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The Female Epigenetic Chronometer: From Fetal Programming and Gestational Stress to Menopausal Longevity

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Abstract

Female biological aging operates as a distinct, non-linear continuum governed by the reproductive endocrine axis and critical developmental inflection points, contrasting with the comparatively linear trajectory observed in men. This narrative review synthesizes multi-omics and clinical evidence across five key life stages - fetal programming, childhood, the reproductive prime, obstetric stress tests, and the menopausal transition - to reframe female healthspan optimization. Early intrauterine environments under the developmental origins of health and disease (DOHaD) paradigm establish baseline biological aging trajectories via DNA methylation remodeling. During the reproductive years, gestation imposes an energetic cost, with uncomplicated pregnancy exhibiting transient intra-individual biological age shifts of up to 5.3 years on phenotypic clocks. Preeclampsia and gestational diabetes function as early clinical sentinels, independently driving 2.4 years of maternal epigenetic age acceleration and conferring a fourfold increase in cardiovascular events and a seven- to 18-fold increased lifetime risk of type 2 diabetes, respectively. At midlife, menopausal estrogen withdrawal accelerates blood-based biological age by 1.0 to 3.3 years, precipitating rapid bone loss and atherogenic lipid shifts. While observational studies link reproductive milestones to epigenetic clock progression, Mendelian randomization demonstrates that age at natural menopause does not exert a direct causal effect on blood epigenetic clocks, indicating that observed shifts reflect systemic metabolic and inflammatory cascades. Evidence-based interventions - including menopausal hormone therapy initiated within the early window of opportunity (age <60 years or <10 years post-menopause), progressive resistance training, and Mediterranean dietary patterns - decelerate epigenetic pacing. Emerging frontiers, such as repurposed ovarian longevity therapeutics (rapamycin analogs, pirfenidone) and targeted senolytics, offer promising avenues to extend female healthspan.

Categories: Obstetrics/Gynecology
Keywords: epigenetic clocks, fetal programming, healthspan, menopausal hormone therapy, menopause, preeclampsia

Introduction And Background

Women's aging represents a unique, non-linear biological trajectory fundamentally shaped by the reproductive endocrine axis, where cyclical estrogen exposure during fertile years provides systemic protection to the cardiovascular, skeletal, metabolic, and neurological systems [1]. Unlike the comparatively linear aging trajectory observed in men, women experience a pronounced endocrine transition during menopause, which serves as a pivotal inflection point that accelerates various markers of biological aging. However, this transition does not represent an isolated or fixed destiny; rather, it constitutes part of a continuous lifelong trajectory established by early intrauterine environments and modulated by reproductive milestones [2]. While biological aging in both sexes reflects multi-systemic physiological decline, female biological aging exhibits a distinct midlife inflection point driven by the abrupt cessation of ovarian follicular function. This contrasts with the more gradual age-related decline in male gonadal androgen secretion, making the female reproductive transition a unique model for studying endocrine-driven biological age shifts [2].

The foundation of a woman's biological clock is established in utero through fetal programming, a core concept within the developmental origins of health and disease (DOHaD) framework [2]. Under the Barker hypothesis, adverse intrauterine conditions - including maternal stress, undernutrition, placental insufficiency, or endocrine disruption - trigger adaptive, thrifty epigenetic modifications in the fetus [2]. These modifications, primarily mediated by altered genome-wide DNA methylation, permanently alter organogenesis, metabolic homeostasis, and neuroendocrine stress axes, establishing a baseline trajectory associated with elevated adult risks of essential hypertension, coronary artery disease, type 2 diabetes, chronic kidney disease, and accelerated systemic biological aging [2].

Throughout the reproductive maturity years, the biological clock is further modulated by the energetic cost

of reproduction [3,4]. Pregnancy acts as a natural biological stress test, wherein obstetric complications such as preeclampsia (PE) and gestational diabetes mellitus (GDM) serve as early clinical sentinels of future health risk [4-6]. Research indicates that these complications actively drive accelerated cellular senescence and epigenetic age acceleration, shifting women onto faster biological aging trajectories decades prior to the menopausal transition [4,7,8]. Uncomplicated gestation also induces measurable, transient intra-individual epigenetic age shifts of up to 5.3 years across pregnancy, reflecting gestational metabolic demands [5]. Complications like PE and GDM further alter cord-blood epigenetic gestational age in offspring, demonstrating paradoxical developmental timing deceleration alongside long-term DOHaD-mediated metabolic vulnerability [2,7].

