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Endocrine and Metabolic Mechanisms Underlying Fatigue in Perimenopausal Women

Aditi Vohra

Doctoral Researcher
Department of Home Science, Kurukshetra University
Kurukshetra (Haryana) India
Email: aditikap09@gmail.com

Abstract

Fatigue is a common and often debilitating symptom experienced by women during the perimenopausal transition. This phase, marked by significant hormonal and metabolic fluctuations, leads to complex physiological changes that contribute to persistent tiredness and low energy levels. The current paper explores the endocrine and metabolic underpinnings of fatigue in perimenopausal women, focusing on hormonal changes (including estrogen, progesterone, thyroid, and cortisol), insulin resistance, anemia, mitochondrial dysfunction, and sleep disturbances. Also highlights effective clinical interventions and management strategies to alleviate fatigue during this transitional period. A better understanding of these mechanisms is essential for clinical recognition, intervention, and improving women's quality of life during this transitional period.

Keywords: Hormonal changes, metabolic, thyroid, estrogen, menstrual irregularity.

1. Introduction

Perimenopause marks the transitional phase preceding menopause, typically beginning in the mid-to-late 40s. This stage is characterized by menstrual irregularity and significant hormonal fluctuations. Women often report a spectrum of physical and emotional symptoms, with fatigue being one of the most common yet least understood (Avis et al., 2009). Too often, fatigue is dismissed as a vague complaint or attributed to aging or stress. However, research suggests that it stems from complex biochemical and physiological shifts driven by hormonal instability (Gold et al., 2006).

The underlying mechanisms of fatigue during this period are multifaceted. Estrogen withdrawal affects neurotransmitter balance and sleep regulation, while cortisol dysregulation amplifies stress responses. In addition, metabolic disturbances—ranging from insulin resistance and thyroid dysfunction to iron deficiency—play a critical role (Santoro et al., 2015). This paper delves into the metabolic and endocrine dimensions of fatigue in perimenopausal women, aiming to offer insights that inform clinical management. Hormonal imbalances, particularly involving estrogen and progesterone, are central to the development of fatigue in this demographic. These endocrine shifts not only influence mood and sleep but also interact with broader metabolic processes (Borges et al., 2024). The sections that follow outline the key hormonal, metabolic, and neurological mechanisms contributing to fatigue in perimenopausal women.

Hormonal Fluctuations

• Erratic levels of estradiol and declining progesterone disrupt the ovarian-pituitary-hypothalamic axis, undermining hormonal regulation and contributing to symptoms such as fatigue (Prior & Hitchcock, 2011).
• Events like "luteal out of phase" (LOOP) surges—unexpected estradiol spikes during the luteal phase—may intensify this imbalance, further exacerbating fatigue.

Metabolic Changes

• Weight gain and increased visceral fat are common during perimenopause and are linked to the development of metabolic syndrome (MetS), which involves insulin resistance, hypertension, and abnormal lipid profiles—all contributing to chronic fatigue (Palla et al., 2020; Borges et al., 2024).

• Shifts in energy metabolism, such as disrupted fatty acid β-oxidation and phospholipid metabolism, reduce energy availability, amplifying fatigue symptoms (Ke et al., 2015).

Neurological Implications

• Estrogen is critical for maintaining brain energy metabolism. Its declining influence on estrogen receptors during perimenopause can trigger a hypometabolic brain state, manifesting as cognitive fog and fatigue (Brinton et al., 2015).

• Sleep disturbances, which become more frequent in this phase, are strongly associated with MetS and further drain energy reserves (Gaston et al., 2019).

Endocrine Factors

• The decline in anabolic hormones such as growth hormone and DHEA, along with estrogen, promotes fat accumulation and insulin resistance—core features of MetS that underlie fatigue (Milewicz & Demissie, 2002).
• While hormone therapy may offer symptom relief, its success in combating fatigue is inconsistent, especially when metabolic issues persist (Toffol et al., 2015).

