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Serum Estrogens and Depression in the Transition to Menopause- Systematic Review

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ABSTRACT/SUMMARY

Objective: To establish the relationship between the reduction of serum estrogens and depression in women in the transition towards menopause and to analyze the influence of menopausal hormone therapy.

Material and Methods: A systematic review of the literature in different electronic databases (Embase, Lilacs, among others) was made, through free and standardized search terms. Outcomes assessed included transition to menopause, depression, serum estradiol (E2), follicle stimulating hormone (FSH), and menopausal hormone therapy (THM).

Results: 73 publications were included. It was found that there is an association of depression with climacteric, and it was observed that the appearance of depression increases during the transition phase towards menopause. A significant negative association between circulating levels of E2 and intensity of depression was explored, as the severity of depression decreased with higher estradiol levels. In FSH levels, the opposite outcome was observed, as high FSH levels were positively related to the severity of depression. THM is an effective treatment for depression in women transitioning to menopause.

Conclusions: Low serum levels of E2 and elevated levels of FSH are positively associated with the onset and severity of depression. Doctors should establish guidelines for screening for depression in women during the transition to menopause.

Keywords: Menopause, Depression, Estrogens, Menopause Hormone Therapy.

INTRODUCTION

Depression ("Major Depressive Disorder" or "Clinical Depression") is defined as an emotional disorder that causes feelings of constant sadness and loss of interest in performing different activities of daily living; it usually affects a person's feelings, thoughts, and behavior, and can be associated with a wide variety of physical and emotional problems (sadness, loss of interest or pleasure, feelings of guilt or low self-esteem, sleep or appetite disorders, feeling tired, and lack of concentration) [1-3]. In its most severe form, depression can lead to suicide [4,5] and increase the risk of mortality [6].

Depression is a major global health problem [7]. It is estimated that it affects more than 350 million people worldwide and that one in four people will suffer it throughout their lifetime, regardless of age or social status [1,3,8].

The prevalence of depression is found in approximately 6% of the population; interestingly, the incidence does not differ between high- and low-income countries, which show a prevalence of 5.5% to 5.9%, respectively, indicating that the incidence of depression is independent of economic development and lifestyle [1,7]. However, lifetime prevalence of depression has been reported to range from 20% to 25% in women and from 7% to 12% in men [9]. thus, women are twice as likely to suffer depression as men [10].

Depression is often the result of complex interactions between social, psychological, and biological factors, while mental health is sensitive to traumatic events and their social and economic consequences [11,12]. Currently, depression accounts for approximately 50% of psychiatric consultations and 12% of all hospital admissions, as it has become a major determinant of inferior quality of life [13].

In the case of women in climacteric conditions, the risk of depression increases during the transition towards menopause [14]; in fact, women who experience vasomotor symptoms report prominent levels of depressive symptoms [15]. In the transition towards menopause, a wide variety of risk factors related to depression have been detected, notably: Demographic factors (age, body mass index (BMI), unemployment, financial problems), health factors (history of depressive disorders), psychosocial factors (disturbing life events, anxiety and symptoms), hormonal factors (Higher levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and low levels of estradiol (E_2) and menopausal symptoms (hot flashes, night sweats, sleep disorders, etc.) [16,19].

The diagnosis of depression is usually made through clinical assessment, since this assessment offers an array of signs and symptoms, so the need for questionnaires and/or diagnostic tests is unusual; cardinal symptoms (anhedonia, crying, sadness, etc.) are decisive [20]. Multiple self-administered depression detection instruments or scales have been developed and are easy to use and evaluate, do not require trained personnel, and manage to make a syndromic diagnosis in a brief time. Highlights include Beck Depression Inventory (BDI) [21], Montgomery-Asber Depression Rating Scale (MADRS) [22], and Hamilton Depression Rating Scale (HDRS) [23], among others.

