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Review

Combined Effects of Inflammation and Aging in Premature Ovarian Insufficiency: Unraveling Mechanisms and Advancing Therapeutic Strategies

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Abstract

Objectives: Premature ovarian insufficiency (POI) affects approximately 3.5% of women worldwide, and its pathogenesis is increasingly associated with the interplay of genetic, autoimmune, and environmental factors. This review aims to: (1) examine the synergistic effects of chronic inflammation and biological aging in accelerating ovarian reserve depletion; (2) evaluate the efficacy and limitations of current management strategies; and (3) explore the potential of emerging regenerative therapies, with an emphasis on integrating precision medicine frameworks in POI care. **Mechanism:** A systematic literature search was conducted across PubMed, Web of Science, and ClinicalTrials.gov from database inception to December 3, 2024. Search terms included combinations of "premature ovarian insufficiency", "primary ovarian insufficiency", "ovarian aging", "inflammation", "senescence", "therapy", and "regenerative medicine". The review encompassed preclinical studies, clinical trials, and meta-analyses. Publications were screened by title, abstract, and full text for relevance, with a focus on human studies and high-impact translational research that elucidates pathogenic mechanisms or therapeutic innovations. **Findings in Brief:** The pathogenesis of POI is critically driven by a self-reinforcing cycle wherein chronic inflammation, mediated via nuclear factor kappa B (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, interacts with cellular aging to amplify oxidative stress and follicular apoptosis. This process is further exacerbated by senescence-associated secretory phenotypes (SASPs). Current standard of care, such as hormone replacement therapy (HRT), effectively manages symptoms but shows limited efficacy in restoring ovarian function or fertility. Antioxidant therapies have yielded inconsistent outcomes. Emerging regenerative strategies, including stem cell therapies, exosomal microRNA (miRNA) delivery, and platelet-rich plasma (PRP) applications, demonstrate potential for ovarian rejuvenation in preclinical and early clinical studies, yet require further validation. **Conclusions:** Advancing POI management requires a shift beyond symptomatic relief toward targeting the underlying inflammation aging axis. Integrating multimodal therapies with biomarker-guided precision medicine represents a feasible strategy to disrupt the self-perpetuating disease cycle. Future research should prioritize robust clinical trials to validate regenerative approaches and establish patient-specific therapeutic algorithms, aiming not only to alleviate symptoms but also to preserve or restore ovarian function.

Keywords: premature ovarian insufficiency (POI); inflammaging; cellular senescence; oxidative stress; therapeutic strategies

1. Introduction

Premature ovarian insufficiency (POI) is a clinical syndrome defined by hypergonadotropic hypogonadism manifesting before the age of 40 years and represents a spectrum of ovarian dysfunction disorders [1]. The condition was first described in 1942 by Fuller Albright et al. [2], who introduced the term "primary ovarian insufficiency". The condition is now uniformly classified as POI following a multidisciplinary consensus facilitated by the National Institutes of Health (NIH) and the American Society of Reproductive Medicine [3].

At its core, inflammation is a coordinated response of the innate immune system to injury or infection, characterized by immune cell activation and the release of proinflammatory cytokines. These mediators orchestrate complex signaling cascades, regulate chemokine dynamics, and modulate genes governing critical cellular pathways, including meiosis, senescence, and apoptosis [4]. Within the ovarian microenvironment, inflammatory dysregulation can impair folliculogenesis and ovulation, compromise oocyte competence, and is increasingly implicated in the pathogenesis of POI. This association is further reinforced by the frequent presence of infection-triggered autoantibodies in patients with POI and by the potential for fluctuating estrogen levels to amplify inflammatory signaling, creating a self-perpetuating cycle that may accelerate disease progression [5].

The interplay between inflammation and organismal aging has attracted considerable scientific attention. Aging, characterized by progressive functional decline, is closely associated with a state of chronic, low-grade inflammation. Notably, a 2023 study identified inflammation as a central biomarker of aging, illustrating how inflammatory molecular patterns not only accompany but also actively drive cellular senescence and tissue aging, thereby intertwining the two processes in a bidirectional relationship [6].

This review synthesizes current understanding of the dynamic triad of inflammation, aging, and POI. It explores the mechanistic connections linking these elements and how their convergence contributes to ovarian pathophysiology. A critical appraisal of existing therapeutic strategies follows, addressing both their underlying rationale and limitations. By highlighting gaps in current management paradigms, this review proposes novel, targeted interventions designed to disrupt the inflammation-aging-POI axis. Ultimately, this work aspires to refine the conceptual framework around POI and support the development of more effective, mechanism-driven therapies.

2. Pathophysiology of POI

2.1 Definition and Clinical Presentation of POI

POI is a clinical syndrome diagnosed in women under the age of 40 years, characterized by the cessation of menses for at least 4–6 months, elevated serum follicle-stimulating hormone (FSH) levels, typically within the menopausal range, and reduced estradiol concentrations [7]. This condition reflects a profound depletion of the ovarian follicle pool. Notably, the peak number of oocytes is established during fetal development, at approximately 20 weeks of gestation, followed by a continuous decline throughout the reproductive life. Menopause marks the complete depletion of this follicular reserve. The pathogenesis of POI is thus conceptualized as arising from either a congenital deficiency in the initial primordial follicle count or an abnormally accelerated rate of follicular depletion [1]. Current research increasingly focuses on elucidating the immunological drivers of this process and on developing targeted immunotherapeutic strategies.

2.2 Epidemiology and Prevalence

A global meta-analysis published in Climacteric reported an overall POI prevalence of 3.5% among women. Subgroup analyses revealed notable variation, with the highest prevalence observed in cases of iatrogenic origin (11.2%) and autoimmune etiology (10.5%). Geographically, North America exhibited the highest prevalence (11.3%), followed by South America (5.4%). Interestingly, the prevalence was higher in developing countries (5.3%) compared with developed countries (3.1%). Although this difference was not statistically significant ($p > 0.05$), an increasing trend in prevalence over the past two decades has been observed [8]. The risk of POI is strongly age-dependent, rising from approximately 1 in 10,000 women aged 18–25 years, to 1 in 1000 among those aged 25–30 years, and further to 1 in 100 in the 35–40 age group. Familial aggregation is observed in approximately 15% of cases, underscoring a significant genetic contribution to its etiology [9].

2.3 Genetic, Environmental, and Idiopathic Factors Contributing to POI

The etiology of POI is multifactorial, encompassing genetic, autoimmune, iatrogenic, infectious, and environmental or lifestyle-related factors. Genetic causes can be broadly classified into chromosomal abnormalities and single-gene disorders. Turner syndrome (45,X) represents the most common chromosomal cause [9]. Numerous gene mutations have been implicated, including expansions of trinucleotide repeat sequences (e.g., *CGG* repeats) in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene (associated with fragile X premutation) [3], mutations in forkhead box L2 (*FOXL2*) [10], pathogenic variants in the SWIM domain-containing protein 7 (*ZSWIM7*) gene [11], and mutations in breast cancer gene (*BRCA*)1 and *BRCA2* [12], among others.

