Selección de Resúmenes de Menopausia

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Long-term hormone therapy for perimenopausal and postmenopausal women

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Background: Hormone therapy is widely provided to control menopausal symptoms and has been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005. Objectives: To assess the long-term effects of prolonged use (at least one year) of hormone therapy on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures and cognition in perimenopausal and postmenopausal women. Selection criteria: We included randomised, double-blind trials in which peri- or postmenopausal women took hormone therapy or placebo for at least one year. We included various oestrogen formulations, with or without progestogens. We focused on studies assessing hormone therapy's effects on long-term clinical outcomes, including death, coronary events and cancer. Hormone therapy's efficacy in managing menopausal symptoms was beyond the scope of this review, and is assessed in other Cochrane reviews. Main results: We included 24 studies - with two newly added in this update - involving 45,660 participants. We derived nearly 70% of the data from two well-conducted studies: the Heart and Estrogen/progestin Replacement Study (HERS 1998) and the large, multi-component Women's Health Initiative research programme, which included two hormone therapy arms (WHI 1998). Across all the studies, most participants were postmenopausal American women with one or more comorbidities. The mean participant age in most studies was over 60 years. Only one included study focused on perimenopausal women. We present full results for all included studies with available data in the main review. The results presented below are drawn from WHI 1998, in which the combined hormone therapy arm and the oestrogen-only arm were run concurrently, with women assigned to the appropriate trial based on their uterus status. One study with 16,608 postmenopausal women with an intact uterus compared combined continuous hormone therapy (conjugated equine oestrogen and medroxyprogesterone acetate) to placebo, and measured outcomes at an average of 5.6 years of follow-up. Based on this study, combined continuous hormone therapy probably makes little to no difference to the risk of a coronary event (RR 1.17, 95% CI 0.95 to 1.44; moderate-certainty evidence). It may increase the risk of stroke (RR 1.39, 95% CI 1.09 to 2.09; low-certainty evidence) and venous thromboembolism (RR 2.03, 95% CI 1.55 to 6.64; low-certainty evidence). Compared to placebo, combined continuous hormone therapy probably increases the risk of breast cancer (RR 1.27, 95% CI 1.03 to 1.56; moderate-certainty evidence) and probably makes little to no difference to the risk of lung cancer (RR 1.06, 95% CI 0.77 to 1.46; moderate-certainty evidence). It may increase gallbladder disease requiring surgery (RR 1.64, 95% CI 1.30 to 2.06; 14,203 participants; low-certainty evidence), and probably reduces the risk of all clinical fractures (RR 0.78, 95% CI 0.71 to 0.86; moderate-certainty evidence). One study including 10,739 postmenopausal women who had undergone a hysterectomy compared oestrogen-only (conjugated equine oestrogen) hormone therapy to placebo, and measured outcomes at an average of seven years' follow-up. Based on this study, oestrogen-only hormone therapy probably makes little to no difference to the risk of coronary events (RR 0.94, 95% CI 0.78 to 1.13), venous thromboembolism (RR 1.32, 95% CI 1.00 to 1.74) and breast cancer (RR 0.79, 95% CI 0.61 to 1.01), all with moderate-certainty evidence. It may make little to no difference to the risk of lung cancer (RR 1.04, 95% CI 0.73 to 1.48; low-certainty evidence). Oestrogen-only hormone therapy probably increases the risk of stroke (RR 1.33, 95% CI 1.06 to 1.67) and gallbladder disease requiring surgery (RR 1.78, 95% CI 1.42 to 2.24), and probably reduces the risk of all clinical fractures (RR 0.73, 95% CI 0.65 to 0.80), all with moderate-certainty evidence. We judged most included studies to have a low risk of bias for most domains. The overall certainty of evidence for the main comparisons was moderate. The main limitation was that only about 30% of women were 50 to 59 years old at baseline, the age group most likely to consider hormone therapy for vasomotor symptoms. Authors' conclusions: Long-term follow-up of women using hormone therapy suggests that the risk profiles vary between combined hormone therapy and oestrogen-only therapy. Oestrogen-only hormone therapy probably makes little to no difference to coronary events, and probably increases the risk of stroke and gallbladder disease. It probably makes little to no difference in the risk of breast cancer, and probably reduces the risk of all fractures. Combined hormone therapy may increase the risk of thromboembolism and probably increases the risk of breast cancer. These results should be interpreted with caution as they are based on one study using oral hormone therapy, which may not represent the risks of the hormone therapy currently used in clinical practice.

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The APOE4-estrogen-microglia axis in perimenopausal cognitive changes: mechanisms and therapeutic implications

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Alzheimer's disease (AD) exhibits marked sex differences, with women bearing a disproportionate burden of disease, particularly after midlife. Among the major factors contributing to this vulnerability, the apolipoprotein E ϵ4 allele (APOE4) and the abrupt endocrine transition of perimenopause have emerged as two critical and potentially synergistic drivers of neurodegeneration. Microglia, the resident immune cells of the central nervous system, lie at the center of this interaction because they integrate genetic, hormonal, metabolic, and inflammatory signals that shape amyloid clearance, synaptic remodeling, and neuroimmune homeostasis. Accumulating evidence indicates that APOE4 impairs microglial phagocytosis, disrupts lipid handling and lysosomal function, promotes pro-inflammatory activation, and compromises neurovascular integrity. In parallel, estrogen normally restrains microglial inflammatory signaling and supports phagocytic, metabolic, and reparative functions through estrogen receptor-dependent pathways. During perimenopause, fluctuating estrogen deficiency removes these protective constraints, thereby increasing the susceptibility of microglia to APOE4-driven dysfunction. This review synthesizes current evidence supporting an integrated pathogenic framework centered on the "APOE4-estrogen deficiency-microglia axis." We discuss how this axis promotes chronic neuroinflammation, synaptotoxicity, amyloid and tau pathology, mitochondrial dysfunction, blood-brain barrier disruption, and large-scale network disconnection, ultimately accelerating cognitive decline in women. We also summarize relevant experimental models, including APOE-targeted murine paradigms, ovariectomy and accelerated ovarian failure models, human induced pluripotent stem cell-derived microglia, and emerging single-cell and spatial omics approaches. Finally, we highlight translational opportunities, including precision hormone-based interventions, selective estrogen receptor modulation, TREM2-centered microglial therapies, APOE4-directed molecular and genetic strategies, and biomarker-guided multi-target interventions during the perimenopausal "window of opportunity." By integrating molecular mechanisms with translational perspectives, this review proposes a precision medicine framework for preventing or delaying neurodegenerative progression in high-risk perimenopausal women.

