PERSONAL PERSPECTIVE

Menopausal transition, mood, and cognition: an integrated view to close the gaps

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Abstract

Epidemiological and clinic data support the notion that some women may be at higher risk for developing mood and anxiety symptoms and cognitive complaints during certain periods in life that are marked by intense hormone variations and psychosocial stressors. The complexity of the so-called windows of vulnerability poses a particular challenge to professionals involved in the care of female patients. Menopausal transition is perhaps a paramount example; the process itself is marked by progressive, dynamic changes in hormone levels and reproductive function that interact with the aging process, changes in metabolism, sexuality, lifestyle behaviors, and overall health.

The putative compounded burden of health challenges associated with this transition has become a main focus of attention of physicians and researchers who aim to identify preventive and/or early intervention strategies to promote healthy aging in midlife women. Recent studies have provided further evidence that the menopausal transition may be not only a window of vulnerability for depression and cognitive impairment but also a critical “window of opportunity” for the success of hormone-based treatments.

The need for further investigation and better understanding of common underlying mechanisms seems intuitive. An ultimate goal could include preventive strategies for women presenting with various risk factors for cardiovascular, cognitive, and mood disorders as well as treatments that could be tailored to multiple symptom domains during the menopausal transition.


The interplay between the hormone milieu, physiological changes, and psychological symptoms that may occur across the life cycle of a woman has long intrigued clinicians and researchers. Accumulating epidemiological and clinic data support the notion that some, but not all, women may be at higher risk for developing mood and anxiety symptoms and cognitive complaints during certain periods in life that are marked not only by intense hormone variations and psychosocial stressors but also by changes in personal, family, and professional responsibilities. The complexity of the so-called windows of vulnerability poses a particular challenge to professionals involved in the care of female patients, and isolated efforts have produced a limited understanding of the multifaceted nature of these phenomena.

Menopausal transition is perhaps a paramount example; the process itself is marked by progressive, dynamic changes in hormone levels and reproductive function that interact with the aging process, changes in metabolism, sexuality, lifestyle behaviors, and overall health. Moreover, health-related conditions and psychological stressors that are not unique to midlife might converge with the biological changes of the menopausal transition to ultimately contribute to the emergence of a broad constellation of symptoms. As a result, the putative compounded burden of health challenges associated with this transition has become a main focus of attention of physicians and researchers who aim to identify preventive and/or early intervention strategies to promote healthy aging in midlife women.

For some, an association between the menopausal transition and emergence of clinically significant depressive or cognitive problems remains controversial, perhaps reflecting the array of different theories and methodological approaches...
that have guided research in this field to date. For many years, the premise had been that the absolute hormone levels (ie, low estrogen concentrations) would constitute the main trigger for the occurrence of reproductive-related mood, sleep, and cognitive disorders; hence, most treatment studies were focused primarily on postmenopausal women and ultimately produced mixed results. Newer research studies have been redirected toward periods of hormone instability rather then hormone deficiency. Through these studies, investigators have accumulated further evidence that the menopausal transition may be not only a window of vulnerability for depression and cognitive impairment but also a critical “window of opportunity” for the success of hormone-based treatments.

Interestingly, different areas of medicine targeting the interaction between the aging process in women and health-related outcomes now seem to converge on the notion of a “critical window” associated with the menopausal transition and the importance of its timing for preventive or therapeutic strategies. Recent evidence from the Study of Women’s Health Across the Nation, for example, suggests a subtle disadvantage in processing speed and verbal episodic memory in women during the menopausal transition; in addition, memory performance returns to premenopausal levels when women reach postmenopausal years. 

This observation is quite consistent with recent epidemiological data from the Penn Ovarian Aging and the Harvard Study of Moods and Cycles showing a heightened prevalence of mood symptoms during the menopausal transition versus the premenopausal and postmenopausal years.

Menopausal transition also increases the susceptibility to cardiovascular events, and key factors need to be monitored during this transition, including risk factors for metabolic syndrome, obesity, and hypertension. Menopausal transition and the decline in estrogen levels during this period have been associated with heightened risk for adverse cardiovascular events, including larger adventitial carotid artery diameters, changes in lipids, and increased blood pressure. Unlike mood, the impact of the menopausal transition on cardiovascular function seems to carry into the postmenopausal period. Nevertheless, evidence from clinical trials supports the concept of a window of opportunity for hormonal intervention in cardiovascular disease.

Ongoing large-scale clinical studies, including ELITE (Early Versus Late Intervention Trial With Estrogen) and KEEPS (Kronos Early Estrogen Prevention Study), offer an opportunity to evaluate this window of opportunity theory from both a cardiovascular and a cognitive perspective.

In sum, there is a confluence of data to support the notion of the menopausal transition as being a critical period of vulnerability for mood, cognitive, and cardiovascular problems. Given this, one could speculate about overlapping etiologies and overlapping preventive or therapeutic strategies for women during this critical window.

An age-stratified analysis of the Women’s Health Initiative data revealed that several of the adverse events initially associated with menopausal hormone therapies (MHTs) in the overall group were not evident in younger postmenopausal women between 50 and 59 years of age and/or women who had recently transitioned into menopause. For example, there seemed to be a cardioprotective effect of MHT (particularly estrogen based) when hormone therapies were administered to women within 10 years of the final menstrual period, possibly because of the fewer preexisting coronary conditions in this subgroup.

In addition, total mortality rates were 30% lower in younger postmenopausal women randomized to MHT versus placebo. Timing of initiation should therefore be factored in when assessing the pros and cons of MHT for midlife women.

Similarly, several studies have investigated the efficacy of MHT to alleviate depressive symptoms, major depressive disorders, and cognitive complaints in postmenopausal women. Estrogen therapies (particularly transdermal estradiol) have shown significant efficacy in placebo-controlled trials when administered to perimenopausal women. Depressed, postmenopausal women, however, showed little or no response to estrogen therapy. Moreover, most placebo-controlled studies on estrogen therapy for the management of depression, including perimenopausal and postpartum subpopulations, have used transdermal estradiol. Clinical trials demonstrate that conjugated equine estrogens plus medroxyprogesterone acetate results in decreased memory for words regardless of age at initiation. Conversely, conjugated equine estrogens alone is not associated with decreased memory for words even in older women.

Different formulations of MHT (eg, transdermal estradiol vs oral conjugated estrogens, estrogen alone versus estrogen-progestin therapies) should therefore be considered when assessing the pros and cons of MHT for midlife women.

In a large, community-based cohort study, abrupt estrogen deprivation after oophorectomy in younger women (before the age of 48 y) was associated with an increased lifetime risk for the development of mood and anxiety disorders, cognitive disorders, and cardiovascular disease. The initiation of estrogen-based therapies immediately after the surgical procedure seemed to attenuate the risk for later cognitive disorders and cardiovascular disease, but not the risk for mood disorders. Early hormone treatment may be particularly critical for women with premature ovarian failure or early surgical onset of menopause.

The common features of windows of vulnerability and opportunity for the occurrence and management of cardiovascular, mood, and cognitive conditions in midlife women are not only intriguing but also encouraging. The need for further investigation and better understanding of common underlying mechanisms seems intuitive. As researchers attempt to disentangle the genetic, psychological, and neurochemical components of these windows, it will be imperative to consider a more comprehensive diagnostic approach to midlife women. A challenging, but not impossible, goal includes preventive strategies for women presenting with various risk factors for cardiovascular, cognitive, and mood disorders as well as treatments that could be tailored to multiple symptom domains during the menopausal transition.
REFERENCES


