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Perspective

Perimenopausal Hormone Replacement Treatments as a Geroprotective Approach - Adapting Clinical Guidance

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ABSTRACT: The decline in ovarian endocrine function represents a pivotal event in female aging, initiating systemic biological deterioration well before the end of reproductive capacity. We propose that Hormone Replacement Therapy (HRT) may constitute an early stage geroprotective intervention with mechanistic relevance across the 12 hallmarks of aging. Despite extensive clinical use, HRT remains underutilized as a geroprotector. Although there is promising data, prospective, biomarker-driven interventional studies are required to test this paradigm. This narrative review outlines the role of HRT as a geroprotective therapy, preferably offered and started within 10 years of menopause onset, in clinically eligible women in perimenopause. We emphasize the need for specific clinical guidelines that reflect and manage the endocrine, inflammatory, and metabolic profiles unique to perimenopause. The development of age- and phase-specific biomarkers will be critical to optimize HRT use and ensure precision delivery of longevity-focused care for women.

Keywords: hormone replacement therapy, perimenopause, geroprotective intervention, female reproductive aging, hallmarks of aging, geromedicine

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Introduction

Due to its unique biology, the ovary is one of the earliest organs to decline functionally with age, often preceding deterioration of other systems [1]. The ovary functions as a key regulator of the female aging trajectory, with its gradual failure accelerating aging processes at the molecular, cellular and systemic levels, such as genomic instability, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, shortening telomeres, systemic inflammation, and adverse metabolic profiles [2].

Aging is the result of a combination of many pathological, physiological, and psychological processes, where the endocrine system can achieve a bidirectional effect on the aging process by regulating the hormone levels in the body [3]. Clinically, loss of estrogens accelerates biological aging through endothelial dysfunction, bone loss, and neurodegeneration [4]. Reproductive aging in women is clinically evident by three clinical stages: perimenopause, menopause, and postmenopause, which reflect the progressive decline in ovarian endocrine function with the drastic decline in endogenous estrogens production. Perimenopause, also known as menopausal transition, is the period leading up to menopause when a woman's ovaries gradually decrease estrogen production [5]. Clinically, perimenopause starts about several years before the final menstrual period with fluctuating ovarian hormone levels and menstrual irregularity, often accompanied by vasomotor symptoms, genitourinary discomfort, sleep disturbances, mood changes, and emerging cognitive difficulties. Seventy to ninety percent of women experience memory lapses or "brain fog" during this transition, frequently linked to hot flashes and insomnia. Estrogen levels decline further during menopause, for 12 consecutive months after the final menstrual period [5]. Menopause marks the irreversible cessation of ovarian follicular activity and hormonal secretion, resulting in the functional decline of many organs and aggravation of multiple symptoms, while also increasing the risk of osteoporosis, sarcopenia, cardiovascular disease, metabolic syndrome, and cognitive impairment [6]. Postmenopause lasts for the rest of a woman's life; persistent vasomotor symptoms and hormonal decline contribute to measurable cognitive and behavioural impairments in mid- to late life while reductions in muscle mass accelerate the development of sarcopenia.

The "timing hypothesis," originally proposed in the field of cardiology, suggests that HRT offers greater cardiovascular benefits when initiated during the perimenopausal period rather than after menopause. While this hypothesis was initially focused on reducing the risk of coronary artery disease and slowing atherosclerosis progression [7], evidence across multiple medical disciplines now supports perimenopause as a critical therapeutic window for targeted menopausal interventions. Starting HRT during this period may not only modulate biological aging and reduce overall morbidity, but also prevent vaginal and urogenital changes, mitigate rapid bone loss [8], slow metabolic aging [9], and potentially provide neuroprotective effects [10].

Current clinical guidelines focus on HRT use mainly for symptomatic menopausal patients [11]. Recent commentaries have proposed revisions to existing guidelines, emphasizing the need for stratified approaches that reflect endocrine, inflammatory, and metabolic heterogeneity across the menopausal continuum [11, 12]. Thus, HRT could be both a time-limited relief of vasomotor symptoms as well as a continued proactive geroprotective strategy in healthy, mid-life women, independent of ongoing symptom status, aligned with NAMS 2022 guidelines [13]. The development, validation and use of life-phase-specific biomarkers of aging could be employed to optimize the timing, formulation, and delivery of HRT [12]. In this context, HRT may serve not only as a therapeutic modality for symptom management, but also as a targeted precision intervention to prevent age-related functional decline in women.