Hormonal Influences on Fatigue

Estrogen modulates neurotransmitters like serotonin and dopamine, which are vital for mood and energy. As levels fall, mood disruptions, poor sleep, and fatigue become more prominent. Similarly, declining progesterone—recognized for its calming, sleep-promoting effects—contributes to these sleep-related energy deficits. Cortisol, regulated by the hypothalamic-pituitary-adrenal (HPA) axis, often becomes dysregulated during this time. Abnormal cortisol patterns, particularly elevated evening levels, interfere with sleep quality and lead to daytime exhaustion. Chronic stress further destabilizes the HPA axis, deepening fatigue (Pardigm, 2022).

Thyroid Function Alterations

Perimenopausal women face a higher risk of thyroid dysfunction, especially hypothyroidism, which slows metabolism and causes fatigue, weight gain, and cognitive dullness. Compounding this, iron deficiency—

commonly resulting from heavy menstrual bleeding—can impair thyroid hormone synthesis and worsen fatigue symptoms (Paloma Health, 2023).

Hormonal Changes and Circadian Regulation

A reduction in estrogen disrupts thermoregulation and circadian rhythms, both critical for sustaining sleep quality (Park, 2024; Moe, 1999). As estrogen levels drop, women become more vulnerable to awakenings triggered by body temperature fluctuations and misaligned sleep-wake cycles. Hormone replacement therapy (HRT) has demonstrated efficacy in alleviating vasomotor symptoms, potentially improving sleep, though its use remains limited due to associated risks (Moe, 1999).

Psychological and Behavioural Contributors

Mental health concerns, particularly anxiety and depression, are closely tied to sleep complaints during perimenopause. These psychological stressors intensify insomnia and perpetuate fatigue. Lifestyle factors, such as prolonged medication use or reliance on dietary supplements, may also interfere with sleep regulation and interact with hormonal instability (Chang et al., 2010). Studies indicate that 39 to 47 percent of perimenopausal women experience sleep-related issues, a notable increase compared to their premenopausal counterparts (Kravitz et al., 2008).

Intervention Strategies

Effective management of perimenopausal sleep disturbances requires a holistic, evidence-based approach. Non-hormonal interventions such as cognitive-behavioural therapy for insomnia (CBT-I) and neurokinin B antagonists have shown encouraging outcomes by addressing underlying psychological mechanisms. While complementary therapies are gaining popularity, current evidence does not robustly support their efficacy in treating menopausal sleep disorders (Carmona et al., 2025).

Healthcare providers are advised to adopt a biopsychosocial framework that considers the interplay between hormonal changes, psychological health, and behavioural factors. Tailored interventions that integrate medical and lifestyle-based solutions may offer the most promising outcomes for restoring sleep quality and reducing fatigue.

Lifestyle Factors Influencing Fatigue in Perimenopausal Women

Fatigue during perimenopause is influenced by multiple lifestyle-related factors that can intensify the symptoms associated with this transitional stage. These include physical inactivity, poor nutrition, psychological stress, sleep disturbances, substance use, and socioeconomic challenges. Understanding these influences is essential for effective management and improved quality of life (Chiu et al., 2021).

Physical Inactivity and Exercise Habits

A sedentary lifestyle common during perimenopause can lead to reduced muscle mass and metabolic rate, contributing to fatigue. In contrast, regular physical activity enhances energy levels, mood, and sleep quality. Despite these benefits, many women do not engage in consistent exercise, missing out on its fatigue-reducing and symptom-alleviating effects (Chiu et al., 2021; Chopra et al., 2022).

Nutritional Deficiencies

Fatigue can also stem from inadequate intake of key nutrients, particularly vitamin B12, vitamin D, and magnesium. These deficiencies impair energy metabolism and can exacerbate fatigue. Ensuring a balanced and nutrient-rich diet is vital for maintaining energy levels and overall well-being (Chang et al., 2010).

