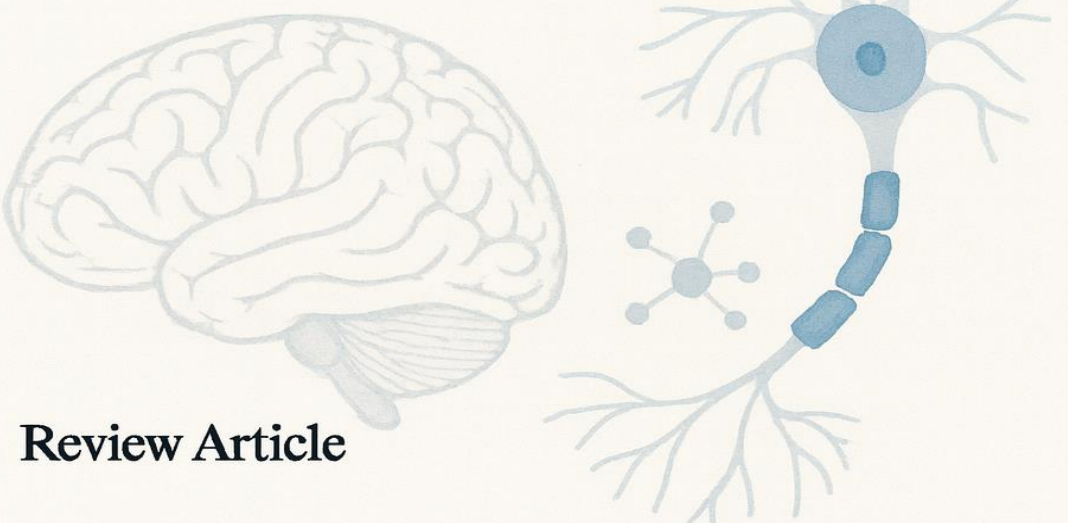
Hormone Deficiency in Women Over 65 and the Risk of Neurodegeneration: Clinical Implications for Parkinson's Disease, Multiple Sclerosis, and Dementia



Review Article

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Hormone Deficiency in Women Over 65 and the Risk of Neurodegeneration: Clinical Implications for Parkinson's Disease, Multiple Sclerosis, and Dementia

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Introduction

The female brain undergoes profound hormonal transitions throughout life, culminating in the postmenopausal state where sex steroids and neurosteroids fall to their lowest sustained levels. While menopause typically occurs in the early fifties, the subsequent decades of life, particularly after the age of 65, represent a period of heightened vulnerability to neurodegenerative disorders. Epidemiologic data consistently demonstrate that older women are at increased risk for Alzheimer's disease and other dementias, while Parkinson's disease and multiple sclerosis show distinct patterns of sex differences in prevalence and clinical course that are influenced by hormonal status.

The decline of estradiol, progesterone, testosterone, dehydroepiandrosterone (DHEA), and pregnenolone leaves the aging brain deprived of essential neuroprotective factors. These hormones and neurosteroids are not simply reproductive regulators but also modulators of synaptic plasticity, mitochondrial resilience, neuroinflammation, and glial function. Their deficiency in older women contributes to the accumulation of pathological proteins, impaired neurotransmission, and reduced repair capacity of myelin and neuronal networks.

This review will examine the clinical relationships between hormone deficiency in women over 65 and the development of Parkinson's disease, multiple sclerosis, and dementias, with a focus on Alzheimer's disease and frontotemporal dementia. Emphasis will be placed on forward-looking clinical implications, particularly the role of hormone replacement and integrative strategies to prevent or delay neurodegeneration.

Hormone Deficiency and the Aging Female Brain

The postmenopausal years are characterized by near-complete loss of ovarian estradiol production, a precipitous decline in progesterone, and progressive reductions in circulating testosterone and adrenal precursors such as DHEA and pregnenolone. The initial "critical window" of menopause has been well-studied, but far less attention has been paid to women over 65, who live decades in a chronically hormone-deficient state. By this age, neurosteroidogenesis in the brain itself is also diminished, depriving neurons and glia of local supplies of estradiol, progesterone, and their metabolites that normally act in an autocrine and paracrine fashion to maintain homeostasis.

Estradiol supports synaptic density, glucose metabolism, and clearance of amyloid-beta, while progesterone promotes myelin repair, suppresses inflammatory cytokine cascades, and enhances GABAergic tone. Testosterone and its metabolites provide trophic support to dopaminergic neurons, while DHEA and pregnenolone act as upstream substrates with pleiotropic effects on neuroplasticity, cognition, and stress regulation. In their absence, aging women are at increased risk for neurodegenerative cascades that manifest clinically as Parkinson's disease, multiple sclerosis progression, or dementia.

