Mitochondrial dysfunction in perimenopausal mood disorders: From hormonal shifts to neuroenergetic failure (Review)

YANG YU[1,2], HAN YAPENG[3], ZELIN LIU[4], LEI FANG[5], JIANUO LI[6], YIFENG LUAN[2], WENZHONG LI[1], HUIFANG CONG[2] and XIUHONG WU[7]

[1]Department of Second Clinical Medical School, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China; [2]Department of Gynecology, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China; [3]Department of Acupuncture, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150000, P.R. China; [4]Department of Orthopedics, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150001, P.R. China; [5]Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, P.R. China; [6]Department of Basic Medical Sciences, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China; [7]School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China

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Abstract. Perimenopause represents a key transition from a reproductive to non-reproductive state in women, characterized by physiological and psychological changes. Mood disturbances during this period, such as depression, anxiety and cognitive decline, are increasingly understood as complex neuroendocrine and metabolic disorders. Mitochondrial homeostasis carries out a key role in the pathophysiology of these affective symptoms. Disruptions in mitochondrial biogenesis, mitophagy and calcium regulation contribute to synaptic dysfunction and neuroimmune changes. These mitochondrial alterations interact with inflammatory pathways and hormonal signals, exacerbating neuropsychiatric symptoms. A more comprehensive understanding of the molecular mechanisms of mitochondrial dysfunction in menopausal mood disorders unveils potential therapeutic strategies, including mitochondria-targeted antioxidants, hormone replacement therapy, and lifestyle interventions designed to restore mitochondrial integrity and cerebral bioenergetic function.

Correspondence to: Dr Huifang Cong, Department of Gynecology, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, 24 Heping Road, Harbin, Heilongjiang 150040, P.R. China
E-mail: hljchf196210@sina.com

Professor Xiuhong Wu, School of Pharmacy, Heilongjiang University of Chinese Medicine, 24 Heping Road, Harbin, Heilongjiang 150040, P.R. China
E-mail: hljwxh7811@163.com

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Contents

1. Introduction

Perimenopause marks a key transitional phase from reproductive maturity to menopause, characterized by the progressive decline in ovarian function and reproductive capacity (1). It typically begins with noticeable menstrual irregularities and concludes 12 months after the final menstruation, most commonly occurring between the ages of 40 and 55, although it may start as early as the mid-30s in some women (2). A hallmark hormonal change during perimenopause is the gradual decline and fluctuation of ovarian hormones, particularly estrogen (E2) and progesterone (3). This hormonal imbalance not only disrupts the menstrual cycle and ultimately leads to its cessation but also triggers a range of multisystem symptoms, including vasomotor disturbances (such as hot flashes and night sweats), mastalgia, musculoskeletal pain, vaginal dryness, fatigue and neuropsychiatric symptoms such as anxiety, depression and cognitive impairment (4-7).

Perimenopausal mood disorders are common yet often underdiagnosed, exerting notable negative effects on occupational performance, interpersonal relationships and overall social functioning (8). Evidence suggests that these mood disturbances not only reduce quality of life but also contribute to the development of somatic comorbidities through dysregulation of the stress axis, endocrine instability and immune dysfunction (9,10). Current therapeutic options include psychotherapy (such as cognitive behavioral therapy),

pharmacotherapy (such as antidepressants and anxiolytics) and hormone replacement therapy (HRT). However, the considerable variability in individual responses to treatment highlights the complex and heterogeneous nature of the underlying pathophysiology (11,12). Understanding the biological mechanisms of perimenopausal mood disorders is therefore important to advancing personalized treatment strategies.

Among the emerging mechanisms, mitochondrial dysfunction has been identified as a central pathological contributor. Mitochondria are vital organelles responsible for ATP production and are integral in regulating oxidative stress, calcium homeostasis, apoptosis and synaptic plasticity (13,14). Increasing evidence has associated impaired mitochondrial function with various affective disorders, including major depressive disorder, anxiety and stress-related conditions (15-17). Disruptions in mitochondrial homeostasis, characterized by impaired bioenergetics, excessive reactive oxygen species (ROS) generation and heightened inflammatory signaling, can damage neuronal structure and function, particularly in brain regions critical for mood regulation, such as the hippocampus and prefrontal cortex (18).

During perimenopause, E2 fluctuations exacerbate these risks. E2 regulates mitochondrial biogenesis, dynamics and antioxidant defense through both genomic pathways [such as nuclear receptor-mediated regulation of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α)] and non-genomic mechanisms (such as membrane receptor signaling and mitochondrial DNA protection) (18). As E2levels decline, mitochondrial instability increases, resulting in greater neuroenergetic vulnerability. Current interventions targeting these mechanisms include HRT, mitochondria-targeted pharmacological agents, antidepressants combined with psychotherapy and lifestyle-based strategies involving physical activity, dietary regulation and sleep hygiene (18). These integrated approaches aim to restore mitochondrial function, reduce oxidative stress and enhance both emotional and physical well-being in perimenopausal women. Future research should explore the bidirectional crosstalk between sex hormones and mitochondrial signaling, paving the way for more precise and safer therapeutic strategies tailored to individual pathophysiological profiles.

2. Perimenopausal mood disorders

Perimenopause denotes the transitional phase from reproductive to non-reproductive life in women, typically spanning the 2-8 years preceding menopause and the first year following the final menstruation (19). This period is characterized by substantial fluctuations in sex hormone levels, particularly cyclical declines in E2 and progesterone, which contribute to both endocrine and clinical heterogeneity (20-22). These hormonal changes underpin a range of symptoms, including menstrual irregularities, vasomotor disturbances and alterations in mood and cognitive function.

Epidemiological characteristics. Extensive evidence highlights a marked increase in the prevalence of psychiatric symptoms during perimenopause (23). Epidemiological studies suggest that ~70% of women experience some form of emotional disturbance, including irritability, anxiety and depressive symptoms (24). While some women report mild mood instability, others may develop moderate-to-severe depression or anxiety that notably impairs daily functioning and social adaptation (10). A meta-analysis of 55 studies revealed a global pooled prevalence of depressive disorders in perimenopausal women at 33.9% (95% CI: 27.8-40.0%) (25). Another large population-based study involving 9,141 women revealed that perimenopausal women are at considerably higher risk of developing depressive symptoms compared with their premenopausal counterparts (26).

The onset of perimenopausal mood disorders is influenced by a complex interaction of biological and psychosocial risk factors. Low educational attainment, unemployment or part-time employment, high perceived stress, menstrual irregularity, constipation poor family relationships (27) and high neuroticism are all associated with an increased risk of depression (28). By contrast, increased household income and access to comprehensive healthcare serve as protective factors (29-32). Notably, a personal history of affective disorders predicts symptom recurrence or exacerbation during perimenopause (8,33). In women with bipolar disorder, perimenopause is often associated with a worsening of mood symptoms (29-32). One study revealed that 68% of perimenopausal women diagnosed with bipolar disorder experienced major depressive episodes, with a markedly higher frequency compared with their reproductive years (7). Similarly, longitudinal tracking of 13 women with bipolar disorder across premenopausal, perimenopausal and postmenopausal stages revealed notable mood instability during the perimenopausal transition (33).

Clinical manifestations. Fluctuating decline in ovarian function during perimenopause results in considerable hormonal instability, particularly in E2 and progesterone levels. These endocrine fluctuations disrupt neurotransmitter systems and neural circuits involved in emotional regulation, leading to mood symptoms that are heterogeneous, episodic and often co-occurring with somatic and cognitive disturbances. Epidemiological studies suggest that perimenopausal women have a 2- to 4-fold increased risk of developing major depressive disorder compared with their premenopausal counterparts (34,35).