Epigenetic dysregulation constitutes another critical layer in the pathogenesis of POI. This includes alterations in DNA methylation, histone modifications, and the regulatory functions of non-coding RNAs (ncRNAs). Advanced genomic technologies, particularly next-generation sequencing (NGS), have accelerated the discovery of novel causative genes and ncRNAs involved in POI. Jiao et al. [13] proposed an integrative epigenetic framework to elucidate the molecular mechanisms underlying POI. DNA methylation, which involves the addition of methyl groups to cytosine residues within cytosine-phosphate-guanine (*CpG*) dinucleotides, is a key epigenetic modification that undergoes extensive reprogramming during germ cell development and senescence [14]. Aberrant methylation patterns can lead to gene silencing, disrupted transcription, and, ultimately, impaired ovarian function. Furthermore, dysregulation of specific microRNAs (miRNAs), including miR-146a [15], miR-181a [16], miR-127-5p [17], and miR-379-5p [18], has been consistently reported in POI. These miRNAs are thought to promote granulosa cell apoptosis and accelerate follicular atresia.

Beyond genetic and epigenetic factors, environmental exposures and lifestyle factors are increasingly recognized for their potential role in accelerating ovarian reserve decline [19]. Immune dysregulation is also closely linked to POI. The physiological processes of follicular rupture and the preovulatory luteinizing hormone (LH) surge are inherently inflammatory, involving controlled release of cytokines [5]. However, the precise mechanisms by which this physiological inflammation transitions into a pathological autoimmune state targeting the ovary remain poorly defined and constitute a vital area for future research.

2.4 Risk Factors and Their Converging Pathways in POI Pathogenesis

The etiology of POI is notably heterogeneous, with a substantial proportion of cases classified as idiopathic. Established risk factors, however, can be systematically categorized into several key domains: genetic factors (e.g., chromosomal abnormalities such as Turner syndrome, fragile X premutation, and mutations in genes critical for ovarian function), iatrogenic factors (including chemotherapy, radiotherapy, and ovarian surgery), autoimmune conditions, infectious causes, and environmental or lifestyle exposures. Notably, genetic and iatrogenic factors are each implicated in approximately 20–25% of cases each, whereas autoimmune conditions contribute to 4–30% of cases [20]. Emerging evidence underscores the significant role of epigenetic dysregulation and environmental toxicants. Despite their diverse origins, these risk factors are thought to converge on common pathogenic pathways, such as accelerated follicular atresia, granulosa cell apoptosis, and stromal damage, ultimately leading to depletion of the ovarian reserve and the clinical manifestation of POI.

3. Inflammation and Aging: Molecular and Cellular Mechanisms

3.1 Overview of the Aging Process and Its Impact on Ovarian Function

Cellular senescence is defined by an irreversible cell cycle arrest, accompanied by impaired cellular function, increased reactive oxygen species (ROS) production, elevated proinflammatory signaling, and the expression of senescence-associated markers such as β-galactosidase, p16, p53, and p21 [21]. This functional decline results from the lifelong, physiological accumulation of irreparable damage to biomolecules, an inevitable consequence of normal metabolism, and underscores the critical importance of cellular repair mechanisms. Within the ovary, the aging process is notably pronounced. Tarin's theory [22] posits that oocytes and granulosa cells exhibit a reduced capacity to neutralize ROS, a primary physiological inducer of cellular damage associated with aging [23]. It is important to recognize that aging is a systemic process, affecting not only the ovaries but also multiple organ systems, such as the lungs, which similarly undergo progressive functional decline over time [21].

With advancing age, the ovarian follicle pool progressively declines. This reduction is accompanied by decreased secretion of inhibin B, followed by reductions in estradiol and inhibin A levels. These hormonal shifts disrupt the tightly regulated feedback mechanisms regulating folliculogenesis. During the menopausal transition, a marked decrease in inhibin B results in elevated FSH levels, which in turn further accelerates depletion of the antral follicle cohort [24,25,26]. Ovarian aging ultimately culminates in ovarian failure, a phase clinically termed perimenopause, which is initiated when the follicular pool falls below a critical threshold [27] (Fig. 1).

The assessment of ovarian aging commonly relies on ultrasonographic measures, such as antral follicle count (AFC) and ovarian volume. Serum anti-Müllerian hormone (AMH) has emerged as a key biomarker for evaluating ovarian reserve, as its levels remain relatively stable throughout the menstrual cycle and correlate with the size of the remaining follicular pool [24]. In the early stages of ovarian aging, diminished follicular sensitivity to FSH leads to an inadequate ovarian response to physiological stimulation, manifesting as ovulatory dysfunction and menstrual cycle irregularities [24].

3.2 Role of Chronic Inflammation in Aging

In contrast to acute inflammation, chronic inflammation is characterized by a persistent, low-grade inflammatory state. Aging is intrinsically associated with this form of systemic chronic inflammation, which is linked to cellular senescence, immunosenescence, organ dysfunction, and the development of age-related diseases [28]. The connection between inflammation and aging was formally proposed as early as 1964 by Walford's immunological theory of aging [29]. This theory conceptualizes inflammation from an evolutionary perspective as a driver of immune senescence, describing a state of low-grade, chronic damage resulting from elevated systemic inflammatory levels. Key features include a declined immune response to both endogenous and exogenous antigens, reduced antitumor surveillance, and impaired clearance of senescent cells. Concurrently, the aging process itself inflicts damage upon the immune system, creating a self-reinforcing cycle that exacerbates immunosenescence [21].

Experimental evidence supports the role of chronic inflammation in tissue aging. For instance, Mei and Zheng [30] demonstrated that, in a postmenopausal mouse model of renal aging, animals exhibited inflammatory pathological changes, including glomerular enlargement, mesangial expansion, and inflammatory cell infiltration, providing mechanistic insight into how inflammation contributes to renal aging. In a separate study, You et al. [31] conducted a retrospective analysis showing that serum levels of Annexin A1 (ANXA1) are negatively correlated with age in humans. Complementary studies in mouse models revealed that ANXA1 expression decreases with age and is associated with vascular dysfunction. Notably, 68-week-old ANXA1 knockout mice exhibited worse vascular function than 100-week-old wild-type controls, highlighting the role of ANXA1 in mitigating age-related vascular decline [31].