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Association between early menopause and adverse cardiovascular events in postmenopausal women: a systematic review and meta-analysis stratified by smoking status and type 2 diabetes mellitus

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Background: The impact of early menopause on adverse cardiovascular events may be modified by smoking and type 2 diabetes mellitus (T2DM). This study aims to investigate the effect of early menopause on adverse cardiovascular events in women, with stratification by smoking status and T2DM status. Methods: Studies were retrieved from four databases (Embase, Web of Science, PubMed, and Cochrane Library) from their inception to January 2026. In this study, early menopause was defined as natural menopause occurring before age 45 years, encompassing both premature menopause (<40 years) and early menopause (40-45 years). This systematic review was registered with PROSPERO (Registration No.: CRD420251238709). Results were presented as hazard ratios (HR) or relative risks (RR) with corresponding 95% confidence intervals (95% CI). Results: In this study, a total of seven cohort studies involving over 1.77 million postmenopausal women were included. Among non-smoking women, early menopause was associated with a higher risk of heart failure (HF: HR = 1.23, 95% CI = 1.02-1.49, p = 0.031, I 2 = 87.9%, n = 2) and coronary heart disease (CHD: RR = 1.26, 95% CI = 1.18-1.35, p < 0.001, I 2 = 0.0%, n = 2). In contrast, among smoking women, we did not find statistically significant evidence of an association between early menopause and either HF (HR = 1.15, 95% CI = 0.88-1.52, p = 0.311, I 2 = 73.7%, n = 2) or CHD (RR = 1.63, 95% CI = 0.90-2.96, p = 0.105, I 2 = 97.2%, n = 2). For women without T2DM, early menopause was associated with a higher risk of both HF (HR = 1.19, 95% CI = 1.00-1.43, p = 0.050, I 2 = 94.1%, n = 2), a borderline finding that should be interpreted with caution, and significantly associated with stroke (HR = 1.11, 95% CI = 1.09-1.13, p < 0.001, I 2 = 0.0%, n = 2). For women with T2DM, early menopause was associated with a higher risk of HF (HR = 1.29, 95% CI = 1.11-1.50, p = 0.001, I 2 = 54.3%, n = 2), but not find with stroke risk (HR = 1.11, 95% CI = 0.99-1.25, p = 0.062, I 2 = 59.6%, n = 2). In both the T2DM and non-T2DM groups, no statistically significant evidence of an association between early menopause and with all-cause mortality was found (T2DM: HR = 1.20, 95% CI = 0.83-1.74, p = 0.333, I 2 = 54.3%, n = 2; without T2DM: HR = 1.18, 95% CI = 0.94-1.47, p = 0.148, I 2 = 53.3%, n = 2, respectively). Conclusion: Early menopause is associated with the risk of adverse cardiovascular events in women, with divergent results by smoking status and T2DM.

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Tibolone Use Associated With Elevated Hepatocellular Carcinoma Risk: Findings From a Nationwide Cohort

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Tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic activity, is widely prescribed for menopausal symptoms, but its association with hepatocellular carcinoma (HCC) remains unclear. Using data from 117,271 women aged ≥ 45 years in the Korean National Health Insurance Service-Health Screening Cohort, we evaluated tibolone use between 2003 and 2007 and identified incident HCC from 2009 through 2019, implementing a 1-year lag period. Participants were propensity score-matched (1:10) by demographic, lifestyle, and metabolic factors. During a median 11-year follow-up, women with ≥ 180 cumulative days of tibolone use showed a higher HCC risk compared with non-users (hazard ratio [HR], 1.88; 95% CI, 1.07-3.29), which persisted after adjustment for key covariates (adjusted hazard ratio [aHR], 1.74; 95% CI, 0.99-3.06). A dose-response trend was observed (P for trend = 0.043). These findings suggest a possible link between sustained tibolone use and HCC risk, warranting confirmation in larger populations and longer follow-up, ideally through well-designed prospective studies.

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Menopausal 'brain fog' or dementia? a practical guide for clinicians

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Cognitive symptoms commonly described by patients as menopausal 'brain fog' are increasingly recognised during the menopause transition and can cause significant distress, anxiety and concern about early dementia. This BMS Tool for Clinicians provides a practical clinical overview of how to distinguish menopause-related cognitive symptoms from mild cognitive impairment and dementia. Brain fog around the time of menopause is typically subjective, fluctuating and associated with perimenopausal symptoms such as sleep disturbance, vasomotor symptoms and mood change, while dementia is more likely to be progressive, objectively impairing and associated with functional decline. The Tool summarises key features for history-taking, assessment and escalation, including consideration of medical, psychological and lifestyle contributors. It highlights the importance of reassurance, education, management of modifiable factors, workplace support and appropriate use of hormone therapy where indicated. A structured approach can help clinicians validate patient concerns while identifying red flags that require further cognitive assessment or specialist referral.