"Gerotherapeutics" are interventions that treat aging-related existing pathologies by targeting fundamental hallmarks of aging, such as cellular senescence and mitochondrial dysfunction [14]. Meanwhile, "geroprotectors" slow, reverse, or mitigate biological aging processes or their downstream pathophysiologic consequences delay age-related decline by maintaining physiological homeostasis e.g., mitigating endocrine aging to preserve metabolic, cognitive, and musculoskeletal function [15, 16]. Hereby, we suggest that HRT exemplifies a translatable geroprotective strategy.

The first way of warranting, clinically validating and adopting HRT as a geroprotector can be promoted through the clinical practice of healthy longevity medicine, also referred to as geromedicine. As a translational, systems-oriented discipline, healthy longevity medicine aims to extend healthspan through biomarker-driven, personalized, and proactive approaches to aging [17]. In this context, HRT might have the potential to be repositioned beyond its conventional role in only managing troublesome menopausal symptoms, to preserving physiological resilience and mitigating the accelerated biological aging associated with ovarian decline. The use of aging biomarkers could enable clinicians to tailor the type, dosage, and mode of HRT delivery to match individual aging patterns.

Ovarian function as a biomarker of aging

The progressive decline in ovarian endocrine function before any other organ systems of the female body constitutes a critical transition in female aging, initiating multisystem biological deterioration that extends beyond the cessation of fertility [1, 2]. After the development of the fetal ovary, the pool of ovarian follicles, made up of oocytes and their layers of supporting cells, declines exponentially throughout life coupled with a decrease in oocyte quality and fecundity. Production of the major hormones secreted by the ovarian follicular cells, estrogens and progestogens, declines with the loss of these cells. Menopause marks the irreversible loss of ovarian follicles, hormonal secretion and results in functional decline of many organs and aggravation of multiple symptoms [6, 18].

The important geroprotective physiologic role of the ovary is challenged by the association between timing of menopause, end of ovarian function and health. Early menopause before age 45, is associated with increased risks of cardiovascular disease, osteoporosis, cognitive decline, and all-cause mortality [17]. Later menopause after age 55, signifying a longer ovarian lifespan and prolonged exposure to endogenous estrogens, confers protective effects on vascular, skeletal, and neurological systems. This is complemented with reduced risks of cardiovascular disease, overall morbidity and increased life expectancy [19]. Several observational studies link later menopause to greater odds of surviving into advanced age, supporting ovarian longevity as a biomarker of healthy aging [4, 20]. This data supports the preliminary conceptual notion that replacing vital ovarian steroids, particularly estrogens and progesterone through HRT, may also act as a gerotherapeutic intervention by mimicking the beneficial multi-systemic effects of these endogenous sex hormones. Thus, the ovaries are not only vital for reproduction but also impact overall health. This concept will need to be further explored and supported by future clinical trials.

Ubiquitous Actions of Estrogens and Progesterone

Estrogens, primarily estradiol (E2), exert pleiotropic effects throughout the body via binding to estrogen receptors (ERα and ERβ) and membrane-bound receptors such as GPER (G protein-coupled estrogen receptor). These receptors are expressed in virtually all organs, including brain, cardiovascular system, bone, skin, immune cells, and adipose tissue [21].

Similarly, progesterone actions are affected throughout the body via nuclear receptors (PR-A and PR-B) and other classes of receptors, or a combination of both [22]. Activation of progesterone receptors leads to transcriptional activity regulation, which in turn leads to longer-lasting responses. These responses involve progesterone receptor membrane components (PGRMC) and membrane progestin receptors (mPRs).

In the context of aging, the ubiquity of estrogen and progesterone receptors translate into the importance of their impact on general health before and after menopause. With menopause, the sudden withdrawal of sex steroids leads to systemic disturbances, disrupts multiple homeostatic systems and accelerates degenerative aging (Table 2).

Table 1. Highlighted Activities of Estrogen and Progesterone on Hallmarks of Aging.