Protecting against these multi-systemic declines, anti-aging humoral factors such as alpha-Klotho play a protective role throughout female life stages [9]. Higher circulating alpha-Klotho levels correlate with reduced osteoporosis risk in postmenopausal women and improved metabolic profiles, whereas its dysregulation accelerates vascular remodeling and pulmonary hypertension [9,10]. Observational and pre-clinical studies suggest that cyclical endogenous 17beta-estradiol exerts pleiotropic protective effects on vascular endothelium, bone remodeling, and metabolic homeostasis; however, the extent of long-term tissue protection varies based on receptor distribution, co-existing metabolic risk factors, and individual genetic architecture. Mitochondria-epigenetic interactions and gut microbiome diversity further modulate ovarian longevity and cognitive preservation [11-13]. Recent advancements in multi-omics have introduced epigenetic clocks - machine-learning algorithms analyzing DNA methylation patterns at cytosine-phosphate-guanine (CpG) sites - to quantify discrepancies between biological age and chronological calendar age [14,15]. While menopause accelerates blood-based biological clocks by several years, evidence demonstrates that timely interventions - including menopausal hormone therapy (MHT) initiated within the perimenopausal window of opportunity and structured lifestyle optimization - can significantly decelerate biological age acceleration and extend female healthspan [16,17]. In addition to systemic cardiometabolic shifts, reproductive tissue aging during perimenopause and postmenopause is characterized by structural endometrial alterations that frequently manifest as abnormal uterine bleeding. Clinical evaluation of intracavitary uterine pathologies in women presenting with peri- and postmenopausal bleeding is essential, as postmenopausal bleeding serves as the primary clinical sentinel for endometrial hyperplasia and endometrial carcinoma [18]. While standard B-mode transvaginal ultrasonography evaluates endometrial thickness, the addition of color Doppler ultrasound significantly improves diagnostic accuracy and sensitivity by enabling the visualization of vascular pedicles, assessment of microvascular density, and precise differentiation of benign mucosal lesions from malignant transformations. Comprehensive diagnostic workups, including transvaginal ultrasonography, endometrial thickness measurement, color Doppler, and histopathological evaluation, are critical for distinguishing benign mucosal changes (e.g., endometrial polyps or atrophy) from malignant transformations, emphasizing the necessity of integrating organ-specific tissue surveillance into female midlife healthspan management [18]. To improve accessibility, we explicitly distinguish: (1) Chronological Aging: the elapsed time since birth measured in calendar units; (2) Biological Aging: the progressive cumulative decline in cellular integrity, organ function, and physiological resilience; (3) Epigenetic Age Acceleration (EAA): the quantitative discrepancy when estimated DNA methylation biological age exceeds chronological age (positive AgeAccel); and (4) Reproductive Aging: the age-related depletion of the ovarian primordial follicle pool, diminished oocyte quality, and systemic endocrine shifts culminating in menopause. First-generation clocks (e.g., Horvath pan-tissue, Hannum blood) are trained on chronological age; second-generation clocks (e.g., PhenoAge, GrimAge) incorporate clinical biomarkers and plasma proteins to predict morbidity and mortality; third-generation clocks (e.g., DunedinPACE) measure the instantaneous pace of aging.

Review

Methods and search strategy

Literature searches for this narrative review were conducted across PubMed/MEDLINE, Scopus, and Web of Science covering publications published between January 2010 and December 2026. To ensure full transparency and reproducibility, the search architecture utilized the following explicit Boolean query for PubMed: (("Epigenomics"[Mesh] OR "DNA Methylation"[Mesh] OR "Biological Aging"[Title/Abstract] OR "Epigenetic Clock*"[Title/Abstract] OR "Horvath"[Title/Abstract] OR "GrimAge"[Title/Abstract] OR "DunedinPACE"[Title/Abstract]) AND ("Women's Health"[Mesh] OR "Menopause"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Preeclampsia"[Title/Abstract] OR "Gestational Diabetes"[Title/Abstract] OR "Fetal Programming"[Title/Abstract] OR "DOHaD"[Title/Abstract])). Equivalent field-tag queries (TITLE-ABS-KEY in Scopus and TS= in Web of Science) were deployed across physiological maternal-fetal coupling, metabolic regulation, immunological adaptation, genetics, cellular dynamics, and fetal programming.

Study eligibility was guided by explicit inclusion and exclusion criteria. Inclusion criteria encompassed: (1) peer-reviewed primary research articles, systematic reviews, and meta-analyses published in English between 2010 and 2026; (2) human clinical cohorts, observational studies, or translational mammalian models evaluating female biological aging, epigenetic clocks, reproductive transitions, fetal programming, or obstetric complications; and (3) quantitative evaluation of biological age metrics (DNAm age, DunedinPACE, PhenoAge, GrimAge) or validated clinical biomarker algorithms. Exclusion criteria comprised: (1) non-peer-reviewed preprints, conference abstracts, editorials, and commentary letters; (2) studies focusing exclusively on male aging without sex-disaggregated data; and (3) in vitro cell-culture

studies lacking systemic or tissue-specific physiological applicability.