Typical depressive symptoms include persistent low mood, anhedonia, fatigue, impaired concentration, excessive guilt and pessimism regarding the future. Atypical features, such as irritability and widespread somatic complaints (such as myalgia), are also commonly reported (36). Notably, some women show reduced responsiveness to standard antidepressant therapy. The presence of severe life stress, a prior history of depression or psychotropic medication use further elevates the likelihood of progression to major depressive episodes, which may carry an increased risk of suicidal ideation and behavior (37,38).

Anxiety is another prevalent symptom cluster, often characterized by sustained tension, excessive worry, irritability and distractibility. Autonomic symptoms, such as palpitations, sweating and tremors, are frequently observed in conjunction with anxiety (39). In perimenopausal women, 60-70% report experiencing 'brain fog', a constellation of mild cognitive deficits, including forgetfulness, reduced attention and slowed thinking (40,41). While these symptoms are generally

transient, persistent cognitive decline may heighten the risk for late-life neurodegenerative disorders, such as Alzheimer's disease and vascular dementia. This suggests that perimenopause may represent a key window for early intervention in cognitive aging (42).

Somatic symptoms, including hot flashes, night sweats, palpitations, headaches and musculoskeletal pain, are also common and can create a bidirectional feedback loop with mood disturbances, exacerbating both psychological and physical symptoms. Sleep disorders are highly prevalent, manifesting as difficulty falling asleep, frequent nighttime awakenings, early morning waking and non-restorative sleep (43-45). Poor sleep quality not only impairs daytime cognitive and physical functioning but is also associated with anxiety, depression and vasomotor symptoms. Notably, the interaction between vasomotor symptoms and emotional states appears to be bidirectional and temporally complex, collectively contributing to notable declines in quality of life (46,47).

Pathophysiological mechanisms. Perimenopause represents a phase of profound endocrine remodeling, during which rapid and irregular fluctuations in sex hormones, particularly E2 and progesterone, markedly impact brain regions, such as the hippocampus and prefrontal cortex, involved in mood regulation (48). Several hormones, including ovarian steroids, progesterone, testosterone, cortisol and their neuroactive derivatives, have been implicated in the development and modulation of perimenopausal mood disorders (22,49).

E2 carries out a key role in this context. Following menopause, serum E2 levels reduce from premenopausal levels of 5-35 ng/dl to ~1.3 ng/dl (50,51). This sharp decline is considered a key biological event contributing to affective instability and cognitive impairment during the menopausal transition (52,53). E2 exerts neuroprotective and regulatory effects within the central nervous system (CNS). E2 deficiency induces cerebral hypoperfusion and vasoconstriction, reducing oxygen supply to brain tissue and exacerbating cognitive deficits (52). E2 receptors (ERs) α and β are widely expressed across emotion-related neural circuits, with particularly high activity in the ventral corticolimbic-brainstem axis (54,55). ERα primarily regulates nuclear gene transcription, while ERβ localizes to mitochondrial membranes, modulating mitochondrial metabolism and cellular stress responses (56).

E2 deficiency disrupts the synthesis and signaling of key neurotransmitters, such as acetylcholine, glutamate (Glu) and neuroprotective peptides, all of which are essential for cognitive function (57). Furthermore, E2 modulates dopaminergic and serotonergic systems. Its withdrawal accelerates dopaminergic neuronal degeneration, weakening reward circuitry and impairs serotonin (5-HT) synthesis and reuptake, particularly during the night, contributing to vasomotor symptoms such as hot flashes and nocturnal sweats (58,59). Dysfunctional ERβ signaling may also alter 5-HT transporter (SERT) activity and increase 5-HT_1A receptor binding in the amygdala, enhancing the processing of negative emotions and heightening vulnerability to depression and anxiety (60,61).

Progesterone levels also fluctuate considerably during perimenopause due to irregular ovulation and declining luteal function. One of its key neuroactive metabolites, allopregnanolone (ALLO), acts as a potent positive allosteric modulator of the γ-aminobutyric acid (GABA)_A receptor, enhancing inhibitory neurotransmission and exerting anxiolytic and antidepressant effects (22,62-64). However, the inconsistent synthesis of ALLO under conditions of hormonal instability may destabilize GABAergic signaling, promoting mood lability and increasing affective vulnerability (65,66). Additionally, concurrent fluctuations in ovarian hormones and neurosteroids may impair GABA_A receptor sensitivity, disrupting hypothalamic-pituitary-adrenal axis homeostasis and heightening stress responsiveness, thereby elevating susceptibility to anxiety and depressive symptoms (67,68).

Collectively, these findings emphasize the multifactorial and hormone-sensitive nature of perimenopausal mood disorders, shaped by complex interactions among E2, progesterone, neurosteroids, neurotransmitters and neuroendocrine stress systems.

Therapeutic strategies

HRT. HRT remains a primary intervention for alleviating mood disturbances associated with E2 withdrawal in perimenopausal women. Substantial clinical evidence supports its efficacy in reducing depressive and anxiety symptoms. In a randomized controlled trial, 17β-estradiol treatment markedly improved depressive symptoms compared with placebo (68 vs. 17% remission rate), highlighting its antidepressant potential (69). HRT has also demonstrated benefits in improving irritability, sleep disturbances and other affective symptoms, and, in some cases, serves as an adjunct to psychotropic medications to enhance treatment response and overall functioning (54,70).

However, the implementation of HRT requires careful evaluation of the risk-benefit balance. Although it may reduce the incidence of hip fractures and endometrial cancer, long-term use is associated with increased risks of coronary artery disease, stroke, breast cancer and dementia (71). These risks are especially relevant for women > 50 years or those using HRT for >5 years (72). By contrast, initiating HRT before the age of 50 years may present a more favorable safety profile. For asymptomatic women, the potential risks may outweigh the benefits, particularly concerning breast cancer incidence (71,73).

To overcome the limitations of conventional HRT, alternative formulations have been developed. Tissue-selective E2 complexes, which combine E2s with selective E2 receptor modulators, aim to retain therapeutic benefits while minimizing adverse effects (74). Additionally, plant-based phytoE2s, such as black cohosh extracts, have been explored for their potential mood-enhancing effects. While early results are promising, further research is necessary to confirm their long-term efficacy and safety in perimenopausal populations (75).

Antidepressant therapy. Selective 5-HT reuptake inhibitors (SSRIs) and 5-HT-norepinephrine (NE) reuptake inhibitors (SNRIs) are considered first-line pharmacological treatments for perimenopausal depression and anxiety. These medications function by inhibiting the presynaptic reuptake of 5-HT and/or NE, thereby increasing synaptic neurotransmitter availability and enhancing mood regulation (76). SSRIs specifically target SERT, while SNRIs inhibit both SERT and the NE transporter, making them particularly effective for patients with concurrent anxiety and reduced motivation.