In the initial treatment of depression, preference is given to psychotherapy, reserving pharmacotherapy for cases of insufficient improvement [24,25]. Consultation with psychiatry is mandatory in patients with severe depression and urgently in any patient with psychotic symptoms or suicidal thoughts and behaviors. First-line drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine [26].

For women in transition to menopause who experience depression, the standard of care is antidepressant treatment (provided they do not have a history of bipolar disorder or current hypomania). This can be initiated by the primary care professional in uncomplicated cases when the diagnosis is clear and there are no suicidal thoughts. Follow-up should be done within 1 to 2 weeks to assess side effects and dose titration [27].

Previous studies suggest that menopausal hormone therapy (MHT) improves the somatic and depressive symptoms experienced by women in transition to menopause, being much more effective than placebo [28-30]. The impact of estradiol treatment on depression appears to be independent of the effect of the hormone on vasomotor symptoms and sleep [31].

In this review, the main objective was to investigate the relationship of low serum estrogen levels with depression in women in the transition to menopause and to analyze the influence of THM on improvement in depression. The findings of this study are expected to help health professionals (especially general practitioners, endocrinologists, and gynecologists) worldwide recognize and treat depression early in the climacteric. this is of significant importance in the prevention of depression in middle-aged women.

MATERIAL AND METHODS

The final research question of this review is described in **Table 1**, following the PICOT model, for digital search of health information (P-Patient; I-Intervention; C-Comparison; O-Outcome; T-Time) [32]. Transition to menopause is associated with an increased risk of depression (2 to 5 times) [18,33,34]. Do low estradiol levels during the transition to menopause influence the onset of depression? The question was refined by consultation with three experts, where the transition to menopause was defined as the variable period that occurs approximately four years before menopause [35].

Table 1. Evaluation question in the PICOT structure	
P	Women in transition to menopause
I	Depression
C	Serum levels of estradiol (E_2), follicle stimulating hormone (FSH), and menopause hormone therapy (THM)
O	Primary Depression in the transition to menopause Negative association between low E_2 levels and depression Relationship of high FSH levels to depression Secondary Improvement of depression with THM
T	As reported in publications

The following inclusion criteria were considered:

- Types of studies: Cross-sectional, case-control, cohort studies, randomized clinical trials, textbooks, systematic reviews, and meta-analyzes, which had the full text available for full evaluation when included in the review.
- Type of population: Studies that included women with depression in transition to menopause.
- Type of intervention: The technology of interest was depression and comparators, serum levels of estradiol and follicle stimulating hormone (FSH) and menopausal hormone therapy (THM).

Primary outcomes included depression in the transition to menopause, a negative association between low E_2 levels and depression, and a relationship between high FSH levels and depression; As a secondary result, improvement of depression with THM.

The exclusion criteria were studies that were not available in full text (posters or abstracts), because not all information on the characteristics and outcomes of these references was available for inclusion in the analysis, studies involving less than 20 women and studies in which homeopathic therapy was preferred.

Search strategy.

A search of the scientific literature was made using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (Wiley platform), CINAHL, CASTEN, Database of Abstracts of Reviews of Effects (DARE platform), EMBASE (Elsevier), Lilacs (Virtual Health

Library – BVS, iAHx interface), Medline via PUBEO, SCOOS, and WES. The search was limited to studies published from January 1, 1980, through October 31, 2022, in english and spanish.

The first step included terms to define population and, later, search terms for technologies of interest. The criteria that defined the population as free text and controlled vocabulary (Mesh and DeCS) were: "Climacteric," "Menopause" and "Depression" [Mesh]. The terms for the health technologies of interest that were associated through the Boolean operator odds ratio (OR) were: "Estradiol," "Follicle Stimulating Hormone" and "Estrogen Replacement Therapy." In short, the portion of search terms that defined the population was linked to the terms of the health technologies of interest through the Boolean operator "AND." In addition, a manual "snowball" search was conducted based on the list of references for each article selected by the reviewers in other publications that met the inclusion criteria.

Screening of references and selection of publications.

