Journal of Rehabilitation Research Current Updates ISSN:3068-9333

PRIME OPEN ACCESS

Volume 2, Issue 2

Research Article

Date of Submission: 24 Mar, 2026
Date of Acceptance: 24 Apr, 2026
Date of Publication: 11 May, 2026

Between Silence and Senescence: Decoding the Accelerated Aging Phenotype and Immunological Paradox in Primary Ovarian Insufficiency Through a Multi-Omics Lens

Aqsa Akram[1*] and Namra Ashfaq[2]

[1]Department of Obstetrics & Gynaecology, Shalamar Hospital, Lahore, Pakistan

[2]Department of Obstetrics & Gynaecology, Arif Memorial Hospital, Lahore, Pakistan

***Corresponding Author:** Aqsa Akram, Department of Obstetrics & Gynaecology, Shalamar Hospital, Lahore, Pakistan.

Citation: Akram, A., Ashfaq, N. (2026). Between Silence and Senescence: Decoding the Accelerated Aging Phenotype and Immunological Paradox in Primary Ovarian Insufficiency Through a Multi-Omics Lens. *J Rehabil Res Curr Updates, 2*(2), 01-11.

Abstract

Background

Primary Ovarian Insufficiency (POI), defined by the European Society of Human Reproduction and Embryology (ESHRE) as oligomenorrhea or amenorrhea for at least four months with two serum FSH measurements exceeding 25 IU/L more than four weeks apart in women under 40, affects approximately 1–3.7% of the global female population [1]. Beyond its reproductive consequences, POI is increasingly understood as a systemic accelerated aging event---a state in which the biological age of a woman in her late twenties or thirties approximates that of a woman in her early-to-mid fifties, as evidenced by converging multi-omics signatures across proteomic, metabolomic, and inflammatory dimensions [2,3].

Objective

To characterize the multi-omics aging signature in POI, compare it quantitatively and qualitatively with natural menopause, and critically examine the dual role of the immune system as both an agent of follicular destruction and a potential mediator of ovarian repair and regeneration.

Methods

Structured narrative synthesis of peer-reviewed publications from October 2023 to February 2026, retrieved from PubMed, EMBASE, and Cochrane, employing proteomic arrays, untargeted and targeted metabolomic profiling, multiplex cytokine panels, single-cell RNA sequencing, epigenetic clock analyses, and immune phenotyping studies in women with POI and comparator populations.

Results

POI demonstrates a canonical Senescence-Associated Secretory Phenotype (SASP) proteomic signature with 73% overlap with the natural postmenopausal proteome, ceramide and mitochondrial energy dysregulation equivalent to women aged 52–58, IDO1-mediated tryptophan–kynurenine pathway activation producing quinolinic acid neurotoxicity, and chronic inflammaging with IL-6 elevated 3.2-fold, TNF-α 2.8-fold, and IFN-γ 10.3-fold in autoimmune POI versus premenopausal controls. Epigenetic clocks reveal biological age advancement of 8–15 years. Simultaneously, the immune system harbors regenerative capacity through M2 macrophage polarization, Treg expansion, ILC2-mediated stromal remodeling, and mesenchymal stem cell (MSC)-facilitated immune reset [4-10].

Conclusions

POI constitutes an accelerated biological aging state that is distinct from, but substantially convergent with, natural menopause. Clinical screening for osteoporosis, cardiovascular disease, and neurocognitive decline must be recalibrated to biological rather than chronological age from the time of diagnosis. Immune modulation---through low-dose IL-2, MSC infusion, and targeted biologics---represents an underexplored but rapidly maturing therapeutic frontier with early-phase trial evidence of follicular rescue.

Keywords: Primary Ovarian Insufficiency, Multi-Omics, Accelerated Aging, Proteomics, Metabolomics, SASP, Autoimmune POI, Immune Modulation, Neurodegeneration, Cardiovascular Risk, Regulatory T-cells, Ovarian Regeneration, Inflammaging, Epigenetic Clock, Tryptophan-Kynurenine Pathway

Domain	Biomarker	Significance in POI	Clinical Action
Proteomic (SASP)	IL-6, TNF-α, MMP-9 PAI-1, CXCL8 Clustering	Elevated 2.8–3.2× vs controls; comparable to natural menopause cytokine levels (ages 50–55); 73% proteome overlap with postmenopausal SASP [2,3,5]	Annual inflammatory marker monitoring; optimize HRT; consider anti-inflammatory agents; baseline epigenetic clock at diagnosis
Metabolomic (Lipid)	Ceramide C16:0 Ceramide C24:1 Sphingomyelin species	Significantly elevated; inverse correlation with AMH; positive correlation with FSH; CVD risk predictor matching women aged 50–60 [8,16]	Statin therapy evaluation; dietary lipid modification; annual lipid panel from diagnosis; cardiovascular risk scoring at baseline
Metabolomic (Mitochondrial)	Lactate:Pyruvate ratio Succinate, Fumarate OXPHOS intermediates	Respiratory chain inefficiency; OXPHOS perturbations matching mitochondrial aging profile of women aged 52–58; TCA cycle disruption [22]	CoQ10 supplementation trial; structured aerobic exercise prescription; annual metabolic review; refer to metabolic specialist if severe
Neuroinflammatory (Trp-Kyn)	Kyn:Trp ratio Quinolinic acid IDO1 activity Kynurenic acid	IDO1 upregulation → quinolinic acid accumulation → NMDA excitotoxicity; depression and anxiety 3× higher in POI vs controls; serotonin depletion documented [11,24,25]	PHQ-9/GAD-7 validated screening every visit; annual neurocognitive battery; psychiatric referral if Kyn:Trp elevated; tryptophan-targeted nutritional support
Immune Phenotyping	Treg % NK cytotoxicity Macrophage M1:M2 ratio AOA titers (21-OHase Ab)	Treg depletion documented in autoimmune POI; M1-dominant macrophage polarization; AOA present in 10–64% of cases depending on assay and population [4,17,19,26]	Annual AOA and thyroid/adrenal autoantibody panel; low-dose IL-2 trial candidacy assessment; MSC referral in refractory cases; immunosuppression protocols where evidence-based
Clinical Aging Index	DEXA Z-score Pulse wave velocity Cognitive battery (MoCA/MMSE)	BMD loss 2.5–3.5%/yr in untreated POI (vs 0.5–1.5%/yr postmenopause); arterial stiffness equivalent to women aged >50 yrs; cognitive decline documented in longitudinal POI cohorts [21,23,27]	Biennial DEXA from diagnosis; cardiac CT calcium score at diagnosis; annual neuropsychological testing; endothelial function testing (FMD) at baseline
Epigenetic Aging Clock	DNAm PhenoAge GrimAge (blood) Horvath clock	Biological age 8–15 years advanced over chronological age in POI cohorts using three independent validated epigenetic clock algorithms; advancement partially attenuated by HRT [12,28]	Baseline epigenetic age assessment at diagnosis; repeat at 2-year intervals; use to guide HRT intensity, preventive strategy tier, and screening frequency

Table 1: Proposed Composite Biomarker Panel for Aging Phenotype in POI

Table 1 presents the recommended multi-omics biomarker domains for clinical characterization of the POI accelerated aging phenotype, with evidence-based clinical actions for each domain [2,3,5,7,8,11,12].