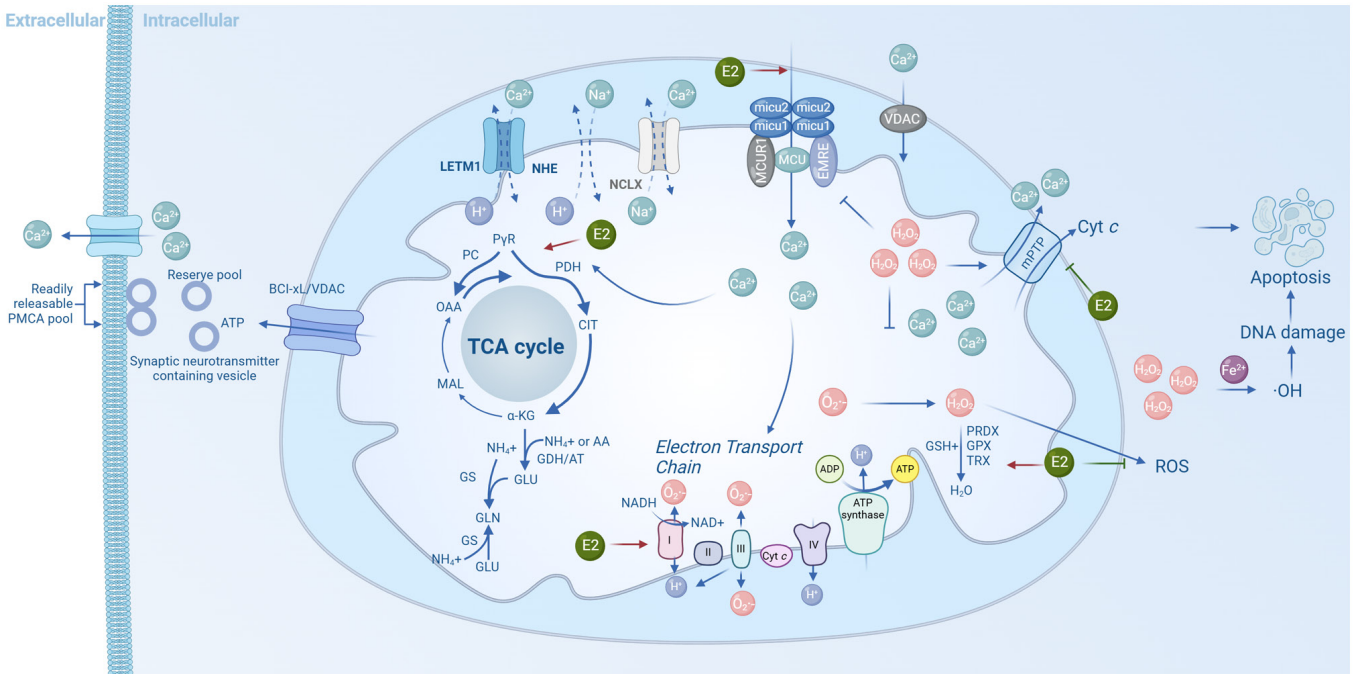

Figure 1. Key mitochondrial processes in neuronal homeostasis. Mitochondrial Ca^{2+} uptake via VDAC and the MCU complex activates TCA cycle dehydrogenases (PDH, isocitrate dehydrogenase and α-KG dehydrogenase), promoting NADH/flavin adenine dinucleotide (reduced form) production and ATP synthesis. Electron leakage from complexes I/III generates superoxide (O_2^-•), converted to H_2O_2 and detoxified by antioxidant systems (superoxide dismutase 2, GPX, PRDX, TRX and GSH). Excess ROS triggers mPTP opening, cyt *c* release and apoptosis. Glutamate is synthesized from α-ketoglutarate via GDH or transaminases, supporting neurotransmission and nitrogen metabolism. E2 enhances bioenergetics and antioxidant defense (red arrows), while inhibiting ROS and apoptosis (green arrows). α-KG, α-ketoglutarate; ATP, adenosine triphosphate; Ca^{2+}, calcium ion; Cyt *c*, cytochrome *c*; E2, 17β-estradiol; GDH, glutamate dehydrogenase; GPX, glutathione peroxidase; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; NADH, nicotinamide adenine dinucleotide (reduced form); O_2^-•, superoxide anion radical; PDH, pyruvate dehydrogenase; PRDX, peroxiredoxin; ROS, reactive oxygen species; SOD2, superoxide dismutase 2; TCA cycle, tricarboxylic acid cycle; TRX, thioredoxin; VDAC, voltage-dependent anion channel.

Studies suggest that SSRIs may also have indirect effects on estradiol levels, potentially enhancing cognitive and neuroprotective benefits (77). Due to their favorable efficacy and tolerability profiles, SSRIs and SNRIs are widely recommended by international guidelines for managing perimenopausal affective symptoms (71,73). However, considerable interindividual variability in treatment response persists. Adverse effects such as nausea, diarrhea, insomnia and sexual dysfunction may affect some patients, and ~30% may fail to achieve sufficient symptom relief with a single agent (78). Therefore, personalized medication selection and continuous monitoring of therapeutic efficacy and tolerability are key for optimizing patient outcomes.

3. Mitochondrial homeostasis and its disruption

Mitochondrial function. Mitochondria are the primary bioenergetic organelles in eukaryotic cells, responsible for generating ATP through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) (79,80). This energy production process is driven by the electron transport chain (ETC) and ATP synthase, which together convert nutrients into usable cellular energy (81). Reducing equivalents such as NADH and flavin adenine dinucleotide ($FADH_2$) donate electrons to the ETC, ultimately leading to ATP synthesis and maintaining cellular homeostasis. The TCA cycle metabolizes pyruvate into carbon dioxide while producing NADH and $FADH_2$, which fuel the ETC (82).

Mitochondria also exhibit dynamic behavior regulated by continuous cycles of fission and fusion. These processes are key for maintaining mitochondrial integrity and function. Fission allows for the removal of damaged mitochondria and supports cellular adaptation under stress, while fusion promotes the mixing of mitochondrial contents and enhances network connectivity to optimize energy distribution (83).

In the CNS, mitochondria are key not only for sustaining neuronal energy demands but also for regulating neurotransmitter synthesis, calcium buffering, oxidative stress responses and apoptotic signaling (84) (Fig. 1). These functions are particularly vital in neurons, which have high metabolic demands. Neurons rely heavily on ATP to maintain resting membrane potential, recycle synaptic vesicles and support neurotransmitter release. Mitochondria dynamically redistribute within neurons in response to local energy needs, often clustering near synaptic terminals during periods of high activity to meet localized energy demands (85). This spatial and functional plasticity is essential for maintaining synaptic transmission, neuronal excitability and overall neurophysiological stability.

Mitochondria and neurotransmitter regulation. Mitochondria carry out a direct and essential role in the synthesis, metabolism and release of various neurotransmitters. Their functional integrity is important for maintaining synaptic transmission and emotional stability within the CNS (85).

Glu, the primary excitatory neurotransmitter in the brain, also serves as a precursor for the inhibitory neurotransmitter GABA (86). The synthesis of Glu is highly dependent on mitochondrial metabolism, particularly through the TCA cycle, which generates α-ketoglutarate (α-KG), a key substrate for Glu biosynthesis. Glu is then converted to GABA via Glu decarboxylase, representing a key biochemical shift from excitation to inhibition (87). In astrocytes, glutamine (Gln), the major precursor of Glu, is synthesized via Gln synthetase and transferred to neurons, where it is converted back into Glu by phosphate-activated glutaminase, further entering mitochondrial pathways.

Mitochondrial regulation of calcium homeostasis. Mitochondria function as major intracellular calcium (Ca^{2+}) buffers, carrying out a key role in maintaining cytosolic calcium homeostasis (84). Calcium signaling not only facilitates intracellular signal transduction but also supports mitochondrial bioenergetics by modulating the mitochondrial membrane potential ($\Delta\Psi m$), which is essential for ATP production. In the mitochondrial matrix, moderate elevations in Ca^{2+} levels activate key dehydrogenases of the TCA cycle, such as isocitrate dehydrogenase (IDH) and α-KG dehydrogenase (α-KGDH), thereby enhancing NADH production, fueling the ETC, and increasing ATP synthase activity (88).