Psychological and Emotional Health

Emotional factors such as stress, anxiety, and depression significantly contribute to fatigue in perimenopausal women. These psychological conditions not only affect mood but are also closely linked with poor sleep, thereby compounding feelings of tiredness (Libbus et al., 1995). Addressing mental health through appropriate interventions can play a pivotal role in fatigue management.

Sleep Quality

Sleep disturbances are frequently reported during perimenopause and are a key factor in fatigue. Poor sleep, often resulting from anxiety, depression, or hormonal fluctuations, intensifies fatigue symptoms. Additionally, the increased prevalence of sleep disorders like sleep apnea during menopause further impacts energy levels (Hall & Leach, 2005).

Substance Use

Lifestyle habits such as smoking and alcohol consumption have been causally linked to increased fatigue. Emerging evidence from Mendelian randomization studies suggests that these substances negatively impact energy, while cessation efforts can lead to notable improvements (Li et al., 2022; Nair, 2022).

Socioeconomic and Demographic Influences

Socioeconomic factors, including income level, education, and employment status, shape lifestyle behaviours related to fatigue. Women from lower socioeconomic backgrounds may face heightened stress and limited access to health-promoting resources, which can negatively influence their diet, activity levels, and overall health (Chopra et al., 2022).

Role of Health Education and Support

Health education initiatives that promote lifestyle modifications—such as stress management, balanced nutrition, and regular physical activity—can empower women to manage perimenopausal symptoms more effectively. Multidisciplinary support programs, including peer groups and psychological interventions, have shown promise in reducing fatigue and enhancing coping strategies (Allah et al., 2024; O'Connell, 2005).

Broader Health Considerations

While lifestyle factors are key contributors, fatigue may also arise from underlying medical conditions, chronic diseases, or side effects of medications. A comprehensive and individualized approach is necessary for accurate diagnosis and effective management, ensuring that all contributing factors—both lifestyle-related and physiological—are addressed (Hall & Leach, 2005).

Table 1: Factors Contributing to Fatigue in Perimenopausal Women

Factor	Mechanism	Symptoms and Impact on Fatigue	References
Estrogen/Progesterone Imbalance	Disruption of neurotransmitters, sleep disturbances	Mood swings, insomnia, increased fatigue	Haufe & Leeners, 2023
Cortisol Dysregulation	Activation of the HPA axis, impaired glucose metabolism	Sleep disruption, energy deficits	Balbo et al., 2010
Insulin Resistance	Decreased glucose uptake	Energy deficits, weight gain	Mäkinen et al., 2013
Thyroid Dysfunction	Slowed metabolism	Lethargy, cognitive impairment	Przybylak et al., 2021
Iron Deficiency Anemia	Reduced oxygen transport	Weakness, decreased endurance	"Iron Deficiency Anemia," 2023
Vasomotor Symptoms	Sleep fragmentation	Daytime sleepiness, reduced alertness	Crovetto, 2023
Sleep Apnea	Intermittent hypoxia, sleep fragmentation	Excessive daytime sleepiness, fatigue	Lal et al., 2021
Physical Inactivity	Decreased muscle mass, metabolic rate	Lower energy levels, increased fatigue	Eggelbusch, 2024
Nutritional Deficiencies	Impaired energy metabolism	Fatigue, weakness	Binquryan et al., 2024

Management Strategies for Fatigue in Menopausal Women

Hormone Replacement Therapy (HRT) is a commonly employed treatment to relieve menopausal symptoms such as vasomotor disturbances and sleep issues that can profoundly affect quality of life. However, the decision to initiate HRT must be individualized, based on a thorough evaluation of the woman's health status, symptom profile, and personal preferences (Borozan et al., 2024). In addition to HRT, a combination of lifestyle modifications, stress management techniques, and medical interventions can provide a holistic and effective strategy for managing fatigue and other menopausal symptoms (Scharbo-DeHaan, 1994).