Prior to the beginning of the process, the criteria for the inclusion of the articles were socialized and questions regarding the development of the selection were clarified. The screening of the references was done by three investigators (LOS, JLN and KTA) independently, without knowing the results of the other reviewers. The articles selected by each of the reviewers were then compared, and dilemmas regarding the selection of articles were resolved by consensus among the reviewers, reexamining the title and abstract; if more information was needed, the full text was obtained to finally make the decision whether or not to include it in the selection. In case of disagreement, a fourth investigator (FJE) was used.

Evaluation of the quality of the evidence.

The evaluation of the quality of evidence and the risk of bias was done for each article in a matched fashion by three researchers (LOS, JLN and KTA). The selected articles were evaluated using the tool designed by the Cochrane Collaboration for the detection of risk of bias [36]. In assessing the quality of the evidence set, for each of the outcomes, the tool developed by Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [37] was used.

Ethical aspects.

As a systematic review of the literature, it is considered a risk-free investigation (resolution 8430 of 1993, article 11) [38].

RESULTS

The search carried out in the different databases reported a total of 1740 references, after eliminating the duplicates, a total of 873 references were extracted; of which 30 that met the inclusion criteria according to title and summary were selected for full text review. **(Figure 1)** describes the PRISMA flow for the screening of the fiducials.

