Journal of Women Health Care and Gynecology
2026 Volume 6, Issue 2
DOI: 10.59657/2993-0871.brs.26.110

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Reproductive Aging Through the Lens of GLP-1 Signaling

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Abstract

Reproductive aging has traditionally been attributed to declining ovarian reserve, germ cell damage, and progressive gonadal dysfunction. However, accumulating evidence indicates that reproductive aging is also closely linked to systemic metabolic dysfunction, chronic inflammation, and impaired cellular homeostasis. This article examines reproductive aging in both female and male reproductive systems through a systems-level aging framework and highlights glucagon-like peptide-1 (GLP-1) signaling as an important metabolic regulator influencing these processes. GLP-1 signaling improves insulin sensitivity, mitochondrial function, and inflammatory balance, thereby indirectly supporting ovarian and testicular physiology. Although GLP-1 signaling does not reverse intrinsic reproductive aging, it may significantly modulate the progression and clinical manifestation of reproductive decline.

Keywords: reproductive aging; GLP-1 signaling; metabolic dysfunction; inflammation; mitochondrial dysfunction; ovarian aging; male reproductive aging; hypothalamic-pituitary-gonadal axis; insulin sensitivity; cellular senescence; aging hallmarks; reproductive health; PCOS

Reproductive Aging as A Systemic Metabolic Process

Reproductive aging is one of the most predictable yet least modifiable aspects of human physiology. Although it has traditionally been linked to depletion of the ovarian reserve and germ cell damage, this process is increasingly being recognized within a broader biological framework [1-3]. Recent advances in aging research suggest that the decline in reproductive capacity reflects systemic disturbances in energy utilization, inflammation, and cellular repair pathways [4-6]. This emerging perspective positions reproductive aging as an important marker of overall health, with implications extending beyond fertility to metabolic dysfunction and the progression of age-related diseases. Aging across tissues is characterized by the progressive disruption of interconnected hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, dysregulated nutrient sensing, cellular senescence, and chronic inflammation [7]. These processes are linked through tightly integrated feedback networks. Mitochondrial dysfunction increases oxidative stress and accelerates genomic and epigenetic damage; chronic inflammation disrupts insulin signaling and metabolic homeostasis; and impaired nutrient sensing further reduces autophagy and cellular resilience [8-10]. Within this interconnected framework, reproductive aging may be viewed as an early and highly sensitive indicator of systemic network failure. Reproductive tissues are particularly dependent on metabolic stability. The hypothalamic-pituitary-gonadal (HPG) axis coordinates energy availability with reproductive hormone secretion, while gonadal function relies heavily on mitochondrial integrity, redox balance, and tightly regulated inflammatory signaling [11-13]. This dependence renders reproductive competence especially vulnerable to even subtle disturbances in metabolic homeostasis. Consequently, reproductive aging is shaped not only by intrinsic limitations of the germline but also by the cumulative effects of systemic metabolic and inflammatory dysregulation [3,14]. Within this systems-level framework, glucagon-like peptide-1 (GLP-1) signaling emerges as a mechanistically important upstream interface. Although traditionally studied in the context of glucose regulation and appetite control, GLP-1 receptor signaling also influences broader metabolic regulatory networks [15-17]. GLP-1 enhances intracellular cyclic adenosine monophosphate (cAMP) levels through Gs protein-coupled receptor activation and subsequently activates downstream pathways, including protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (Epac2). These pathways further engage phosphoinositide 3-kinase-protein kinase B (PI3K-Akt), AMP-activated protein kinase (AMPK), and mechanistic target of rapamycin (mTOR)

signaling, collectively regulating nutrient sensing, mitochondrial function, autophagy, and inflammatory responses across multiple tissues [18-21]. The central conceptual premise is that GLP-1 signaling functions not as a direct reproductive regulator, but rather as a systemic metabolic modulator capable of influencing multiple hallmarks of aging simultaneously. Improved insulin sensitivity reduces inflammatory and endocrine disturbances originating from adipose tissue, thereby stabilizing hypothalamic regulation of the reproductive axis [22,23]. Enhanced mitochondrial efficiency lowers oxidative stress, thereby supporting the cellular microenvironment in which reproductive tissues function [24,25]. In parallel, suppression of nuclear factor kappa B (NF-κB)-driven inflammatory signaling may help restore endocrine and paracrine balance across metabolic and reproductive systems [26,27].

