REVIEW ARTICLE

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Etiology, symptoms and treatment of peri-menopausal depression

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Abstract

Introduction and Objective. Menopause is associated with the onset of a variety of symptoms that have a significant impact on a woman's daily functioning. Many women develop depressive disorders as their hormone levels fluctuate and their stress response pathways change. The goal of this study was to collect up-to-date information on the etiology, symptoms, and treatment of peri-menopausal depression.

Review Methods. PubMed and Google Scholar databases were searched for articles on menopausal women's mental health published between 1991 and 2022. Ninety articles were discovered and categorized by content and topic. The 35 most pertinent and current articles were selected.

Brief description of the state of knowledge. According to a review of the literature, major depressive disorders are most common in women during the menopausal transition due to hormonal fluctuations which are at their peak. This is because previously unknown negative menopausal symptoms have emerged, such as sleep **disturbances, hot flashes, excessive sweating, weight gain, and mood disorders.**

Summary. Women with a proclivity for depressive behavior and a lower level of education are more likely to develop more severe psychiatric symptoms. Adequate pharmacotherapy, as well as prevention in the form of regular exercise and psychotherapy, should be implemented early in the development of mood disorders. In addition to implementing pharmacotherapy, women going through menopause should be encouraged to exercise and receive psychological counseling.

Key words

Mental Health, Anxiety, Depression, Menopause, Hormone Replacement Therapy, Mood

INTRODUCTION

Etiology. Menopause, as defined by the WHO (World Health Organization), is the final cessation of menstruation caused by the loss of follicular activity in the ovaries, after which there is no more bleeding for a period of 12 months. This process is unrelated to any other physiological or pathological causes. It is most common in women between the ages of 44 and 56 [1]. Due to the decreased production of estrogen and progesterone, menopause is associated with a variety of psychological and physiological symptoms which typically begin mildly and then worsen later in the transition, when a prolonged period of amenorrhea and hypoestrogenism predominate. Hot flashes, hyperhidrosis, weight gain, sleep disturbances, mood swings, irritability, and anxiety are common menopausal symptoms, as are sexual problems, decreased libido, urinary incontinence, and low-energy fractures [1–4].

All these symptoms have a negative impact on a women's quality of life and can lead to serious mental disorders, the most prominent of which is depression. The prevalence of depressive symptoms in menopausal women is estimated to range from 8.5% – 25.7%, with major depressive disorder accounting for up to 42% [5, 6]. Symptoms peak during the menopausal transition, followed by a significant alleviation [7].

Depression is a serious mental illness marked by sadness, loss of interest and pleasure, guilt, low self-esteem, sleep and appetite disturbances, fatigue, and impaired concentration. Several factors, such as: family history and genetics, chronic stress, history of trauma, female gender, poor nutrition, unresolved grief or loss, personality traits, medication use can make depression more likely. It has a significant impact on the patients' quality of life and ability to function in all aspects of life, both socially and professionally. Depression symptoms can be mild, almost imperceptible, but depression can also manifest as a Major Depressive Disorder (MDD) – the most common type of disability worldwide. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), it is characterized by a variety of mood, cognitive, and behavioural disturbances that cause clinically significant distress and impaired functioning. Self-monitoring scales from the Center for Epidemiologic Studies of Depression [CES-D] and the Beck Depression Inventory, among others, are commonly used to assess depressive symptoms. Differential diagnoses should include dysthymia, premenstrual dysphoric disorder, and a depressive episode of bipolar disorder [8].

It has been established that peri-menopausal women are twice as likely as pre-menopausal women to experience depressive symptoms [9]. Peri-menopausal depressive symptoms impair the quality of life, cause social maladjustment, and increase disability [5]. Sleep disruption

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is another factor that contributes to the poor health of menopausal women. Constant fatigue from sleep deprivation exacerbates depressive symptoms, impairs concentration and memory, and causes irritability and decreased efficiency, all of which lower self-esteem and daily functioning [10].

Understanding the factors affecting the mental health of menopausal women will help raise public awareness of mental disorders in middle-aged women, prompting society to intervene to improve women's quality of life.

The aim of this study was to conduct a literature review on depressive disorders in peri-menopausal women and provide an overview of the etiology of peri-menopausal depression, as well as an overview of available treatments for the disorder.

MATERIALS AND METHOD

Scientific articles in Polish and English published between 2015 – 2022 were manually searched in the PubMed database. Menopause, Depression, Anxiety, Mood, Mental Health, Memory, Sleep, and Hormone Replacement Therapy were the key words used. The 26 most relevant articles in terms of topic and content were chosen from a pool of 65. To supplement the literature, a review of the bibliographies of the individual articles was conducted.