Table 1. Recommended composite multi-omics biomarker panel for POI aging phenotype characterization and clinical decision-making. Reference numbers in square brackets denote supporting evidence for each domain.

Introduction

Primary Ovarian Insufficiency (POI), historically referred to as premature ovarian failure, is defined by the European Society of Human Reproduction and Embryology (ESHRE) as the occurrence of oligomenorrhea or amenorrhea for at least four months in a woman under 40 years, with two serum FSH measurements exceeding 25 IU/L more than four weeks apart [1]. With an updated global prevalence of 1–3.7% across 34 countries, POI represents both a reproductive tragedy and an under-recognized systemic health emergency [13]. Diagnostic delay averaging 3.7 years from symptom onset further compounds the cumulative biological harm accruing from untreated estrogen deficiency and chronic inflammation during the critical reproductive years [13].

The conceptual architecture of POI has undergone a fundamental recalibration over the past decade. No longer viewed solely through the lens of gonadal failure and infertility, POI is now increasingly conceptualized as a condition with profound systemic consequences that are analogous to, yet mechanistically distinct from, physiological menopause. The central thesis gaining momentum in reproductive endocrinology and the emerging field of geroscience is that POI induces an accelerated aging phenotype: a biological state in which a woman in her late twenties or thirties bears closer biological resemblance---by the metrics of proteomics, metabolomics, epigenetics, and inflammatory burden---to a woman a decade or more her senior [2,3,12]. This reframing carries enormous clinical implications for the calibration of preventive medicine, particularly the initiation of screening protocols for osteoporosis, cardiovascular disease (CVD), and neurocognitive decline [14-16].

Simultaneously, the immunological dimension of POI has emerged as one of the most intellectually rich and clinically consequential questions in reproductive medicine. Autoimmune mechanisms account for a variable but significant proportion of POI cases---estimates range from 4% to as high as 30% depending on diagnostic criteria and the antibody panel employed [1,4,17]. Yet the immune system in POI is not simply a saboteur. Emerging data from single-cell transcriptomics, murine model experiments, and early-phase human clinical trials suggest that the immune milieu simultaneously harbors keys to ovarian repair through macrophage polarization, T-regulatory cell dynamics, innate lymphoid cell type 2 (ILC2) activity, and immune-mediated stromal remodeling [4-10,18,19].

This article synthesizes evidence from multi-omics studies published between October 2023 and February 2026 to address two overarching research questions: first, does POI generate a biologically aging phenotype that is quantitatively and qualitatively distinct from, yet convergent with, natural menopause? And second, can the immune system, when appropriately modulated, be transformed from an ovarian adversary into a therapeutic ally capable of preserving or restoring follicular function? The synthesis integrates proteomic arrays, untargeted metabolomics, multiplex cytokine panels, epigenetic clock analyses, single-cell RNA sequencing data, and immunotherapy trial outcomes to construct a unified multi-omics framework for understanding and managing POI as an accelerated aging state.

The clinical urgency of this framework cannot be overstated. Women with POI face a substantially elevated lifetime risk of hip fracture, major cardiovascular events, Parkinson's disease, dementia, and all-cause mortality compared with eumenorrheic peers---risks that are substantially attenuated but not eliminated by hormone replacement therapy (HRT) [16,19,20]. Current clinical guidelines, which calibrate screening thresholds to chronological age, systematically fail women with POI by initiating preventive interventions a decade too late. A biologically age-adjusted clinical model, grounded in multi-omics evidence, offers a more rational and potentially life-saving alternative [15,19].

Poi As A Model Of Accelerated Aging: The Multi-Omics Evidence

Conceptual Framework: Biological vs. Chronological Age

Biological age, as distinct from the passage of time measured chronologically, encompasses a constellation of molecular and cellular parameters: epigenetic modifications quantified by DNA methylation clocks, telomere attrition rates, proteomic composition drift, metabolic efficiency decline, mitochondrial biogenesis capacity, and inflammatory burden. In women with POI, biological age surpasses chronological age by 8–15 years using three independently validated multi-parameter aging clocks---PhenoAge, GrimAge, and the Horvath methylation clock---applied to peripheral blood samples [12,21]. Crucially, this advancement is observed even after adjusting for years of estrogen deficiency, suggesting that the accelerated biological aging of POI is not attributable solely to estrogen withdrawal but is driven, at least in part, by upstream immune dysregulation, chronic oxidative stress, and mitochondrial dysfunction operating as co-drivers of the aging cascade [3,7].

The estrogen-independent aging contribution is supported by multi-omics analyses demonstrating that specific aging signatures in POI---particularly those involving mitochondrial proteome disruption, ceramide-mediated lipotoxicity, and IDO1-driven tryptophan pathway dysregulation---are present even in women receiving adequate HRT, albeit at attenuated levels [7,11,19]. This has important therapeutic implications: HRT, while essential and effective, addresses the hormonal but not the immunological or metabolic dimensions of the POI aging phenotype. A comprehensive preventive strategy must therefore be multi-targeted.

The radar chart comparison of multi-omics aging domain scores between POI women aged 25–38, naturally postmenopausal women aged 50–55, and premenopausal controls demonstrates near-congruence between the POI and natural menopause profiles across nine biological aging domains, with both groups substantially elevated above controls [3,6]. This visual and quantitative equivalence underpins the core clinical argument: women with POI should receive the preventive medical attention currently extended to women in their early-to-mid fifties.

Proteomic Evidence: The SASP Signature and Matrix Remodeling

The Senescence-Associated Secretory Phenotype (SASP) represents the hallmark proteomic output of cellular senescence---a complex secretome encompassing pro-inflammatory cytokines, matrix metalloproteinases (MMPs), growth factors, extracellular vesicles, and bioactive lipids that collectively propagate inflammation and tissue dysfunction [2,5]. Plasma proteomic arrays from POI cohorts have revealed statistically significant upregulation of CXCL1, CXCL8 (IL-8), MMP-3, MMP-9, plasminogen activator inhibitor-1 (PAI-1), and clusterin relative to age-matched eumenorrheic controls---a canonical SASP profile previously characterized in naturally postmenopausal women aged 50–55 [2-5]. The biological significance of MMP-9 elevation extends beyond the ovary: MMP-9-mediated degradation of extracellular matrix in vascular walls contributes directly to the arterial stiffness and elevated pulse wave velocity documented in women with POI [16,22,23].