Parkinson's Disease and Hormone Deficiency

Parkinson's disease (PD) is classically more common in men, yet women who develop PD often experience later onset but a more rapid decline in cognitive and functional status. Estrogens have been shown to exert neuroprotective effects on dopaminergic neurons of the substantia nigra and to modulate dopamine release in the striatum. Postmenopausal estrogen deficiency is therefore associated with greater vulnerability of the

nigrostriatal system to oxidative stress and mitochondrial dysfunction, both of which are hallmarks of PD pathophysiology (Saunders-Pullman et al., 2009).

Clinical data suggest that women with longer lifetime exposure to estrogens, whether through later menopause or exogenous replacement, have a lower risk of PD onset and slower motor progression. Progesterone and DHEA are also implicated: animal models demonstrate that progesterone reduces dopaminergic cell loss after toxin exposure, while DHEA enhances mitochondrial function and reduces neuroinflammation. Women over 65 who are hormone-deficient may therefore be more susceptible to rapid motor decline and non-motor features of PD such as depression, fatigue, and cognitive impairment.

Forward-looking clinical implications include the judicious use of hormone replacement therapy (HRT) in older women with prodromal or early PD, combined with lifestyle strategies that optimize mitochondrial health. Although prospective trials in this age group are limited, the converging epidemiologic and translational evidence supports a positive role of estrogens, progesterone, and DHEA in delaying PD onset or mitigating severity.

Multiple Sclerosis and Hormone Deficiency

Multiple sclerosis (MS) is classically a disease of young adults, with female predominance during reproductive years. However, a distinct subset of patients develops late-onset MS, and older women with MS experience accelerated progression of disability. The hormonal environment is critical: pregnancy, with its high levels of estradiol and progesterone, is associated with reduced MS relapses, while the postpartum decline in hormones triggers rebound activity.

In women over 65, the chronic deficiency of estradiol and progesterone leads to diminished remyelination capacity and unchecked neuroinflammation. Progesterone is particularly important in this context: it promotes oligodendrocyte differentiation and myelin repair while dampening proinflammatory cytokines such as TNF-α and IL-1β. Estradiol, meanwhile, enhances regulatory T-cell activity and supports synaptic resilience in the hippocampus. The absence of these protective influences accelerates neurodegenerative aspects of MS, leading to cognitive impairment, gait instability, and fatigue that are often underappreciated in older women.

Clinical implications suggest that late-life hormone replacement may help preserve neurological reserve in women with MS, even if disease-modifying therapies are ongoing. Although randomized data are sparse, the consistent mechanistic rationale points toward a role for progesterone and estradiol in maintaining function and quality of life in aging female patients.

Dementia: Alzheimer’s Disease and Frontotemporal Dementia

Alzheimer’s Disease

Alzheimer’s disease (AD) disproportionately affects women, with nearly two-thirds of patients being female. While longer life expectancy contributes to this imbalance, hormonal factors are central. Estradiol deficiency after menopause removes a key regulator of amyloid precursor protein processing, promoting the accumulation of amyloid-beta plaques. Estradiol also suppresses hyperphosphorylation of tau protein, reduces oxidative stress, and supports hippocampal synaptogenesis (Brinton, 2008). Without these protections, older women experience accelerated cognitive decline.

Progesterone further contributes by modulating neuroinflammation and enhancing GABAergic stability, while DHEA and pregnenolone influence memory and stress responses. Low levels of these hormones in women over 65 correlate with poorer cognitive trajectories and higher risk of AD diagnosis. Testosterone, though present in lower amounts in women, may also exert protective effects against cortical atrophy and memory decline.

Clinically, the "critical window" hypothesis emphasizes that earlier initiation of HRT near menopause may yield the strongest protective benefits. However, growing evidence suggests that even in older women, targeted hormone strategies—particularly transdermal estradiol combined with micronized progesterone—may stabilize cognition and delay progression when carefully monitored. Adjunctive strategies, including DHEA supplementation, lifestyle interventions, and nutraceuticals that support mitochondrial and synaptic health, can further augment this approach.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is less common than AD but often devastating, with profound behavioral and executive dysfunction. Sex differences in FTD are less well-defined, yet hormonal influences are increasingly recognized. Androgen and estrogen deficiency may contribute to vulnerability of the frontal and temporal cortices by diminishing synaptic plasticity and stress resilience. Unlike AD, FTD pathology is less centered on amyloid and more on tau and TDP-43 proteins, but estradiol still exerts modulatory effects on these pathways.

Clinical correlations show that women with lower lifetime estrogen exposure may be at higher risk of FTD, though data remain limited. Neurosteroids such as pregnenolone and allopregnanolone, which decline significantly after 65, play a role in mood regulation and cognitive flexibility—functions that are severely disrupted in FTD. Hormone deficiency in older women may therefore accelerate the onset of behavioral disinhibition, apathy, and language deficits characteristic of this dementia.