Within the ovary, these systemic effects are most prominently reflected in granulosa cell function. Improved metabolic signaling promotes steroidogenic balance by reducing hyperinsulinemia-driven androgen excess and restoring follicular endocrine homeostasis [28,29]. At the intracellular level, activation of PI3K-Akt signaling enhances phosphorylation of forkhead box O1 (FOXO1), limiting its nuclear translocation and thereby suppressing pro-apoptotic gene programs while supporting granulosa cell survival [30,31]. Enhanced mitochondrial biogenesis and function, partly mediated through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), may improve energy availability within the follicular microenvironment, indirectly supporting oocyte quality and developmental competence [32,33]. Collectively, these mechanisms are particularly relevant in polycystic ovary syndrome (PCOS), where metabolic dysfunction, hyperandrogenism, and inflammation converge to accelerate features of reproductive aging [34,35]. In this context, GLP-1 signaling may attenuate the metabolic drivers that exacerbate reproductive decline without directly reversing intrinsic germline aging processes. Beyond the ovary, improvements in vascular and inflammatory signaling associated with GLP-1 activity may also influence uterine receptivity [36-38]. Enhanced endothelial nitric oxide signaling may improve tissue perfusion, while reduced inflammatory tone may support stromal function and decidualization [39,40]. However, these effects remain indirect and are likely secondary to correction of systemic metabolic dysfunction rather than direct modulation of uterine receptor signaling.

In the male reproductive system, GLP-1 signaling appears to act predominantly through systemic metabolic regulation [41,42]. Improved insulin sensitivity and reduced adiposity may help restore HPG axis function and support testosterone production by Leydig cells. Reduced oxidative stress may also preserve Sertoli cell integrity and maintain germ cell homeostasis [43,44]. Nevertheless, key features of male reproductive aging-including telomere attrition, meiotic errors, and cumulative DNA damage-remain largely unaffected, underscoring the limitations of metabolic intervention.