Comparative analysis against natural postmenopausal proteomes revealed 73% overlap in differentially expressed proteins between POI and natural menopause groups [2,5]. The 27% POI-specific portion of the proteomic signature is particularly revealing: it includes AMHR2 fragments, inhibin alpha subunit (INHA), and zona pellucida glycoprotein ZP3---antigens implicated in autoimmune ovarian targeting and detected in women with anti-ovarian antibodies [4,17]. The presence of these autoimmune-associated fragments suggests that autoimmune ovarian targeting contributes an

accelerating dimension to the aging phenotype in POI that operates above and beyond what estrogen deficiency alone would be expected to produce.

Matrix remodeling proteomics comparing POI with natural menopause have identified shared fibrotic signatures---specifically involving fibronectin-1, collagen VI, and SPARC---alongside POI-distinct elevations in periostin and versican that may reflect the specific pattern of follicular microenvironment disruption in autoimmune oophoritis [22]. These findings have implications for the development of imaging biomarkers capable of detecting early ovarian fibrosis before complete follicular depletion, potentially enabling earlier therapeutic intervention.

Metabolomic Signatures: Lipid Dysregulation and Tryptophan–Kynurenine Pathway Activation

Untargeted metabolomic studies using high-resolution mass spectrometry have identified three principal metabolic perturbation clusters in women with POI, each with distinct clinical correlates and aging implications.

The first cluster involves ceramide dysregulation. Ceramide species C16:0 and C24:1 are significantly elevated in the serum of women with POI relative to both premenopausal controls and age-matched eumenorrheic women, correlating inversely with AMH and positively with FSH---a pattern consistent with their established role as cardiovascular risk mediators in aging populations [8,20]. Ceramides impair endothelial nitric oxide synthase activity, promote insulin resistance through PKCζ/θ activation, and induce mitochondrial outer membrane permeabilization---collectively establishing a lipotoxic vascular environment equivalent to that observed in women aged 50–60 [8,20,24]. The ceramide-CVD risk axis is further amplified by elevated sphingomyelin species and lysophosphatidylcholines identified in POI lipidomic analyses.

The second metabolic cluster involves oxidative phosphorylation (OXPHOS) perturbations. Mitochondrial metabolomics comparing POI women with both premenopausal controls and postmenopausal women of different age strata found that OXPHOS intermediate ratios in POI---including elevated lactate:pyruvate ratio, succinate accumulation, and fumarate perturbations---matched the mitochondrial aging profile of women aged 52–58, consistent with respiratory chain complex I and III inefficiency [7,25]. The clinical translation of this finding encompasses fatigue, reduced exercise tolerance, and accelerated metabolic aging---symptoms that are prevalent but often underattributed in clinical POI management [25].

The third and arguably most clinically consequential metabolic perturbation involves the tryptophan–kynurenine (Trp-Kyn) pathway. Under conditions of chronic immune activation, indoleamine 2,3-dioxygenase 1 (IDO1) is upregulated in immune cells, diverting tryptophan away from the serotonin synthesis pathway toward kynurenine catabolism [11,26,27]. In POI, IDO1 upregulation driven by the chronic inflammatory microenvironment produces progressive accumulation of quinolinic acid---an N-methyl-D-aspartate (NMDA) receptor agonist that at elevated concentrations causes excitotoxic neuronal damage and promotes neuroinflammation [11,26]. The kynurenine-to-tryptophan (Kyn:Trp) ratio is elevated in women with POI and correlates with depression severity scores, providing a molecular bridge between the immunological dysregulation of POI and its well-documented psychiatric comorbidity burden [26,27]. Rates of depression and anxiety in women with POI are approximately three times higher than in age-matched controls, a finding now explicable at least in part by this neuroimmune metabolic axis [26,27].

Inflammatory Marker Panels: Quantifying Inflammaging in POI

The concept of "inflammaging"---chronic, low-grade, sterile systemic inflammation that is a hallmark feature of biological aging in multiple organ systems---has been quantitatively and rigorously documented in POI across multiple independent study cohorts [3,6,24,28]. A 2024 multi-center study from the European POI Consortium simultaneously measured 52 cytokines using multiplex bead-based immunoassays in POI women (aged 28–38), naturally postmenopausal women (aged 50–58), and premenopausal controls (aged 25–38) [6]. The inflammatory cytokine composite scores of POI women did not differ statistically from those of naturally postmenopausal women (p = ns), while both groups differed substantially from premenopausal controls ($p < 0.001$).

Specific cytokine elevations in POI are quantitatively striking and clinically actionable. IL-6 was elevated 3.2-fold in idiopathic POI versus premenopausal controls, consistent with its role in accelerated bone resorption through osteoclast activation, endothelial dysfunction, and insulin resistance [2,6]. TNF-α was elevated 2.8-fold, contributing to the SASP amplification loop through NFkB pathway activation. Most remarkably, IFN-γ was elevated 10.3-fold in autoimmune POI specifically---a degree of immune activation that substantially exceeds that seen in natural menopause (where IFN-γ elevation approximates 2.5-fold) and reflects the active cellular immune assault on granulosa cells characteristic of autoimmune oophoritis [4,6].

The IFN-γ elevation pattern in autoimmune POI is mechanistically linked to NK cell activation---the earliest identifiable cellular event in the autoimmune follicular destruction cascade, as demonstrated by single-cell RNA sequencing of ovarian biopsies [4]. NK cell-secreted IFN-γ recruits and activates CD8+ cytotoxic T lymphocytes (CTLs) that infiltrate granulosa cell layers, triggering apoptotic cascades amplified by Th17-derived IL-17A. This innate-to-adaptive immune transition creates a self-perpetuating inflammatory circuit in the follicular microenvironment [4,17,24].

C-reactive protein (CRP), while a less specific aging biomarker, is consistently elevated in women with untreated POI at levels comparable to those in postmenopausal women on no HRT---an observation with direct clinical utility, as

elevated CRP in POI is a surrogate indicator of heightened CVD risk that warrants early preventive intervention [20,28]. The chronic elevation of multiple acute-phase reactants in POI also accelerates telomere attrition through oxidative DNA damage mechanisms, providing a mechanistic link between inflammaging and the epigenetic age advancement documented by methylation clocks [12,21].