The precise regulation of mitochondrial calcium flux is mediated by a network of transmembrane channel complexes. Under resting conditions, Ca^{2+} enters the intermembrane space through voltage-dependent anion channels located on the outer mitochondrial membrane. It then crosses the inner membrane into the matrix through the OXPHOS mitochondrial calcium uniporter (MCU) complex, which includes core subunits such as MCU, MICU1, MCUR1 and EMRE (89). These components work together to regulate Ca^{2+} uptake in a tightly controlled manner, ensuring efficient and safe calcium accumulation (90,91). During neuronal excitation, mitochondrial calcium uptake via the MCU is essential for sustaining synaptic activity. Calcium buffering within mitochondria supports synaptic vesicle fusion and neurotransmitter release by shaping local calcium transients, thereby optimizing the efficiency and timing of synaptic transmission.

In addition to their intrinsic calcium-handling systems, mitochondria are functionally and structurally connected to the ER at specialized membrane contact sites known as mitochondria-associated membranes. These microdomains facilitate calcium transfer between organelles. Upon stimulation, inositol 1,4,5-trisphosphate receptors on the ER release stored Ca^{2+} near the mitochondrial outer membrane, where it is taken up via the voltage-dependent anion channel-MCU pathway. Conversely, sarco/endoplasmic reticulum Ca^{2+}-ATPase pumps recapture cytosolic Ca^{2+} back into the ER, contributing to calcium clearance and recycling (81).

Redox balance and oxidative stress regulation. Mitochondria carry out a central role in maintaining cellular redox balance, acting as both the primary source of ROS and a key platform for their detoxification and stress response. Under normal physiological conditions, electrons from NADH and $FADH_2$ are transferred through the mitochondrial ETC to molecular oxygen, driving ATP synthesis. However, during this process, especially at Complex I and Complex III, some electrons may prematurely reduce oxygen, generating superoxide anion ($O_2^{-}\bullet$), the major intracellular ROS (92,93). Superoxide is rapidly dismutated by mitochondrial superoxide dismutase (SOD2) into hydrogen peroxide (H_2O_2), which can then form highly reactive hydroxyl radicals (OH•) via Fenton chemistry in the presence of transition metals such as Fe^{2+}. While ROS at low levels function as signaling molecules involved in transcriptional regulation, proliferation, differentiation and immune responses (94,95), excessive ROS production can overwhelm the antioxidant defense system, leading to oxidative stress. This imbalance results in protein oxidation, lipid peroxidation, DNA damage and mitochondrial dysfunction, ultimately causing cell death or senescence (92).

The generation of ROS is further exacerbated under conditions of elevated mitochondrial membrane potential ($\Delta\Psi m$) or an imbalanced $NADH/NAD^+$ ratio. To mitigate this, mitochondria are equipped with robust enzymatic and non-enzymatic antioxidant systems. In addition to SOD2, enzymes such as glutathione peroxidase (GPx) and the thioredoxin-2/peroxiredoxin-3 system convert H_2O_2 into water, preventing harmful accumulation. Glutathione, a major non-enzymatic antioxidant, maintains the reduced intracellular environment and participates in free radical neutralization (96).

ROS also activate nuclear antioxidant signaling pathways that enhance cellular adaptive capacity. For example, ROS can promote the dissociation of nuclear factor erythroid 2-related factor 2 (Nrf2) from its repressor Keap1, enabling its nuclear translocation and subsequent activation of antioxidant enzyme genes, including SOD, GPx and heme oxygenase-1 (HO-1) (97). Simultaneously, ROS activate mitochondrial biogenesis and stress adaptation pathways through coactivators and transcription factors such as PGC-1α and FOXO3a, thereby enhancing mitochondrial resilience (98,99).

Moreover, mitochondrial quality control is maintained through mitophagy, a process that selectively removes damaged or ROS-overproducing mitochondria (100). This process is mediated by the PINK1/Parkin pathway: Upon collapse of the $\Delta\Psi m$, PINK1 stabilizes on the outer membrane and recruits the E3 ubiquitin ligase Parkin, which tags damaged mitochondria for autophagic degradation (101). This mechanism effectively prevents the propagation of ROS-induced damage and preserves cellular homeostasis.

Mitochondria in the balance of cell survival and apoptosis. Mitochondria are key regulators of the dynamic balance between neuronal survival and apoptosis, serving as key checkpoints in determining cell fate. While physiological apoptosis is essential for eliminating damaged or dysfunctional neurons to maintain brain homeostasis, aberrant activation of apoptotic pathways can disrupt neural circuits and contribute to the pathogenesis of mood disorders and neurodegenerative diseases (102,103).

Under normal mitochondrial homeostasis, anti-apoptotic members of the BCL-2 family, such as BCL-2 and BCL-xL, are anchored in the outer mitochondrial membrane. These proteins inhibit apoptosis by binding to and neutralizing pro-apoptotic factors such as Bax and Bak, preventing their oligomerization and subsequent increase in mitochondrial outer membrane permeability, thereby promoting neuronal survival (104). In

