

The Impact of Oxidative Stress Imbalance on Ovarian Function and Its Mechanisms

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Abstract: Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a critical role in female reproductive health, particularly in ovarian function. This review provides a comprehensive and updated synthesis of the impact of oxidative stress on ovarian physiological processes, including follicular development, oocyte quality, steroid hormone synthesis, luteal function, and ovarian aging. We delve into the underlying molecular mechanisms—mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory signaling (NF- κ B, NLRP3), and epigenetic alterations—and discuss how these pathways converge to drive specific cell death modalities (apoptosis, pyroptosis, ferroptosis) in granulosa cells and oocytes. The review consolidates current knowledge on diagnostic biomarkers, associated pathological conditions (polycystic ovary syndrome, premature ovarian insufficiency, endometriosis), and emerging intervention strategies. What distinguishes this review from existing literature is its systematic integration of mechanistic pathways with clinical phenotypes, its explicit discussion of conflicting evidence and knowledge gaps, and its forward-looking perspective on targeted therapies (mitochondria-directed antioxidants, stem cell-derived exosomes, traditional Chinese medicine) and lifestyle interventions. Our aim is to provide a theoretical foundation for understanding oxidative stress-mediated ovarian dysfunction and to offer practical insights for future research and clinical management.

Keywords: oxidative stress, ovarian function, follicular development, reactive oxygen species, antioxidant defense

Introduction

The ovary, as a central organ of the female reproductive system, is endowed with both reproductive and endocrine functions, making it indispensable for fertility and hormonal homeostasis. Its physiological activities, including folliculogenesis, ovulation, and steroidogenesis, are inherently linked to cellular metabolic processes that generate ROS as by-products. Under physiological conditions, ROS serve as crucial signaling molecules, participating in the regulation of key ovarian events such as follicle development and the ovulatory process.¹ However, the ovary's high metabolic activity renders it particularly susceptible to oxidative stress when the delicate balance between ROS production and the endogenous antioxidant defense system is disrupted. This imbalance, where ROS generation exceeds cellular scavenging capacity, leads to oxidative stress, a state recognized as a fundamental mechanism associated with aging and the deterioration of fertility.² The consequences of such oxidative stress imbalance are profound and multifaceted, impacting various cellular components of the ovary, including granulosa cells, oocytes, and theca cells, thereby disrupting the finely tuned processes of follicular recruitment, growth, selection, and atresia. Ultimately, this disruption contributes to a decline in ovarian reserve, diminished oocyte quality, endocrine dysfunction, and a consequent recession in fertility potential.

The detrimental impact of oxidative stress on ovarian function is not merely a consequence of normal aging but is also implicated in the pathogenesis of various ovarian-related disorders. A significant body of evidence underscores the role of oxidative stress in conditions such as premature ovarian failure (POF), also referred to as premature ovarian insufficiency

(POI). In POF, characterized by hypergonadotropic hypogonadism and follicular dysplasia in women under forty, elevated levels of ROS and oxidative stress markers like malondialdehyde (MDA) are consistently observed, alongside a reduction in antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). Experimental models, often induced by agents like D-galactose (D-gal) or cyclophosphamide (CTX), replicate this oxidative damage, leading to increased follicular atresia, granulosa cell apoptosis, and hormonal disturbances. Interventions with compounds possessing antioxidant properties, such as amygdalin or chrysin, have been shown to ameliorate these effects by inhibiting oxidative stress, reducing inflammation, and suppressing apoptosis in granulosa cells, thereby improving ovarian function. Similarly, oxidative stress is a key driver of ovarian aging, a process marked by a gradual loss of the primordial follicle pool and declining endocrine function. In aged rat models, markers of oxidative damage are elevated, while interventions like resveratrol can delay ovarian aging by reducing oxidative damage and activating pathways such as those involving Sirt1.³ Furthermore, environmental factors and lifestyle exposures can exacerbate ovarian oxidative stress. For instance, maternal exposure to a high-fat diet (HFD) or environmental pollutants like heavy metals (eg, copper, arsenic, cadmium) can induce oxidative stress through direct or indirect mechanisms, leading to adverse effects on ovarian function in both experimental animals and women, including follicular atresia, decreased estrogen production, and conditions resembling premature ovarian insufficiency. These findings collectively highlight oxidative stress as a common pathological nexus linking diverse etiologies to ovarian dysfunction.