While no trials have directly tested HRT in FTD, the broader evidence base suggests that hormone restoration could support executive function and delay cortical atrophy. Positive clinical approaches involve integrating hormonal support with behavioral therapies and caregiver interventions to preserve autonomy and quality of life.

Clinical Implications and Forward-Looking Perspectives

The convergence of evidence across Parkinson's disease, multiple sclerosis, and dementias points to a central theme: hormone deficiency after age 65 leaves the female brain vulnerable to neurodegeneration. Estradiol, progesterone, testosterone, DHEA, and pregnenolone act as multifaceted neuroprotectants, and their loss removes critical safeguards against protein aggregation, mitochondrial decline, and inflammatory damage.

From a clinical perspective, the implications are profound. Hormone replacement therapy, long debated due to cardiovascular and cancer risks, must now be reconsidered in the context of brain health. The goal is not to recreate reproductive hormone levels but to restore physiologic balance that supports cognition, mood, and neuronal survival. Transdermal estradiol, micronized progesterone, and carefully monitored DHEA supplementation represent promising strategies, even in women beyond the traditional "window" of menopause.

Moreover, the synergy between hormones and lifestyle measures cannot be overstated. Exercise, nutrition rich in omega-3 fatty acids and antioxidants, cognitive engagement, and management of cardiovascular risk factors all work in tandem with hormones to preserve neural integrity. Emerging approaches, including neurosteroid analogues and selective hormone receptor modulators, further expand the toolkit for clinicians aiming to protect the aging female brain.

Looking forward, the most positive perspective is one of empowerment: by recognizing hormone deficiency as a modifiable contributor to neurodegeneration, clinicians can offer women over 65 a proactive path to preserving independence, cognition, and quality of life.

Assessing Post-Menopausal Hormones

Accurate assessment of hormonal status in women over 65 is essential to identify deficiencies that contribute to neurodegenerative risk. While symptom-based evaluation provides some insight, laboratory-based diagnostics remain the cornerstone for individualized treatment. Conventional panels often measure only estradiol, progesterone, testosterone, and occasionally DHEA sulfate, offering an incomplete picture of the complex interplay between hormones, metabolism, and neuroinflammation in the aging brain.

The Millennium's **28-point biomarker panel** provides a comprehensive approach by integrating neuroendocrine, metabolic, and inflammatory markers into a unified assessment framework. This panel goes beyond isolated hormone measurements, identifying subtle deficiencies and imbalances across the full spectrum of sex steroids, adrenal hormones, and key signaling intermediates that modulate brain health. By simultaneously capturing indices of inflammation, oxidative stress, and metabolic reserve, the panel allows clinicians to connect laboratory findings directly with clinical manifestations such as cognitive decline, mood disturbance, fatigue, and gait instability.

The advantage of this expanded biomarker approach is the ability to generate a **personalized hormonal map** for each patient. Rather than applying generic protocols, results from the 28-point biomarker panel guide the tailoring of estradiol, progesterone, testosterone, DHEA, or pregnenolone support according to the unique biochemical needs of the individual. This level of precision ensures that interventions target the actual drivers of dysfunction, maximizing neuroprotective benefit while minimizing unnecessary exposure.

Within the context of Parkinson's disease, multiple sclerosis, and dementias, this assessment becomes particularly valuable. Subtle deficiencies in neurosteroids may precede overt clinical decline, and early detection allows for timely initiation of restorative protocols. By incorporating the 28-point biomarker panel into routine evaluation of post-menopausal women, clinicians gain a powerful tool to align laboratory findings with clinical strategies—helping to preserve brain health and delay the onset or progression of neurodegenerative disease.

Conclusion

Women over 65 represent a rapidly growing demographic at high risk for Parkinson's disease, multiple sclerosis progression, Alzheimer's disease, and frontotemporal dementia. The unifying factor across these conditions is the chronic deficiency of neuroprotective hormones and neurosteroids. Estradiol, progesterone, testosterone, DHEA, and pregnenolone collectively defend the brain against inflammation, proteinopathy, and synaptic decline. Their absence contributes directly to the emergence and worsening of neurodegenerative disease.

A forward-looking clinical approach emphasizes hormone restoration—not as a reproductive intervention, but as a neuroprotective strategy. Combined with integrative lifestyle measures and emerging therapies, hormone support has the potential to delay or even prevent the devastating impact of neurodegeneration in older women. Future research must refine protocols, clarify safety, and individualize treatment, but the direction is clear: addressing hormone deficiency is central to protecting the female brain in aging.

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