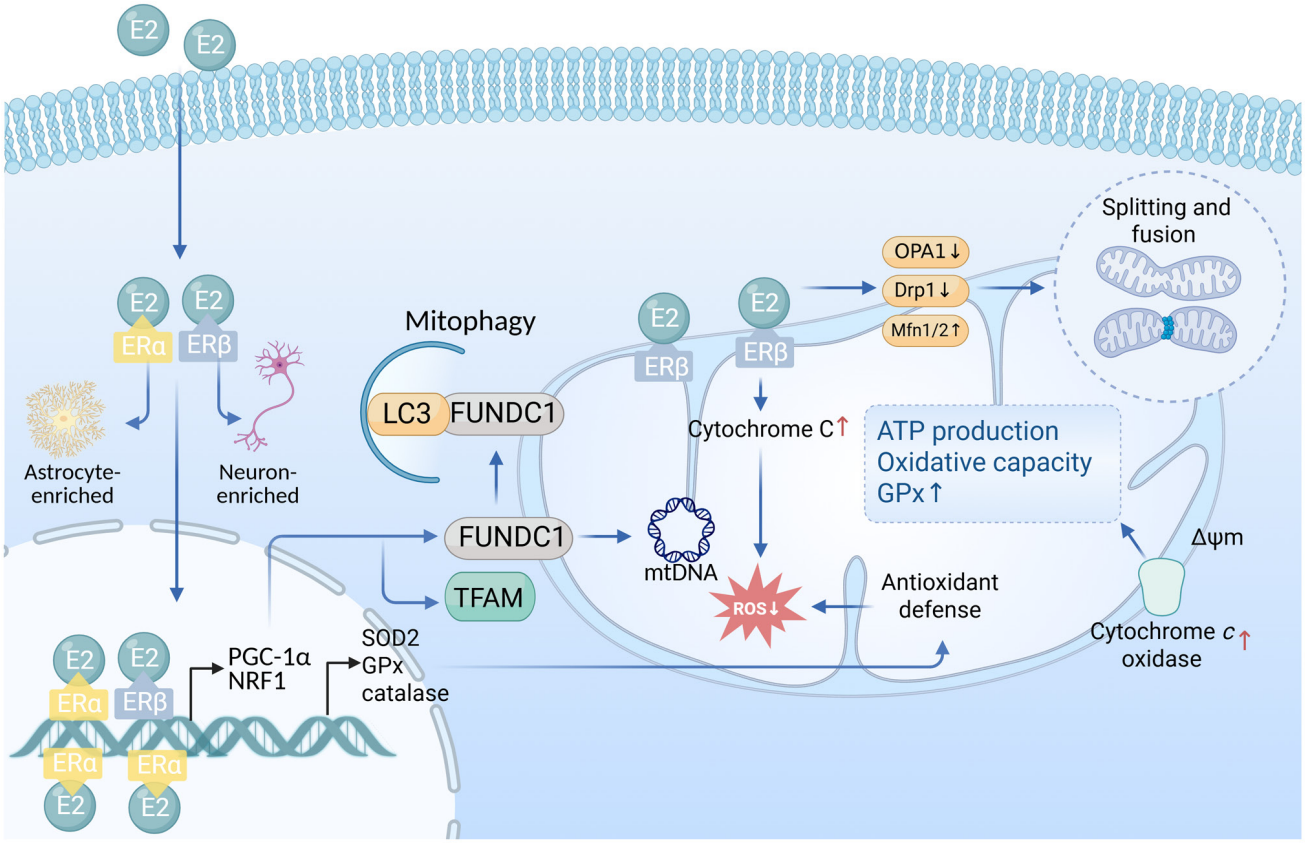

Figure 2. Estrogenic regulation of mitochondrial function. E2 engages ERα and ERβ to regulate mitochondrial function via genomic and non-genomic pathways. ERβ is mainly located in mitochondria in neurons, while ERα shows predominant nuclear expression in astrocytes. Genomically, it upregulates TFAM and antioxidant enzymes (SOD2, GPx and catalase), enhancing oxidative phosphorylation and redox balance. Non-genomically, E2 stabilizes mitochondrial dynamics (↑Mfn1/2, OPA1 and ↓Drp1) and promotes mitophagy via ERβ-FUNDC1 signaling. Drp1, dynamin-related protein 1; E2, 17β-estradiol; ERα, estrogen receptor α; ERβ, estrogen receptor β; FUNDC1, FUN14 domain containing 1; GPx, glutathione peroxidase; Mfn1/2, mitofusin 1/2; OPA1, optic atrophy 1; SOD2, superoxide dismutase 2; TFAM, transcription factor A, mitochondrial.

response to cellular stressors, including oxidative damage, calcium overload or DNA damage, pro-apoptotic pathways are activated. For instance, signaling through the Bad/p53 complex or the JNK-Bim axis promotes the conformational activation and translocation of Bax to the mitochondrial outer membrane. This destabilizes the membrane, leading to a decrease in ΔΨm and the opening of the mitochondrial permeability transition pore (mPTP) (105). Upon mPTP opening, cytochrome *c* (Cyt *c*) is released from the mitochondrial intermembrane space into the cytosol, initiating the intrinsic (mitochondrial) apoptotic pathway. In the cytoplasm, Cyt *c* binds to apoptotic protease-activating factor-1 and procaspase-9, forming the apoptosome. This multiprotein complex activates executioner caspases, such as caspase-3, initiating a cascade of proteolytic events that ultimately lead to the programmed death and clearance of damaged neurons (106).

E2ic regulation of mitochondrial function. E2 regulates mitochondrial function through both classical nuclear receptor signaling and rapid non-genomic pathways, collectively coordinating mitochondrial biogenesis, morphology, metabolic activity and responses to cellular stress (Fig. 2) (107).

At the transcriptional level, E2 binds to its receptor isoforms, ERα and ERβ, to activate several nuclear-encoded mitochondrial regulatory factors, including nuclear respiratory factor 1 (NRF1) and PGC-1α (107,108). NRF1 and PGC-1α work synergistically to promote the expression of key genes such as mitochondrial transcription factor A (TFAM), which facilitates mtDNA transcription, replication and translation, thus supporting the structural and functional integrity of OXPHOS complexes (109-111). Notably, ERβ is also localized to the mitochondrial membrane, where it exerts direct non-genomic control over mitochondrial respiration (112,113). By modulating Cyt *c* oxidase (complex IV) activity and stabilizing Δψm, ERβ enhances respiratory efficiency and reduces electron leakage (113).

E2 further upregulates key mitochondrial antioxidant enzymes, including SOD2, GPx and catalase, thereby enhancing ROS-scavenging capacity (109). It may also indirectly reduce ROS production by increasing Cyt *c* mRNA and protein expression, thereby strengthening antioxidant defenses (114). Beyond metabolic and redox control, E2 influences mitochondrial morphology by suppressing the recruitment and activation of the fission-related protein dynamin-related protein 1 (Drp1) and promoting the expression of fusion proteins such as mitofusin 1/2 (Mfn1/2) and optic atrophy 1 (OPA1) (115). These actions together support mitochondrial network integrity and ensure efficient energy distribution (116).

Table I. Regulatory effects of estrogen on mitochondrial function and after its decline.

Author/s, year	Regulatory mechanisms	Role of estrogen	Effects of estrogen decline	(Refs.)
Gaignard *et al*, 2017; Velarde, 2014; Klinge, 2008	Mitochondrial gene expression	Activates NRF1 and PGC-1α via ERα/ERβ, promoting mitochondrial biogenesis and respiratory complex expression.	Downregulates NRF1 and PGC-1α, impairs mtDNA replication, reduces energy-related gene expression by ~40%.	(107,110,111)
Salnikova *et al*, 2021; Kim *et al*, 2024; Yin *et al*, 2021	Fission and fusion balance	Inhibited Drp1, promoted the expression of Mfn1/Mfn2 and Opa1, and maintained mitochondrial homeostasis.	Increases Drp1 activity (~1.5-fold), reduces fusion proteins, leading to fragmentation and abnormal morphology.	(115-117)
Kemper *et al*, 2014; Rettberg *et al*, 2014; Miao *et al*, 2024	Respiration and ATP synthesis	Enhances ETC activity, supports COX function, stabilizes Δψm, and boosts ATP production.	Decreases ATP yield (~30%), OCR and glucose utilization.	(108,112,118)
Gujardo-Correa *et al*, 2022; Stirone *et al*, 2005; Miao *et al*, 2024	Antioxidant defense	Induces SOD2, GPx, and catalase expression, reducing mitochondrial ROS accumulation.	Decreases SOD2, increases ROS by 50-80%, causing oxidative damage to membranes, proteins and DNA.	(109,114,118)
Plovanich *et al*, 2013; Hunter *et al*, 2012	Calcium homeostasis	Regulates MCU-mediated Ca^{2+} influx, supporting ATP synthase activity and calcium signaling.	MCU dysfunction reduces Ca^{2+} uptake (~40%), impairing respiration and triggering apoptotic pathways.	(126,127)
Liu *et al*, 2021; Li *et al*, 2023	Mitophagy	FUNDC1 is upregulated by PGC-1α to promote mitochondrial clearance of damage.	Autophagy disorder leads to damage mitochondrial accumulation and a further increase in ROS, creating a vicious cycle.	(99,158)

NRF1, nuclear respiratory factor 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; ERα, estrogen receptor α; mtDNA, mitochondrial DNA; Drp1, dynamin-related protein 1; Mfn, mitofusin; Opa1, optic atrophy protein 1; ETC, electron transport chain; COX, cytochrome c oxidase (complex IV); OCR, oxygen consumption rate; SOD2, superoxide dismutase 2; GPx, glutathione peroxidase; ROS, reactive oxygen species; MCU, mitochondrial calcium uniporter; FUNDC1, FUN14 domain containing 1.

