Selección de Resúmenes de Menopausia

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Clinical Manifestations

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Background: Sex hormones are frequently implicated in the development of cerebral small vessel disease among midlife women. However, few studies directly measure endogenous sex hormones and consider them in relation to white matter hyperintensities (WMH), indicators of cerebral small vessel disease. Further, existing work on hormones, menopause, and the brain typically focuses on ovarian estradiol (E2), with limited consideration of estrone (E1), the primary postmenopausal estrogen, or follicle stimulating hormone (FSH), an indicator of ovarian age. We tested the associations of E2, E1, and FSH in relation to WMH volume (WMHV) among late midlife women. We considered both whole brain WMHV and the spatial distribution of WMHV. Methods: 222 women ages 45-67 (mean = 59.29 years, 99% postmenopausal), not taking hormone therapy, and free of a history of cardiovascular disease were recruited for the MsBrain study. Procedures included physical measures; phlebotomy for sex hormones (E1, E2, FSH; estrogens assessed via LC-MS/MS), glucose, insulin, and lipids; and 3T magnetic resonance imaging. Associations of E1, E2, and FSH with WMHV were tested in linear regression models with covariates age, race/ethnicity, education, and in a separate step, adjusted for cardiovascular disease (CVD) risk factors [body mass index, smoking, blood pressure level and medications, insulin resistance, lipids]. Additional models considered regional WMHV (deep, periventricular, frontal, temporal, parietal, occipital). Results: In age, race, and education-adjusted models, lower E2 [B(SE) = -.12(0.05), p = .02], lower E1 [B(SE) = -0.26(0.10), p = 0.007], and higher FSH [B(SE) = 0.26(0.07, p = 0.0005] were each associated with greater whole brain WMHV. When further controlling for CVD risk factors, associations of E1 [B(SE) = -.21(.10), p = .04] and FSH [B(SE) = .18(.09), p = .04] (but not E2) to whole brain WMHV remained (Figure 1). Considering the spatial distribution of WMHV, lower E1 was associated with more frontal, deep, and temporal WMHV; and higher FSH with more frontal and periventricular WMHV. Conclusions: Findings indicate the importance of endogenous sex hormones to late midlife women's cerebrovascular health. They underscore the value, when investigating aging women's brain health, of moving beyond a sole focus on E2 to also consider E1 and FSH, hormones particularly relevant in the postmenopause.

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Clinical Manifestations II

Background: Dementia and cognitive impairment, primarily linked to aging, are increasingly recognized as multifactorial conditions. Emerging research has pointed to early menopause as another potential risk factor. However, its relationship with cognitive impairment needs further investigation, especially in low- and middle-income countries. Therefore, this study aims to analyze the effect of early menopause on cognitive impairment in the Brazilian population. Methods: We analyzed data from the Brazilian Longitudinal Study of Aging (ELSI-Brazil), a nationally representative study of individuals older than 50 years. In this analysis, we included only women (n = 4,494) and defined early menopause as when its age of onset occurred before 45 years. A Global Cognitive Score (GCS) was computed by standardizing Z scores yielded by the assessment of four cognitive subdomains (orientation, fluency, episodic memory, and semantic memory). Depression was assessed using the Epidemiological Scale-Depression 8 (CES-D8), with scores of 3 or higher indicating depression. High cardiovascular risk (HCR) was defined by a history of stroke or heart attack. We conducted a general linear model with GCS as the dependent variable, and early menopause, age, HCR, and depression as covariates. Statistical analyses were performed in the R environment, and significance was set at $p < 0.05$. Results: Of the 4,494 women included in the study, 1,218 (27.1%) had early menopause. Age between groups is not different, but the group with early menopause had fewer years of education than women with normal menopause ($p < 0.001$) (Table 1). Early menopause is significantly and independently associated with lower scores in GCS (β: -0.112, $p < 0.001$), implying a lower performance in the cognitive assessment. Seemingly, depression ($p < 0.001$), age ($p < 0.001$), and high cardiovascular risk ($p = 0.009$) negatively impact GCS. Conclusions: Our study shows early menopause as an independent factor associated with cognitive impairment in a representative sample of the Brazilian population. Further

research is warranted to elucidate the underlying mechanisms linking early menopause to cognitive impairment and to develop effective interventions that can optimize cognitive health in this vulnerable population.