Hallmark	Estradiol and Progesterone Effects
Genomic Instability	Estrogens can promote genomic stability by regulating DNA damage response and DNA repair mechanisms [63]. However, estrogen can also induce DNA damage and genomic instability, particularly through R-loop formation and excessive proliferation. This ability has been connected to resistance to breast cancer therapy [63].
Telomere Attrition	Human telomerase reverse transcriptase (hTERT) gene is a target of both estrogen and progesterone. Sex hormones acting on the TERT gene increase telomerase activity and Tamoxifen, a selective estrogen receptor modulator, was demonstrated to reduce telomerase activity [64]. Telomere lengths were longer in postmenopausal women who had a history of long-term HRT than in postmenopausal women without HT [65].
Epigenetic Alterations	Estrogen alters DNA methylation patterns in a tissue- and age-dependent manner, impacting gene expression related to inflammation and cellular stress. Interactions among ER-alpha, the SRC proteins and p300/CBP indicate a specific role for the SRC and p300/CBP coactivators, as well as targeted histone acetylation, in ERalpha-mediated transcription [66]. E2 deprivation leads to a global downregulation in gene expression, and more specifically of TET2 demethylase that may be involved in the DNA hypermethylation following short-term E2 deprivation [67]. Progesterone, via progesterone receptor (PR)-dependent pathways and through alternative receptors, such as membrane-associated PRs (distinct from the classical PR), can modulate gene actions particularly in genes associated with neuroplasticity and mitochondrial function [68].
Loss of Proteostasis	Estrogen promotes protein synthesis by fine-tuning the expression of the eukaryotic translation initiation factor 3 subunit f (eIF3f) [69].

	Estrogen enhances proteostasis by upregulating heat shock proteins which assist in proper protein folding, prevent the aggregation of misfolded proteins, and aid in protein degradation, all crucial for cellular health [70].
Dysregulated Nutrient Sensing	Estrogen regulates nutrient sensing by modulating the insulin/IGF-1 signaling pathway. Estrogen receptor activation enhances insulin sensitivity and reduces circulating IGF-1 levels, thereby mimicking calorie restriction-like metabolic effects [71]. Estrogen activates AMPK (AMP-activated protein kinase), a key energy sensor, and regulates energy balance and metabolism. This interaction can influence processes like thermogenesis in brown adipose tissue, potentially impacting energy expenditure and body weight [72]. Progesterone affects glucose metabolism by inhibiting glucose uptake through various steps of insulin signaling [73].
Mitochondrial Dysfunction	Estrogen promotes mitochondrial biogenesis and function through transcription of nuclear respiratory factor-1 (NRF-1, NRF1) which are critical for oxidative phosphorylation and ATP production, as well as reduces mitochondrial ROS production and preserves mitochondrial membrane potential, contributing to cellular energy stability during aging [74]. Estrogen modulates PINK1/Parkin-dependent mitophagy, enhances mitophagy and upregulates autophagy related genes like LC3B, BNIP3 and Beclin-1 [74]. Progesterone supports mitochondrial integrity by regulating expression of mitochondrial transcription factor A (TFAM) and inhibiting cytochrome c release, thereby reducing apoptosis and promoting cell survival under stress [75].
Cellular Senescence	Estrogen inhibits cellular senescence by modulating the expression of senescence-associated genes, protecting against DNA damage and promoting mitophagy [76]. Estrogen decreases circulating senescence markers in postmenopausal women [77]. Progesterone can induce cellular senescence and can involve the upregulation of senescence-associated cell cycle inhibitors. The induction of senescence by progesterone can have both beneficial (endometrium, ovarian cancer) and detrimental effects [78].
Stem Cell Exhaustion	Estrogen stimulates stem cell division, in hematopoietic stem cells, embryonal stem cells, and mesenchymal stem cells [79]. Estrogen deficiency has been linked to compromised maintenance and self-renewal of muscle stem cells, leading to impaired regeneration [80]. Progesterone modulates the differentiation of stem and progenitor cells. Converts hormone receptor-positive cells to a more stem-like state, which may have implications for tissue regeneration and cancer development [81].
Altered Intercellular Communication	Estrone increases intracellular cell-to-cell communication by increasing connexin [82] and gap junctional intercellular communications. Progesterone modulates immune responses and reduces inflammation, thereby maintaining a conducive environment for cellular interactions reproductive tissues and the immune system [83].
Chronic Inflammation	Estrogen has critical anti-inflammatory activity through inhibition of inflammatory mediators, such as monocyte chemoattractant protein-1, macrophage inflammatory protein-2, and TNF-alpha, induced by lipopolysaccharide in the brain [84]. Estrogens exhibit an anti-inflammatory effect that is associated with improved outcomes during severe infection and wound healing and repair [85]. Progesterone downregulates the induction of inflammatory reactions, the activation of immune cells and the production of cytokines, which are critical mediators of immune responses [86].
Dysbiosis	Estrogen and gut dysbiosis, an imbalance of gut bacteria, have a complex, bidirectional relationship (estrobolome). Estrogen helps maintain microbial diversity and intestinal barrier integrity by promoting the growth of beneficial commensal bacteria such as Lactobacillus and Bifidobacterium, which are involved in mucosal immunity and metabolic regulation. Dysbiosis can affect estrogen levels and, conversely, estrogen levels can influence the gut microbiome leading to multiple morbidities of aging [87]. Progesterone might exert indirect influence on the microbiome, especially during pregnancy, when elevated levels alter microbial composition to favour metabolic adaptation [88].
Compromised Extracellular Matrix Integrity	Estrogen preserves extracellular matrix (ECM) structure by stimulating fibroblast production of collagen, elastin, and hyaluronic acid via ERα activation, particularly in skin, vasculature, muscles, tendons, bone and the intervertebral disc [89]. Progesterone influences ECM remodelling and homeostasis, particularly in reproductive tissues. It likely exerts similar activities in aging connective tissue [90].