Mitochondrial homeostasis disruption in perimenopausal mood disorders. During menopause, the abrupt decline in E2 has been revealed to disrupt mitochondrial homeostasis, leaving measurable bioenergetic signatures across both central and peripheral tissues (99,107-112,114-117) (Table I). Clinical studies indicate that postmenopausal women exhibit a ~30% reduction in ATP production efficiency, which associates directly with decreased activity of mitochondrial complex IV, COX (118). Translational neuroimaging studies, combining ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS), reveal a concurrent decline in cerebral metabolic rate of glucose consumption (CMRglc) and OXPHOS efficiency in perimenopausal women (118). Notably, the extent of metabolic decline is inversely correlated with Beck Depression Inventory-II (BDI-II) scores, suggesting an association between impaired brain energetics and depressive symptom severity (119). Furthermore, reduced glucose utilization in the brain has been associated with decreased Cyt *c* oxidase activity in peripheral blood platelets, indicating a parallel dysfunction of mitochondrial metabolism in both the CNS and peripheral tissues (120). This pattern of metabolic disruption appears to result not merely from chronological aging, but from hormone-driven 'endocrine aging' that destabilizes mitochondrial function. Collectively, these findings highlight mitochondrial E2 dependence as a key mechanistic factor underlying perimenopausal mood disorders.

Mitochondrial bioenergetic dysfunction. E2 deficiency during perimenopause is a major driver of mitochondrial bioenergetic impairment, with the ETC being a primary target. Experimental studies indicate that E2 enhances the expression

and activity of several ETC complexes, including Complex I (NDUFB8), Complex IV (MTCO1) and Complex V (121). In the absence of E2, the Erβ-PGC-1α-NRF1 transcriptional axis is downregulated, leading to reduced expression of OXPHOS subunits, decreased ΔΨm and impaired coupling between substrate oxidation and ATP synthesis (122). In ovariectomized rats, mitochondrial oxygen consumption rate in skeletal muscle decreases by ~25% at rest, with maximal respiratory capacity reduced by up to ≤40% (123). These deficits associate with diminished expression of Complex I and IV subunits, highlighting the structural and functional deterioration of the ETC as a key mechanism underlying energy failure due to E2 deficiency.

Additionally, E2 regulates the TCA cycle through epigenetic mechanisms. E2 withdrawal suppresses sirtuin 1-mediated deacetylation of key metabolic enzymes, resulting in downregulation of IDH 3α (IDH3α) and α-KGDH, both rate-limiting enzymes in the TCA cycle (124,125). This suppression limits NADH production, reducing electron supply to the ETC and slowing TCA cycle throughput.

E2 also positively regulates the expression and assembly of the MCU complex. When E2 levels decline <50 pg/ml, dysfunctional MCU assembly limits mitochondrial Ca^{2+} uptake, impairing ATP synthase activation and disrupting calcium-dependent apoptotic signaling (126). Mitochondrial Ca^{2+} is essential for activating key dehydrogenases in the TCA cycle, such as pyruvate dehydrogenase (PDH), IDH and α-KGDH, which facilitate NADH and $FADH_2$ production. These reducing equivalents fuel the ETC, enhancing ATP synthesis and supporting mitochondrial bioenergetics. In perimenopausal women, E2 deficiency reduces mitochondrial Ca^{2+} sensitivity, impairing respiratory efficiency and energy output (127). Moreover, dysregulated mitochondrial Ca^{2+} buffering disrupts the spatial and temporal precision of calcium transients required for synaptic vesicle release. This leads to inefficient neurotransmission and contributes to excitatory/inhibitory (E/I) imbalance, often manifested as elevated extracellular Glu levels and reduced GABAergic tone. Such imbalances compromise synaptic plasticity, long-term potentiation and network stability in limbic regions (128).

Furthermore, E2 deficiency impairs fatty acid oxidation by downregulating carnitine palmitoyltransferase I, a key enzyme responsible for mitochondrial fatty acid uptake and β-oxidation. This defect limits the utilization of alternative energy substrates and reduces overall metabolic flexibility (125). E2 also influences glucose metabolism at multiple regulatory points. Its absence leads to reduced expression of glucose transporters GLUT1 and GLUT4 in the brain, and GLUT3 and GLUT4 in peripheral tissues. Additionally, increased phosphorylation of PDH inhibits its activity, impairing pyruvate utilization and mitochondrial entry. These combined effects result in reduced glucose uptake and decreased lactate production, reflecting a broad suppression of glucose oxidative capacity (129).

Impaired antioxidant defense. E2 deficiency markedly disrupts mitochondrial antioxidant defense systems, exacerbating oxidative stress and contributing to mitochondrial dysfunction. The phenolic hydroxyl group of E2, particularly on the A-ring, acts as a direct free radical scavenger by donating hydrogen atoms to neutralize ROS, thereby exerting non-enzymatic antioxidant effects (118). In perimenopausal women, a decline in circulating E2 levels is associated with a 50-80% increase in ROS production, positioning E2 loss as a key driver of mitochondrial oxidative stress. E2 deficiency downregulates the Erβ-PGC-1α-NRF1 transcriptional axis, leading to suppressed SOD2 expression and impaired clearance of mitochondrial ROS, initiating a vicious cycle of oxidative damage and mitochondrial destabilization (122). Concurrently, reduced expression of OXPHOS subunits further impairs mitochondrial electron flow, resulting in decreased ΔΨm and diminished coupling efficiency. These alterations increase the $NADH/NAD^+$ ratio, which inhibits Complex I activity and promotes electron leakage to oxygen, generating additional superoxide radicals and intensifying oxidative injury (130).

Excessive ROS not only impair ETC function but also activate pro-inflammatory and pro-apoptotic pathways. For example, elevated ROS levels can trigger the assembly of NLRP3 inflammasomes, promote mPTP opening and initiate caspase-mediated apoptosis. These downstream effects contribute to neuroinflammation and neuronal loss, thereby reinforcing the pathological association between E2 decline, mitochondrial dysfunction and mood disorders during perimenopause (131).

Imbalance in mitochondrial dynamics. E2 decline also promotes mitochondrial fission, resulting in fragmented mitochondria with disorganized cristae and reduced inter-organelle connectivity. Such fragmentation impairs substrate and protein exchange across the mitochondrial network, compromises ΔΨm and reduces coupling efficiency between electron transport and ATP synthesis.

Mechanistically, E2 deficiency increases the expression and activation of the fission protein Drp1, particularly through phosphorylation at Ser616. By contrast, the expression of key fusion proteins, Mfn1/2 and Opa1, is downregulated (117). This imbalance between enhanced fission and suppressed fusion leads to structural fragmentation, metabolic uncoupling and deterioration of respiratory chain function, all of which contribute to bioenergetic failure.

To illustrate the association between E2 signaling, mitochondrial integrity and mood regulation, a conceptual framework outlining the hormone-mitochondria-mood axis is proposed (Fig. 3). As summarized, declining E2 levels during perimenopause disrupt key mitochondrial processes, such as biogenesis, antioxidant defense, calcium homeostasis, mitophagy and energy metabolism, through multiple nuclear and cytoplasmic signaling pathways (132). These impairments collectively compromise neuronal function and synaptic plasticity in emotion-related brain regions, such as the hippocampus and prefrontal cortex, contributing to the onset of affective and cognitive symptoms (133).