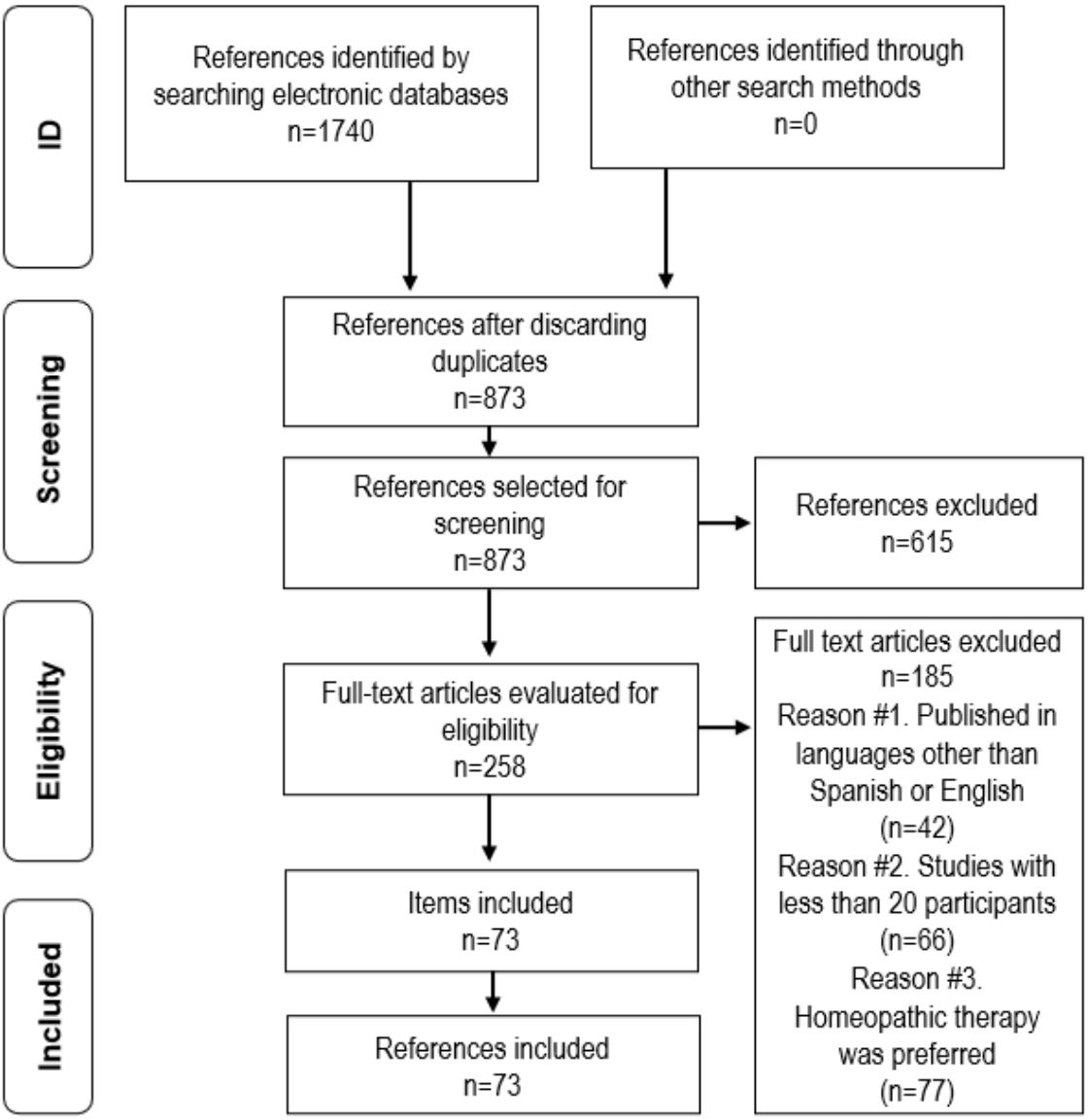

Figure 1. PRISMA flow diagram for screening and reference selection.

Depression in the transition towards menopause

Relationship of the transition towards menopause to the onset of depression: For this outcome, 4 studies of important relevance [39-42] were identified, totaling 4227 women participants. These prospective cohort studies have shown that transition to menopause and its changing hormonal environment are strongly associated with the onset of depression, with a three-fold increased risk of developing a major depressive episode during perimenopause compared to pre-menopause.

In the meta-analysis by Kruif et al. [43] We included 11 studies and found an increased risk of depressive symptoms during perimenopause compared with premenopause (OR: 2.0; IC95%: [1.48-1;< 0,001). There was a greater severity of depressive symptoms in perimenopause compared to premenopause (Hedges: 0.44; IC95%: 0.11–0.73, p = 0.007). The probability of vasomotor symptoms and depression was 2.25 (IC95%: 1.14–3.35; p<0.001) during perimenopause. This study establishes evidence that vasomotor symptoms are positively related to depressive symptoms during the transition to menopause.

Negative association between low E2 levels and depression

Relationship between low serum levels of E_2 and the presence of depression: in their research Chu et al. (44), out of a population of 1748 Chinese women aged 40 to 65 years, related to biopsychosocial risk factors for depression during transition to menopause in southeastern China, reports a prevalence of depressive symptoms of 47.43%. The association between menopausal syndrome and severity of depression was significant (OR: 6.69; IC95%: 5.39– 8.29). The outcome found a significant negative association between circulating levels of E_2 and the intensity of depression. Depression severity decreased in participants with higher estradiol levels (OR: 1.35; IC95%: 1.06– 1.73).

In the study of Malik et al. [45], in a population of 400 natural postmenopausal women, from urban areas in India, the psychological symptoms, somatic symptoms and genital urinary symptoms of menopause correlate with the drop in estrogen levels; it is found that there is a greater inverse correlation of low serum estrogen levels with psychological symptoms (depression, anxiety, mood swings), (p<0,001).

In their investigation, Freeman et al. [46], with a randomly stratified sample based on a population of African American (n = 218) and white (n = 218) women aged 35 to 47 years, decreasing E_2 levels during the transition to menopause were associated with more depressive symptoms.

Relationship of high FSH levels to depression

Relationship of high serum FSH levels and the onset of depression: in the study by Chu et al. [44], the analysis of serum FSH levels observed the opposite result of serum E_2levels, as the elevated FSH concentration was significantly related to the severity of depression (OR: 1.62; IC95%: 1.00– 2.62). On the other hand, Freeman et al, [46], explains that FSH is unlikely to contribute directly to depressive symptoms, but, as a marker of ovarian aging, they provide hormonal evidence that the transition to menopause is associated with the dysphoric mood observed at this stage.