At the cellular level, oxidative stress exerts its damaging effects primarily on granulosa cells and oocytes, which are critical for follicular integrity and oocyte competence. Granulosa cells, which provide essential support for oocyte growth and steroid hormone production, are highly vulnerable to oxidative damage. Exposure to oxidative stressors like cisplatin or hydrogen peroxide (H₂O₂) can induce granulosa cell apoptosis, mitochondrial dysfunction, and a decline in steroidogenic capacity. Protective mechanisms involve the enhancement of mitochondrial function and the upregulation of antioxidant pathways. For example, growth hormone (GH) has been shown to protect against cisplatin-induced granulosa cell apoptosis by alleviating oxidative stress and enhancing mitochondrial function via the Sirt3-Sod2 pathway.⁴ Similarly, in polycystic ovary syndrome (PCOS), a condition characterized by hyperandrogenism and abnormal folliculogenesis, oxidative stress in granulosa cells is significantly heightened. Hyperandrogenemia in PCOS can induce excessive oxidative stress, for instance, by increasing the flux of the polyol pathway, which in turn impairs ovarian function.⁵ The oocyte itself is also a direct target of oxidative damage. Oocytes from models of POF or aging exhibit excessive ROS, increased mitochondrial DNA damage, and abnormal morphology.⁶ The quality of oocytes, crucial for successful fertilization and embryonic development, is particularly compromised under conditions of oxidative stress during in vitro maturation (IVM) or due to post-ovulatory aging. Accumulation of ROS in oocytes cultured in vitro is a major factor impairing maturation rates, spindle assembly, and subsequent embryo developmental potential. Antioxidant supplementation, such as with coenzyme Q10, N-acetyl-L-cysteine (NAC), or specific compounds like α -ketoglutarate, has been demonstrated to reduce ROS levels, improve oocyte quality, and enhance embryonic development outcomes. These insights underscore the centrality of oxidative balance in maintaining the functional integrity of both somatic and germ cell compartments within the ovary.

The molecular mechanisms underpinning oxidative stress-induced ovarian damage are complex and involve a network of signaling pathways and cellular processes. Key pathways include the PI3K/Akt/FoxO3a axis, the Nrf2 antioxidant response pathway, and pathways regulating mitochondrial function and mitophagy. In models of POF, oxidative stress can dysregulate the PI3K/Akt/FoxO3a signaling pathway, and its modulation by agents like quercetin can restore ovarian function and inhibit oxidative stress.⁷ The transcription factor Nrf2 is a master regulator of the cellular antioxidant response. Activation of Nrf2, often in concert with SIRT1, can upregulate the expression of antioxidant enzymes like SOD and catalase, providing a defense against oxidative insult. Resveratrol, for example, alleviates ovarian oxidative stress by upregulating Nrf2 and SIRT1 while downregulating FoxO1 and P53.² Mitochondria are both a major source of ROS and a primary target of oxidative damage. Mitochondrial dysfunction, characterized by loss of membrane potential, reduced mitochondrial DNA copy number, and impaired oxidative phosphorylation, is a hallmark of oxidative stress in ovarian cells. Enhancing mitophagy, the selective autophagy of damaged mitochondria, is a crucial quality control mechanism. Compounds like HEP14 have been shown to improve ovarian function in aged mice by inducing mitophagy and effectively clearing ROS, mediated through the activation of the PKC-ERK1/2 pathway.⁸ Conversely, impaired mitophagy can exacerbate damage. In primary ovarian insufficiency, inhibition of

PINK1-Parkin mediated mitophagy by He's Yang Chao Recipe was associated with improved ovarian function and reduced oxidative stress.⁹ Furthermore, oxidative stress can trigger inflammatory responses and programmed cell death pathways such as apoptosis, pyroptosis, and even ferroptosis in granulosa cells, contributing to follicular atresia. The interplay between oxidative stress, inflammation (evidenced by elevated cytokines like TNF- α , IL-1 β , IL-6), and cell death forms a vicious cycle that accelerates ovarian functional decline. Understanding these intricate molecular dialogues is essential for developing targeted therapeutic strategies.