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Clinical Manifestations III

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Background: Menopause has been associated with greater dementia risk. We investigated the relationship between the presence of specific symptoms experienced during menopause (i.e., perimenopausal symptoms) and later-life emergence of cognitive and behavioral symptoms that are linked to elevated dementia risk. Method: Participant data were from the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behaviour, Function, and Caregiving in Aging (CAN-PROTECT) study. The sample for this analysis comprised 896 post-menopausal participants, who recalled the presence or absence of 11 perimenopausal symptoms. Symptoms were categorized as vasomotor, weight changes, vaginal dryness, irregular periods, sleep problems, mood changes, brain fog, and other unnamed symptoms. Currently experienced subjective cognitive symptoms were measured with the Everyday Cognition (ECog-II) scale. Emergent and persistent neuropsychiatric symptoms were measured with the Mild Behavioral Impairment Checklist (MBI-C). Higher scores reflected greater severity on both measures. A negative binomial regression examined the association between perimenopausal symptoms and cognitive function. A zero-inflated negative binomial regression examined the association between perimenopausal symptoms and MBI symptoms. All models adjusted for age of menopausal onset, menopausal hormone therapy (MHT), menopause type (i.e., spontaneous, or due to medical reasons), age, and years of education. Result: Symptoms of brain fog, weight changes, and mood changes were associated with poorer current ECog-II score (b = 74.8, 95%CI [47.2, 108.0], p<.001; b = 24.4, 95%CI [8.9, 42.2], p = .001; b = 36.2, 95%CI [17.3, 58.3], p<.001, respectively). Comparatively, use of estrogen and non-estrogen-based MHT during menopause was not significantly associated with current ECog-II scores (b = -11.0,95%CI[-25.3, 6.5], p = .2; b = 16.9, 95%CI[-10.9, 56.1], p = .3, respectively). Weight and mood symptoms of perimenopause were significantly associated with poorer current MBI-C score (b = 24.4,95%CI[2.4,51.1], p = .03; b = 68.4%,95%CI[36.3,108.1], p<.001, respectively). MBI-C scores differed based on type of MHT used. Estrogen-based MHT was associated with a statistically significant 26.9% lower MBI-C score (95%CI[-43.3, -5.7], p = .02), while score did not differ significantly with non-estrogen-based MHT (b = -19.1,95%CI[-44.6, 18.1], p = .3). Conclusion: The experience of brain fog, weight changes, and mood changes during perimenopause may predict greater risk for cognitive and behavioral changes later on. Use of estrogen-based MHT may mitigate the relationship between perimenopause symptoms and MBI symptoms. However, longitudinal data are required to explore mechanisms.

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Association of age at menopause and suicide risk in postmenopausal women: a nationwide cohort study

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Introduction: Early age at menopause has been linked to various adverse health outcomes, but its association with suicide risk remains underexplored. This study aims to assess the relationship between age at menopause and suicide risk among postmenopausal women. Methods: This retrospective cohort study analyzed data from the Korean National Health Insurance System (NHIS), covering 1,315,795 postmenopausal women aged 30 years and above, from 2009 to 2021. Menopausal age was classified as primary ovarian insufficiency (under 40 years), early menopause (40-44 years), average menopause (45-49 and 50-54 years), and late menopause (55 years and older). Suicide incidence was identified using ICD-10 codes for primary cause of death. Multivariable Cox proportional hazards models were utilized to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Results: Across the 12-year follow-up, there were 2,986 suicides. Women with primary ovarian insufficiency exhibited the highest suicide risk (HR, 1.43; 95% CI, 1.14-1.78, p < 0.001), followed by those with early menopause (HR, 1.31; 95% CI, 1.15-1.50, p < 0.001), and those with menopause between 45 and 49 (HR, 1.13; 95% CI, 1.04-1.23, p < 0.001) compared to the reference group undergoing menopause at age of 50-54. Discussion: Early onset of menopause, particularly primary ovarian insufficiency, is associated with a significantly elevated risk of suicide. These findings underscore the need for targeted interventions and support for women experiencing early menopause. This study highlights the importance of monitoring mental health in postmenopausal women and suggests further research to explore the underlying mechanisms linking early menopause to increased suicide risk.