Improvement of depression with THM

Relationship of THM to improvement of depression: In this outcome, research by Schmidt et al. [29], in women aged 44 to 55 years who met the diagnostic criteria for perimenopause-related depression, after 3 weeks of treatment with E_2, standardized mood rating scale scores and visual analogue scale symptom scores (sadness,

anhedonia, and social isolation) they decreased significantly compared to baseline scores ($p<0.01$) and were significantly lower than the scores of women receiving placebo ($p<0.01$), which did not show significant improvement. Neither the presence of hot flashes nor the duration of treatment (3 vs 6 weeks) influenced the outcome. A full or partial therapeutic response was observed in 80% of women who received E_2 and 22% of those who received placebo.

In their study Soares et al. [28], in perimenopausal women (40 to 55 years) who met the criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) [47], were randomized to receive 17β-estradiol transdermal patches (100 micrograms) or placebo. Remission of depression was observed in 68% of women treated with 17β-estradiol compared with 20% in the placebo group ($p= 0.001$). Specifically, a sustained antidepressant benefit was observed after discontinuation of estradiol treatment despite the worsening of somatic symptoms. These findings suggest independent effects of estrogens on mood and vasomotor symptoms.

In Denmark, a prospective, double-blind (12-month) randomized study of 105 women in early post menopause confirmed that THM is superior to placebo in suppressing somatic and psychic symptoms of menopausal syndrome (48). Moreover, in a cross-sectional study in San Francisco, California, with 6602 postmenopausal women, estrogen users were at a lower risk of reporting depressive symptoms, compared with non-users (OR: 0.7; IC95%: 0.5–0.9; $p = 0.01$) [49].

In a randomized, double-blind, placebo-controlled trial of 172 euthymic women in perimenopause and early post menopause (45 to 60 years), mood benefits of transdermal estradiol (0.1 mg/day) with oral micronized progesterone (200 mg/day) compared with placebo they were evident in preventing the development of depressive symptoms among women in the transition to menopause [50]. In another randomized double-blind study comparing the effects of placebo and conjugated equine estrogens (0.625 and 1.25 mg) on psychological function for 3 months in 36 asymptomatic women (45 to 60 years), the results state that women treated with estrogen had fewer depressive symptoms than those treated with placebo [51]. These findings are similar to those published by Derman et al. [52], with the use of sequential 17β-estradiol and norethindrone acetate in women aged 40 to 60 years, who spontaneously complained of menopausal symptoms.

DISCUSSION

This research included a systematic review of the scientific literature to establish the relationship between estrogen reduction and depression in the transition to menopause and to analyze the influence of THM on depression improvement. It was found that depressive symptoms are associated with low serum levels of E_2, such as those that occur during the transition to menopause, so that estrogen deficiency plays a significant role in the appearance of depression.

In their study, McEwen BS et al. [53] states that ovarian steroids have many effects on the brain throughout life; These hormones affect areas of the brain and central nervous system (CNS) that are not involved in reproduction, such as the basal forebrain, hippocampus, caudate putamen, midbrain raphe, and brain stem curemulous locus. Thus, ovarian steroids have effects throughout the brain, including effects on catecholaminergic neurons in the brainstem and midbrain, serotonin pathways in the midbrain, and the cholinergic system of basal forebrain. Regulation of the serotonin system is related to the presence of estrogen-sensitive and progestogen-sensitive neurons in the midbrain raphe, while the influence of ovarian steroids on cholinergic function involves the induction of choline acetyltransferase and acetylcholinesterase. Because of these widespread influences on these various neural systems, it is not surprising that ovarian steroids produce measurable cognitive effects after oophorectomy and during aging. Kendall et al. [54]concluded that testosterone and estrogen, but not dihydrotestosterone, reverse the effects of castration in men, suggesting that the interaction between steroids and antidepressants is mediated by estrogen receptors.