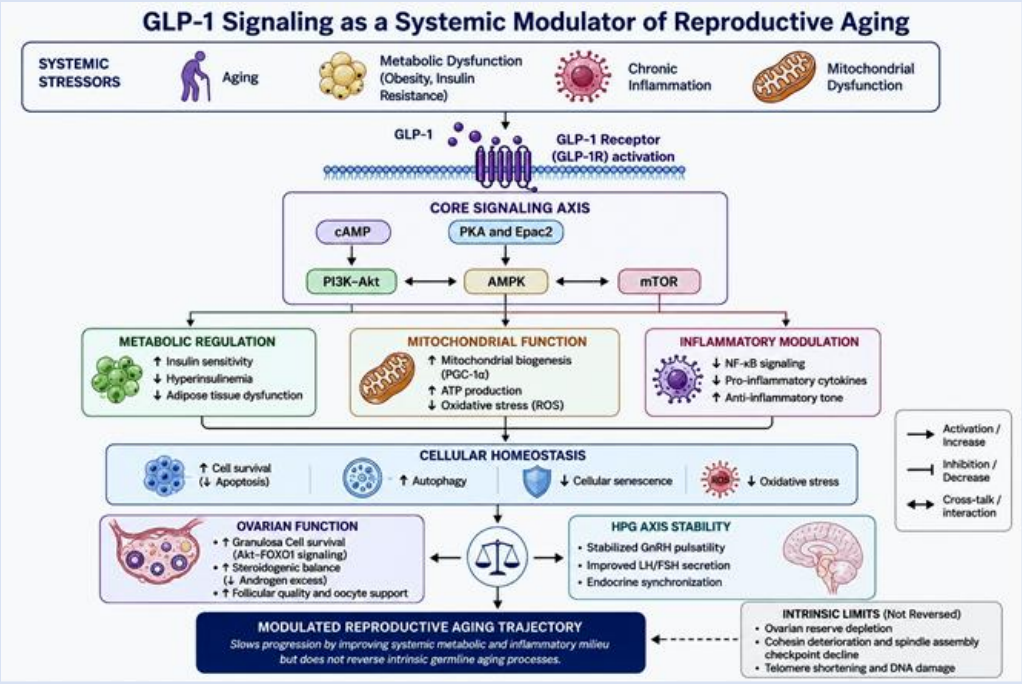

Figure 1: GLP-1 signaling as a systemic modulator of reproductive aging.

Aging-associated systemic stressors converge on GLP-1R activation, initiating cAMP-dependent signaling via PKA and Epac2 and integrating with PI3K-Akt, AMPK, and mTOR pathways. These interconnected axes coordinate metabolic regulation, mitochondrial function, and inflammatory control, converging on cellular homeostasis (enhanced survival and autophagy; reduced senescence and oxidative stress). At the tissue level, these effects support ovarian function and stabilize hypothalamic-pituitary-gonadal (HPG) axis dynamics. Overall, GLP-1 signaling acts as a systemic metabolic modulator that shapes–rather than reverses–the trajectory of reproductive aging within intrinsic biological limits. This figure was generated using ChatGPT (OpenAI, GPT-5.3) via text-to-image conversion and subsequently refined through manual editing for clarity and presentation.

Abbreviations: GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; Epac2, exchange protein directly activated by cAMP 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; FOXO1, forkhead box O1; HPG axis, hypothalamic–pituitary–gonadal axis; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ROS, reactive oxygen species.

Importantly, GLP-1 signaling operates within a broader nutrient-sensing network that regulates organismal aging, including AMPK, mTOR, sirtuins, and insulin/insulin-like growth factor 1 (IGF-1) pathways [45,46]. Within this integrated framework, GLP-1 receptor agonists function as systemic metabolic reprogrammers rather than tissue-specific reproductive agents [45,46]. Their influence on reproductive biology is therefore indirect, mediated through restoration of energy balance, mitochondrial efficiency, and inflammatory homeostasis across the organism. At the same time, reproductive aging remains constrained by irreversible structural determinants. In females, depletion of the finite ovarian reserve, deterioration of cohesin complexes accumulated during prolonged meiotic arrest, and decline of spindle assembly checkpoint fidelity represent fundamental biological limitations [47,48]. In males, the progressive accumulation of genomic instability and telomere shortening imposes comparable constraints [49,50]. These irreversible processes establish the biological boundaries within which metabolic interventions can operate.

In synthesis, GLP-1 signaling should not be regarded as a direct anti-aging pathway for reproduction, but rather as a metabolic interface linking multiple hallmarks of aging and shaping the systemic environment in which reproductive aging unfolds. Its role is therefore better understood as modulatory rather than restorative: GLP-1 signaling does not reverse intrinsic reproductive aging, but it may influence the rate and phenotypic manifestation of reproductive decline by recalibrating upstream metabolic and inflammatory networks.

Declarations

Conflict of Interest

The author does have anything to declare.

Funding

None.

Generative AI statement

The authors confirm that no content in this manuscript was generated by artificial intelligence (AI) tools without appropriate oversight. Any use of AI-assisted technologies (e.g., for language editing or formatting) has been transparently acknowledged, and the authors have reviewed and verified all content for accuracy, originality, and compliance with ethical standards. The authors take full responsibility for the work, including any errors or inaccuracies.

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Cite this article: Chakrabarti SK. (2026). Reproductive Aging Through the Lens of GLP-1 Signaling, *Journal of Women Health Care and Gynecology*, BioRes Scientia Publishers. 6(2):1-6. DOI: 10.59657/2993-0871.brs.26.110

Article History: **Received:** May 08, 2025 | **Accepted:** July 10, 2026 | **Published:** July 20, 2026