REVIEW AND DISCUSSION

Risk factors. Doltic et al. conducted a study on the mental health and quality of life of peri-menopausal women. Based on the data obtained, they discovered that various socio-demographic and health parameters were associated with aspects of mental health in pre- and postmenopausal women. Their findings were as follows:

1) lower-income pre-menopausal women are more likely to report depression;
2) post-menopausal women who live on the outskirts of town, are unmarried and lead a sedentary lifestyle are more likely to suffer from depression;
3) pre-menopausal women with a higher BMI (Body Mass Index) are more likely to experience anxiety;
4) a lower level of education contributes to higher levels of anxiety in post-menopausal women;
5) the presence of gynecological diseases is associated with poorer memory in pre-menopausal women;
6) a lower level of education correlates with poorer memory in post-menopausal women;
7) menopausal symptoms have an equal impact on memory and concentration in both pre- and post-menopausal women;
8) being married, drinking alcohol and increasing physical activity improve sleep in pre-menopausal women;
9) lack of regular rest improves sleep in post-menopausal women? [5].

Women of all ages are more likely than men to suffer from depression. Women have twice the lifetime prevalence of depressive disorders as men – 18–21%. Menopause is a time when depressive disorders become more prevalent. The risk of developing depression during this period is 1.5 – 4 times higher than during pre-menopause, especially in women who have vasomotor symptoms and other risk factors for mood disorders and depression [11]. Women with a 2-year decline in total serum estradiol have a more than 3-fold increased risk of depressive symptoms [12].

Menopausal transition. The menopausal transition is defined by the Stages of Reproductive Ageing Workshop +10 (STRAW+10) criteria as the late reproductive phase (-3), early menopausal transition (-2), late menopausal transition (-1) and FMP (Final Menstrual Period-stadium 0), and early post-menopause (+1).

Ovarian reserve decreases during the late reproductive phase. To maintain a regular ovulatory cycle, hormonal changes compensate for the decreasing number of follicles. Anti-mullerian hormone (AMH) and inhibin B levels fall, causing the pituitary to produce more follicle-stimulating hormone (FSH-follitropin) [13].

Mulhall et al. investigated the link between menopause and the risk of depressive and anxiety symptoms in a community-based sample of middle-aged Australian women. The Goldberg Depression Scale and the Goldberg Anxiety Scale were used to assess depression and anxiety symptoms. It was discovered that being peri-menopausal was associated with an increased risk of depressive symptoms, whereas being post-menopausal increased anxiety symptoms. Both the peri-menopausal and post-menopausal periods are associated with an increased risk of greater depressive and anxiety symptoms in women with a negative history of major depressive and anxiety disorders. In women with this history, the risk of symptoms does not differ from menopausal status [14].

To maintain normal estradiol levels, there is a continuous depletion of ovarian follicles and a decrease in AMH, inhibin B, and a greater increase in FSH, as well as an increase in follicular aromatase activity during the early menopausal transition phase. Following ovulation, the levels of progesterone and inhibin A decrease, resulting in an increase in FSH levels[13].

Late menopause is characterized by an increase in FSH and LH (Lutropin) and a continued decrease in estradiol and progesterone [13].

When 12 months have passed since the last menstrual period, the woman has entered the early post-menopausal phase. During this stage, ovarian reserve is undetectable, and FSH and LH levels continue to increase while estrogen and gestagen levels decrease [13].

Because estrogen receptors (ERs) are widely distributed in the brain, estrogen may have neurotransmitter-protective effects [15]. Hormone fluctuations can thus result in the development of psychiatric disorders. According to the study, peri-menopausal women are more likely to report depressive symptoms (31%) than pre-menopausal women (28%). Early peri-menopause affects 28% – 47% of women, and they are more likely to have elevated depressive symptoms at this stage than at the pre-menopausal stage[16].

Neuroseroids in menopausal transition. Hormonal changes and neurosteroids are thought to contribute to a GABA (Gamma-AminoButyric Acid) imbalance between GABA-A and GABA-B, increasing vulnerability to depression during this period of life[17]. Animal models suggest that ovarian hormone fluctuations increase the risk of peri-menopausal depression, due to changes in neurosteroids derived from progesterone. The reduced ring A metabolite of progesterone is one of the best studied neurosteroids (ALLO), which stimulates GABA A receptors by increasing GABA-induced Cl-ion channels [18]. GABA is the most important inhibitory neurotransmitter in the human nervous system.

ALLO, by modulating the GABA receptor, increases GABAergic transmission in response to stress, and thus negatively modulates the pituitary-hypothalamic-adrenal (HPA) axis [19]. ALLO not only inhibits the Hypothalamic–pituitary–adrenal (HPA) axis, but also affects the arcuate nucleus of the striatum which connects the stress-responsive pathways (HPA) to the limbic structures [20].

ALLO is primarily formed from progesterone, but estradiol is also responsible for the concentration of this neurosteroid through modulation of enzymes involved in the conversion of progesterone to ALLO, 5α-reductase and 3-hydroxysteroid dehydrogenase [21]. With menopausal transmission and ovarian function extinction, the adrenal glands are the sole source, resulting in significant fluctuations in ALLO concentrations [22]. The fluctuation of ALLO concentration affects the GABA receptor, resulting in an over- or under-inhibitory GABAergic effect [23, 24]. GABA receptor dysfunction is one of the causes of Premenstrual Dysphoric Disorder (PMDD), as well as post-partum and peri-menopausal depression [25, 26]. ALLO also modulates the release of glutamate via presynaptic GABAA receptors, and glutamate transmission is a key factor in the etiology of MDD[27, 28].