Given the central role of oxidative stress in ovarian pathophysiology, identifying and developing effective intervention strategies has become a major focus of research. These strategies primarily aim to bolster the endogenous antioxidant defense system or directly scavenge excess ROS. A wide array of natural compounds and pharmacological agents have demonstrated protective potential. Antioxidants such as resveratrol, quercetin, melatonin, and proanthocyanidins have shown efficacy in various experimental models of ovarian aging, POF, and PCOS by reducing oxidative stress markers, enhancing antioxidant enzyme activities, inhibiting apoptosis, and improving steroidogenesis. For instance, melatonin alleviates ovarian function damage induced by dexamethasone in laying hens by enhancing antioxidant enzymes and inhibiting the FOXO1 pathway.¹⁰ Similarly, the quercetin/cyclodextrin complex ameliorates symptoms in a PCOS rat model by decreasing oxidative stress markers and improving antioxidant activity.¹¹ Beyond small molecules, physical therapies like photobiomodulation (PBM) have emerged as non-invasive approaches. PBM treatment in naturally aging mice was found to restore ovarian function by alleviating oxidative stress, reducing chronic inflammation, and improving mitochondrial function.¹² In the context of assisted reproductive technologies (ART), optimizing in vitro culture conditions is critical. Supplementation of culture media with antioxidants like L-carnitine, curcumin, or punicalagin can mitigate oxidative stress damage during ovarian tissue culture, follicle growth, oocyte maturation, and embryo development, thereby improving outcomes. Furthermore, addressing systemic or environmental sources of oxidative stress, such as through dietary management or avoidance of pollutants, represents a preventive approach. The exploration of novel delivery systems, such as antioxidant-enriched hydrogels or stem cell-conditioned media, holds promise for enhancing the efficacy and targeted delivery of therapeutic agents.¹³ As research progresses, a multi-faceted approach combining lifestyle modifications, antioxidant supplementation, and advanced biomedical interventions may offer the most effective means to preserve ovarian function and combat infertility associated with oxidative stress.

Despite the extensive body of research linking oxidative stress to ovarian dysfunction, several critical gaps remain unresolved. First, the clinical translation of antioxidant therapies has yielded inconsistent results, partly due to heterogeneity in study designs, populations, and outcome measures. Second, the role of specific cell death pathways—particularly pyroptosis and ferroptosis—in ovarian pathophysiology is only beginning to be understood, and their interplay with classical apoptosis remains poorly defined. Third, biomarkers for assessing ovarian oxidative stress status lack standardization, limiting their utility in routine clinical practice. Fourth, the transgenerational effects of oxidative stress on offspring ovarian function are underinvestigated. Fifth, emerging interventions (eg, stem cell-derived exosomes, mitochondria-targeted antioxidants, epigenetic modulators) remain at preclinical stages, and their safety and efficacy in humans require rigorous validation. This review aims to address these gaps by: (i) providing a balanced synthesis of established and controversial findings; (ii) highlighting mechanistic convergence and divergence across different ovarian pathologies; (iii) critically appraising current evidence for antioxidant interventions; and (iv) outlining a roadmap for future research and clinical translation.

The Impact of Oxidative Stress on Ovarian Follicle Development and Atresia Interference with Primordial Follicle Pool Activation and Maintenance

Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, critically disrupts the activation and maintenance of the primordial follicle pool, the cornerstone of female reproductive lifespan. Excessive ROS directly inflicts damage on the genetic material of oocytes within primordial follicles. Studies have shown that exposure to environmental toxins like ochratoxin A (OTA) or chemotherapeutic agents such as cyclophosphamide (Cyc) leads to increased DNA damage markers like γ H2AX in germ cells, impairing meiosis progression and primordial follicle formation.¹⁴ This damage, if unrepaired, accumulates and compromises oocyte genomic stability and long-term survival, accelerating the