Estrogen and progesterone effects on the hallmarks of aging (Table 1)

The concept of the "hallmarks of aging" was first proposed in 2013 and expanded in 2023 to provide a unifying framework for understanding the biological mechanisms underlying aging [14, 23]. This concept emerged from the need to categorize the complex, conserved processes that contribute to age-related functional decline across species and integrate cellular,

molecular, and systemic mechanisms that drive aging and age-associated diseases. The known geroprotective clinical effects of HRT can be viewed in relation to the effects of estrogen and progesterone on the "hallmarks of aging" (Fig. 1). Table 1 highlights these key biological activities. The emerging wide-ranging regulatory health effects of estrogen and progesterone position them conceptually as important modulators of female longevity and healthspan which will need to be supported by future clinical data. These effects involve complex interactions with multiple cellular and biological pathways, a comprehensive analysis of which exceeds the scope of this article and will be addressed in a subsequent dedicated review.

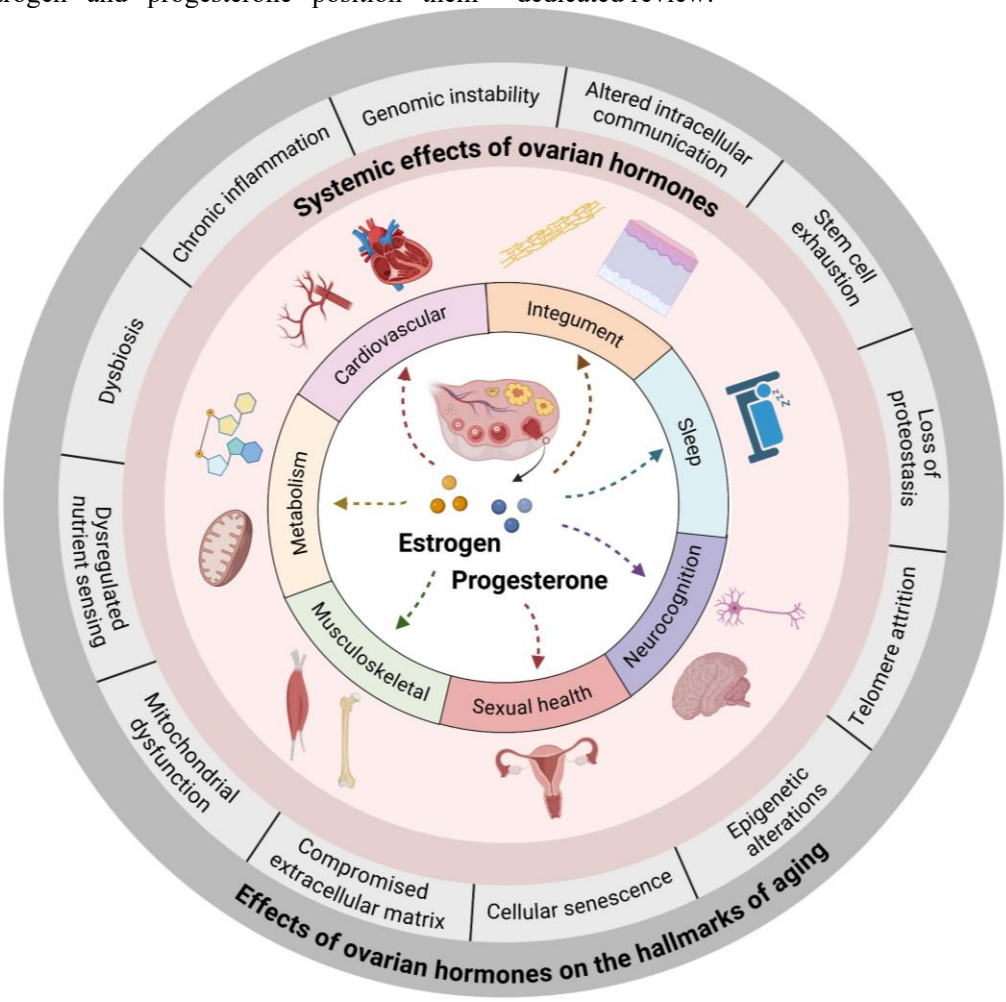

Figure 1. The effects of estrogen and progesterone on hallmarks of aging.

Estrogen actions *in vitro* have demonstrated to enhance genomic stability, support telomere maintenance, modulate epigenetic patterns, and promote mitochondrial efficiency, preserve proteostasis, suppress chronic inflammation, and maintain intercellular communication and extracellular matrix integrity (Table 1). Estrogen exerts multifaceted geroprotective effects across the 12 hallmarks of aging through genomic and non-genomic signaling. It helps preserve genomic stability by enhancing DNA repair pathways and reducing oxidative DNA damage, while modulating telomere attrition via upregulation of telomerase in certain tissues. In epigenetic regulation, estrogen influences DNA methylation, histone acetylation, and chromatin remodeling, thereby maintaining youthful transcriptional patterns [24]. Estrogen supports proteostasis by promoting autophagy, reducing endoplasmic reticulum stress, and stabilizing protein turnover [25]. It contributes to mitochondrial function through improved biogenesis, ATP production, and antioxidant defenses, mitigating deregulated nutrient sensing by sensitizing insulin, IGF-1, AMPK, and mTOR pathways [2, 26]. Estrogen reduces cellular senescence and SASP (Senescence-Associated Secretory Phenotype) production, thereby lowering chronic inflammation, and helps maintain stem cell exhaustion by supporting proliferation and survival signals in neural, hematopoietic, and mesenchymal stem cells [27, 28]. Estrogen modulates dysbiosis through effects on gut

barrier integrity and microbiome composition [29]. Progesterone action complements these benefits by modulating autophagy, maintaining general hormonal and immune balance, and supporting tissue regeneration and stem cell homeostasis. Together, these hormones could help preserve cellular resilience, metabolic equilibrium, and systemic integrity to mitigate aging effects. Furthermore, both clinical and basic research emphasize that the type and route of estrogen and progesterone administration significantly affect these biological processes [30].