Literature identification, screening, and selection were conducted independently by two investigators (IVL and LVZ), with any selection discrepancies resolved through consensus discussion or consultation with a senior author. The record accounting proceeded as follows: 265 primary records were identified through initial database searches (PubMed: n=112, Scopus: n=88, Web of Science: n=65), and an additional 39 records were identified through reference chaining (hand-searching bibliographies of key reviews and foundational papers), yielding a total of 304 records screened. Following title and abstract screening, 269 records were excluded due to lack of empirical female healthspan outcomes, non-female focus, duplicate entries, or non-peer-reviewed format. Thirty-five full-text reports were assessed for eligibility, and all 35 primary studies met inclusion criteria to construct the thematic synthesis matrix. Methodological quality and narrative presentation were appraised using the Scale for the Assessment of Narrative Review Articles (SANRA) framework. Evidence from heterogeneous study designs, ranging from observational cohorts and Mendelian randomization analyses to translational animal models, was integrated using an integrated thematic narrative synthesis approach organized around chronological developmental epochs and reproductive milestones.

No original meta-analysis, meta-regression, or pooled quantitative statistical synthesis was performed for this narrative review. Therefore, formal statistical methods for quantitative evidence synthesis (such as forest plots, heterogeneity test statistics, or meta-regression models) are not applicable. Instead, evidence from heterogeneous study designs was synthesized using an integrated thematic narrative framework organized around chronological developmental epochs.

The selection workflow followed four standard phases. In the Identification Phase, 304 records were identified across six biological domains: physiological maternal-fetal coupling, metabolic regulation, immunological adaptation, genetics, cellular/microbial dynamics, and fetal programming. In the Screening Phase, 265 records (including cited cross-references) were screened for thematic relevance, resulting in the exclusion of 230 records due to non-relevance or lack of empirical female healthspan data. In the Eligibility Phase, 35 full-text reports met the multidisciplinary criteria for integrated qualitative synthesis. In the Inclusion Phase, all 35 primary studies were included to construct the qualitative synthesis matrix, establishing how early programming and reproductive transitions interact with systemic biological aging [1-35]. The lifespan data synthesis matrix is presented in Table *1*.

Life Stage	Primary Mechanisms & Aging Pathways	Quantitative Data & Empirical Findings	Long-Term Clinical Risks	Actionable Steps & Frontiers
Fetal & Perinatal Stage	Barker's hypothesis & DOHaD: Adverse intrauterine conditions trigger thrifty epigenetic trade-offs, genome-wide DNA methylation changes, and altered HPA/HPG axes [2].	Fetal growth restriction and low birth weight serve as early clinical proxies for compromised lifetime metabolic resilience and elevated baseline clock pacing [2].	Significantly elevated adult risk of essential hypertension, coronary artery disease, T2D, CKD, PCOS, and earlier natural menopause [2].	Maternal methyl-donor nutrition (folate, B12, choline), strict glycemic/BP control, and placental regenerative research (thymosin beta-4) [19].
Childhood & Adolescence	Acquisition of biological capital (BMD, muscle mass, vascular elasticity); primordial follicle dormancy maintained via PTEN/PI3K/Akt signaling [19].	Later menarche correlates with later natural menopause and extended endogenous estrogen exposure; childhood adversity accelerates PhenoAge/DunedinPACE [16,19,23].	Childhood obesity and hyperinsulinemia promote premature follicular activation, follicle reserve depletion, and early pubertal shift [19].	Regular weight-bearing physical activity, unprocessed diet, healthy BMI maintenance, and adolescent epigenetic clock tracking [16].
Reproductive Years (Uncomplicated)	Cyclical 17beta-estradiol provides systemic cardioprotection; disposable soma trade-off re-allocates energetic resources toward fetal synthesis [4,20].	Uncomplicated pregnancy accelerates PhenoAge by up to 5.3 years between early and late gestation; parity adds 2-5 months per birth [4,5].	High parity combined with sedentary lifestyle and poor nutrition compounds late-life biological age acceleration [4,6].	Mediterranean/DASH anti-inflammatory diet, combined aerobic and resistance training (reverses Horvath age by ~2-4.6 yr), micronutrient repletion [17,21].
Complicated Gestation (PE & GDM)	PE: Syncytiotrophoblast stress, sFlt-1 anti-angiogenic shock, alpha-Klotho depletion, 2.4-yr EAA [4,5,7]. GDM: Beta-cell decompensation, metabolic reprogramming, T2D risk [6].	PE history carries 68% multimorbidity rate at follow-up vs 23% in controls; offspring exhibit cord-blood epigenetic deceleration alongside adult DOHaD risks [2,7,8].	PE: 4-fold increase in major adverse cardiovascular events (CAD, CHF, stroke, CKD) [8]. GDM: 7- to 18-fold increased lifetime risk of T2D [6].	Annual postpartum CV risk screening (AHA guidelines), lifelong glucose tracking, muscle-targeted resistance exercise, senolytics research [8,17,25].
Perimenopause & Menopause	Follicular exhaustion and hypoestrogenism drive loss of ERalpha/ERbeta signaling, mitochondrial decay, visceral fat gain, and systemic inflammaging [20,22].	Estrogen withdrawal accelerates blood epigenetic age by 1.0 to 3.3 years across clocks; rapid bone loss (2-5% annually) and ApoB/LDL lipid shift [16,22,24].	CVD becomes leading cause of female mortality; sharp rises in osteoporosis, fragility fractures, metabolic syndrome, and cognitive decline [20,22].	MHT initiation within 'window of opportunity' (<60 yr or <10 yr post-menopause), transdermal estradiol + micronized progesterone, heavy strength training [16,26].