depletion of the finite ovarian reserve.¹⁵ In conditions like classic galactosemia (CG) or in BRCA1/2 mutant models, elevated oxidative stress is associated with increased DNA damage (p-H2A.X) and activation of DNA repair pathways within primordial follicles, which can paradoxically lead to accelerated follicular atresia and a diminished follicle pool.^{16,17} The oocyte itself employs defense mechanisms, such as high expression of the antioxidant enzyme superoxide dismutase 1 (SOD1), to maintain low intracellular ROS levels essential for sustaining dormancy; a decline in this defense, as seen with aging or genetic deletion, results in oxidative damage and triggers cell death pathways like ferroptosis in primordial follicles.¹⁸ Furthermore, oxidative stress perturbs key signaling pathways that govern the primordial follicle's decision to remain dormant or activate. A central mechanism involves the dysregulation of the PTEN/PI3K/AKT/FOXO3a axis. Under physiological conditions, this pathway is tightly controlled to prevent premature activation. However, oxidative stress can disrupt this balance. For instance, maternal exposure to fine particulate matter (PM2.5) or the presence of a *Brcal* mutation leads to upregulated phosphorylation of AKT and the subsequent nuclear extrusion of the dormancy guardian FOXO3a, thereby promoting aberrant primordial follicle activation and hastening ovarian reserve decline.^{19,20} Conversely, in CG, oxidative stress is linked to a significant reduction in phospho-AKT levels in granulosa cells and oocytes, suggesting an impaired activation and survival signal that also contributes to pool depletion.¹⁶ The role of oxidative stress in pathway dysregulation is further highlighted by interventions; the PI3K inhibitor LY294002 can reverse PM2.5-induced overactivation, and antioxidants like apigenin can restore AKT/FOXO3a signaling disrupted by 4-vinylcyclohexene diepoxide (VCD), thereby protecting the primordial follicle pool.^{19,21} The vulnerability of primordial follicles is exacerbated by a compromised follicular microenvironment. A reduction in the activity of crucial antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), leaves follicles more susceptible to oxidative insult. In models of glutathione deficiency (*Gclm*^{-/-} mice), accelerated primordial follicle loss is observed alongside ovarian oxidative stress.²² Similarly, exposure to shikonin decreases SOD activity and glutathione (GSH) levels, promoting follicle atresia.²³ Protective agents often exert their effects by bolstering this antioxidant shield. Melatonin, N-acetylcysteine (NAC), and compounds like paeoniflorin (PF) or capsaicin have been shown to enhance the activity of endogenous antioxidants (eg, SOD, GPx), increase GSH levels, or upregulate the NRF2 antioxidant response pathway, thereby mitigating oxidative damage and preserving primordial follicle counts.^{24–27} This protective effect is crucial in contexts like ischemia-reperfusion injury following ovarian tissue transplantation, where oxidative stress is a major driver of follicular loss.²⁸ In summary, oxidative stress orchestrates a multi-faceted attack on the primordial follicle pool through direct genotoxic damage to oocytes, dysregulation of critical dormancy pathways like PI3K/AKT/FOXO3a, and the weakening of intrinsic antioxidant defenses, collectively leading to premature activation, impaired survival, and accelerated depletion of ovarian reserve.

Inhibition of Preantral and Antral Follicle Growth

Oxidative stress exerts a profound inhibitory effect on the growth and development of preantral and antral follicles, primarily by inducing granulosa cell apoptosis, thereby compromising the essential nutritional support and signaling to the oocyte and leading to follicular developmental arrest or delay. In vitro culture models consistently demonstrate that the accumulation of reactive oxygen species (ROS) is a key limitation for preantral follicle survival and growth.²⁹ Antioxidant supplementation, such as ascorbic acid, has been shown to promote follicular development and maintain morphological integrity in bovine preantral follicles by stabilizing ROS levels.³⁰ Similarly, compounds like astaxanthin and sodium butyrate enhance in vitro follicular growth, antral formation, and oocyte maturation rates while concurrently reducing oxidative stress markers like malondialdehyde (MDA) and intracellular ROS.^{31,32} The protective role of antioxidants is further evidenced by studies on N-acetyl-cysteine (NAC), which sustains preantral follicle growth and cell viability during long-term culture,³³ and stem cell-conditioned medium, which improves follicular survival and growth while reducing ROS levels in spent media.³⁴ This granulosa cell apoptosis, triggered by oxidative stress, is a direct mechanism disrupting the follicular unit, as seen in models where environmental toxicants like bisphenol A (BPA) promote ROS production and apoptosis in mouse pre-antral follicle granulosa cells.³⁵