Epigenetic Aging: The Clock Evidence

The development of epigenetic aging clocks---algorithms that translate DNA methylation patterns at carefully selected CpG sites across the genome into a biological age estimate---has provided the most objective and quantitative evidence to date that POI constitutes an accelerated aging state [12,21,23]. Three independent epigenetic clock algorithms (DNAm PhenoAge, GrimAge, and the original Horvath clock) have been applied to peripheral blood DNA from women with POI in a 2024 multi-parameter analysis. All three clocks consistently returned biological age estimates 8–15 years above chronological age in POI cohorts, with the greatest acceleration observed in women with autoimmune subtype POI and the smallest but still significant acceleration in idiopathic POI [12].

GrimAge, which predicts time-to-death and is heavily weighted by smoking-related methylation patterns and plasminogen activator inhibitor-1 (PAI-1) methylation, returned particularly high biological age estimates in POI---consistent with the PAI-1 protein elevation observed in the SASP proteomic analysis and the known association between elevated PAI-1 and increased risk of thromboembolism, myocardial infarction, and all-cause mortality [12,21]. HRT partially attenuated epigenetic age acceleration, reducing the biological age gap from 8–15 years to 4–8 years in women on adequate estrogen replacement---providing further molecular evidence for the partial but incomplete protection afforded by hormone therapy against POI-associated aging [12,21].

Telomere length analysis, a complementary aging biomarker, demonstrated significantly shorter leucocyte telomere lengths in women with POI compared with age-matched controls, with shortening equivalent to that seen in women 10–12 years older---a finding replicated across European, Asian, and South American POI cohorts [21,23]. The mechanistic drivers of accelerated telomere attrition in POI include both oxidative damage from the chronic inflammatory microenvironment and reduced telomerase activity---the latter potentially a downstream consequence of impaired reproductive hormone signaling on telomerase expression in bone marrow progenitor cells [23].

Clinical Implications: A Recalibrated Screening Framework

The convergence of proteomic, metabolomic, epigenetic, and inflammatory evidence for accelerated biological aging in POI demands a fundamental reconsideration of clinical screening timelines and preventive medicine protocols. The current paradigm---in which screening thresholds for osteoporosis (DEXA at age 65), cardiovascular risk (formal assessment at 40–50), and neurocognitive decline (memory clinic referral at 60+) are calibrated to general population chronological age---systematically fails women with POI by initiating preventive interventions approximately a decade after the biological aging trajectory has already placed them at elevated risk [14,15,29].

Based on multi-omics aging equivalence data, a biologically grounded screening protocol for POI should commence at diagnosis, irrespective of chronological age [15,29,30]. DEXA scanning should be initiated at POI diagnosis with biennial reassessment, given documented BMD loss rates of 2.5–3.5% per year in untreated POI---approximately three times the rate observed in natural menopause [23]. Cardiovascular risk profiling, including fasting lipid panel with ceramide subspeciation, endothelial function testing by flow-mediated dilatation, and coronary calcium scoring by CT, should be performed at diagnosis in accordance with postmenopausal cardiovascular guidelines shifted forward by a decade [15,20]. Neurocognitive screening using validated brief tools such as the Montreal Cognitive Assessment (MoCA) should be incorporated into annual follow-up visits from diagnosis, given the quantifiable Trp-Kyn pathway activation and documented cognitive decline in longitudinal POI cohorts [16,26,27].

The Immune System in Poi: Adversary, Ally, And Therapeutic Target

The Autoimmune Assault: Mechanisms of Immune-Mediated Follicular Destruction

Autoimmune oophoritis is characterized by lymphocytic infiltration of developing follicles, with destruction of granulosa cells mediated through convergent humoral and cellular immune mechanisms. Anti-ovarian antibodies (AOAs) directed against steroidogenic enzymes---particularly 17-alpha hydroxylase, 3-beta hydroxysteroid dehydrogenase, and cytochrome P450 side-chain cleavage (P450scc)---are documented in 10–64% of POI cases, with the wide range reflecting heterogeneity in assay methodology, antibody panel composition, and study population autoimmune background rates [17,24]. The co-occurrence of POI with other autoimmune endocrinopathies is clinically significant and commonly underappreciated: autoimmune adrenocortical insufficiency (Addison's disease) is found in 10–20% of AOA-positive women with POI, and autoimmune thyroiditis in approximately 25%---necessitating systematic annual autoimmune surveillance rather than opportunistic testing [1,17].

A landmark 2023/2024 single-cell RNA sequencing study of ovarian biopsies from women with autoimmune POI delineated the cellular immune choreography of follicular destruction with unprecedented resolution [4]. NK cell activation---identified by upregulation of granzyme B, perforin, and IFN-γ---represents the earliest event, preceding CD8+ CTL infiltration into granulosa cell layers. CTLs subsequently execute perforin/granzyme-mediated apoptosis of granulosa cells, with the transcriptomic signature of CD8+ T cells showing a hybrid activated/exhausted phenotype that

may reflect the chronicity of the autoimmune assault. Th17 cell accumulation follows, with IL-17A-driven disruption of tight junction integrity in the follicular basement membrane and amplification of the pro-inflammatory circuit through IL-17A-CXCL8 cross-talk [4,17].

The temporal evolution of macrophage polarization in the autoimmune oophoritis microenvironment is of particular pathophysiological and therapeutic significance. Active autoimmune oophoritis is characterized by M1-dominant macrophage polarization (elevated HLA-DR, CD86, IL-12, TNF-α) that amplifies granulosa cell apoptosis and disrupts follicular vascularization. As follicular depletion progresses and the inflammatory substrate is exhausted, a transition toward M2 polarization (elevated CD163, CD206, IL-10, TGF-β) is observed in the largely follicle-depleted "burnt-out" ovarian tissue [4,18]. This temporal M1→M2 shift may represent a futile endogenous repair attempt that arrives too late---but it also establishes the biological rationale for therapeutic strategies aimed at forcing premature M2 polarization to preserve residual follicles before depletion is complete [18,19].

The Regenerative Potential: Immune System as Ovarian Repair Mediator

The recognition that the immune system is not uniformly destructive in POI but harbors regenerative capacity represents one of the most significant conceptual advances in the field. M2-polarized macrophages are the primary cellular source of TGF-β, VEGF, and IGF-1 within the ovarian microenvironment---growth factors critically implicated in follicular activation, granulosa cell proliferation, and ovarian stromal vascularization [18]. In murine models of cyclophosphamide-induced POI, deliberate M2 macrophage polarization via systemic IL-4 administration resulted in statistically significant partial recovery of antral follicle counts and measurable improvement in ovarian stromal blood flow by contrast-enhanced ultrasound---demonstrating proof-of-concept that macrophage polarization state is a pharmacologically tractable determinant of follicular fate [18].

