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Menopausal hormone therapy and Alzheimer's disease: A literature review

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ABSTRACT

This paper presents a review of the current literature on the possible relationship between menopausal hormone therapy and Alzheimer's disease. Increasing life expectancy in modern society is steadily leading to health problems in older women. Approximately 46.8 million people worldwide currently have cognitive disorders, and 2/3 of them are women. At the age of ≥65 years, every sixth woman and every eleventh man experience a form of higher nervous system pathologies. Older people are most often diagnosed with Alzheimer's disease. It is a neurodegenerative disease that leads to problems with memory and cognitive functions and is characterized by changes in behavior and social-adaptive position of a person in society.

One theory states that dementia is caused by changes in the endocrine status during menopause, particularly a decrease in estrogen levels. Currently, hormonal drugs are being considered a way to reduce the risk of neurological disorders. The possibility of preventing dementia, particularly Alzheimer's disease, has long been of interest to leading experts in this field. The prevention of these diseases and prolongation of active longevity are becoming more relevant than ever. The relationship between menopausal hormone therapy and the risk of Alzheimer's disease is receiving increasing attention.

Keywords: dementia; Alzheimer's disease; cognitive disorders; menopause; estrogens; phytoestrogens; oophorectomy; hormonal therapy.

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Менопаузальная гормональная терапия и болезнь Альцгеймера (обзор литературы)

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АННОТАЦИЯ

В работе представлен обзор современной литературы, посвящённой возможной связи менопаузальной гормональной терапии и болезни Альцгеймера. Увеличение продолжительности жизни в современном обществе неуклонно ведёт к проблемам здоровья женщин старшей возрастной группы. По статистическим данным, в настоящее время когнитивными расстройствами страдает около 46,8 млн человек в мире, причём 2/3 из них составляют женщины. В возрасте от 65 лет у каждой шестой женщины и каждого одиннадцатого мужчины наблюдается одна из форм патологий высшей нервной системы. У людей старшей возрастной группы чаще всего диагностируют болезнь Альцгеймера — нейродегенеративное заболевание, приводящее к проблемам с памятью и когнитивными функциями мозга, характеризующееся изменениями в поведении и в социально-адаптационном положении человека в обществе.

Одна из основных теорий объясняет возникновение деменции изменением эндокринного статуса в период менопаузы, в частности снижением уровня эстрогенов. В настоящее время рассматривается эффективность назначения гормональных препаратов как способа уменьшения риска развития расстройств неврологического характера. Возможность профилактики деменции, в частности болезни Альцгеймера, давно интересует ведущих специалистов в этой области. Профилактика этих заболеваний и продление активного долголетия становятся как никогда актуальными. Всё больше внимания уделяется связи между менопаузальной гормональной терапией и риском развития болезни Альцгеймера.

Ключевые слова: деменция; болезнь Альцгеймера; когнитивные расстройства; менопауза; эстрогены; фитоэстрогены; овариэктомия; гормональная терапия.

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ЭКО•ВЕКТОР

The authors searched eLybrary, MEDLINE, PubMed, and Cyberleninka databases through September 2023. Registries of ongoing trials and reference lists from previous studies and systematic reviews were also screened.

Menopause is a natural process during which women experience cessation of ovarian functions and decreased estrogen levels. This change in endocrine status can lead to decreased metabolic activity, which may serve as a basis for neurological, neuroendocrine, and vascular dysregulation, increasing the risk of developing various nervous system pathologies [1–2].

Dementia is a chronic noncommunicable disease that has become a pandemic. According to the World Health Organization (WHO), 10 out of 100 women aged >65 years are diagnosed with dementia, primarily Alzheimer's disease (AD). In 2015, approximately 47.5 million people were suffering from dementia, and it is expected to nearly double to 82 million by 2030 [1–2].

During normal aging, the brain employs compensatory mechanisms, which are most notably demonstrated through neuronal hypertrophy and an increase in the population of satellite glia. Hypertrophy can also be observed in AD, vascular dementia, and chronic cerebral ischemia with decreased levels of sex-specific steroids [3].

ESTROGEN'S ROLE IN BRAIN FUNCTION

The estrogen receptor network is a major regulatory system in the brain. Changes in estrogen availability or its receptor network can influence intracellular signaling, neural circuit function, and energy availability. In the brain, neural structures that control numerous bodily functions contain many estrogen receptors. These estrogen receptors are found in plasma membranes, mitochondria, and cell nuclei, with a high concentration in the hypothalamus, a major center for thermoregulation, sleep, and circadian rhythms. Moreover, critical areas of the brain for learning and memory retention, such as the prefrontal cortex, hippocampus, amygdala, and posterior cingulate cortex, contain estrogen receptors.