3.2.1 Immune Cell-Driven Ovarian Microenvironment Disruption

Aging and POI are associated with a profound shift in the ovarian immune landscape. Specific immune cell populations infiltrate the ovary or undergo functional changes

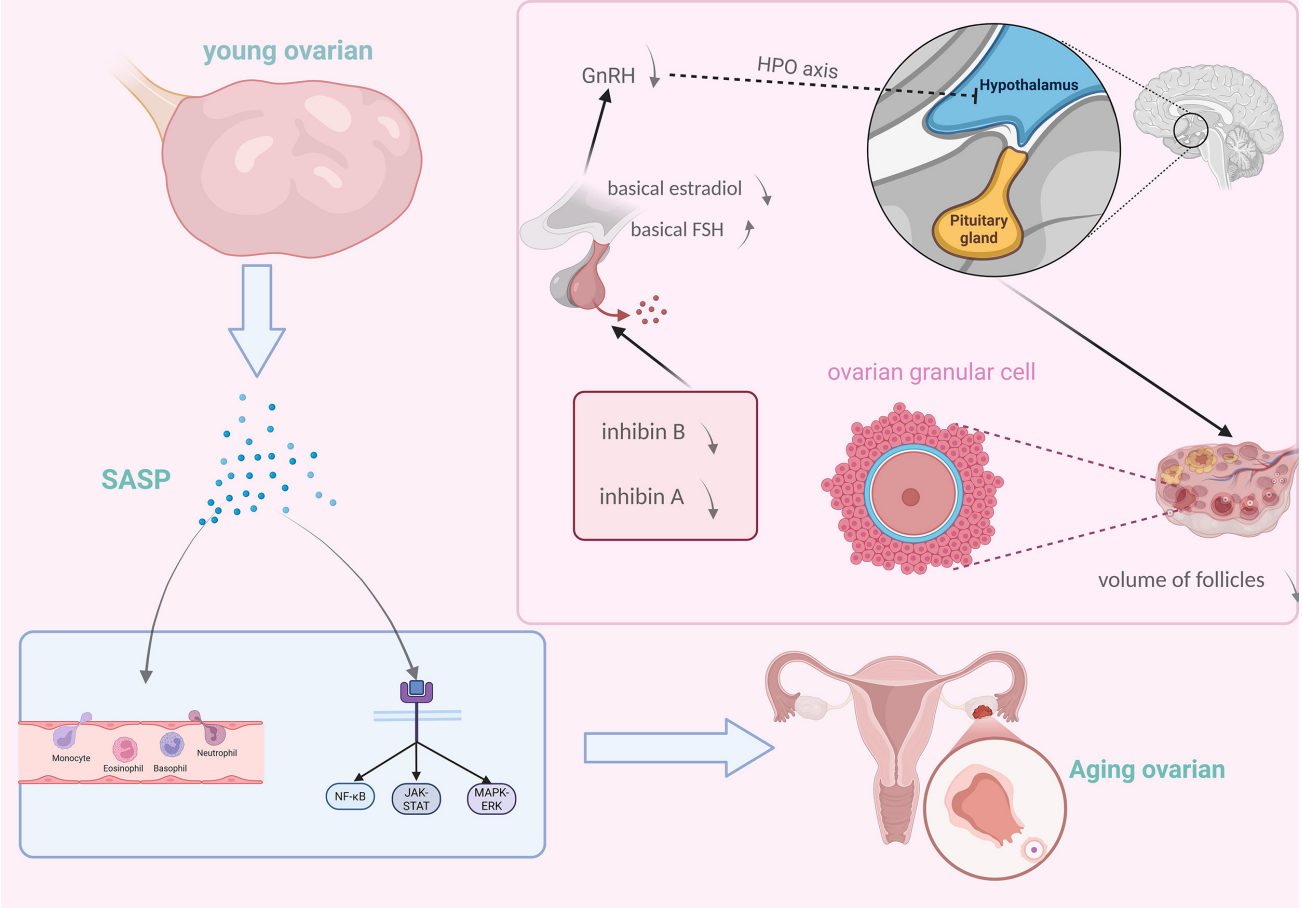

Fig. 1. Hormonal changes in the hypothalamic-pituitary-gonadal axis during aging human body. HPO, hypothalamic-pituitary-ovary; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; SASP, senescence-associated secretory phenotypes. The figure was created by BioRender (https://www.biorender.com/).

within it, actively contributing to a proinflammatory and prosenescent microenvironment.

3.2.1.1 Macrophages. Senescent or M1-polarized macrophages are a major source of proinflammatory cytokines (e.g., interleukin [IL]-1β, tumor necrosis factor-α [TNF-α]) and exhibit a high SASP index within the ovary. Their secretory profile directly disrupts follicular function and promotes the senescence of granulosa and stromal cells [32].

3.2.1.2 T Lymphocytes. Dysregulation of T helper cell subsets, particularly an imbalance between proinflammatory T helper 17 (Th17) cells and regulatory T cells (Tregs), is implicated in POI. This imbalance perpetuates local inflammation and may facilitate autoimmune attacks against ovarian antigens.

3.2.2 Autoimmune Conditions: A Systemic Etiology and Amplifier

Beyond local immune cell dysfunction, POI is frequently associated with systemic autoimmune diseases (e.g., Addison's disease, autoimmune thyroiditis). This connection represents a critical etiological pathway through which autoimmunity accelerates ovarian aging.

3.2.2.1 Systemic Inflammation. Autoimmune diseases create a state of chronic, systemic inflammation characterized by elevated levels of circulating cytokines and autoantibodies.

3.2.2.2 Ovarian Targeting. In susceptible individuals, this systemic milieu can lead to the production of anti-ovarian antibodies or the recruitment of self-reactive lymphocytes to the ovary, thereby initiating or exacerbating the local immune-mediated damage and inflammatory cascade described above [33]. This process establishes a vicious cycle in which systemic autoimmunity promotes local ovarian inflammation, which in turn amplifies further systemic immune dysregulation.

3.2.3 Inflammatory Cytokines, Mediators, and SASP

The actions of dysregulated immune cells and systemic autoimmunity converge at the molecular level through the sustained release of inflammatory factors. Inflammatory cytokines and mediators are signaling

molecules released primarily by immune cells and certain parenchymal cells [32]. During aging, their dysregulated overproduction can disrupt normal immune function. For example, injured endothelial cells can promote excessive hematopoietic stem cell (HSC) differentiation via IL-1 or TNF-α, potentially leading to HSC exhaustion [6]. Senescent cells, including macrophages, exhibit a pronounced SASP. SASP is a key mediator of the paracrine effects of senescent cells, comprising a complex mixture of ILs, chemokines, growth factors, and proteases. These factors can induce local inflammation, alter the tissue microenvironment, induce cell cycle arrest in neighboring cells, and contribute to systemic aging. In the ovarian context, a high SASP index in ovarian macrophages and T cells is implicated in disrupting the ovarian microenvironment and accelerating ovarian aging [32].