Regulatory T-cells (Tregs) exert pro-tolerogenic effects that are essential for the maintenance of immune privilege in the follicular microenvironment. Through IL-10 and TGF-β secretion, CTLA-4-mediated co-stimulation blockade, and generation of an immunosuppressive tissue niche, Tregs protect residual follicles from CTL-mediated apoptosis and NK cell cytotoxicity [3,19,29]. Quantitative Treg depletion---documented by flow cytometric immune phenotyping in women with autoimmune POI---correlates with the severity of follicular loss, providing a direct mechanistic link between Treg deficiency and accelerated follicular depletion [3,29].

Innate lymphoid cells type 2 (ILC2s), which produce IL-5 and IL-13, have been identified as promoters of ovarian stromal remodeling in a manner distinct from Tregs and macrophages [10]. Single-cell transcriptomics of murine ovaries demonstrates ILC2 enrichment in peri-follicular stromal compartments, where their cytokine secretion promotes M2 macrophage differentiation and anti-fibrotic matrix remodeling. In ILC2-deficient murine POI models, adoptive transfer of wild-type ILC2s attenuated ovarian fibrotic remodeling, preserved primordial follicle density at higher levels than PBS-treated controls, and restored partial fertility---providing compelling preclinical evidence for ILC2 as a hitherto underappreciated immune guardian of the primordial follicle pool [10].

Mesenchymal Stem Cell Immunotherapy and the Paracrine Immune Reset Hypothesis

Mesenchymal stem cells (MSCs) exert their therapeutic effects in POI predominantly through paracrine immune modulation rather than direct differentiation into ovarian cell types. The MSC secretome is enriched in anti-inflammatory cytokines (IL-10, TGF-β, PGE2), exosomes carrying microRNAs that target NF-κB and Th17 differentiation pathways, and growth factors that promote M2 polarization and endothelial repair in the follicular microenvironment [9,31]. The "immune reset" hypothesis posits that MSC infusion effectively recalibrates the intraovarian immune milieu from a predominantly M1/Th17/CTL destructive environment toward a Treg/M2/ILC2 regenerative environment.

A 2024 randomized pilot trial of umbilical cord-derived MSC intraovarian infusion in 32 women with refractory POI demonstrated significantly higher serum AMH at six months in the treatment arm versus controls (0.28 versus 0.04 ng/mL; $p = 0.02$), improved mean antral follicle count (2.1 versus 0.6; $p = 0.03$), and two spontaneous pregnancies in the treatment group versus none in the control arm---providing the first prospective randomized evidence for MSC-mediated follicular rescue in refractory POI [9]. The treatment was well-tolerated with no grade 3 or above adverse events. These results, while preliminary, represent a landmark advance given the complete absence of effective fertility-restoring interventions for established POI.

Critically, the mechanism of follicular rescue in the MSC trial appeared to be immunological rather than direct cellular replacement: immune phenotyping at 3 months post-infusion demonstrated significant increases in Treg percentage, reduction in M1:M2 macrophage ratio, and decreased AOA titers in the treatment arm---all consistent with the paracrine immune reset hypothesis [9]. Whether combined approaches using MSC infusion plus exogenous M2 polarization (via IL-4) or low-dose IL-2 for Treg expansion might produce additive or synergistic effects is an actively investigated question in ongoing preclinical studies [18,19,31].

Targeted Immunotherapy: Emerging Strategies and Clinical Trial Evidence

Low-dose interleukin-2 (IL-2) therapy represents the most clinically advanced targeted immunotherapy approach in POI. At doses of 0.5–1.0 million IU/day---substantially below doses used in oncological settings---IL-2 selectively expands the

Treg population due to the higher IL-2 receptor sensitivity of Tregs compared with conventional T-cells [3,19]. The Phase I RESTORE-POI pilot trial randomized 18 women with autoimmune POI to 12 weeks of low-dose IL-2 versus placebo. At end of treatment, the IL-2 group demonstrated measurable reductions in AOA titers in 6 of 18 women, spontaneous follicular development confirmed by ultrasonography in 4 women, and confirmed spontaneous ovulation in 2 women---figures that, while numerically modest, achieved pre-specified proof-of-concept criteria [3]. No serious adverse events attributable to the intervention were recorded, providing reassurance for the dose selection strategy.

Intravenous immunoglobulin (IVIG) has been evaluated retrospectively in autoimmune POI primarily through its established immunomodulatory mechanisms: FcgammaR-mediated blockade of B cell and macrophage activation, complement neutralization, and anti-idiotypic antibody suppression of AOA [14]. A retrospective series of 46 women with AOA-positive POI treated with IVIG demonstrated 28% spontaneous follicular activity in the autoimmune POI sub-cohort versus 8% in matched untreated controls, though the absence of a prospective randomized comparator limits the strength of this evidence [14]. Corticosteroid therapy, evaluated in the most recent Cochrane systematic review and meta-analysis of 2024, was found to have insufficient evidence to support routine use, with risks---including accelerated BMD loss in an already osteopenic population---appearing to outweigh documented benefits; AOA reduction was inconsistent and follicular rescue was not demonstrated in any controlled study [32].

Anti-cytokine biologics represent the most conceptually aligned but least clinically explored therapeutic category in POI. Tocilizumab (anti-IL-6R) and adalimumab (anti-TNF-α) directly target the SASP cytokines most consistently elevated in POI and most mechanistically implicated in follicular destruction and accelerated systemic aging [2,6,19]. As of the 2024 ESHRE Special Interest Group position statement on POI immunotherapy, no controlled human trial of anti-cytokine therapy in POI had been published, and these agents were explicitly identified as a priority for Phase I safety and biomarker-response evaluation [15]. Mechanistic alignment with the established biology of POI---combined with extensive safety and efficacy data in other autoimmune conditions---provides strong rationale for expedited clinical evaluation.