During menopause, estrogen levels significantly decrease. Although the brain typically compensates for this process, some women may experience reduced, absent, or limited adaptive compensation in a few estrogen-regulated neuronal networks, and this results in a complex neurological phenotype of menopause [4–5].

During perimenopause, estrogen regulation of glucose metabolism in the brain is impaired, leading to a hypometabolic state. Preclinical studies have indicated that when estrogen levels in the brain decrease significantly during perimenopause, the systems responsible for glucose metabolism in the brain stop functioning properly. This leads to the induction of an adaptive starvation response and an increase in fatty acid oxidation to generate and use ketone bodies by mitochondria as an alternative fuel. Hypometabolism, reduced mitochondrial function, and oxidative damage contribute to neuronal dysfunction, increasing the risk of AD development [6–8].

A study showed that a decrease in estrogen levels can negatively affect the regulation of glucose metabolism in brain regions responsible for cognitive functions [7].

In AD, the expression levels of estrogen α-receptors increased in the nuclei of hypothalamic and anterobasal neurons. This finding can be used as a diagnostic criterion for AD in pathohistological practice. MB1 is a novel splicing variant of estrogen α receptors. Its expression increases in peri- and postmenopausal women, indicating the accumulation of mutant estrogen α receptors in the hypothalamic nuclei when circulating estrogen levels decrease [9].

RELATIONSHIP BETWEEN THE FEMALE SEX AND NEURODEGENERATIVE DISEASES

Cognitive disorders (CD) refer to the deterioration of cognitive functions, including attention, memory, speech, perception, praxis, and control functions. This deterioration is detected subjectively and/or objectively and is compared with the individual's initial or average age educational levels. CD is caused by organic pathology and functional impairment of the brain caused by various etiologies. CD affects the effectiveness of learning, professional, social, and everyday activities [1]. CDs represent a diverse range of conditions that stem from neurological, somatic, and psychiatric diseases. In older individuals, CDs are primarily caused by neurodegenerative and cerebrovascular diseases and dysmetabolic disorders. Risk factors for AD development can be categorized as modifiable and nonmodifiable. Advanced age is a significant nonmodifiable risk factor (with varying risks for different age groups); 65–69 years, 0.3%; 70–74 years, 0.6%; 75–80 years, 0.9%; 80–84 years, 2.3%; 85–89 years, 4%; and >90 years, 6.9% [10–11]. Nonmodifiable risk factors for AD include a family history of AD, particularly for early onset (before 65 years of age), genetic polymorphisms, presence of the APOE4 allele, female sex, and history of head injuries [1].

The high incidence of AD cases in postmenopausal women suggests a sex-specific susceptibility to the disease in the absence of adequate estrogen levels [1, 12].

Compelling evidence shows that low estrogen levels during the menopausal transition lead to a systemic inflammatory state. This condition is characterized by the presence of proinflammatory cytokines in reproductive tissues, altered cellular immune profile, increased availability of inflammasome proteins in the central nervous system, and a proinflammatory microenvironment that increases the brain's susceptibility to various stressors [13].

In 2022, a study unveiled that prescribing combined oral contraceptives and menopausal hormone therapy (MHT) after menopause was associated with a reduced risk of AD development. Furthermore, the risk of dementia development

decreased with extended hormone therapy. The study also suggested that hormone therapy may be effective in preventing dementia among patients with depressive disorders [14].

In 2021, C.P. Boyle et al. reported that estrogen therapy shortly before the cessation of normal ovarian hormonal function had protective effects on brain health. However, if a long time had elapsed between menopause onset and MHT prescription, no beneficial effects of estrogen on the brain were observed [15].

RELATIONSHIP BETWEEN ESTROGEN DEFICIENCY AND THE PROGRESSION OF NEURODEGENERATIVE DISEASES

Menopause symptoms and long-term consequences can significantly affect women's health and mood, reducing their quality of life. Thus, seeking for medical advice and exploring treatment options are recommended to manage these symptoms. Although symptoms such as insomnia, irritability, and cognitive impairment are common, they should not be considered natural or inevitable. Initial clinical signs of cognitive decline frequently appear during perimenopause and may not always be accompanied by menstrual dysfunction or autonomic manifestations. A study discovered a statistically significant correlation between the age at which early ovariectomy was performed and the development of dementia. However, the risk of cognitive impairment or dementia did not increase in women who underwent ovariectomy before the age of 45 years but received estrogen replacement therapy before the age of 50 years [16]. During menopause, a complex imbalance of neurotransmitters occurs in the brain, which can lead to the development of depression [12, 17].

The average age of menopause onset worldwide is 48.8 years, with significant variations depending on the geographic region of residence (12, 18, 19). In the Russian Federation, the age range is between 49 and 51 years. Approximately 75% of women aged 45–55 years report experiencing hot flashes, and 28.5% of cases were moderate or severe [20–21]. Vasomotor symptoms are more frequent during the late period of menopausal transition and are particularly noticeable in the first few years after menopause [22]. Sleep disorders are prevalent among perimenopausal women, with rates ranging from 39% to 47%, and postmenopausal women, ranging from 35% to 60% [4, 15].