4. Limitations and prospects

Limitations of current research

Clinical confounders and mechanistic gaps. Perimenopause represents a complex physiological transition characterized by notable hormonal fluctuations and multisystem remodeling. During this stage, E2 and progesterone levels fluctuate along

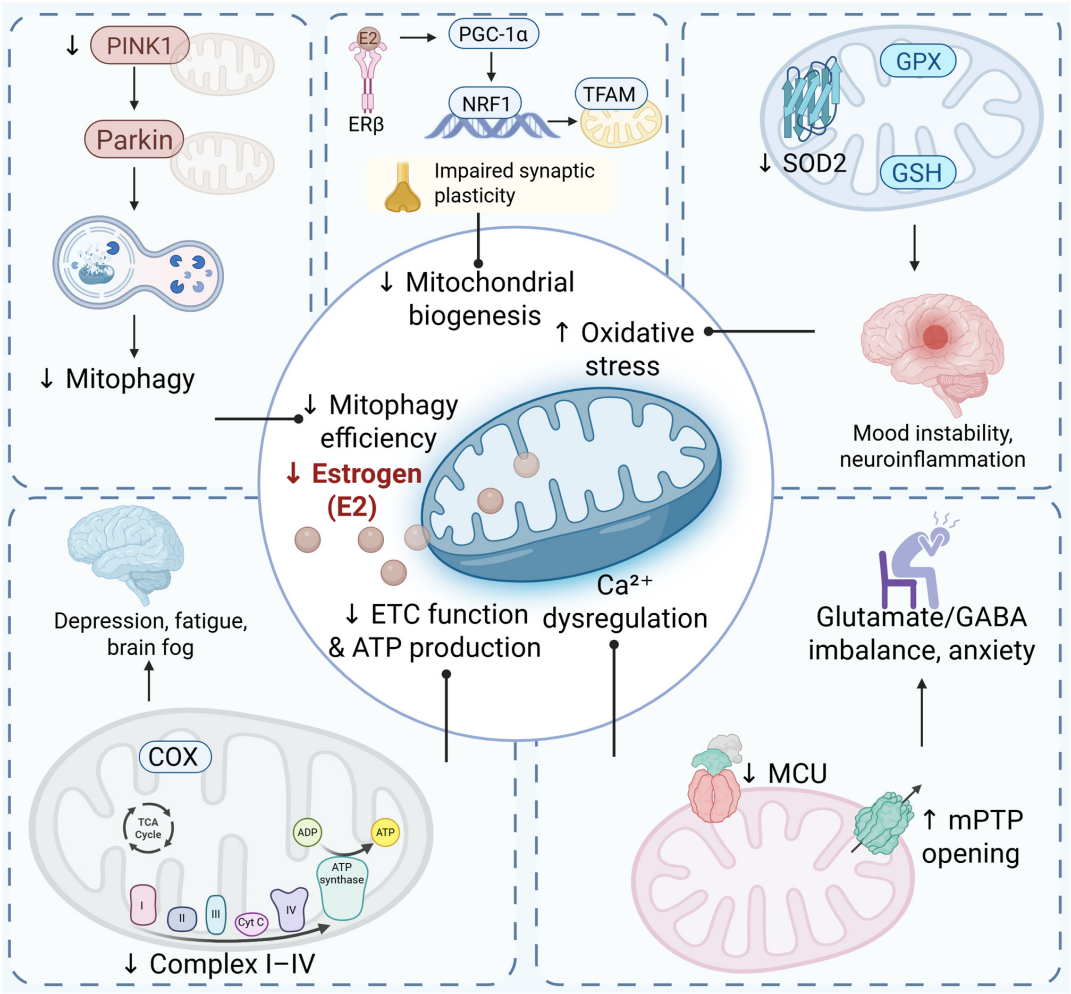

Figure 3. Disruption of the hormone-mitochondria-mood axis in estrogen deficiency. Estrogen deficiency induces multifaceted mitochondrial dysfunction in mood-regulating brain regions, characterized by impaired oxidative phosphorylation, reduced ATP synthesis, excessive reactive oxygen species accumulation, dysregulated fission-fusion dynamics and suppressed mitophagy. These alterations compromise neuronal bioenergetic capacity and redox homeostasis, contributing to synaptic dysfunction and neuroinflammatory cascades. This mechanistic continuum constitutes the hormone-mitochondria-mood axis, wherein endocrine withdrawal drives mitochondrial destabilization, ultimately predisposing individuals to affective and cognitive disturbances during the perimenopausal transition. ATP, adenosine triphosphate; Ca^{2+}, calcium ion; COX, cytochrome c oxidase (complex IV); E2, 17β-estradiol; ETC, electron transport chain; GABA, gamma-aminobutyric acid; GPX, glutathione peroxidase; GSH, reduced glutathione; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; NRF1, nuclear respiratory factor 1; Parkin, Parkin RBR E3 ubiquitin protein ligase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; SOD2, superoxide dismutase 2; TCA, tricarboxylic acid cycle; TFAM, transcription factor A, mitochondrial.

individualized trajectories, profoundly affecting CNS function and mood regulation pathways (134). While the majority of women experience varying degrees of mood disturbances, such as depression, anxiety and cognitive impairment, others may remain largely asymptomatic. The clinical presentation of perimenopausal mood disorders reflects the unique interplay between biological factors and psychosocial influences, encompassing depressive and anxious symptoms, cognitive decline and somatic complaints. This variability is likely due to differences in hormone sensitivity, genetic polymorphisms, psychiatric history and exposure to life stressors. These confounding factors introduce considerable variability, complicating the comparability and generalizability of clinical research findings. Future studies should implement stratified analyses based on individual stress exposures, assessed using validated psychological or life event scales, to differentiate between stress-induced and hormone-driven mitochondrial alterations.

Although growing evidence implicates mitochondrial dysfunction, such as impaired ATP production, elevated oxidative stress, disrupted mitophagy and calcium dysregulation, in the pathogenesis of perimenopausal mood disorders, the underlying mechanisms remain poorly understood (135). To date, no fully integrated pathological cascade has been established associating sex hormone decline, mitochondrial dysfunction, neurotransmitter imbalance and affective symptoms. Much of the mechanistic insight stems from animal models or *in vitro* systems, which may not accurately replicate the physiological complexity of human perimenopause. Additionally, to the best of our knowledge, high-quality, longitudinal clinical studies specifically targeting perimenopausal populations are lacking. This gap restricts the development of robust, evidence-based conclusions and limits the translational potential of mitochondrial biomarkers and targeted interventions in this context. Moreover, individual genetic variations in mitochondrial or E2-responsive genes, such as ESR1, TFAM,

Table II. Comparison of therapeutic strategies targeting imbalances in mitochondrial homeostasis.

Author/s, year	Treatment strategy	Mechanism of action	Evidence	Potential risks/ limitations	(Refs.)
Soares *et al*, 2001; van Staa *et al*, 2008; Rossouw *et al*, 2002	HRT	Replenishes estrogen, restores mitochondrial membrane potential, ATP production and antioxidant defense.	RCTs show notable symptom reduction in perimenopausal depression (remission, 68 vs. 17%)	Potential long-term risks: Cardiovascular disease and breast cancer.	(69,71,73)
Yan 2014; Wagner *et al*, 2012	Mitochondria-targeted drugs	Antioxidants (CoQ10, NAC) reduce ROS; α-lipoic acid enhances energy metabolism and promotes mitochondrial biogenesis via TFAM.	Animal studies confirm improved mitochondrial function and gene expression.	Limited clinical data; long-term safety remains uncertain.	(146,151)
Stahl *et al*, 2005; Parry, 2010	Antidepressants and psychological therapy	SSRIs/SNRIs increase monoamine levels; CBT modifies cognition and alleviates emotional symptoms.	SSRIs and phototherapy improve mood; CBT reduces anxiety and sleep issues .	Side effects (such as nausea and sexual dysfunction); efficacy varies among individuals.	(76,78)
Shon *et al*, 2023; Shavaisi *et al*, 2024	Lifestyle interventions	Diet (such as omega-3 and soy) offers antioxidant/anti-inflammatory effects; exercise improves metabolism and neuroplasticity.	Improves progesterone levels, mood, and gut microbiota; reduces inflammation	Requires long-term adherence; outcomes vary with individual compliance.	(152,153)

HRT, hormone replacement therapy; RCT, randomized controlled trial; CoQ10, coenzyme Q10 (ubiquinone); NAC, N-acetylcysteine; ROS, reactive oxygen species; TFAM, transcription factor A, mitochondrial; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; CBT, cognitive behavioral therapy.