Among the most studied SASP factors are IL-1α and IL-1β, which promote an inflammatory milieu and immunosenescence. Another significant component is C-C motif chemokine ligand 2 (CCL2), the expression of which is regulated by IL-1 [32]. Furthermore, Barkaway et al. [33] demonstrated that elevated C-X-C motif chemokine ligand 1 (CXCL1) in aged mice impairs normal neutrophil migration across damaged tissues, thereby contributing to age-related decline in immune function.

3.2.4 Oxidative Stress and Cellular Damage

Hypoxia is a potent driver of cellular senescence [23]. Senescent cells secrete factors such as vascular endothelial growth factor (VEGF), which can activate pathways like hypoxia-inducible factor 1 (HIF-1) to promote cellular survival under low oxygen tension. However, this adaptive response is associated with reduced mitochondrial respiratory function [34]. The resulting age-related decline in mitochondrial efficiency often leads to increased electron leakage from the electron transport chain and elevated production of ROS. These ROS, in turn, can damage mitochondrial DNA (mtDNA) and proteins, thereby establishing a vicious cycle that further impairs mitochondrial function.

ROS are not solely damaging agents; within a physiological range, they act as crucial signaling molecules that regulate cellular processes and energy metabolism through the activation of transcription factors such as NF-κB and activator protein-1 (AP-1) [35]. Nevertheless, a persistent imbalance between ROS production and antioxidant defenses results in oxidative stress. This condition causes widespread macromolecular damage and may trigger the mitochondrial apoptotic pathway via cytochrome c release, ultimately leading to programmed cell death [36].

Oxidative stress is a well-established mechanism underlying the toxicity of exogenous agents, such as the chemotherapeutic drug cyclophosphamide (CP). Following administration, CP is primarily metabolized in the liver by cytochrome P450 enzymes, yielding the active metabolites phosphoramide mustard and acrolein. Phosphoramide mustard mediates the primary therapeutic (and cytotoxic) effect by inducing DNA interstrand cross-links. In contrast, acrolein contributes to tissue toxicity by depleting antioxidant defenses, generating additional ROS, and promoting lipid peroxidation. This cascade synergizes with endogenous oxidative processes, culminating in damage to DNA, membrane lipids, and other critical cellular components, which collectively drive cell injury [37,38].

3.3 Interaction Between Inflammation and Ovarian Aging

Depletion of the ovarian reserve is the fundamental cause of ovarian aging and a primary determinant of female reproductive senescence [39]. Follicular atresia, which drives the progressive reduction in follicle number, is a major contributor to this depletion. Research indicates a strong bidirectional relationship between inflammation and this process. For example, Cao et al. [40] showed that methyltransferase-like 3 (METTL3)-deficient mice developed a POI-like phenotype in which reduced levels of mature miR-21-5p led to increased expression and secretion of IL-1β in ovarian cells.

Lliberos et al. [41] reported elevated serum levels of proinflammatory cytokines (e.g., TNF) and inflammasome-related factors in aged mice. Intriguingly, genetic knockout of specific inflammasome components, namely nod-like receptor protein 3 (NLRP3) or autism spectrum conditions (ASC), resulted in a higher ovarian reserve and extended reproductive lifespan in aged mice. These effects were accompanied by reduced levels of cytokines like IL-6, IL-18, and TNF-α [41,42]. Human studies further corroborate this inflammatory axis. Machlin et al. [43] reported that cytokine concentrations in follicular fluid increase with advancing age in women. Babayev and Duncan [44] revealed that the ovarian microenvironment in women of reproductive age becomes enriched with proinflammatory factors (e.g., IL-3, IL-7, transforming growth factorβ1 [TGFβ1], macrophage inflammatory protein-1 [MIP-1]) with increasing age. Furthermore, Huang et al. [45] observed a positive correlation between serum C-reactive protein (CRP) levels and age in premenopausal women, independent of confounding factors such as diet.

Single-cell RNA sequencing analyses of ovaries from young and aged mice have further elucidated this interaction, revealing significant age-related differential gene expression in oocytes, granulosa cells, stromal cells, and ovarian immune cells (Table 1, Ref. [46,47,48]) [49].

Among the downregulated genes, Top2B (DNA topoisomerase II beta) is vulnerable to oxidative degradation, and its reduction serves as a sensitive indicator of oxidative DNA damage. Concurrently, the downregulation of GPX1 (glutathione peroxidase 1) and GSR (glutathione reductase) compromises the core ROS-scavenging system, leaving oocytes and granulosa cells exposed to peroxidative injury. In contrast, the upregulated genes—FCER1G, CD53, AIF1, and CX3CL1—point to immune activation and re-

Table 1. Cell types, genotype changes following aging, and specific gene-associated functional alterations identified by single-cell RNA sequencing.

Aging cell type	Labeled gene	Alterations in gene expression	Species	Function
Oocytes	*Top2B* [46]	Downregulation	Human	Decline of double-strand break repair following oxidative stress
	GPX1 and *GSR* [47]	Downregulation	Monkey	Decreased antioxidant function
Granular cell	*ELF4* and *FOSB* [47]	Downregulation	Monkey	Regulation of reductase activity
	FCER1G, *CD53*, *AIF1* and *CX3CL1* [47]	Upregulation	Human	Activation of myeloid leukocytes
Ovarian stromal cells	*XBP1* and *SELK* [48]	Upregulation	Mice	ER stress-induced apoptosis leading to follicular atresia
Endothelial cells	-	-	-	-
Ovarian smooth muscle cells	-	-	-	-

cruitment of inflammatory cells into the ovarian niche. Furthermore, the elevated expression of XBP1 and SELK reflects ER stress and compensatory responses; when excessive, these changes can disrupt calcium homeostasis and ultimately trigger granulosa cell apoptosis, leading to follicular atresia.

4. Signaling Pathways Involved in POI

4.1 Complex Dysregulation Patterns of Key Signaling Pathways in POI

The pathogenesis of POI involves a complex dysregulation of several key intracellular signaling pathways, namely NF-κB, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK). These pathways exhibit cell type, context, and stage-specific alterations rather than uniform hyperactivation or suppression.

4.1.1 NF-κB Pathway: A Double-Edged Sword in Ovarian Homeostasis

The NF-κB pathway is a central regulator of inflammation, immune response, and cell survival. Its role in POI is context-dependent, involving both loss-of-function during folliculogenesis and gain-of-function in chronic inflammation.

Pro-survival and pro-developmental role: In normal ovarian physiology, NF-κB activation is crucial during the transition from secondary to antral follicle. It upregulates gonadotropin receptors, promotes granulosa cell proliferation, and suppresses apoptosis via targets such as X-linked inhibitor of apoptosis (XIAP), thereby establishing a positive feedback loop essential for follicular growth and steroidogenesis [50,51]. Consequently, impairment of this function contributes to the development of POI. Lawrence [52] demonstrated that NF-κB inactivation in mice results in reduced follicle counts, impaired granulosa cell proliferation, increased apoptosis, and decreased hormone levels, culminating in a POI phenotype.