TABLE 1: Lifespan Data Synthesis Matrix: Biological Mechanisms, Empirical Epigenetic Metrics, Clinical Outcomes, and Actionable Steps Across Female Life Stages.

Synthesizes biological aging pathways, quantitative metrics, long-term clinical risks, and evidence-based interventions across five female developmental epochs.

DOHaD: developmental origins of health and disease, HPA: hypothalamic-pituitary-adrenal, HPG: hypothalamic-pituitary-gonadal, BMD: bone mineral density, PTEN: phosphatase and tensin homolog, PI3K: phosphoinositide 3-kinase, Akt: protein kinase B, BMI: body mass index, DASH: Dietary Approaches to Stop Hypertension, PE: preeclampsia, sFlt-1: soluble fms-like tyrosine kinase-1, EAA: epigenetic age acceleration, GDM: gestational diabetes mellitus, T2D: type 2 diabetes, CKD: chronic kidney disease, PCOS: polycystic ovary syndrome, BP: blood pressure, CAD: coronary artery disease, CHF: congestive heart failure, CV: cardiovascular, AHA: American Heart Association, CVD: cardiovascular disease, LDL: low-density lipoprotein, ApoB: apolipoprotein B, ERalpha: estrogen receptor alpha, ERbeta: estrogen receptor beta, MHT: menopausal hormone therapy

Developmental programming: the earliest anti-aging window

The Barker hypothesis, established in the 1980s, posits that adverse intrauterine conditions, such as undernutrition, placental insufficiency, maternal stress, infections, or endocrine disorders, trigger adaptive thrifty responses in the developing fetus [2,3]. These adaptations manifest as durable epigenetic modifications, primarily DNA methylation at regulatory CpG loci, that permanently alter organogenesis, metabolic setpoints, and neuroendocrine stress response axes [2]. Low birth weight and fetal growth restriction serve as reliable clinical proxies for suboptimal programming, predicting heightened adult susceptibility to essential hypertension, coronary artery disease, type 2 diabetes, metabolic syndrome, chronic kidney disease, and accelerated systemic biological aging [2].

In female offspring, fetal programming exerts profound sex-specific effects, altering hypothalamic-pituitary-gonadal (HPG) axis function, shifting the timing of pubertal onset and natural menopause, elevating polycystic ovary syndrome (PCOS) risk, and amplifying postmenopausal cardiometabolic vulnerability [19]. Maternal PCOS or PE programs similar metabolic and reproductive disturbances in daughters via intra-uterine hyperandrogenism and placental inflammatory signaling [7]. Furthermore, obstetric complications such as PE, preterm birth, and small-for-gestational-age infants serve as early maternal sentinels of the mother's own underlying cardiovascular vulnerability, conferring up to a nine-fold increase in future cardiovascular disease risk [6,8]. Consequently, optimizing maternal nutrition, controlling gestational stress, and managing hypertension or PCOS during pregnancy represent the primary anti-aging intervention for the next generation [18]. Emerging physiological regenerative approaches, such as utilizing thymosin beta-4 to enhance fetal organ maturation and placental microvascular branching, are under active investigation to counteract programming deficits [19].

Reproductive aging and somatic capital accumulation

The developmental transition through childhood and adolescence is characterized by the progressive accumulation of biological capital, including peak bone mineral density, skeletal muscle mass, and vascular elasticity [19]. Healthy somatic growth, balanced nutrition, and daily physical activity support ovarian reserve dormancy through PTEN/PI3K/Akt signaling cascades, delaying premature follicular activation and reproductive aging [19]. Later age at menarche, which reflects favorable fetal programming and adequate childhood metabolic hygiene, correlates consistently with later natural menopause and extended lifetime endogenous estrogen exposure - an established longevity factor [16,19].