PGC-1α and NRF1, may influence mitochondrial biogenesis, redox regulation and susceptibility to hormonal decline (136). These polymorphisms may explain the heterogeneous responses to both E2 loss and therapeutic interventions across perimenopausal women.

Limitations of current diagnostic and therapeutic strategies. Although peripheral mitochondrial markers, such as platelet Cyt *c* oxidase activity, have been proposed as minimally invasive proxies for CNS mitochondrial function, their diagnostic utility remains limited. Differences in metabolic demand, regulatory environment and cell-type specificity between platelets and neurons may obscure central pathophysiological signals (137). Therefore, future studies should integrate peripheral bioenergetic markers with neuroimaging and hormonal profiling to establish more reliable, multidimensional diagnostic tools.

HRT can enhance $\Delta\Psi m$, increase ATP synthesis efficiency and upregulate antioxidant enzymes such as SOD2 and GPx, thereby improving neuronal bioenergetics and redox homeostasis while attenuating central oxidative stress (138). Notably, the variability in HRT efficacy may reflect underlying differences in mitochondrial status among individuals. Women with higher baseline oxidative stress or impaired mitophagy may exhibit diminished mitochondrial responsiveness to E2, limiting the therapeutic benefits of HRT (56). Identifying such biomarkers could guide personalized interventions. Mitochondria-targeted therapies, including antioxidants [such as, coenzyme Q10, N-acetylcysteine (NAC) and α-lipoic acid] and mitochondrial nutritional supplements, have emerged as promising alternatives aimed at mitigating oxidative stress and restoring mitochondrial function.

Additionally, emerging mitochondria-targeted compounds, such as SS-31 (elamipretide) and MitoQ, have demonstrated preclinical efficacy in reducing oxidative damage and restoring mitochondrial function in neuronal models of depression and E2 deficiency (139). Although preclinical studies and animal models have revealed improvements in energy metabolism, reductions in ROS production, and beneficial behavioral effects in depression and anxiety paradigms, human studies remain limited. Current clinical trials in perimenopausal populations face challenges such as small sample sizes, short intervention durations and a lack of appropriate control groups, restricting the generalizability and strength of evidence needed for clinical implementation. Another key limitation is the prevailing 'one-size-fits-all' approach in current treatment paradigms, which fails to account for the considerable interindividual heterogeneity in clinical phenotype, hormonal responsiveness, mitochondrial status and genetic background (140).

Future directions

Multi-omics integration and precision medicine. The advent of large-scale multi-omics approaches, including metabolomics, epigenomics and neuroimaging, offers increasing potential to address the heterogeneity of perimenopausal mood disorders and move toward precision medicine. By integrating genetic variations, epigenetic modifications, inflammatory profiles and metabolic signatures with neurofunctional imaging markers, researchers have begun identifying biologically distinct subtypes of depression (141). Recent studies, for instance, have utilized machine learning clustering based on low-frequency amplitude features from functional magnetic resonance imaging, combined with multi-omics data, to classify depression into molecularly distinct subtypes (141,142). These subtypes demonstrate divergent characteristics in neurodevelopment, synaptic regulation and immune-inflammatory dysregulation, and associate with differences in symptom severity.

Extensive evidence has validated the concept of mechanism-based stratification and highlighted the need for personalized interventions tailored to individual molecular and neurobiological profiles (143-145). Moving forward, the integration of artificial intelligence and machine learning is expected to enhance data analysis efficiency and support predictive modeling for disease trajectories and treatment responsiveness in perimenopausal populations. To further elucidate the pathophysiological role of mitochondrial dysfunction and inform treatment development, future studies should integrate omics-based profiling with dynamic neuroimaging to map the spatiotemporal relationship between mitochondrial imbalance and affective symptoms.

Multipathway combination therapies. Mitochondrial dysfunction in perimenopausal mood disorders is often accompanied by oxidative stress and neuronal injury. Antioxidant agents such as coenzyme Q10, vitamin E and NAC reduce ROS production, enhance mitochondrial ATP levels, and restore membrane potential (146). These effects contribute to improved neuroenergetic function and emotional regulation. For instance, vitamin E has demonstrated efficacy in improving vaginal health and modulating hormone levels in perimenopausal women, with a favorable safety profile (147). However, the majority of studies on coenzyme Q10 and NAC have primarily focused on ovarian function, and their long-term efficacy and safety in mood-related contexts remain insufficiently validated (148,149). Natural compounds that activate the Nrf2 signaling pathway, such as curcumin and resveratrol, have also demonstrated promise in reducing oxidative stress, mitigating inflammation and enhancing mitochondrial resilience in preclinical models (150). ALA upregulates mitochondrial TFAM, promoting mtDNA replication and mitochondrial biogenesis, and functions as a cofactor in the ETC, directly enhancing redox function (151).

Given the multifactorial nature of mitochondrial imbalance, multipronged therapeutic strategies are likely more effective than single-target approaches (Table II) (69,71,73 ,76,78,146,151-153). For example, Nrf2 activators upregulate endogenous antioxidant defenses and exert neuroprotective, anti-apoptotic effects, while mitophagy modulators promote the selective clearance of dysfunctional mitochondria. Mitophagy deficits are increasingly implicated in depression pathogenesis; therefore, enhancing mitochondrial quality control may offer therapeutic benefits. A growing body of preclinical evidence supports the antidepressant potential of mitophagy-promoting interventions in animal and cellular models (154). While multi-pathway approaches hold promise, priority should be given to interventions supported by clinical trials, such as phytoE2s (for example genistein), melatonin or lifestyle strategies such as exercise and dietary modulation.

Nanomedicine and mitochondria-targeted delivery. To address limitations in drug targeting and delivery efficiency, the development of mitochondria-targeted nanomedicine has emerged as a promising strategy. Functionalized nanoparticles can penetrate both cellular and mitochondrial membranes, as well as the blood-brain barrier, enabling direct delivery of therapeutics into neuronal mitochondria. This approach enhances drug bioavailability, stability and organelle specificity (155,156).

The structural complexity of mitochondria often restricts the effective delivery of conventional compounds. Nanocarriers, such as ligand-functionalized lipid nanoparticles and MITO-Porter systems, can preferentially accumulate within mitochondria, facilitating the precise release of antioxidants and metabolic modulators (157). However, these experimental strategies are still in the early stages of development and require further validation before clinical application.

5. Conclusion

Perimenopausal mood disorders result from complex interactions between hormonal decline and mitochondrial dysfunction. The present review highlights disrupted mitochondrial homeostasis, including impaired OXPHOS, calcium imbalance, redox stress and defective mitophagy, as a central mechanism linking E2 loss to neuropsychiatric symptoms. E2 modulates mitochondrial function through both genomic and non-genomic pathways, positioning mitochondria as key mediators of hormonal effects on brain health. While preclinical evidence supports mitochondrial targets, clinical translation remains hindered by insufficient biomarker-based stratification and a lack of long-term data. Future research should integrate multi-omics, neuroimaging and artificial intelligence-driven subtyping to develop personalized, mitochondria-targeted interventions. Restoring mitochondrial integrity presents a novel therapeutic approach for enhancing emotional and cognitive resilience in perimenopausal women.

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Authors' contributions

YY and HY drafted the initial version of the manuscript. ZL and LF contributed to the collection, organization, and critical interpretation of the literature. JL and YL assisted in preparing figures and tables and participated in manuscript editing. WL and HC provided intellectual input, supervised the writing process, and revised the manuscript for important content. XW conceived the review topic, guided the overall structure, and finalized the manuscript. All authors read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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