Proinflammatory and detrimental role: Conversely, in the context of immune activation or systemic inflammation, chronic and excessive NF-κB signaling in ovarian stromal and immune cells can drive a feedforward inflammatory loop, producing cytokines (e.g., IL-1β, TNF-α) that further disrupt the follicular microenvironment and accelerate follicular depletion [52]. This dual role explains why NF-κB inhibitors can be protective in immune-mediated POI models [53], whereas their activity remains essential during normal follicular development.

4.1.2 JAK/STAT Pathway: Guardian of Follicular Quiescence and Immune-Endocrine Interface

The JAK/STAT pathway transduces signals from a wide range of cytokines and hormones, serving as a pivotal link between the immune system and ovarian function.

Essential for primordial follicle maintenance: In the ovary, basal JAK/STAT signaling is critical for maintaining primordial follicle dormancy. Inhibition of JAK1/2 (e.g., with ruxolitinib) induces premature follicle activation and subsequent depletion, highlighting its protective role in preserving the ovarian reserve [54,55].

Mediator of inflammatory insult: Paradoxically, in autoimmune or inflammatory conditions associated with POI (e.g., Systemic Lupus Erythematosus [SLE]-like models), excessive cytokine signaling (e.g., type I interferons) through the JAK/STAT axis can create a hostile ovarian environment, impairing granulosa cell function and promoting apoptosis [56,57]. Therapeutic strategies, such as the formula Hu Yang Shenyang, have shown benefit in POI models, in part by normalizing JAK2-signal transducer and activator of transcription 3 (STAT3) overactivation [58].

4.1.3 MAPK/ERK Pathway: Integrator of Mitogenic and Stress Signals

The MAPK/ERK pathway responds to growth factors, hormones, and cellular stress, coordinating cell fate decisions critical for folliculogenesis.

Dysregulation in metabolic and genetic POI: Aberrant MAPK/ERK signaling has been implicated in POI associated with metabolic disorders (e.g., hyperactivation in PCOS endometrium [59]) and inborn errors of metabolism like galactosemia [60].

Therapeutic target for ovarian protection: Given its central role, this pathway represents a viable therapeutic target; compounds like epicatechin appear to alleviate POI symptoms partly by modulating oxidative stress through this pathway [61,62].

4.2 Integrated Crosstalk: Forming a Pathological Network in POI

The pathogenesis of POI is not driven by isolated pathway defects but by their extensive crosstalk among signaling networks, forming a self-sustaining system that bridges inflammatory triggers and aging-related functional decline (Fig. 2). Key integrative nodes include:

NF-κB and JAK/STAT mutual activation: This interaction represents a central mechanism of inflammatory amplification. Cytokines like TNF-α and IL-1β activate NF-κB, which in turn transcriptionally upregulates additional cytokines (e.g., IL-6) and their receptors. These ligands then activate the JAK/STAT pathway in an autocrine or paracrine manner. Conversely, STAT proteins, particularly STAT3, can promote the expression of NF-κB subunits [63], thereby creating a positive feedback loop that exacerbates chronic inflammation within the ovarian stroma [64,65].

MAPK/ERK as a common downstream effector and modulator: Both inflammatory cytokines (via receptor tyrosine kinases) and cellular stress can activate the MAPK/ERK. Once active, ERK can phosphorylate and potentiate the transcriptional activity of NF-κB and STAT3 [66], thereby integrating proinflammatory and pro-survival/apoptotic signals. This positions MAPK/ERK at a critical juncture, linking extrinsic stimuli with intracellular signaling outcomes [67,68].

Negative feedback and dysregulation: Fine-tuning of this network is achieved through negative regulators. For instance, NF-κB can induce the expression of suppressor of cytokine signaling (SOCS) proteins, which inhibit JAK/STAT signaling, forming an intrinsic block on inflammation [69]. Conversely, persistent JAK/STAT activation can upregulate protein inhibitor of activated STATs (PIAS), which may suppress NF-κB activity. In POI, disruption of these feedback mechanisms (e.g., SOCS4 downregulation [55]) may lead to uncontrolled network hyperactivation and accelerated ovarian aging.

4.3 Implications for Therapeutic Strategy: From Single-Target to Network Pharmacology

The extensive crosstalk among these pathways necessitates a shift from single-target to network-based therapeutic strategies. Evidence from rheumatology supports this approach, where combining drugs targeting different nodes (e.g., JAK/STAT and NF-κB inhibitors) is a cornerstone for treating complex diseases like rheumatoid arthritis [70], validating the synergy of intercepting interconnected pathways. Translating this paradigm to POI suggests that, for immune-mediated subtypes, rational drug combinations may more effectively disrupt inflammatory networks, while for other forms, modulation of master regulators (e.g., SIRT1) or context-dependent pathway activity may be more effective. Ultimately, targeting the signaling network as a whole, rather than isolated components, represents the most promising strategy for developing effective POI therapies.

Targeting master regulators: Agents that modulate upstream or nodal regulators affecting multiple pathways (e.g., SIRT1 activators that can suppress both NF-κB and STAT3 acetylation and activity) represent a network-based pharmacology approach to restore overall signaling homeostasis.

5. Current and Emerging Intervention Therapies

The management of POI aims to alleviate symptoms, prevent long-term complications, and, when possible, address underlying pathogenic mechanisms or preserve fertility. Current and investigational strategies can be categorized into anti-inflammatory, antioxidant, hormonal, and novel regenerative approaches.

5.1 Anti-Inflammatory Therapies

Given the established role of inflammation in POI pathogenesis, modulating the immune response represents a logical therapeutic approach.

5.1.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs have been explored in assisted reproduction for POI. Kawachiya et al. [71] reported that NSAIDs significantly reduce the risk of premature ovulation and improve embryo transfer rates, although without a statistically significant impact on clinical pregnancy or live birth rates per transfer. Reviews by Merviel et al. [72] and Livshits and Seidman [73] suggest that adjuvant aspirin or NSAIDs may increase oocyte yield and prevent premature ovulation in natural-cycle *in vitro* fertilization (IVF). However, the evidence is conflicting; Buckley [74] found that the prostaglandin inhibitor indomethacin caused ovulation abnormalities in mice, an effect that was age dependent.