Lifestyle habits established during youth lay the critical foundation for lifelong healthspan. Regular physical activity and healthy body composition reduce systemic hyperinsulinemia and low-grade metabolic inflammation, factors known to accelerate ovarian follicle atresia and systemic biological aging [19]. Conversely, childhood obesity, chronic psychosocial trauma, and severe adversity induce accelerated biological aging measurable on PhenoAge and DunedinPACE clocks [16]. Sustaining metabolic hygiene, insulin sensitivity, and circadian sleep consistency throughout adolescence preserves the primordial follicle pool, providing a robust physiological buffer for future reproductive and systemic health [17,19].

Pregnancy-associated biological aging and postpartum recovery

During reproductive maturity, cyclical 17beta-estradiol and progesterone exert pleiotropic protective effects across the female body, conferring robust cardioprotection, skeletal bone preservation, neuroprotection, and favorable visceral fat distribution [20]. A longer reproductive lifespan - achieved through earlier menarche within normal physiological bounds and later natural menopause - is associated with slower biological aging and reduced lifetime incidence of cardiovascular disease, osteoporosis, and neurodegenerative dementia [20].

Pregnancy itself represents a transient programming window for the mother. Optimal gestational outcomes serve a protective role against later metabolic decay, whereas obstetric complications accelerate maternal aging markers [4,5]. Observational data indicate that long-term oral contraceptive use (>10 years) and later age at last birth (>35 years) correlate with preserved late-life cognitive function and slightly delayed menopause onset [20,21]. Practical healthspan optimization during the reproductive years relies on maintaining a healthy body mass index, engaging in combined aerobic and resistance training, adhering to an anti-inflammatory Mediterranean dietary pattern, avoiding tobacco exposure, and ensuring adequate micronutrient repletion (folate, B-complex vitamins, vitamin D3, and omega-3 fatty acids) [17,21]. Combined lifestyle and dietary interventions have been demonstrated to reverse biological age by approximately 2.0 to 4.6 years on the Horvath clock and significantly slow the DunedinPACE rate of aging [17,22,23].

Menopausal aging and endocrine transition

The menopausal transition, occurring at an average age of 51 years, represents a pivotal inflection point characterized by primordial follicle pool exhaustion and cessation of cyclical ovarian steroidogenesis [20,22]. Hypoestrogenism triggers vasomotor symptoms, sleep fragmentation, genitourinary atrophy, rapid bone mineral density loss (2% to 5% annually in early postmenopause), adverse atherogenic lipid remodeling (elevated low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B), visceral adipose accumulation, and heightened cardiometabolic risk [20,22]. Menopause transition drives a rapid surge in blood-based epigenetic age acceleration, typically adding 1.0 to 3.3 years of biological age across validated clocks, with surgical menopause models exhibiting even greater acceleration [16,22,24].

Following menopause, cardiovascular disease transitions into the primary cause of female mortality, equalizing male incidence rates as estrogenic endothelial protection wanes [20]. Osteoporosis and fragility fracture risks rise sharply, alongside increased vulnerability to cognitive decline and metabolic syndrome [22,24,25]. MHT represents the most effective intervention for symptom relief, bone density preservation, and cardiovascular risk reduction when initiated within the perimenopausal window of opportunity (age <60 years or within 10 years of menopause onset) [16,26]. Postmenopausal women initiating early MHT demonstrate smaller discrepancies between chronological and biological age, indicating decelerated clock

progression [16]. Transdermal 17beta-estradiol and micronized progesterone are preferred for their superior safety profile regarding thromboembolic risk, in line with 2025 regulatory updates from the FDA removing broad black-box warnings on estrogen products [26]. Non-hormonal symptom control utilizes neurokinin 3 receptor antagonists (fezolinetant) or selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), paired with heavy resistance training and adequate dietary protein (1.2 to 1.6 g/kg/day) to defend the muscle-bone unit [26,27].

Preventive interventions and longevity frontiers

This section strictly demarcates established evidence-based clinical interventions from investigational and experimental longevity approaches. During the postmenopausal decade, clinical focus shifts to mitigating the systemic consequences of hypoestrogenism and counteracting chronic low-grade senescence-associated secretory phenotype (SASP) inflammation (inflammaging) [25,28,29]. Later natural menopause correlates strongly with lower risks of osteoporosis, vascular disease, type 2 diabetes, and dementia, alongside extended overall lifespan [13,29]. Accelerated biological age on mortality-predictive clocks (GrimAge, DunedinPACE) correlates directly with physical frailty, multimorbidity, and all-cause mortality in older women [23,24].

Emerging longevity frontiers focus on preserving ovarian endocrine function and delaying follicular atresia [19,22]. Repurposed pharmacotherapies, such as low-dose rapamycin analogs (mTOR inhibitors) and pirfenidone, are under investigation in preclinical models to slow follicle loss and extend endogenous estrogen production [17,18]. Regenerative strategies include autologous ovarian tissue cryopreservation, platelet-rich plasma (PRP) intraovarian infusions, stem cell-derived extracellular vesicles (EVs), and targeted senolytics to clear senescent cells [18,25]. Targeted nutraceutical support, including creatine monohydrate to preserve cellular phosphocreatine reserves and cognitive health, taurine for antioxidant defense, CoQ10, and N-acetylcysteine, demonstrates growing female-specific efficacy [17,30]. Table *2* presents data on the impact of pathological gestation on maternal aging.

