulins.

Transplantation of stem cells derived from menstrual blood mesenchymal stem cells (MSCs) can improve the ovarian microenvironment by reducing apoptosis in granulosa cells and fibrosis of the interstitium of the ovaries, which contributes to an increase in the number of follicles and the return of sex hormone levels to normal values. Transplanted MSCs migrate to the ovarian interstitium in a targeted manner, for its restoration they do not directly affect the differentiation of oocytes. In addition, MSCs have a protective effect on damaged ovaries by partially secreting FGF2. MSCs repair ovarian damage, improve ovarian function, and stimulate regeneration, suggesting that MSC transplantation can provide more than 70% recovery.

Bone marrow-derived mesenchymal stem cells are reported to improve ovarian reserve. In addition, the paracrine factors secreted by these stem cells play an important role in ovarian repair.

Transplantation of human mesenchymal stem cells from the placenta has been demonstrated as an effective way to restore ovarian function in mice with autoimmune-induced PNO. The effect of MSC transplantation on apoptosis of granulosa cells and the expression of AMH and follicle-stimulating hormone (FSH) receptor in autoimmune drug-induced premature mouse ovarian failure. MSC transplantation can significantly improve serum levels of high gonadotropin and low estrogen in mice with PNO, promote follicle development, inhibit excessive follicular atresia and granulosa cell apoptosis, and improve ovarian reserve capacity. The mechanism can be achieved by increasing the expression of AMH and FSH in the ovaries. Although menstrual cycles in patients with POF stop, some women still have residual dormant follicles in their ovaries.

When using MHT in women with PM/RM, it is necessary to weigh the benefits and risks for individual patients, such as the underlying risk factors for cardiovascular disease, breast cancer, or liver disease. Based on many recent double-blind, randomized, placebo-controlled trials and re-analyzed WHI data that show no side in women aged 50-54 years, NAMS recommends low-dose MHT for short periods of time to correct severe menopausal symptoms in low-risk women, especially those with vasomotor symptoms. Most of the causes of early menopause are beyond the patient's control. The only risk factors that they themselves can prevent are bad habits, which play an important role in the development of PM/RM.

Two studies evaluated the effect of MHT on carotid intima-media thickness, which changes with age and is an established indicator of the progression of atherosclerosis. The first prospective randomized controlled trial, "Estradiol Treatment in Early and Late Postmenopause," to test the temporal hypothesis first proposed by Clarkson, according to which the beneficial effects of MHT depend on when MHT begins before plaque formation, showed less progression compared to placebo. Another study, the Kronos Early Estrogen Prevention Study (KEEPS), found that MHT, both oral and low-dose transdermal used in women in early menopause, had no effect on plaque progression. However, women with a coronary artery calcium (CAC) score of ≥ 50 Agastone units, a marker of subclinical atherosclerosis, were excluded from the KEEPS study. Plaque measurements did not show progression of atherosclerosis in either group, possibly because there were only 4 years of follow-up, which may be too short a time to detect progression. Although WHI follow-up data show that timely use of MHT in women aged 50–59 years reduces cardiovascular mortality, the overall event rate (cardiovascular mortality) is too low to reach statistical significance.

POI is a common condition that can have far-reaching consequences for a woman's physical and mental health. Early diagnosis and treatment are crucial. We are increasingly seeing improved access to new diagnostic tools and more effective options for preserving ovarian function in young women. We need to be able to move away from concerns about the safety of hormone therapy, focus on effective management to improve health outcomes for these young women with the condition. Sharing information between researchers and a new international database of women with PNS will improve our understanding and management of the condition. **Conclusion.** After analyzing several studies, we concluded that MHT is of paramount importance for the treatment and prevention of premature and early menopause, which can help improve the quality of life of patients and eliminate complications. The combination of MHT with antioxidant drugs, phytoestrogens should be decided based on the individual properties of the body and concomitant pathologies of patients. Treatment of MSCs requires further study as it does not have large randomized trials. In addition to the main treatment, we agree with the opinion that it is necessary to include the rules of a healthy lifestyle, proper balanced nutrition and physical activity, and reduce the psycho-emotional load.

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