Clinical Evidence Supporting the Role of HRT for Healthy Longevity (Table 2)

There is a growing body of clinical evidence that estrogen and progesterone exert many healthy effects [3]. Table 2 presents a summary and the relevant literature of human data on the geroprotective effects of HRT on multiple organ systems in midlife women. In addition, studies have demonstrated that HRT is cost-effective at USD 2438 per QALY (quality-adjusted life-years) gained and when started early, there is an average gain of 1.5 QALY [31].

Table 2. A Summary of Selected Geroprotective Effects of HRT.

Body system	Beneficial Effect	When to initiate
Cardiovascular Health	Early HRT: Reduces progression of atherosclerosis, coronary events and all-cause mortality [7, 91]. The differences in vascular biology between men and women are related to the cardiovascular and metabolic action/effects of sex steroid hormones [92]. HRT is cost-effective at USD2438 per QALY gained and when started early, there is an increase of 1.5 quality-adjusted life-years [31].	Perimenopausal transition or within 10 years post-menopause
Postmenopausal osteoporosis	Observational studies and randomised trials demonstrated that HRT reduces vertebral and hip fractures by approximately 34% [1-3, 8]. Long-term benefits persist after cessation, with no rebound in fracture risk observed in some cohorts [93]. Transdermal estrogen may provide significant musculoskeletal benefits with a safer profile [94].	Menopause
Sleep quality	Evidence from meta-analyses confirms that HRT with 17β-estradiol improves sleep quality, particularly among women experiencing vasomotor symptoms [95]. Transdermal estrogen delivery appears to confer greater benefit over oral routes [95]. Micronized progesterone has shown efficacy in enhancing sleep quality by reducing sleep onset latency and improving subjective sleep outcomes and in combination with transdermal estradiol to mitigate menopausal sleep disturbances [96].	Perimenopause and menopause
Neurocognition	Estradiol therapy improves verbal memory, working memory, and visuospatial skills when hormone therapy is initiated near the onset of menopause, supporting the timing hypothesis [1-4, 18]. Estradiol enhances sleep spindles, facilitating memory consolidation during non-REM sleep [97]. Progesterone has a broad spectrum of neuroprotective effects in the brain [98].	Perimenopause and early menopause
Metabolic health	HRT, particularly estrogen therapy, has gained recognition for its role in improving metabolic health when initiated early during perimenopause [99]. Early HRT may help counteract increased adiposity, insulin resistance, and other metabolic dysregulations associated with aging [100]. Menopause-related metabolic dysfunction accelerates aging-related diseases, and HRT-mediated metabolic stabilisation could improve both quality of life and lifespan through secondary prevention of coronary heart disease [101].	Perimenopause and menopause