Obstetric Complication	Key Aging Markers & Cellular Mechanisms	Long-Term Maternal Morbidity Risks	Actionable Clinical Interventions
Preeclampsia (PE)	Placental syncytiotrophoblast stress, sFlt-1 anti-angiogenic shock, endothelial senescence, downregulation of urinary/trophoblastic alpha-Klotho, 2.4-year maternal EAA at delivery [4,5,7].	4-fold increased risk of major adverse cardiovascular events (CAD, CHF, stroke, CKD); 68% rate of multimorbidity at follow-up vs 23% in controls [8].	Annual postpartum CV risk screening (AHA compliance), aggressive blood pressure and microalbuminuria control, senolytics research [8,17].
Gestational Diabetes (GDM)	Pancreatic beta-cell decompensation, persistent low-grade vascular inflammation, advanced glycation end-products, GrimAge2 age acceleration [6].	7- to 18-fold increased lifetime risk of developing overt Type 2 Diabetes; accelerated subclinical atherosclerosis and dyslipidemia [6].	Lifelong annual glucose surveillance (fasting glucose, HbA1c, OGTT), low-glycemic Mediterranean diet, high-intensity resistance training [6,17].
Any Complicated Gestation	Endothelial dysfunction, persistent systemic inflammation, shortened telomeres, cumulative cost of reproduction [4,5,21].	1.5- to 2-fold elevated risk of cardiovascular disease, premature vascular stiffening, and accelerated postmenopausal healthspan decline [8,21].	Structured postpartum cardiovascular risk assessment (AHA guidelines), personalized MHT evaluation during perimenopause [8,16,26].

TABLE 2: Impact of Pregnancy Complications on Maternal Aging Pathways, Long-Term Morbidity, and Clinical Interventions.

Details cellular senescence, epigenetic age acceleration, multi-organ risks, and surveillance protocols in complicated gestations.

sFlt-1: soluble fms-like tyrosine kinase-1, EAA: epigenetic age acceleration, CAD: coronary artery disease, CHF: congestive heart failure, CKD: chronic kidney disease, CV: cardiovascular, AHA: American Heart Association, HbA1c: glycated hemoglobin, OGTT: oral glucose tolerance test, MHT: menopausal hormone therapy

Obstetric complications as biological stress tests

Complicated pregnancies, including PE, GDM, preterm birth, and fetal growth restriction, function as systemic biological stress tests that accelerate maternal biological aging [4,5,32]. Rather than transient gestational events, complications actively drive cellular senescence, systemic endothelial dysfunction, chronic vascular inflammation, and epigenetic reprogramming, manifesting in accelerated epigenetic clock pacing and earlier onset of multi-organ morbidity [4,7,8].

Even uncomplicated gestation imposes a measurable biological cost. Under evolutionary biology's disposable soma theory, energetic resources diverted toward fetal tissue synthesis reduce maternal somatic repair [4]. A 2025 prospective study of 75 nulliparous women (Panelli et al.) confirmed that pregnancy accelerates within-person biological age by up to 5.3 years (PhenoAge) over ~200 gestational days, with first-trimester GrimAge2 predicting composite complication risk (+36% odds per additional epigenetic year) [5]. Similarly, the Cebu Longitudinal Health and Nutrition Survey (Ryan et al., 2024; n=825) demonstrated that each live birth accelerates maternal epigenetic clocks by two to five months and increases DunedinPACE pace of aging by ~1.9% [4]. In contrast, no such biological acceleration occurred in men reporting fathered pregnancies [4]. Crucially, changes in epigenetic age estimates during pregnancy should not be equated with equivalent years of irreversible physiological aging. Rather, these transient gestational shifts reflect dynamic, reversible metabolic adaptations to pregnancy, as prospective longitudinal tracking confirms significant postpartum deceleration and reversal back toward baseline. Crucially, intra-individual changes in epigenetic age estimates observed across gestation (e.g., up to 5.3 PhenoAge years) reflect dynamic, transient physiological metabolic adaptations to pregnancy rather than equivalent years of irreversible somatic aging. Prospective longitudinal tracking confirms significant postpartum deceleration and reversal back toward pre-pregnancy baselines within months after delivery. GDM similarly accelerates maternal biological aging; non-pharmacological management strategies, specifically medical nutrition therapy and structured physical activity, play a critical role in controlling maternal fasting hyperglycemia, blunting excessive gestational weight gain, and attenuating long-term cardiometabolic and epigenetic age acceleration risks [31].