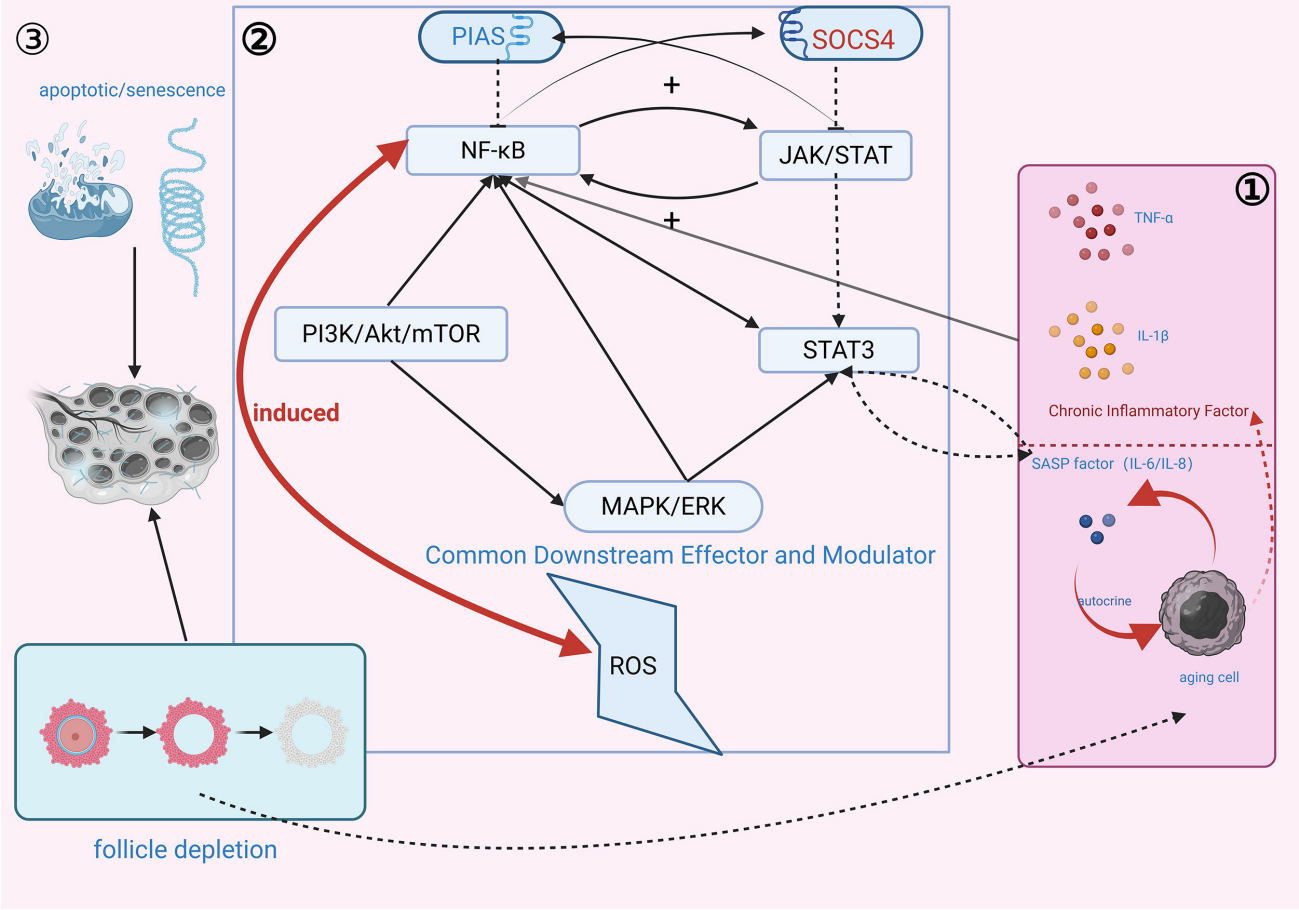

Fig. 2. Proposed model of inflammatory-senescence crosstalk in POI pathogenesis. ①Stage of inflammatory factor action; ②Stage of signaling pathway crosstalk; ③Stage of gross tissue senescence (manifesting as follicle depletion). POI, premature ovarian insufficiency; PIAS, protein inhibitor of activated STATs; NF-κB, nuclear factor kappa B; PI3K/Akt/mTOR, phosphatidyl-inositol-3-kinase/protein kinase B/mammalian target of rapamycin; SOCS4, suppressor of cytokine signaling-4; JAK/STAT, Janus kinase/signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription 3; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinase; ROS, reactive oxygen species. The figure was created by BioRender (https://www.biorender.com/).

5.1.2 Corticosteroids

Corticosteroids: Used for their immunosuppressive and anti-inflammatory properties, corticosteroids have shown some benefit. Riestenberg et al. [75], in a case report, demonstrated that high-dose corticosteroid immune suppression enabled successful controlled ovarian stimulation and oocyte cryopreservation in a patient with autoimmune POI and FSH receptor autoantibodies.Forges et al. [76] reported that corticosteroid therapy reduced serum anti-ovarian autoantibodies (AOA) and improved IVF outcomes. A significant concern, noted by Robertson et al. [77], is that systemic immunosuppression may impair post-implantation placental development, potentially contributing to IVF failure.

5.1.3 Biological Agents Targeting Specific Cytokines

Biological agents targeting specific cytokines: Direct cytokine inhibition remains underexplored in POI. An exception is the work by Zidan et al. [78], who found that donepezil (an acetylcholine inhibitor) protected against chemotherapy-induced POI in mice. Overall, there is a paucity of recent studies investigating targeted cytokine inhibitors for POI.

5.2 Antioxidant Therapies

Counteracting oxidative stress, a key driver of follicular depletion, is a key strategic focus.

5.2.1 Vitamin Supplements

Vitamin supplements: Vitamins with antioxidant properties have been investigated. Vitamin D, known for its roles in calcium metabolism, immune modulation, and potential protection against autoimmune diseases [79], represents a candidate of interest. Wu et al. [80] demonstrated that a B-vitamin complex reduced oxidative stress markers in aging mice. Abdollahifar et al. [81] showed that

vitamin C mitigated ovarian aging in mice. In humans, a meta-analysis by Shang et al. [82] concluded that antioxidants could improve pregnancy rates and oocyte-related outcomes in IVF for diminished ovarian reserve, without significantly reducing miscarriage rates. Conversely, Tarín et al. [83] argued that oral antioxidants may adversely affect oocyte number and quality in IVF and may pose risks at high doses.

5.2.2 Natural Antioxidants

Natural antioxidants: Compounds such as carotenoids and phenolics are of interest. Gammone et al. [84] highlighted the cardiovascular protective role of carotenoids. Li et al. [85] reviewed astaxanthin's anti-fibrotic and anti-aging potential via pathway modulation. Fernandez-Panchon et al. [86] summarized evidence for the *in vivo* antioxidant activity of phenolic-rich foods. Their direct efficacy in POI requires further clinical validation.

5.3 Hormone Replacement Therapy (HRT)

5.3.1 Benefits and Risks

HRT remains the cornerstone for managing hypoestrogenic symptoms and preventing complications.