Sexual health	Initiating HRT early in the perimenopausal phase may mitigate symptoms of Genitourinary Syndrome of Menopause (GSM), thereby enhancing sexual function and overall quality of life [102]. Early HRT improves vaginal health with estrogen therapy, and whether systemic (17β-Estradiol) or localised (Estriol), has been shown to enhance vaginal lubrication, elasticity, and blood flow while reducing dyspareunia [103]. Combined estrogen-testosterone therapy has demonstrated greater sexual satisfaction compared to estrogen alone [104].	Perimenopause

Based on these data, we embrace the conclusion of Taylor et al. (2025) that the current guidelines on the initiation of HRT need to be more inclusive of women outside the symptomatic thresholds [12]. As clinicians and scientists involved in healthy longevity medicine, and based on the beneficial effects demonstrated for HRT, we conclude that HRT should be a geroprotective and a strategic intervention to extend healthspan in women by preventing chronic health conditions exacerbated by estrogen deficiency (e.g., osteoporosis, metabolic dysfunction, and vascular aging). The integration of biological aging markers into clinical decision-making repositions HRT from a reactive, symptom-based therapy to a foundational protective strategy in proactive, precision-based longevity care for women.

Nevertheless, each medical intervention needs to be evaluated for its potential benefits and risks. While menopausal HRT provides significant symptomatic and systemic benefits, its use has been associated with several potential risks. These include an increased risk of venous thromboembolism (VTE), particularly with oral estrogen preparations, an elevated incidence of stroke and coronary events in older women initiating HRT more than 10 years after menopause [32], and a modest but increased risk for breast cancer with combined estrogen–progestin therapy with prolonged use (>5 years) [33]. Endometrial hyperplasia and carcinoma risk also increases with unopposed estrogen therapy in women with a uterus if not counterbalanced by adequate progestogen administration [34].

Recent data refuted some of these concerns. Subgroup analyses from the Women's Health Initiative (WHI) and findings from the ELITE trial support the "timing hypothesis", indicating that the risks of HRT are substantially lower, and potential cardiovascular benefits greater, when therapy is initiated within 10 years of menopause or before age 60 years [35]. Overall mortality and cardiovascular morbidities appear to be neutral or even slightly reduced in these younger cohorts. Furthermore, transdermal estrogen formulations and micronized progesterone are associated with a more favorable safety profile regarding VTE, stroke, breast cancer and metabolic effects [36, 37].

Estrogen-only therapy is appropriate in hysterectomized women, whereas combined estrogen/ progesterone is required for endometrial safety in women with an intact uterus [38]. However, inclusion of progesterone may also be biologically relevant for geroprotection: in a recent study loss of both estradiol and progesterone at menopause has been linked to increased senescence-associated phenotypes in preclinical models which attenuated senescence markers and tissue degeneration by combined HRT [39]. Progesterone may also contribute to musculoskeletal and neurobehavioral health through bone remodeling (greater BMD gains reported with estrogen–progestogen vs estrogen alone) and sleep/brain effects [40, 41]. Cohort analyses reported different breast cancer risks with different progestogens, with lower risk estimates observed for regimens using micronized progesterone compared with several synthetic progestins [37] . Thus, it seems that micronized progesterone should currently be the preferred progesterone in a geroprotective protocol.