Lifestyle Modifications

- **Exercise:** Regular aerobic and resistance training have been shown to improve energy levels, mood, and general well-being. Physical activity also complements HRT by mitigating fatigue and enhancing overall health (Scharbo-DeHaan, 1994; Borozan et al., 2024).
- **Nutrition:** A nutrient-rich diet, particularly one high in iron, B vitamins, and antioxidants, supports energy metabolism and reduces fatigue. Balanced nutrition is essential for managing menopause-related changes (Scharbo-DeHaan, 1994).

- **Sleep Hygiene:** Establishing consistent sleep routines and addressing sleep disturbances are crucial for improving rest and minimizing fatigue. Good sleep practices enhance the effectiveness of HRT and contribute to better quality of life (Borozan et al., 2024).

Stress Management

- **Mindfulness and Meditation:** Practices such as mindfulness meditation help manage stress and emotional disturbances, offering a non-pharmacological complement to HRT (Borozan et al., 2024).
- **Cognitive-Behavioural Therapy (CBT):** CBT is effective in improving psychological resilience, reducing stress, and consequently alleviating fatigue. It serves as a valuable adjunct to medical treatments (Borozan et al., 2024).
- **Relaxation Techniques:** Techniques like deep breathing, progressive muscle relaxation, and guided imagery can reduce stress levels and improve sleep, thereby addressing fatigue holistically (Borozan et al., 2024).

Medical Interventions

- **Treatment of Underlying Conditions:** Identifying and managing health issues such as hypothyroidism, anemia, or chronic illness is essential, as these conditions can independently contribute to fatigue and diminish the benefits of HRT (Walsh, 1999).
- **Personalized HRT Regimens:** Hormone therapy should be tailored to individual needs in terms of formulation, dosage, and administration method. A personalized approach maximizes therapeutic benefits while minimizing risks (Hillard, 1997; Studd & Zakaria, 1997).
- **Ongoing Monitoring and Adjustment:** Regular follow-up is necessary to assess response to treatment and make appropriate adjustments. This ensures safety and optimizes symptom management (Hillard, 1997).

Although HRT can significantly alleviate menopausal fatigue and related symptoms, it is not appropriate for everyone. The potential risks—such as increased incidence of cardiovascular disease, stroke, and breast cancer—must be carefully considered in relation to the anticipated benefits. Factors such as age, medical history, and individual preferences should guide decision-making. For many women, non-hormonal alternatives and lifestyle-based strategies offer effective, lower-risk options for managing menopause-related fatigue (Cameron et al., 2023).

2. Conclusion

Fatigue in perimenopausal women is a complex issue influenced by hormonal changes, metabolic shifts, and lifestyle factors. As estrogen and progesterone levels decrease, women experience disruptions in sleep, energy, and mood, leading to increased fatigue. These hormonal fluctuations can also impact neurotransmitters, which further contribute to feelings of tiredness and reduced vitality.

In addition to hormonal imbalances, lifestyle factors such as poor nutrition, lack of physical activity, and stress can exacerbate fatigue. Nutrient deficiencies, particularly in iron and other essential vitamins, may

worsen the tiredness felt during this stage. A sedentary lifestyle reduces overall energy levels, and the mental and emotional stress of perimenopause can drain women's energy reserves even further.

Addressing perimenopausal fatigue requires a comprehensive approach. Hormone replacement therapy (HRT) may be beneficial for some women, but other treatments such as cognitive-behavioural therapy (CBT) for insomnia and stress management can help alleviate fatigue. Regular physical activity and a balanced diet also play key roles in restoring energy and improving overall well-being.

In conclusion, managing fatigue in perimenopausal women involves both medical and lifestyle interventions. By addressing hormonal imbalances, improving nutrition, increasing physical activity, and managing stress, women can better cope with fatigue and enhance their quality of life during this transitional phase.

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