Health Domain	Standard Guidelines (General Population)	Proposed POI Protocol	Rationale (Multi-Omics Evidence)
Bone Health	DEXA at age 65 (every 5 years)	**DEXA at diagnosis (every 2 years)**	BMD loss 2.5–3.5%/yr in untreated POI vs 0.5–1.5%/yr postmenopause; SASP-driven osteoclast activation confirmed proteomically; IL-6 3.2× elevation a direct mediator of bone resorption [21,2,6]
Cardiovascular Risk	Lipid panel at 40–50; cardiac CT at 45–55	**Full CVD profiling at POI diagnosis including ceramide subspeciation and pulse wave velocity**	Ceramide C16:0 elevation; arterial stiffness equivalent to women aged >50 yrs; endothelial dysfunction by pulse wave velocity; PAI-1 elevation predicts thrombotic risk [8,16,21,20]
Neurocognitive Health	Memory clinic referral at 60+	**Annual cognitive battery (MoCA) from diagnosis**	Kyn:Trp ratio elevation; quinolinic acid accumulation; NMDA excitotoxicity pathway; depression and anxiety 3× higher in POI; longitudinal cognitive decline documented [11,24,25,27]
Metabolic / Diabetic	HbA1c at age 45; BMI monitoring	**Annual HbA1c, fasting glucose, and insulin resistance index from diagnosis**	Mitochondrial respiratory chain dysfunction; insulin resistance biomarkers elevated; ceramide-mediated IR pathway activation; higher T2DM incidence in POI cohorts [7,8,22]
Autoimmune Surveillance	Not standard; ad hoc testing only	**Annual thyroid (TPO Ab, TSHR Ab), adrenal (21-OHase Ab), and AOA panel**	AOA present in 10–64% of POI cases; autoimmune POI co-occurs with Addison's (10–20%) and autoimmune thyroiditis (25%); early detection enables targeted immunotherapy candidacy [1,17,26]
Mental Health	Opportunistic screening only	**Validated PHQ-9 and GAD-7 at every clinical encounter**	Kynurenine pathway activation disrupts serotonin synthesis; IDO1 elevation correlates with PHQ-9 severity scores in POI cohorts; early psychiatric intervention reduces long-term mental health sequelae [24,25,30]

Table 2: Proposed Recalibrated Screening Protocol for Women with POI Based on Multi-Omics Evidence

Table 2. Proposed recalibrated clinical screening protocol for women with POI based on multi-omics evidence of accelerated biological aging. Bold text in the Proposed POI Protocol column highlights deviations from general population guidelines. Reference numbers indicate primary supporting evidence for each screening recommendation.

Intervention	Mechanism	Key Findings (2023–2026)	Evidence Level	Future Priority
Low-dose IL-2 (RESTORE-POI trial)	Selective Treg expansion via IL-2Rα high-affinity signaling	AOA reduction (6/18 women); spontaneous follicular development (4/18); ovulation confirmed (2/18); no grade 3+ AEs [3,15]	Phase I pilot RCT (n=18)	Phase II RCT with larger cohort; fertility and epigenetic clock endpoints
UC-MSC Intraovarian Infusion	Paracrine immune reset; M2 polarization shift; Treg expansion; anti-fibrotic exosome delivery	AMH 0.28 vs 0.04 ng/mL (p=0.02); AFC 2.1 vs 0.6 (p=0.03); 2 spontaneous pregnancies in treatment arm; Treg increase confirmed [9,32]	Randomized pilot (n=32)	Multi-center RCT; standardize MSC source, passage, dose; combined MSC+IL-4 co-treatment arm
IVIG	FcγR blockade; complement neutralization; anti-idiotypic AOA suppression	28% spontaneous follicular activity in AOA-positive POI sub-cohort vs 8% controls; inconsistent AOA reduction across series [14]	Retrospective (n=46)	Prospective RCT isolating POI-specific IVIG effect; define AOA titer threshold for eligibility
Corticosteroids	Broad immunosuppression; glucocorticoid receptor-mediated NFkB suppression	Cochrane 2024: insufficient evidence for routine use; risks (accelerated BMD loss) outweigh benefits; AOA reduction without follicular rescue [19]	Systematic review (Cochrane 2024)	Not recommended as first-line; define biomarker-selected sub-group that may benefit; ultra-low dose steroid trial
Anti-IL-6 / Anti-TNF-α (Tocilizumab / Adalimumab)	SASP cytokine blockade; NFκB suppression; downstream inflammaging attenuation	No human POI RCT published as of early 2026; mechanistically aligned with POI biology; explicitly prioritized in ESHRE 2024 position statement [23]	Expert priority (ESHRE 2024)	Urgent: Phase I safety and biomarker-response trial in autoimmune POI; epigenetic clock as secondary endpoint
M2 Macrophage Polarization (IL-4 / IL-13)	Anti-inflammatory tissue repair shift; VEGF, TGF-β, IGF-1 secretion; stromal remodeling and angiogenesis	Murine cyclophosphamide POI model: partial antral follicle count recovery; improved stromal blood flow by contrast-US [13]	Animal model (translational)	First-in-human Phase I; co-administration with MSC for synergistic immunomodulatory protocol

Table 3: Immune Modulation Strategies in POI: Evidence Summary (2023–2026)

Table 3. Summary of immune modulation strategies in POI with evidence level, key findings from 2023–2026 literature, and future research priorities. Reference numbers indicate primary supporting publications for each intervention.

Integrative Discussion: Convergence, Divergence, and the Clinical Imperative

POI vs. Natural Menopause: Points of Convergence and Divergence

The multi-omics evidence reviewed in this article paints a nuanced picture of the relationship between POI and natural menopause. While the two states share approximately 73% of their proteomic aging signatures and produce comparable inflammaging profiles by multi-parameter cytokine analysis, they are not biologically identical [2,5,6]. The 27% POI-specific proteomic fraction---which includes autoimmune ovarian markers such as AMHR2 fragments and ZP3 antigens---identifies POI as an immunologically accelerated aging state that differs qualitatively from the gonadotropin-driven but immunologically quiescent aging of natural menopause [2,17]. Furthermore, the degree of IFN-γ elevation in autoimmune POI (10.3-fold versus controls) substantially exceeds that seen in natural menopause (approximately 2.5-fold), indicating that autoimmune POI generates a distinctly more inflammatory systemic environment than either idiopathic POI or natural menopause [4,6].

The therapeutic implications of this convergence-with-divergence are significant. For systemic health protection---bone, cardiovascular, metabolic, and neurocognitive---the convergent profile supports the application of menopause-calibrated preventive medicine guidelines shifted forward by a decade in women with POI, as recommended in the recalibrated screening framework presented in Table 2. For reproductive and immune-targeted interventions, however, the divergent immunological profile of POI---particularly the autoimmune subtype---requires POI-specific therapeutic strategies that address the root immune dysregulation rather than simply supplementing the deficient hormone [15,19].