Perimenopausal and postmenopausal women should be offered HRT and counselled after evaluating personal and genetic contraindications in addition to addressing their personal attitudes and wishes. Integrating HRT into longevity strategies also demands addressing disparities in access and cultural biases that currently limit uptake. For example, racial (i.e., differences in menopausal onset and severity) [42] and socioeconomic (i.e., lifestyle, stress, smoking, nutrition) factors influence menopause timing, symptom severity and HRT prescribing patterns, necessitating equitable implementation.

Future large-scale trials must continue evaluating HRT's effects on aging trajectories, including cognitive resilience, metabolic homeostasis, and resulting all-cause mortality across diverse populations. In addition, studies should explore whether synergies between HRT and other geroprotective therapies to optimize protocols for healthy aging in women. For instance, combining low-dose HRT with repurposed agents as Metformin or SGLT-2 agonists could enhance metabolic benefits while mitigating potential risks of conventional HRT use [43, 44].

Healthy longevity medicine has been adopting various aging biomarkers to assess epigenetic, inflammatory and immunologic, metabolic, cardio-

vascular and cognitive states [45]. The combined use of these aging biomarkers should enable clinicians to tailor the type, dosage, and mode of HRT delivery to better match and modulate individual aging trajectories.

Thus, weighing the available evidence, it supports an approach when HRT is initiated early in the perimenopausal period to achieve the expected benefits of HRT on women's healthy longevity. HRT, when individualized, appropriately timed, and correctly formulated, improves quality of life, preserves neurocognition, muscle, bone and cardio-metabolic health, reducing all-cause mortality in women [12, 35, 46].

Biomarker-Guided HRT Optimization

A personalized approach to menopause management increasingly relies on multidimensional biomarker profiling that captures biological aging trajectories beyond chronological age [47]. Epigenetic clocks such as GrimAge [48], DunedinPACE [49], and PhenoAge [50] can quantify systemic aging acceleration and help identify women who may benefit from earlier or more proactive intervention, although their integration into routine clinical practice still requires consensus and longitudinal validation. Inflammatory biomarkers including hsCRP, IL-6, and TNF-α provide insight into chronic low-grade inflammation that often rises in the menopausal transition and may modify both symptom burden and cardiovascular risk [51, 52]; however, their variability necessitates cautious interpretation. Metabolic markers such as HOMA-IR, fasting insulin, and detailed lipid subfractions can differentiate women with emerging insulin resistance or atherogenic lipid phenotypes, helping tailor HRT regimens toward safer and more metabolically favorable profiles [53]. Cardiovascular aging measures, including pulse wave velocity and endothelial function assays, offer mechanistic insight into vascular stiffness and endothelial decline, yet their availability remains limited outside specialized centers [54] Bone turnover biomarkers such as CTX and P1NP, reflecting type I collagen resorption and formation respectively, allow dynamic assessment of bone remodeling[55]. Emerging neurocognitive and sleep biomarkers, including digital phenotyping and objective sleep metrics, may help stratify women at risk of cognitive decline or severe insomnia during the menopausal transition, though normative datasets are still evolving [56]. Finally, ovarian aging markers, particularly AMH levels and FSH dynamics, can inform the tempo of reproductive aging and refine the timing of HRT initiation, while acknowledging that these markers exhibit considerable interindividual variability [57, 58]. In Table 3, we grouped the biomarkers that are the most applicable in the HRT-suitability context, by physiological domain and by clinical readiness (whether they are clinically available, translational, or research-grade). Together, these biomarker domains underscore both the promise and current limitations of a precision-medicine framework for menopause mapping, highlighting the need for integrative algorithms rather than reliance on any single measure.

Table 3. Proposed biomarkers of aging applied in clinical decision making for HRT application in perimenopause.

Domain	Biomarker / Measure	Type	Clinical Availability	Relevance to Aging / HT Evaluation
Epigenetic / Molecular	GrimAge, PhenoAge, Horvath clocks	DNA methylation clocks	Research-grade / emerging	Estimate biological age and mortality risk; useful for longitudinal intervention studies
Epigenetic / Molecular	DunedinPACE	Pace-of-aging metric	Research-grade	Sensitive to short-term intervention effects
Metabolic	HbA1c, Fasting glucose, insulin	Glycemic control, Insulin resistance markers	Clinical routine	Reflects metabolic aging and cardiometabolic risk, Tracks metabolic resilience and intervention response
Inflammatory	hs-CRP, IL-6,	Systemic inflammation, Pro-inflammatory cytokine	Clinical / research	Widely validated inflammatory aging marker, Associated with inflammaging and functional decline
Physiological / Functional	Grip strength, Gait speed / TUG	Muscle function, Mobility performance	Clinical	Strong predictors of morbidity, mortality, and biological aging
Physiological / Functional	Frailty index	Composite clinical score	Clinical	Integrative measure of physiological reserve
Vascular	Blood pressure, Carotid IMT	Hemodynamic marker, subclinical atherosclerosis	Clinical routine	Core cardiovascular aging parameter, Sensitive marker of vascular aging