Furthermore, ROS can activate stress kinase pathways such as p38 MAPK and JNK, which inhibit granulosa cell proliferation and reduce the secretion of critical factors like Anti-Müllerian Hormone (AMH), thereby disrupting the follicular selection process. Pro-inflammatory cytokines, which are often elevated in conditions associated with oxidative stress, such as obesity or polycystic ovary syndrome (PCOS), can directly impair early follicular development. For

instance, $\text{TNF-}\alpha$, $\text{IL-1}\beta$, and IL-6 disrupt granulosa and theca cell function during the preantral-to-antral transition, suppressing FSH-induced granulosa cell proliferation and steroidogenesis while elevating oxidative stress in granulosa cells.³⁶ The activation of p38 MAPK and JNK pathways is a common downstream event of such inflammatory and oxidative insults. In bovine granulosa cells, oxidative stress induced by H_2O_2 leads to differential expression of various transcription factors mediated by the NRF2 signaling pathway, which is intertwined with stress response mechanisms.³⁷ The reduction in AMH, a key regulator of follicular recruitment, is another consequence. Studies show that oxidative stress can compromise AMH levels, as seen in carboplatin-induced ovarian toxicity where antioxidants like melatonin help preserve AMH.³⁸ The expression of growth factors essential for folliculogenesis, such as BMP15 and GDF9, is also altered under oxidative conditions, as observed in buffalo ovarian tissue across different follicular stages.³⁹

Finally, oxidative damage compromises the structural integrity of the follicular unit, particularly the basement membrane, affecting the exchange of materials between the follicle and its environment and potentially inciting a local inflammatory response that further deteriorates the growth milieu. The integrity of the follicular basement membrane and the extracellular matrix is crucial for follicular development. Oxidative stress can disrupt this integrity, as suggested by studies where antioxidants like the ethanolic extract of *Punica granatum* L. preserve follicle morphology and ultrastructure in cultured bovine ovarian tissue, indicating protection against such damage.⁴⁰ Similarly, cryopreservation processes, which induce oxidative stress, can damage preantral follicles, with higher concentrations of cryoprotectants like DMSO leading to increased ROS levels and follicular degeneration.⁴¹ This structural damage facilitates adverse exchanges and inflammatory responses. For example, in a mouse model of ovarian endometriosis, iron accumulation from endometriotic lesions leads to oxidative stress in follicles at all stages, disrupting the follicular microenvironment and contributing to infertility.⁴² Furthermore, exposure to environmental nanoparticles like TiO_2 and ZnO disrupts the cytoskeleton arrangement and ultrastructure of antral follicles, effects mediated partly through oxidative stress pathways.⁴³ The resulting pro-inflammatory state, characterized by cytokine release and fibrotic signaling as seen with cytokine exposure,³⁶ creates a hostile environment that impedes the coordinated cellular interactions necessary for sustained follicular growth and development.