While growing evidence indicates that estrogen influences neuronal function through the serotoninergic, noradrenergic, dopaminergic, and γ-aminobutyric systems [53,54], the mechanism by which estradiol may have an antidepressant effect remains unclear [55]. However, this has not been a reason why THM is not considered as a first-line treatment for psychological symptoms related to menopause; in fact, in their meta-analysis Zweifel et al. [56] reports that estrogens (with or without progesterone) and androgens, alone or in combination, are more effective in improving psychological symptoms in menopausal women; this could be explained by minimizing the fluctuation and/or withdrawal of estradiol, which characterizes the transition to menopause [50], in addition to the direct protective actions of estrogens in hippocampal neurons [57].

Estrogens have been reported to influence neural function through direct effects on neurons and indirect effects on oxidative stress, inflammation, the vascular system, and the immune system [58]. This could play a key role in reducing the risk of depression with the use of THM, since it is compatible with maintaining brain health. In another order of thinking, there is emerging evidence that the presence and severity of certain menopausal symptoms may be associated with the onset of depression; indeed, this is the proposal for the “cascade theory,” in which hot flashes cause sleep disorders and then daytime fatigue, inferior quality of life, and depressive symptoms [59,60]. Thus, the severity of the symptoms of menopause could be a critical determinant that influences the pathogenesis of depression, and in turn explains the efficacy of THM in positively impacting both prevention and management. All of this justifies why THM is an effective treatment for depression in women in the transition to menopause.

In a cohort of 3302 women (black, chinese, hispanic, japanese, and white) aged 42 to 52 years, Avis et al. [61] found that symptoms of menopause, not menopause itself, had a significant negative impact on women's overall emotional functioning in the transition period to menopause. Proper control of depressive disorders and symptoms throughout the transition to menopause is therefore of paramount importance.

While current guidelines recommend traditional antidepressants, psychological therapy, and lifestyle changes as first-line treatment of depression during menopause (62-64). The positive CNS effects of estrogens are increasingly recognized, and estrogen-associated THM usually plays a major role in the treatment of depression associated with menopause [28,31,65]; in part because estrogen itself is involved in the modulation of serotonin through the adjustment of serotonin receptor expression [66-68], which in addition to its protective effects against cognitive impairment, makes it effective in the treatment of psychological conditions in women [28,29].

In short, the benefits of THM may exceed the risks for most symptomatic postmenopausal women who are less than 60 years old or less than 10 years old from the onset of menopause and without contraindications to receiving it [62,69,70]; therefore, it is recommended as first-line medical treatment for vasomotor and urogenital symptoms at menopause [69,71,72], in addition it may reduce depressive symptoms [28,28,73].

The main strength of this study is the use of a systematic literature review methodology to search for and synthesize available evidence on a specific question, such as the "PICOT" strategy [32]. The fact that the review considers clinical trials involving a representative number of women is another strength for the body of evidence. The extensive search of medical literature, extended by "snowball," took care to obtain relevant publications. With regard to limitations, it is mentioned that the inclusion of cohort studies may introduce weaknesses in the results found, because the evidence is of lower quality than that generated by randomized controlled trials

CONCLUSIONS

Women who are in the transition towards menopause have a significant risk of depression. The vasomotor symptoms and mood changes observed during this period can negatively affect many women as they age, which would act as a trigger for the onset of depression.

Low serum levels of E_2 and high concentrations of FSH are positively associated with the onset and severity of depression; Thus, the inverse association between hormonal profiles of E_2 and depressive symptoms establishes convincing evidence that the changing hormonal environment contributes to the dysphoric mood in the transition period to menopause.

THM is associated with a lower risk of depressive symptoms, thus it is an effective treatment for depression in women in the transition to menopause. Early interventions with THM are important for healthcare professionals to increase the mental health well-being of women in the transition to menopause.

Doctors should establish guidelines for screening for depression in women during the transition to menopause. Studies are needed to help understand the effect of THM on depressive symptoms in older women,

and to help determine whether the absence of vasomotor symptoms or the non-use of THM independently modifies the risk of depression.

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