Benefits and risks: For adolescents with POI, low-dose combined oral contraceptives (COCs) or hormone therapy (HT) tailored to the developmental stage are standard [87]. HRT, particularly vaginal administration, improves endometrial thickness, alleviates vasomotor and genitourinary symptoms, provides osteoprotection, and may contribute to cardiovascular prevention [88,89]. It may also enhance the efficacy of adjunct therapies like stem cell-based approaches [88]. Segerer et al. [90] reported improved insulin metabolism with HRT in patients with Turner syndrome receiving growth hormone. However, significant risks remain. HRT has been associated with an increased breast cancer risk [91], and its cardiovascular effects remain debated. Administration route is clinically relevant: percutaneous estrogen avoids first-pass hepatic metabolism, offering a more favorable lipid and inflammatory profile, whereas oral estrogen and progestins like medroxyprogesterone acetate (MPA) can increase thromboembolic risk and adversely affect metabolic parameters [92].

5.3.2 Current Guidelines and Recommendations

Current guidelines and recommendations: The Consensus of clinical diagnosis and treatment of premature ovarian insufficiency (2023 edition) affirms that estrogen replacement is appropriate and necessary for early-onset POI. It emphasizes benefits for cardiovascular health, mental well-being, quality of life, and osteoporosis prevention, with an overall favorable risk profile [93].

5.4 Novel and Experimental Therapies

Regenerative and targeted strategies represent the frontier of POI research.

5.4.1 Stem Cell Therapy

Stem cell therapy: Stem cells (embryonic, adult, or induced pluripotent) may restore ovarian function via homing, paracrine signaling, immunomodulation, and anti-apoptotic effects [94]. Elias et al. [95] demonstrated functional restoration using induced pluripotent stem cells (iPSCs) in a POI model. As of December 2024, 19 clinical trials are registered on ClinicalTrials.gov for stem cell transplantation in POI, although larger-scale validation of safety and efficacy is still required.

Platelet-rich plasma (PRP): PRP is a related regenerative approach. First applied in a CP-induced POI mouse model by Vural et al. [96], it has shown promise in improving oocyte yield and quality in patients with poor ovarian response [97].

5.4.2 Gene Therapy

Gene and exosome/miRNA therapy: Although no clinical gene correction therapies are currently available for genetic forms of POI (e.g., Turner syndrome, *FOXL2* mutations), ongoing research continues to identify pathogenic variants and underlying molecular mechanisms [98,99].

Exosome-based therapy is highly promising. Exosomes derived from mesenchymal stem cells (MSCs) can deliver therapeutic cargo (proteins, miRNAs) to the ovaries. Huang et al. [100] showed that exosomes from human adipose-derived MSCs (hADSC-Exos) improved ovarian function, increased follicle count, and restored hormone levels in a POI model, partly by inhibiting pro-apoptotic SMAD signaling. Current research heavily focuses on stem cell-derived exosomes for ovarian recovery [101,102,103]. For example, Sun et al. [104] found that BMSC-exosomal miR-644-5p inhibited granulosa cell apoptosis by targeting p53, while Nie et al. [105] reported that miRNAs like miR-23a can promote apoptosis via SMAD5, highlighting the precise regulatory potential of this approach.

5.4.3 Targeted Molecular Therapies

Targeted molecular therapies: These strategies aim to inhibit specific apoptotic pathways. The work by Huang et al. [100] and others on exosomal regulation of SMAD and p53 pathways exemplifies this targeted approach [104], advancing toward precise modulation of the intracellular signaling defects underlying POI.

5.5 Preclinical Ovarian Protective Drugs

LCZ696 (sacubitril/valsartan), a medication widely used in cardiovascular diseases such as heart failure, has shown protective potential against CP-induced ovarian dysfunction in preclinical studies. As reported by Khallaf et al. [106], LCZ696 effectively prevented ovarian dam-

age in CP-treated rat models. The underlying mechanism is thought to involve dual modulation of the renin–angiotensin system (RAS) and the natriuretic peptide system, leading to combined anti-inflammatory, anti-fibrotic, and antioxidant effects. By targeting key drivers of the "inflammation–fibrosis cycle", LCZ696 may help interrupt the self-perpetuating pathological cascade in the ovary, thereby slowing the decline of ovarian function.

6. Clinical Implications and Future Directions

6.1 Diagnostic and Prognostic Biomarkers for POI

The diagnosis of POI is established based on key clinical and biochemical parameters: age under 40 years, oligo- or amenorrhea for at least 4 months, and elevated basal serum FSH levels >25 U/L on two occasions at least 4 weeks apart, as outlined in contemporary expert consensus [93]. Beyond diagnosis, identifying biomarkers to prognosticate ovarian response and monitor therapeutic efficacy is an active area of investigation. Current clinical assessments often rely on follicular phase AFCs to gauge functional recovery [107,108]. For instance, Gibbons et al. [107] reported that vaginal progesterone priming prior to assisted reproductive technology (ART) increased serum progesterone levels, suggesting an improved ovarian response. Other studies evaluate treatment impact on long-term sequelae; Cartwright et al. [109] found that both HRT and COCs increased lumbar bone mineral density and reduced bone turnover markers in patients with POI, with HRT demonstrating a superior effect on bone density.

While these diagnostic criteria are well-established, they identify POI at a relatively late stage, often after significant follicular depletion has occurred. Consequently, there is a pressing need for biomarkers capable of predicting POI risk or detecting its onset at a preclinical or early stage. AMH is currently the most robust serum marker of ovarian reserve and may decline years before a rise in FSH, offering a window for earlier detection [24]. Beyond AMH, research is exploring a broader panel of potential early biomarkers. These include markers of immune dysregulation (e.g., specific anti-ovarian antibodies and cytokine profiles like IL-1β, TNF-α), oxidative stress (e.g., advanced oxidation protein products and lipid peroxidation adducts), and cellular senescence (e.g., circulating SASP factors and p16INK4a expression) [32]. Additionally, genetic markers (e.g., specific FMR1 premutation status, autoimmune regulator gene variants) can help identify high-risk subpopulations. However, the translation of these candidate biomarkers into routine clinical practice for early POI detection requires further validation in large, prospective cohorts to establish standardized cutoff values and predictive accuracy.

6.2 Personalized Medicine Approaches

Personalized management of POI is increasingly feasible, particularly for cases with a genetic component. The use of polygenic risk scores (PRS) to estimate an individual's age of natural menopause represents a significant advancement. This tool can inform personalized counseling regarding fertility timelines and the potential need for early intervention with IVF or tailored combination therapies, helping to anticipate and mitigate risks such as poor ovarian response to stimulation. However, the clinical application of PRS is currently constrained by its predictive precision, which at this nascent stage is limited to estimating menopause age within a window of several months [110].

