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Letter to Editor

Midlife blues in women: Hormonal and psychosocial dimensions of a multifactorial syndrome

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Dear Editor,

The midlife period, broadly defined as the age range between 40 and 60 years, represents a critical phase in the human lifespan, marked by biological, psychological and social transitions. A growing body of evidence suggests a U-shaped trajectory of life satisfaction, with the lowest point in midlife, often referred as Midlife Blues.[1] This phase encompasses a constellation of symptom such as mood swings, irritability, fatigue, sleep disturbances, loss of libido, and depressive features. Understanding the aetiology of these symptoms requires a holistic approach that considers hormonal, neurochemical and psychosocial factors.

This period is particularly significant for women, who face substantial hormonal shifts during perimenopause and menopause. Estrogen plays a critical role in mood regulation by enhancing serotonergic function increasing tryptophan availability, serotonin synthesis, and receptor density. Consequently, the decline in oestrogen levels during midlife, particularly in perimenopause and menopause, can impair these pathways, contributing to increases susceptibility to mood disturbances and depressive symptoms.[2]

Meta-analysis of 14 studies including 67,714 women suggested 20-30% of perimenopausal women experience clinically significant depressive symptoms with up to 10% meeting diagnostic criteria for major depressive disorder (MDD).[3]

Clinical evidence suggests that flucations in progesterone and its neuroactive metabolite allopregnanolone contribute to mood dysregulation via effects on GABA-A receptors. Inhibition of allopregnanolone synthesis has been shown to reduce dysphoric mood in women with premenstrual dysphoric disorder, highlighting a shared neuroendocrine mechanism across reproductive mood disorders, including postpartum and menopausal depression.[4]

Additionally, hormonal imbalances involving cortisol, thyroid hormones, and androgens such as testosterone have been implicated in midlife mood disturbances. Elevated cortisol levels due to HPA axis hyperactivity can heighten stress sensitivity; thyroid dysfunction may impair serotonin and dopamine regulation; and declining testosterone levels are associated with reduced dopaminergic activity and diminished motivation.[5-7]

The limbic system, particularly the amygdala and hippocampus, plays a key role in emotional regulation through neurotransmitters such as serotonin and dopamine. These are synthesized from amino acids like tryptophan and tyrosine, requiring cofactors including vitamins B6, B12, folate, magnesium, and zinc. Deficiencies in these nutrients particularly B12 and folate have been linked to depression and poor response to treatment. Additionally, reduced dopamine activity is associated with midlife symptoms such as low motivation, anhedonia, and cognitive slowing. Importantly, midlife mood disturbances arise not only from

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hormonal shifts, but also from the complex interplay of neurotransmitter imbalances, nutritional deficiencies, and psychosocial stressors such as caregiving responsibilities, occupational strain, and 'empty nest' transitions.[8-9]

Women in midlife often face a disproportionate psychosocial burden as part of the “sandwich generation,” balancing caregiving responsibilities for both aging parents and dependent children.[9] These chronic stressors activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated cortisol levels that impair emotional regulation and increase the risk of mood disturbances. Addressing these unique psychosocial pressures is essential for effective prevention and management of midlife blues in women.[10-11]

Emerging research supports several non-pharmacologic strategies for managing midlife mood disturbances. Regular physical activity has been shown to increase endorphin and serotonin levels, with recent randomized controlled trials demonstrating that moderate aerobic exercise performed most days of the week significantly reduces symptoms of mild to moderate depression.[12] Nutritional interventions, including diets rich in omega-3 fatty acids, complex carbohydrates, and proteins, promote neurotransmitter synthesis; a 2020 systematic review confirmed that adherence to a Mediterranean-style diet is associated with lower depression risk and improved mood outcomes.[13] Additionally, light therapy, delivering 10,000 lux for 20-30 minutes daily, remains effective in treating seasonal affective disorder and may benefit individuals experiencing circadian rhythm disruptions common in midlife.[14] These evidence-based lifestyle approaches offer promising adjuncts or alternatives to pharmacotherapy in addressing midlife blues.

In summary, midlife blues in women result from a complex interaction of hormonal changes, neurotransmitter imbalances, and psychosocial stressors. A holistic approach that includes lifestyle modifications such as exercise, nutrition, and light therapy alongside appropriate medical management is essential. Addressing these factors can significantly improve mood and overall well-being during midlife. Continued research is needed to develop personalized interventions for this vulnerable population.

Conflict of Interest

None.

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