When discussing menopausal therapy, therapy with natural estrogens is commonly mentioned while neglecting the importance of gestagens. In general, progestagens have neuroprotective effects when combined with estrogens, including their antagonistic effect, which restore GABAergic activity and protect neurons from NMDA-induced neurotoxicity, and cumulative effects, which have a direct membrane-stabilizing and antiapoptotic action in relation to estrogens. Progestagens, either directly or through intermediate metabolites, increase neuronal survival and restore the expression of sigma-1 receptors. This phenomenon contributes to the normalization of monoamine synthesis and provides antidepressant action [11].

In the future, personalized medicine will allow the selection of individualized regimens of MHT prescription based on the study of estrogen receptors and possible allele variants. A study noted an association between the side effects of MHT and APOE ε4 allele carriers [20]. Another study reported that female APOE4 carriers who underwent MHT exhibited improved short-term memory and larger amygdala volumes than those who did not undergo MHT. Administering MHT early was linked to greater hippocampal volume but only in APOE4 carriers. These findings highlight the significance of a personalized approach to AD prevention [17].

Scientists have explained the protective role of estrogen in preventing AD through different biological processes. Estrogen promotes cholinergic neuron activity, increases cholinergic activity, has antioxidant and anti-inflammatory properties, reduces ischemic damage, and promotes nonamyloidogenic amyloid metabolism. Many studies have supported the role of genetic factors that influence the bioavailability of estrogen in the brain at AD onset. In the brain, estrogen activity is mediated by two nuclear receptors, ERα and ERβ [21–22].

The risk of AD development was significantly lower when hormone replacement therapy was initiated within the first 5 years after menopause onset. Therefore, the duration of estrogen exposure is a crucial factor in reducing the risk of dementia. According to [13], the risk decreases as the exposure time increases.

In 2023, studies have identified three activators of nongenomic estrogen-like signaling (ANGELS), namely, estren, compound A, and compound B. Estren protects against Aβ agonist pathology and restores cholinergic neuronal density to the same extent as E2. It also exerts restorative effects on bone mass loss and cholinergic neurons, without affecting reproductive tissues. However, the mechanism of action of ANGELS remains poorly understood. It has been hypothesized that ANGELS may cause imperfect and transient binding to membrane estrogen receptors, which activates nonclassical signaling through ERα and mitogen-activated protein kinase. The development of ANGELS may affect the treatment of menopausal symptoms and the development of neuroprotective drugs for estrogen-sensitive brain pathologies without compromising women's health [22].

The potential risks of cognitive impairment following ovariectomy in the reproductive age have not been overlooked.

A cohort study conducted at the Mayo Clinic evaluated the possible association between ovariectomy and pathologic aging. In that study, women who underwent ovariectomy at a younger age had an increased risk of cognitive impairment and dementia. The risk nearly doubled when unilateral ovariectomy was performed before the age of 41, and it was more than four times higher when ovariectomy was performed before the age of 34. The study indicated that the risk of dementia was only increased in patients who did not

receive MHT before the age of 50. Estrogen treatment after ovariectomy has been hypothesized to reduce the risk of cognitive impairment or dementia. In addition, younger women who had undergone ovariectomy have a higher risk of parkinsonism and related dementia. However, no association has been found between MHT administration and cognitive function in older women with surgical or natural menopause [9, 12].

According to a 2019 report, 16,669,000 women were aged 50–64 years in Russia [23]. Assuming that only 1.3% of women aged 45–69 in the Russian Federation take MHT, as they do today, the economic effect, calculated through the number of averted days of disability and lives saved, is 9.1 billion rubles annually. This is 2.5 times lower than the share of MHT use in EU countries, which is 3.4% [24].

EFFECT OF MHT ON DISEASE PROGRESSION OR REGRESSION

WHO experts have extensively examined the potential therapeutic and preventive effects of MHT. Previous research on this topic has yielded conflicting results regarding whether MHT increases or decreases the risk of AD development. For instance, the Women's Health Initiative Memory Study conducted in 1989 involved nearly 7,000 women aged 65–79 years who had received either MHT or a placebo at the beginning of the study. Women who received combination MHT had a higher risk of AD development and cognitive deficits than those who received placebo. Although the difference in mean scores between the active therapy and placebo groups was of borderline statistical significance and consistently favored the placebo groups, the difference was too small to be clinically significant. Moreover, the patients had a mean age of 71 years [25].