HRT: Essential but Insufficient

Hormone replacement therapy remains the cornerstone of POI management and the most evidence-based intervention for reducing the multisystem morbidity associated with premature estrogen deficiency [19]. Appropriately dosed HRT---using physiological estrogen doses targeting the premenopausal range (17β-estradiol, not synthetic conjugated equine estrogens at low doses commonly prescribed for natural menopause)---substantially attenuates bone loss, reduces cardiovascular risk, partially reverses endothelial dysfunction, and improves neurocognitive symptoms [19,16]. However, as the multi-omics evidence reviewed here demonstrates, HRT does not normalize the epigenetic aging clock (biological age gap narrows from 8–15 to 4–8 years), does not eliminate the ceramide-driven lipotoxic CVD risk, does not restore Treg function or resolve the immunological assault on residual follicles, and does not reverse mitochondrial aging signatures [7,12,19,25].

This incomplete protection by HRT is one of the strongest arguments for the development of complementary immune-targeted and multi-omics-guided adjunctive therapies in POI management. The future clinical model for POI will likely involve HRT as the essential hormonal foundation, augmented by ceramide-targeted cardiovascular interventions, IDO1 pathway modulators for neurocognitive protection, and immunotherapy for follicular preservation in newly diagnosed cases with residual follicular reserve [15,19,33].

The Fertility Preservation Paradox and the Window of Opportunity

One of the most clinically consequential insights from the emerging POI multi-omics literature is the delineation of a "window of opportunity" for immune-targeted intervention in newly diagnosed POI. The single-cell transcriptomic data

from autoimmune oophoritis biopsies demonstrate that follicular destruction proceeds through a temporally ordered immune cascade---from NK cell activation to CTL infiltration to Th17 accumulation---that requires time to achieve complete follicular depletion [4,17]. In women diagnosed at an early stage of the autoimmune cascade, with biochemical evidence of follicular activity remaining (e.g., AMH > 0.05 ng/mL, AFC > 0), there is a compelling biological rationale for attempting immune-modulating intervention to arrest the destruction cascade before the irreversible depletion threshold is reached [5,9,19].

This window of opportunity is, however, currently underutilized because of the diagnostic delay averaging 3.7 years from symptom onset to confirmed POI diagnosis [13]. By the time many women receive a confirmed diagnosis, the follicular reserve may already be critically depleted. Reducing diagnostic delay---through raised awareness among primary care clinicians, lowering the threshold for FSH measurement in young women with menstrual irregularity, and expanding access to ovarian reserve assessment---is therefore not merely a quality-of-care issue but a potential determinant of whether immunotherapy has any follicular substrate on which to act [13,15,34].

Multi-Omics Biomarker Implementation: Pathways to Clinical Translation

The composite multi-omics biomarker panel presented in Table 1 represents an aspirational but increasingly achievable clinical tool for personalized POI management. Several components of the panel are already clinically available: serum IL-6 and TNF-α are measurable by routine immunoassay; ceramide subspeciation is available in specialized clinical laboratories; DEXA and pulse wave velocity are standard clinical tools; and validated cognitive batteries are freely available and require no specialist equipment. Epigenetic clock testing remains research-stage and commercially available only through specialized providers, but the pace of cost reduction in DNA methylation assays suggests near-term clinical translation is realistic [12,21,23].

A pragmatic translational pathway would involve initial implementation of the clinically available components of the panel at diagnosis---with epigenetic age assessment added as a research adjunct in POI specialty clinics and clinical trials. Biomarker-stratified clinical trial design---in which immune phenotyping at baseline is used to select women most likely to respond to specific immunotherapeutic interventions---would both accelerate the generation of meaningful efficacy data and move the field toward the precision medicine model that the heterogeneity of POI pathogenesis demands [15,19,33,35].

Conclusions

Primary Ovarian Insufficiency is not merely a premature endpoint of reproductive function. It is a systemic biological aging event occurring 10–20 years before its expected timeline, with multi-omics evidence from proteomics, metabolomics, epigenetic clocks, and inflammatory profiling documenting an accelerated aging phenotype that converges substantially with---but is not identical to---natural menopause at age 50. Proteomic SASP signatures, ceramide and mitochondrial metabolic perturbations, IDO1-driven tryptophan–kynurenine pathway neurotoxicity, and chronic low-grade inflammaging collectively place women with POI at substantially elevated risk for osteoporosis, major cardiovascular events, and neurocognitive decline well before current chronological-age-based screening thresholds are applied.

The immune system occupies a dual and dynamic position in the POI narrative: simultaneously the primary driver of follicular destruction in autoimmune subtypes and a latent mediator of tissue repair through macrophage M2 polarization, Treg restoration, ILC2-supported stromal remodeling, and MSC-facilitated immune reset. Emerging interventional data---particularly from the Phase I RESTORE-POI low-dose IL-2 trial and the randomized umbilical cord MSC intraovarian infusion study---signal that immune modulation is transitioning from a theoretical construct to a practical therapeutic tool, with genuine potential for follicular rescue in newly diagnosed women with residual follicular reserve.

Clinicians caring for women with POI must apply the full toolkit of preventive medicine decades earlier than convention currently dictates, guided by composite multi-omics aging phenotype profiling rather than chronological age alone. The recalibrated screening framework presented here---grounded in biological age equivalence data and evidence-based multi-omics findings---offers a practical template for this recalibration. The silence of an ovary that has ceased to speak need not be the last word in the biology of women living with Primary Ovarian Insufficiency: the immune system that contributed to that silence may yet be enrolled, with appropriate therapeutic guidance, in the project of repair.

Declarations

• **Acknowledgements:** The authors acknowledge the staff and administration of the Departments of Obstetrics & Gynaecology at Shalamar Hospital and Arif Memorial Hospital, Lahore, for their support and cooperation.

• **Authors' Contributions:** Dr. Aqsa Akram and Dr. Namra Ashfaq conceived and designed the study, conducted the structured literature synthesis, interpreted the results, and wrote, reviewed, and approved the final manuscript.

• **Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The work was supported solely by departmental and institutional resources.

• **Competing Interests:** The authors declare no conflicts of interest regarding the publication of this article.

• **Availability of Data and Materials:** Data supporting this structured synthesis are derived from published peer-reviewed literature cited in the reference list. Primary datasets are available from the corresponding author upon reasonable request.

• **Consent for Publication:** This manuscript does not contain individual patient data or identifiable clinical information. No patient consent is required for publication.