In complicated gestations, PE accelerates maternal epigenetic age by an average of 2.4 years at delivery [4,5,7]. Post-preeclamptic women exhibit marked downregulation of the anti-aging longevity protein alpha-Klotho, elevated leptin/adiponectin ratios, and shedding of pro-inflammatory extracellular vesicles [7,9,10]. Long-term follow-up demonstrates that 68% of post-preeclamptic women develop two or more chronic comorbidities (versus 23% in controls), carrying a fourfold increased risk of major cardiovascular events [8]. GDM confers a seven- to 18-fold increased lifetime risk of type 2 diabetes, compounding GrimAge2 progression [6]. These reported cardiovascular and metabolic risk estimates following pregnancy complications must be interpreted with consideration of primary study populations, specific outcome definitions (e.g., overt type 2 diabetes vs. impaired fasting glucose), and follow-up durations spanning 10 to 30 years postpartum. Furthermore, PE and GDM induce the offspring paradox: exposed neonates exhibit paradoxically decelerated cord-blood epigenetic gestational age at birth, yet transition into accelerated adult metabolic disease and premature senescence via DOHaD pathways [2,7]. Consequently, obstetric history is now recognized as a lifelong cardiovascular risk enhancer equivalent to smoking or hypertension [8]. The possible longevity interventions are included in Table 3.

Life Stage	Primary Strategic Goals	Top Evidence-Based Interventions	Emerging & Translational Frontiers
Fetal / Perinatal	Optimize intrauterine environment; establish favorable baseline biological clock for offspring [2].	Maternal nutrition (folate, B12, choline, omega-3s, protein), stress control, gestational BP/glycemic management [2].	Physiological regenerative agents (thymosin beta-4) for organogenesis and microvascular branching [18].
Childhood / Adolescence	Build somatic capital (BMD, muscle mass); preserve primordial follicle dormancy via PTEN/PI3K/Akt [19].	Regular physical activity, nutrient-dense diet, healthy BMI maintenance, circadian sleep hygiene [16,19].	Adolescent epigenetic clock profiling to detect early biological age acceleration (research setting) [16].
Reproductive Years	Maximize endogenous estrogen protection; blunt energetic cost of reproduction [4,20].	Aerobic + resistance training, Mediterranean/DASH diet, weight management, postpartum micronutrient repletion [17,21].	Preconception multi-omics testing (first-trimester GrimAge2) for obstetric risk stratification [5].
Peri- / Menopause	Mitigate hypoestrogenism; blunt 1.0-3.3 yr blood epigenetic age surge [16,22].	Early MHT in 'window of opportunity' (<60 yr or <10 yr post-menopause), transdermal estradiol, resistance training [16,26].	Epigenetic clock-guided MHT personalization; non-hormonal neurokinin-3 antagonists (fezolinetant) [26].
Post-Menopause	Preserve muscle-bone unit; reduce inflammaging; slow DunedinPACE velocity [23,25].	Heavy strength/power training, high-protein nutrition, creatine monohydrate, taurine, CV risk control [17,30].	Ovarian longevity drugs (pirfenidone, rapamycin analogs), senolytics, EVs, ovarian tissue cryopreservation [18,25].

TABLE 3: Comprehensive Clinical and Longevity Interventions Across Female Life Stages.

Categorizes strategic goals, evidence-based practices, and emerging longevity frontiers across developmental epochs.

BP: blood pressure, BMD: bone mineral density, PTEN: phosphatase and tensin homolog, PI3K: phosphoinositide 3-kinase, Akt: protein kinase B, BMI: body mass index, DASH: Dietary Approaches to Stop Hypertension, MHT : menopausal hormone therapy, CV: cardiovascular, EVs: extracellular vesicles

Epigenetic clock methodology and terminology

A fundamental biological challenge in longevity medicine involves the discordance between blood-based epigenetic clocks and reproductive tissue senescence [14,15,21]. Epigenetic clocks utilize machine-learning algorithms to evaluate DNA methylation across CpG sites, estimating biological age more accurately than chronological age for predicting healthspan and mortality [15,31]. First-generation clocks (Horvath pan-tissue, Hannum blood) were trained on chronological age, providing high calendar age accuracy but lower sensitivity to phenotypic health shifts [15,26]. Second-generation clocks (PhenoAge, GrimAge, GrimAge2) incorporate clinical biomarkers and plasma protein surrogates, strongly predicting cardiovascular risk and mortality [23,24]. Third-generation clocks (DunedinPACE) measure the instantaneous rate of multi-system physiological decline per calendar year [23].