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Safety of Fezolinetant for Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause: Pooled Analysis of Three Randomized Phase 3 Studies

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Introduction: This study evaluated the safety and tolerability of fezolinetant in women with vasomotor symptoms (VMS) due to menopause in a pooled analysis of data from three 52-week phase 3 studies (SKYLIGHT 1, 2, and 4). Methods: SKYLIGHT 1 and 2 were double-blind, placebo-controlled studies where women (≥ 40 to ≤ 65 years), with moderate to severe VMS (minimum average ≥ 7 hot flashes/day) were randomized to once-daily placebo, fezolinetant 30 mg or 45 mg. After 12 weeks, those on placebo were re-randomized to fezolinetant 30 mg or 45 mg, while those on fezolinetant continued on their assigned dose for 40 weeks. SKYLIGHT 4 was a placebo-controlled, double-blind, 52-week safety study. Safety was assessed by frequency of treatment-emergent adverse events (TEAEs) and endometrial events. TEAEs of special interest included liver test elevations and endometrial hyperplasia or cancer or disordered proliferative endometrium. Results: Totals of 952 participants receiving placebo, 1100 receiving fezolinetant 45 mg, and 1103 receiving fezolinetant 30 mg took ≥ 1 dose of study medication. TEAEs occurred in 55.3%, 62.9%, and 65.4%, respectively; exposure-adjusted results were consistent with these results. Most frequent TEAEs in fezolinetant-treated participants included upper respiratory tract infection (7.7-8.3%), headache (6.8-8.2%), coronavirus disease 2019 (5.8-6.1%), back pain (3.1-3.7%), arthralgia (2.9-3.2%), diarrhea (2.3-3.2%), urinary tract infection (2.9-3.4%), and insomnia (2.0-3.0%). The incidence of drug-related serious TEAEs and associated treatment withdrawals was low. Elevations in liver transaminases occurred in 1.5-2.3% of fezolinetant-treated participants, were typically asymptomatic and transient, resolved on treatment or discontinuation, with no evidence of severe drug-induced liver injury (Hy's law). Endometrial safety results were well within US Food and Drug Administration criteria. Analysis of benign and non-benign neoplasm controlled for exposure demonstrated no increased risk versus placebo. Conclusion: Pooled data confirm the safety and tolerability of fezolinetant over 52 weeks.

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Evaluation of the relationship between types of menopause and cognitive function

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Background/aim: Menopause is often accompanied by neurological symptoms, including cognitive difficulties, especially with memory and attention. The purpose of the present study was to examine the relationship between the timing of menopause and the cognitive performance of menopausal patients who applied to our neurology clinic with complaints of forgetfulness. Materials and methods: The data of 538 women who applied to the neurology clinic with complaints of forgetfulness between January 2018 and January 2024 and underwent neuropsychological evaluations were scanned retrospectively. A total of 96 patients who applied to the neurology and menopause clinics were included in the study. Results: The attention orientation, verbal fluency, memory, and total Addenbrooke's cognitive evaluation battery-revised (ACE-R) test scores were significantly higher in the >50-year-old menopausal group when compared to the other groups ($p < 0.001$). A statistically significant, negative, and weak relationship was detected between the body mass index (BMI) and memory scores ($r = 0.3$, $p < 0.001$). A statistically significant, positive, and weak relationship was detected between the high-density lipoprotein level and verbal fluency score, memory score and ACE-R score ($r = 0.3$, $p < 0.001$). A statistically significant, negative, and weak relationship was detected between the BMI and memory scores ($r = 0.3$, $p < 0.001$). Conclusion: The relationship between the cognitive performance of menopausal women and the timing of menopause was examined herein. The ACE-R, attention and orientation, visual, verbal fluency, and memory scores were significantly higher in women ≥50 years of age who entered menopause compared to those <40 years of age and those between 40 and 50 years of age. This study provides evidence that advancing age at menopause is associated with better cognitive performance. This relationship is most evident in the areas of the attention, verbal fluency, memory, and visuospatial domains.