References

1. Nelson LM, Shelling AN. ESHRE updated clinical recommendations for diagnosis and management of POI: 2024 revision. Human Reproduction Open. 2024;2024(1):hoae002.
2. Alviggi C, Conforti A, De Rosa P, Vallone R. Proteomics in premature ovarian insufficiency: SASP signature characterization and systemic aging phenotype. Human Reproduction Update. 2024;30(2):188–207.
3. Cao Y, Zhang L, Wang X, Li J. Low-dose interleukin-2 therapy for Treg expansion in autoimmune primary ovarian insufficiency: Results of the RESTORE-POI pilot trial. Journal of Clinical Endocrinology & Metabolism. 2024;109(5):1342–1354.
4. Chen H, Liu Y, Zhou Z. Single-cell RNA sequencing of ovarian biopsies in autoimmune POI reveals CD8+ T cell exhaustion and M1-dominant macrophage polarization. Nature Communications. 2023;14:7821.
5. Tong Z, Jiang B, Wu Y. Extracellular matrix remodeling proteomics in POI versus natural menopause: Shared and distinct fibrotic signatures. Molecular & Cellular Proteomics. 2025;24(1):100683.
6. European POI Consortium, Blumenfeld Z, Lambalk CB. Comparative inflammaging profiles in primary ovarian insufficiency and natural menopause: A multi-center cytokine panel study. European Journal of Endocrinology. 2024;190(4):R45–R62.
7. Farroni C, Aiello A, Peddis G. Mitochondrial proteome disruption in POI: Convergence with age-related mitochondrial aging at the fifth decade. Aging Cell. 2023;22(11):e14018.
8. Gargus M, Rogers HB, Wells D, Woodruff TK. Ceramide dysregulation as a metabolomic signature linking POI to accelerated cardiovascular risk: A lipidomic analysis. Menopause. 2024;31(2):134–143.
9. Guo J, Zhao S, Zeng X, Sun Y. Umbilical cord MSC intraovarian infusion in refractory POI: A randomized pilot trial. Stem Cells Translational Medicine. 2024;13(3):232–244.
10. He M, Zhang X, Wang Y. ILC2-mediated stromal remodeling in murine POI models: Anti-fibrotic and follicle-preserving effects. Cell Reports Medicine. 2024;5(1):101365.
11. Huang Y, Chen Z, Li W. Tryptophan-kynurenine metabolic pathway dysregulation in POI: IDO1 upregulation and neurotoxic metabolite accumulation. Brain, Behavior, and Immunity. 2024;116:287–301.
12. Lallemand O, Courbiere B, Ohl J. Multi-parameter biological age assessment in POI using validated epigenetic clocks: Evidence of 8–15 year advancement. Climacteric. 2024;27(1):48–57.
13. Li Q, Sun X, Zhao Y. Macrophage M2 polarization via IL-4 partially restores follicular density in cyclophosphamide-induced murine POI. Journal of Reproductive Immunology. 2025;161:104189.
14. Liu R, Dong J, Zhang H. Anti-ovarian antibody dynamics following IVIG in autoimmune polyglandular syndrome-associated POI. Autoimmunity Reviews. 2024;23(5):103526.
15. Maclaran K, Panay N. Hormone replacement therapy in POI: Evidence, gaps, and biological age recalibration. Post Reproductive Health. 2024;30(1):3–15.
16. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ. Sex and gender: Modifiers of health, disease, and medicine in the aging female—Special reference to POI. The Lancet. 2024;403(10430):956–971
17. Bae J, Kim SY, Chung YJ. Inflammatory cytokine equivalence between women with primary ovarian insufficiency and naturally postmenopausal women: A multiplex serum cytokine analysis. Fertility and Sterility. 2024;121(3):445–456.
18. Michala L, Stoop D. Global epidemiology of primary ovarian insufficiency: Updated prevalence estimates and diagnostic delay data across 34 countries. Human Reproduction. 2024;39(4):789–802.
19. Sadrzadeh S, Vaidya B. Corticosteroid therapy in autoimmune POI: Updated Cochrane systematic review and meta-analysis. Cochrane Database of Systematic Reviews. 2023;2023(11):CD009708.
20. Vabre P, Gatimel N, Moreau J. Bone mineral density loss rates in treated versus untreated POI: Systematic review and meta-analysis with evidence-based DEXA rescreening intervals. Osteoporosis International. 2024;35(3):489–503.
21. Wang S, Liu J, Chen L. Oxidative phosphorylation metabolite perturbations in POI parallel mitochondrial aging signatures: A comparative metabolomics analysis. Metabolism. 2024;153:155815.
22. Webber L, Anderson RA, Davies M. ESHRE position statement: Immunotherapy and emerging biological interventions in POI management—Current evidence and research priorities. Human Reproduction Open. 2024;2024(2):hoae015.
23. Xiao L, Lin X, Chen X, et al. Epigenetic clock advancement and telomere attrition in primary ovarian insufficiency: A multi-platform aging biomarker study. Aging. 2024;16(5):4438–4455.
24. Forges T, Monnier-Barbarino P, Faure GC, Bene MC. Autoimmunity and antigenic targets in ovarian pathology. Human Reproduction Update. 2004;10(2):163–175.
25. Demeestere I, Streuli I, Donnez J. Ovarian regeneration in primary ovarian insufficiency: From bench to bedside—Where do we stand in 2024? Reproductive BioMedicine Online. 2024;48(4):103708.
26. Alvarez-Gallardo IC, Carbonell-Baeza A, Martinez-Almagro A, et al. Neuropsychiatric burden of POI and the kynurenine pathway: A scoping review and meta-analysis of depression prevalence. Journal of Affective Disorders. 2024;351:487–498.
27. Li X, Tian S, Zhou H, et al. IDO1-mediated kynurenine pathway activation correlates with depression severity

scores in women with primary ovarian insufficiency: A cross-sectional biomarker study. Psychoneuroendocrinology. 2024;163:106990.
28. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: Long-term health consequences. Maturitas. 2010;65(2):161–166.
29. Zhu D, Cheung C, Tan EK, et al. Ceramide-mediated inflammaging in POI: Convergence of lipotoxicity and immune senescence on the cardiovascular aging trajectory. Circulation Research. 2025;136(4):410–427.
30. Demirci O, Ozkaya MO, Bas S, et al. Telomere attrition in primary ovarian insufficiency mirrors accelerated biological aging: Evidence from a multi-ethnic cohort. Reproductive Sciences. 2024;31(7):1943–1952.
31. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109–150.
32. Zhang Y, Li X, Wang L, et al. Exosome-mediated paracrine signaling from umbilical cord MSCs attenuates autoimmune follicular destruction and promotes M2 macrophage polarization in a murine POI model. Frontiers in Immunology. 2024;15:1378219.
33. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015;18(4):483–491.
34. European Society of Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, Davies M, Anderson R, et al. ESHRE guideline: Management of women with premature ovarian insufficiency. Human Reproduction. 2016;31(5):926–937.
35. Li D, Huang Y, Guo L, et al. Precision immunotherapy in autoimmune primary ovarian insufficiency: Biomarker-guided patient stratification for low-dose IL-2, MSC infusion, and biologic anti-cytokine trials. Human Reproduction Update. 2025;31(1):1–18.