6.3 Potential for Combination Therapies

Combination therapies that target multiple pathological pathways simultaneously hold promise for enhancing treatment efficacy. Preclinical evidence established a foundation: a 2019 study showed that co-administration of granulocyte colony-stimulating factor (G-CSF) with PRP significantly accelerated ovarian recovery in a mouse model of POI [111]. This approach has since translated into promising clinical applications. A seminal 2020 case report detailed a 37-year-old woman with severe POI (AMH <0.02 ng/mL) who underwent intraovarian injection of PRP combined with gonadotropins. The treatment led to improved folliculogenesis, hormonal profiles, and oocyte maturation, culminating in a successful embryo transfer and live birth [112]. Further supporting this strategy, Aboutalebi et al. (2022) [113] demonstrated in mice that the combination of PRP with pentoxifylline (PTX) effectively promoted functional ovarian recovery.

6.4 Areas for Further Research

Despite progress, fundamental gaps in knowledge remain. Although a strong genetic predisposition is well recognized and research has focused on gene variants and signaling pathway dysregulation, the precise molecular mechanisms initiating POI remain elusive. This review underscores the critical, yet incompletely understood, role of chronic inflammation, suggesting potential avenues for therapies targeting inflammatory pathways, as well as the use of inflammatory markers as prognostic tools. Furthermore, although innovative approaches like autologous PRP combined with hormonal regimens show potential for restoring ovarian function, the current evidence base is limited by small-scale studies and case reports [112]. Accordingly, a key priority for the field is to conduct large-scale, rigorous clinical trials to validate the efficacy and safety of these emerging therapies and to develop robust, biomarker-driven frameworks for personalized POI management.

6.5 Limitations

First, a significant proportion of the mechanistic evidence, particularly regarding the inflammation-aging axis, is derived from animal models, and its direct translatability to human POI requires further validation. Second, clinical studies on emerging therapies (e.g., stem cells, exosomes,

PRP) are often limited by small sample sizes, short follow-up, and heterogeneous protocols, precluding definitive conclusions about their long-term efficacy and safety. Third, although genetic and inflammatory biomarkers are promising, their predictive and prognostic utility in routine clinical practice remains to be standardized and validated in large cohorts. Finally, and crucially, a fundamental limitation lies in the current therapeutic landscape itself. Existing approaches, primarily HRT, are largely palliative, aimed at managing symptoms and sequelae rather than reversing ovarian dysfunction or restoring fertility. This underscores the pressing, unmet need for novel mechanism-based treatments that can genuinely alter the disease prognosis, which this review seeks to address.

Additionally, our systematic search closed on December 3, 2024; thus, the 2025–2026 studies (Refs. [20,37,38]) added during revision per reviewers' request were not part of the original screening, and await systematic integration in future updates.

7. Conclusions

7.1 Summary of Key Findings

In conclusion, this review synthesizes the available evidence to propose that dysregulated chronic inflammation and accelerated cellular senescence constitute a central, self-perpetuating axis in POI pathogenesis, moving beyond mere association to a causal mechanistic framework. This "inflammation-senescence axis" not only explains the ovarian follicular depletion and stromal dysfunction characteristic of POI but also integrates its systemic manifestations and comorbidities.

Critically, this mechanistic understanding directly informs a paradigm shift in therapeutic strategy, from symptomatic management to targeted mechanism-based interventions. Promising approaches, including anti-cytokine therapies, senolytics, and antioxidant agents, aim to disrupt this vicious cycle, potentially preserving ovarian function and improving long-term outcomes.

However, translating this promise into clinical reality faces significant challenges. These include the predominant reliance on preclinical models, a lack of standardized early diagnostic biomarkers, and the absence of long-term data from targeted clinical trials. Therefore, the future of POI research must prioritize the validation of these mechanisms in human studies, the development of sensitive early detection panels, and the rigorous clinical evaluation of novel combination therapies that simultaneously target inflammation, senescence, and oxidative stress. By bridging these gaps, the field can advance toward the ultimate goal of modifying the disease course and restoring ovarian health.

7.2 Toward a New Clinical Paradigm: From Symptom Management to Precision Prevention and Therapy

The mechanistic association between inflammation and ovarian aging compels a fundamental shift in clinical practice, moving from reactive hormone replacement to proactive, stratified management.

Refining risk stratification beyond genetics: While PRS currently offers limited standalone utility, its predictive performance can be significantly enhanced by integration with dynamic, quantifiable biomarkers of the inflammation-aging axis. A clinically actionable risk model should combine:

Genetic susceptibility (PRS): For underlying predisposition.

Early-life and environmental exposures: Low birth weight, metabolic status.

Real-time biomarkers: Circulating inflammatory cytokines (e.g., IL-6, TNF-α), markers of cellular senescence (e.g., SASP factors, p16INK4a), and oxidative stress markers. This multi-modal approach can identify high-risk individuals for early intervention before overt POI develops.

Implementing mechanism-guided adjunctive therapies: For diagnosed patients, management must extend beyond HRT to address the underlying pathophysiology. Clinical trials should prioritize evaluating adjunctive, mechanism-targeted agents, such as:

Repurposed immunomodulators: Testing whether specific, low-dose NSAIDs (e.g., celecoxib) or cytokine inhibitors can improve ovarian reserve parameters (e.g., AFC, AMH) in subsets with elevated inflammatory markers.

Senolytics and senomorphics: Investigating agents that clear senescent cells or suppress the SASP to ameliorate the inflammatory ovarian microenvironment.

7.3 Defining a Translational Research Agenda: From Bench to Bespoke Therapies

Future research must transition from descriptive association to causal experimentation and targeted translation. We propose the following prioritized, testable framework:

Hypothesis-driven mechanistic research:

Specific Aim 1: To determine whether JAK/STAT inhibition in a defined autoimmune oophoritis model preferentially rescues the primordial follicle pool compared with broad-spectrum anti-inflammatory agents.

Specific Aim 2: To test whether temporal, stage-specific modulation of NF-κB (protective vs. destructive) can be achieved pharmacologically to support folliculogenesis while suppressing inflammation.

Therapeutic development and testing:

Priority 1 (repurposing): Conduct a phase II trial of anakinra (IL-1 receptor antagonist) in POI patients with a high-inflammatory phenotype, using changes in ovarian stromal blood flow or AMH trend as the primary endpoint.

Priority 2 (combination strategies): Systematically evaluate in preclinical models whether PRP or exosomes derived from young, healthy donors enhance the engraftment and efficacy of co-administered mesenchymal stem cells by modulating the recipient ovarian inflammatory niche.

Technology-enabled personalization: Develop patient-derived ovarian cell models (e.g., from induced pluripotent stem cells) to serve as "avatars" for high-throughput drug screening and personalized therapy selection.

Author Contributions

TC—writing-original draft, visualization, investigation. XLin—supervision, validation, writing-review & editing. XLi—methodology, writing-review & editing. QZ—conceptualization, methodology, supervision, writing-review & editing. DZ—conceptualization, methodology, supervision, writing-review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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