Neurocognitive	Cognitive test batteries	Neurocognitive function	Clinical / research	Tracks brain aging and cognitive resilience
Digital / Wearables	Sleep architecture metrics	Digital biomarker	Emerging / clinical	Reflects neuro-aging and circadian health
Composite / Multi-domain	Multi-omic aging indices	Integrated biomarker panels	Research-grade	High predictive value for biological age and intervention responsiveness

Regulatory Landscape, Access and Risk-Benefit-Stratification

The recent U.S. FDA regulatory actions have revised menopausal HRT labelling, initiating removal of most boxed warnings and reframing HRT as a systemic individualized, timing-dependent intervention [59]. These changes were based on a re-evaluation of WHI data, in which 18-year follow-up showed no increase in all-cause, cardiovascular or cancer mortality and a more favorable mortality profile in women who initiated therapy between ages 50 and 59 years [60]. Randomized and observational studies, demonstrated that HRT started near menopause can reduce coronary events and all-cause mortality with low absolute rates of breast cancer, stroke and venous thromboembolism, supporting the "timing hypothesis [61, 62]. This official FDA update is expected to lessen clinician hesitation, reduce medicolegal concerns, and improve appropriate access to HRT for symptomatic midlife women.

Risk–benefit stratification is central to our proposal to use HRT as a geroprotective intervention rather than solely as treatment for symptoms. Therefore, candidates must be assessed individually according to age, time since menopause, baseline cardiometabolic status, breast and endometrial cancer risk, venous thromboembolism history, and personal and family history of cardiovascular disease and hormone-sensitive malignancies. Our proposal agrees with the WHI study by emphasizing the "timing hypothesis": WHI enrolled mainly older women with higher baseline risks, often many years beyond menopause. We propose initiation of HRT to younger, recently menopausal, otherwise healthy women, in whom vascular biology, atherosclerotic burden, and global risk profiles are fundamentally different. Table 4 categorizes patients into low, intermediate, and high-risk tiers based on commonly available clinical variables; it is intentionally presented as a pragmatic scaffold rather than a validated scoring system, intended to guide individualized decision-making and stimulate future validation.

Table 4. Proposed general risk stratifications when considering HRT in perimenopause.

Risk Tier	Example Characteristics	Clinical Implication
Low Risk	Age <60, <10 years since menopause, BMI <30, normotensive, no CVD, non-smoker	Candidate for early HRT consideration
Intermediate Risk	Mild metabolic syndrome, family history of CVD, former smoker	Individualized HRT with enhanced monitoring
High Risk	Prior VTE, stroke, active malignancy, uncontrolled CVD	HRT generally not recommended

Prescribing HRT as a preventive intervention in a non-disease state demands robust informed consent, including explicit discussion of known and potential risks, the uncertainty around long-term geroprotective benefits, and the current limitations of the evidence base. At this stage, this approach should include well designed, long-duration clinical trials and registries, with continued re-evaluation of the outcome.

Conclusion

Evidence supports a need for a paradigm shift in HRT guidelines, emphasizing early initiation, safer formulations, and personalized approaches to maximize longevity benefits. Basic research and clinical evidence support perimenopausal therapeutic administration of estrogen and progesterone for women without clinical contraindications. When applied in a personalized and evidence-based manner, HRT may target core aging mechanisms, offering a promising strategy to extend healthspan and prevent age-related decline. Positioning HRT as a geroprotector rather than solely for symptom relief reframes its value within the broader context of healthy aging. To unlock its full potential in healthy longevity medicine, future research should prioritize long-term outcomes, elucidate underlying biological mechanisms, and promote equitable access, ultimately advancing a more proactive and inclusive approach to women's health across the lifespan. In the future, the parallel challenges and opportunities in developing geroprotective strategies for men should be pursued. Currently, due to the unique biology of the female

menopause transition provides a clearer interventional window and a stronger existing evidence base for hormone-based interventions.

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