The MIRAGE study (Investigation of the Genetic Epidemiology of Alzheimer's Disease) found that MHT in women aged 50–63 years was associated with a reduced risk of AD development [25–26]. However, a 2004 study showed that the overall risk of dementia in women receiving combined hormonal therapy was twice that of women in the matched placebo group. The absolute risk of dementia is relatively low, at 45 per 10,000 postmenopausal women aged >65 years who received combined hormonal therapy for 1 year [27]. A large population-based study in Taiwan yielded similar results. The study analyzed the medical records of 35,024 women who received MHT and 70,048 women who were not prescribed MHT. The participants were followed until diagnosis of dementia, death, or the end of December 2013, whichever came first. The mean follow-up duration was 12.2 years. During follow-up, the MHT cohort had a significantly higher cumulative incidence of dementia than the comparison cohort, resulting in an adjusted hazard ratio of 1.000 (95% CI 1.35–1.13). A higher cumulative dose of MHT prescription was observed to increase the risk of dementia, as indicated by previous studies [26, 28]. The MHT group showed significantly higher risks of AD and vascular dementia, regardless of the age of menopause onset. Although higher MHT doses were associated with a higher risk of dementia, the duration of hormone use, whether ⩽13.5 or ⩾13.5 years, did not appear to affect the risk [26].

A recent large-scale study that ended in 2020 reported conflicting findings. The study evaluated the risk of dementia and AD in women who received MHT. The study included 118,501 women aged ⩾55 years with a primary diagnosis of dementia and 497,416 women in the control group. All patients had received MHT for at least 3 years before follow-up. Overall, the risk of dementia associated with MHT did not increase. On the contrary, a decreased overall risk of dementia was found in patients and control women aged <80 years who received estrogen-only therapy for ⩾10 years [29]. However, an increased risk of AD was found in women who used estrogen–hemostagen therapy for >5 years.

Regarding hormone therapy, phytoestrogens, which have a place in modern medicine, must be considered. In a meta-analysis of 10 placebo-controlled randomized trials conducted in 2015, P.F. Cheng et al. reported that soy isoflavone supplements improved cognitive function and visual memory in postmenopausal women [30]. They emphasized the significance of geographical features and treatment duration as crucial factors that affect the outcome.

The SOPHIA study evaluated the effect of prescribing soy to postmenopausal patients. Isoflavones were supplemented in women at a dose of 110 mg/day. After 12 weeks of daily supplementation, cognitive function was assessed. The results showed a significant improvement in the ability to memorize pictures, sustained attention, and task planning [31]. The authors described two mechanisms by which phytoestrogens exert their effects: estrogen-mediated and non-estrogen-mediated mechanisms. Importantly, phytoestrogens do not compete with estrogens but protect neurons through their means. Estrogen-mediated mechanisms include all reactions involving estrogens. Phytoestrogens can replace estrogens by binding to receptors. These mechanisms include reducing tau protein phosphorylation, reducing amyloid-β deposition, stimulating calcium efflux, and enhancing acetylcholine release. Estradiol (and phytoestrogens) act as natural antioxidants for membrane lipid peroxidation and mitigate amyloid-β toxicity to neurons. Phytoestrogens significantly improve cerebral blood flow, increasing the supply of oxygen and nutrients to brain cells [32].

Currently, dementia has become a pandemic chronic noncommunicable disease. As previously mentioned, women are at a higher risk of developing cognitive disorders. Studies show that 10 of 100 women aged >65 years will be diagnosed with dementia, primarily AD. Recent studies have suggested that MHT may have a beneficial effect on some risk factors for dementia and support the normal functioning of defense mechanisms that prevent dementia development. However, MHT is not recommended for improving cognitive

function in women with pre-existing dementia [33-34]. Although it can help reduce menopausal symptoms and control the risk of cardiovascular disease and osteoporosis, its effect on cognitive function is not guaranteed. Thus, an individualized decision about hormonal therapy based on the advice of a specialist is important.

The relationship between MHT and AD remains debatable and requires further research. When deciding whether to start or continue MHT, the individual characteristics of each patient must be considered. MHT can have both positive and undesirable side effects [34–36].

Hormone replacement therapy can be a challenging yet reassuring multimodal approach for developing personalized neurocognitive management of the nervous and endocrine systems in a three-tiered age-related system of health maintenance: emotional, cognitive, and mental. It may be useful in AD prevention and treatment.

Recent studies have indicated that MHT may protect against AD if initiated within 5 years after menopause. However, the late initiation of MHT and its administration to women with type 2 diabetes may be a risk factor for AD [35–36].

Thus, to ensure oncological safety standards and stabilize the immune response, MHT should be prescribed based on indications. The treatment course should be relatively long, i.e., by years instead of months, and should begin during the menopausal transition period. Therefore, the minimum effective dose of estrogen must be selected. Further studies on the relationship between immune and reproductive aging may lead to the discovery of new clinical and laboratory markers of risks associated with age-related immune system dysfunction and the adjustment of these risks to hormonal therapy [8, 37].

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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