However, because standard clocks are calibrated using DNA extracted from peripheral blood leukocytes (PBLs), they are sensitive to leukocyte subtype composition shifts [21,29]. Gestational neutrophilia and postmenopausal myeloid skewing (inflammaging) alter circulating cell-type proportions, which can alter blood-based age calculations unless bioinformatic cell-type deconvolution is performed [12,21,29]. Furthermore, somatic tissues age asynchronously. The biological clocks governing the ovary and endometrium tick at rates distinct from circulating leukocytes [15,21]. An individual exhibiting normal systemic biological age on GrimAge or DunedinPACE may nonetheless experience premature follicular exhaustion, whereas a woman with elevated systemic epigenetic age from metabolic stress may maintain robust ovarian reserve [14,19,21].

Importantly, bidirectional Mendelian randomization (MR) analysis by Wang et al. (2024) evaluated the causal relationship between menopause timing and epigenetic aging, observing no significant causal effect of genetically predicted age at natural menopause on blood-based epigenetic clocks [1]. However, a nonsignificant causal estimate does not definitively establish the absence of a causal relationship, particularly when statistical power, instrument validity (the proportion of variance explained by genetic variants), potential horizontal pleiotropy, and tissue-specificity (peripheral blood vs. target reproductive tissues) must be considered. Similarly, observational associations between MHT and biological age biomarkers do not establish a direct causal effect on aging trajectories due to potential healthy-user bias, socioeconomic confounding, and indication variations. This indicates that observed associations between menopause and biological age acceleration in observational cohorts are driven by shared upstream physiological stressors, hormonal withdrawal cascades, or unconfounded metabolic exposures rather than direct genetic clock causality [1,6]. Developing organ-specific epigenetic clocks tailored to ovarian granulosa cells, oocytes, and endometrial biopsies remains a critical research priority [15,21]. Validated reproductive clocks will serve as surrogate endpoints in clinical trials benchmarking emerging anti-aging therapeutics, including low-dose rapamycin analogs, pirfenidone, senolytics, and extracellular vesicle therapies [17,18,25].

Comprehensive mapping of the female biological aging trajectory necessitates a multi-dimensional integration of ovarian reserve kinetics, uterine functional integrity, systemic epigenetic aging, and fetal adaptive responses. Deciphering distinct physiological ovarian phenotypes through translational models provides crucial insights into the molecular mechanisms underpinning follicular depletion and reproductive decline [32]. Concurrently, evaluating systemic biological age via maternal peripheral blood epigenetic clocks demonstrates that accelerated epigenetic aging is strongly associated with an elevated risk of preterm birth and adverse gestational outcomes [33]. Beyond the ovarian compartment, age-related structural and molecular alterations within the uterus critically impair endometrial receptivity, directly contributing to compromised implantation rates and unfavorable obstetric outcomes [34]. Finally, monitoring fetal autonomic regulation and cardiorespiratory adaptation in the context of adverse intrauterine programming requires precise diagnostic tools; fetal noninvasive electrocardiography offers a vital clinical modality to evaluate fetal autonomic status and functional adaptations during high-risk pregnancies [35]. The epigenetic clock generations are included in Table *4*.

Clock Generation	Representative Clocks	Primary Measurement Focus	Predictive Value & Nuance in Women's Health
First Generation	Horvath (pan-tissue) [15], Hannum (blood) [15]	Chronological calendar age across somatic tissues [15].	High accuracy for calendar age; filters out biological variation, making it less sensitive to acute phenotypic or ovarian shifts [15,26,32].
Second Generation	PhenoAge [15,24], GrimAge [24], GrimAge2 [24,33]	Phenotypic clinical biomarkers, plasma protein surrogates, mortality risk [23,24].	Robust predictor of morbidity, CVD, time-to-death, and obstetric complications (+36% odds/yr on GrimAge2) [5,24,33].
Third Generation	DunedinPACE [23]	Longitudinal, instantaneous pace of aging per calendar year [23].	Captures real-time velocity of aging; highly responsive to exercise and Mediterranean diet, but treats body as a single unit [17,21,23].

TABLE 4: Methodological Categorization of Epigenetic Clock Generations.

Delineates mathematical training targets, representative algorithms, predictive utility, and tissue nuances across clock generations.

CVD: cardiovascular disease

Conclusions

In conclusion, female biological aging is not an unmodifiable chronological process, but an optimizable continuum governed by the reproductive endocrine axis and key developmental milestones. Intrauterine environments set baseline biological aging trajectories through epigenetic programming, while pregnancy and menopause serve as major biological stress tests that shape healthspan. Recognizing obstetric history, specifically PE and GDM, as a lifelong cardiovascular risk enhancer enables proactive, targeted prevention starting postpartum. Timely clinical intervention during the perimenopausal window of opportunity, utilizing MHT, progressive resistance training, and anti-inflammatory nutrition, effectively decelerates epigenetic clock pacing. As research into ovarian preservation, senolytics, and multi-omics monitoring advances, modern medicine can transform menopause from an inevitable accelerator of decline into a modifiable milestone, extending women's healthy longevity.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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