Menopause causes an increase in oxidative stress. Reduced estrogen levels exacerbate antioxidant status [29]. Stress causes an increase in ALLO, which has an inhibitory effect on the GABA receptor via hormone fluctuations. The stress response is prolonged, thereby exacerbating anxiety symptoms. This mechanism contributes to the onset of peri-menopausal depression.

Treatment. Several studies have found that Hormone Replacement Therapy (HRT) significantly improves mood in peri-menopausal and post-menopausal women.

Gordon et al. conducted a study to see if transdermal estradiol combined with micronized progesterone (TE+IMP) could prevent the onset of depressive symptoms in initially euthymic peri-menopausal and early post-menopausal women. Estradiol (0.1mg/d) or placebo was applied transdermally for a period of 12 months. Every 3 months, women receiving active TE also received oral micronized progesterone (200 mg/d for 12 days), and women receiving placebo received identical placebo tablets. Twelve months of TE+IMP therapy was found to be more effective than placebo in preventing the development of clinically significant depressive symptoms in women who were initially euthymic, peri-menopausal, or early post-menopausal [30].

Furthermore, Birkhäuser discovered that estrogen, like anti-depressants, modulates serotonin and norepinephrine metabolism, affecting mood, mental and cognitive function. There is evidence that estrogen therapy can improve mood, reduce anxiety, and depression during the menopausal transition. Estrogen may be used as a first-line treatment for depressive symptoms in peri-menopausal and early post-menopausal women with vasomotor symptoms, but is of little use in late post-menopause [11].

Soares et.al conducted one of the larger studies of estrogen therapy for peri-menopausal depression. A 12-week placebo-controlled study involving 50 peri-menopausal women with varying degrees of depression found that 68% of women treated with 100 mg of transdermal estradiol experienced depression remission, compared to 20% in the placebo group. Despite the recurrence of vasomotor symptoms 4 weeks after discontinuing therapy, the anti-depressant effect was still evident [31]. Another placebo-controlled study involving 34 women with peri-menopausal depression found that estradiol therapy for 3–6 weeks improved symptoms in 80% of the women, but only 22% in the placebo group [32].

In addition to hormone therapy, anti-depressants from the SSRI (selective serotonin reuptake inhibitor) and SNRI (serotonin norepinephrine reuptake inhibitor) families are effective. They continue to be first-line drugs for the treatment of depression in people who have had multiple depressive episodes in the past, and who have severe symptoms. Paxil, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, and desvenlafaxine have all been studied.

In the treatment of severe post-menopausal depression, Zhou et al. compared the efficacy and safety of venlafaxine and fluoxetine. The study lasted 8 weeks and was multicentre, randomized, single-blind, and actively-controlled. It included 172 women, 82 of whom were given venlafaxine and 90 were given fluoxetine. Venlafaxine was found to be more tolerated than fluoxetine, and led to greater progress in the treatment of post-menopausal major depressive episodes (MMD, Major Menopausal Depression) [33, 34].

Citalopram in combination with SSRIs, as well as duloxetine and venlafaxine in combination with SNRIs, have been shown to improve not only mood but also the severity of vasomotor symptoms [35].

CONCLUSIONS

As estrogen levels fall, menopausal women experience symptoms that have a negative impact on their lives: sleep is disrupted by hot flashes and night sweats, and sleep deprivation reduces concentration and memory. Chronic fatigue and weight gain amplify negative self-perception resulting in the deterioration of the quality of life. In order to avoid the serious consequences of depression, it is necessary to identify high-risk groups for developing mental disorders during menopause and include them in psychological counseling early in the menopausal transition. Menopausal women at increased risk of developing mental disorders, as well as women already experiencing depressive symptoms, should be under the constant supervision of a gynaecology and psychiatry specialist. HRT is used to balance estrogen levels, but if hormone therapy is insufficient, adding venlafaxine to the treatment produces excellent results. Women entering menopause should be encouraged to engage in physical activity and seek psychological counseling.

Table 1. Treatment of symptoms of peri-menopausal depression

Symptom	Treatment	Mechanism
Impaired cognitive functions	HRT	Modulation of serotonin and norepinephrine metabolism [11]
Anxiety	HRT	Modulation of serotonin and norepinephrine metabolism [11]
Major Menopausal Depression	Venlafaxine	Inhibition of serotonin and norepinephrine re-uptake [34]
Lowered mood	Citalopram	Serotonin re-uptake inhibition [35]
Sleep deprivation	HRT	Treatment for vasomotor symptoms [36]
	Escitalopram	Serotonin re-uptake inhibition [37]
Eating disorders	Estrogen-modulating strategies (estrogen+fluoxetine)	Serotonin re-uptake inhibition effects of Fluoxetine are enhanced with estrogens [38]

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