Regulation of Dominant Follicle Selection and Ovulation Process

Ovulation is a complex physiological event that inherently involves localized inflammation and a controlled increase in reactive oxygen species (ROS) generation, which are essential for follicular rupture and oocyte release.⁴⁴ This process is tightly regulated by the luteinizing hormone (LH) surge and involves a cascade of molecular events, including the activation of inflammatory pathways and the production of prostaglandins, cytokines, and proteases necessary for extracellular matrix breakdown.⁴⁴ However, excessive oxidative stress disrupts this precise balance, leading to ovulatory dysfunction. In conditions like polycystic ovary syndrome (PCOS), elevated oxidative stress is a hallmark and is closely associated with ovulation disorders.^{45,46} Studies using single-cell transcriptomics have revealed a significant upregulation of oxidative stress pathways in women with ovulation dysfunction, including PCOS and primary ovarian insufficiency, alongside distinct alterations in immune cell populations.⁴⁷ This imbalance can impair the normal inflammatory cascade required for ovulation. For instance, in endometriosis-associated infertility, oxidative stress decreases the expression of EZH2 and H3K27Me3 in ovarian granulosa cells, which in turn upregulates IL-1 receptor 2 (IL-1R2), a decoy receptor that suppresses the essential $\text{IL-1}\beta$ -mediated inflammatory signaling necessary for ovulation, contributing to conditions like luteinized unruptured follicle syndrome.⁴⁸ Furthermore, excessive ROS directly impacts the expression of genes critical for cumulus expansion, such as PTGS2 (prostaglandin-endoperoxide synthase 2) and HAS2 (hyaluronan synthase 2).⁴⁸ Cumulus expansion is vital for the formation of a functional cumulus-oocyte complex (COC) that facilitates oocyte maturation and its release from the follicle. Oxidative stress can damage this process, compromising COC function. Research indicates that oxidative stress induced by hydrogen peroxide (H_2O_2) in granulosa cells leads to increased apoptosis and inflammation, which are detrimental to follicular health.⁴⁹ In PCOS models, hyperandrogenism can induce hyperactivity of the polyol pathway, leading to a further increase in oxidative stress flux that damages ovarian function and follicular maturation.⁵ The negative impact of oxidative stress extends to the oocyte itself. Elevated ROS levels in the follicular fluid microenvironment, often seen in conditions like PCOS or with advanced maternal age, are associated with reduced oocyte competence, impaired meiotic maturation, and lower fertilization and embryo development rates.^{50,51} Antioxidant defenses are crucial to counteract this. For example, the selenium-dependent antioxidant enzyme GPX1 and its selenium-uptake receptor LRP8 show increased expression in

granulosa cells of developing follicles, correlating with steroidogenic activity to neutralize ROS produced during hormone synthesis.⁵² Interventions that modulate oxidative stress, such as short-term metformin therapy in clomiphene-resistant PCOS patients, have been shown to improve follicular fluid redox balance by lowering total oxidant status (TOS) and the oxidative stress index (OSI) while increasing total antioxidant status (TAS), resulting in a higher number of mature follicles and improved fertilization rates.⁵³ Similarly, antioxidant supplementation, including N-acetylcysteine (NAC), vitamin E, and natural compounds like Swertiamarin or Carnosol, has demonstrated potential in ameliorating oxidative damage, restoring follicular development, and improving ovulation outcomes in both animal models and clinical settings.^{54–57} Therefore, while physiological ROS generation is a necessary component of the ovulatory signal, pathological oxidative stress acts as a key disruptor, interfering with the hormonal, inflammatory, and proteolytic equilibrium required for dominant follicle selection, cumulus expansion, and successful ovulation, ultimately contributing to female infertility.

Oxidative Stress Damage to Oocyte Quality and Developmental Potential

Induction of Asynchrony Between Nuclear and Cytoplasmic Maturation of Oocytes

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is a critical factor disrupting the precise coordination between nuclear and cytoplasmic maturation in oocytes, ultimately compromising their developmental competence. High levels of ROS directly interfere with the assembly and stability of the meiotic spindle apparatus and the proper alignment of chromosomes, thereby increasing the risk of aneuploidy. This is evidenced by studies showing that exposure to polystyrene nanoparticles (PS-NPs) during meiotic maturation in mouse oocytes leads to impaired spindle assembly and chromosome misalignment.⁵⁸ Similarly, in a model of hyperglycemic and hyperlipidemic (HGHL) conditions mimicking metabolic stress, mouse oocytes exhibited significant spindle abnormalities and chromosome misalignment, which are hallmarks of compromised nuclear maturation and contributors to aneuploid embryos.⁵⁹ These disruptions in the nuclear maturation process, driven by oxidative stress, create a fundamental asynchrony with cytoplasmic events, as the oocyte progresses to metaphase II with a genetically unstable configuration. Consequently, even if fertilization occurs, the resulting embryo carries a high risk of developmental failure due to this initial chromosomal instability. Beyond the nucleus, oxidative stress profoundly impairs cytoplasmic maturation by damaging mitochondrial function. Mitochondria are not only the primary source of ATP but also key regulators of calcium homeostasis and redox signaling. The accumulation of PS-NPs in mouse oocytes was associated with increased oxidative stress and mitochondrial aggregation, indicating dysfunctional organelle distribution and likely reduced efficiency in energy production.⁵⁸ In the HGHL model, altered mitochondrial distribution patterns were also observed, further linking metabolic and oxidative stress to organelle dysregulation.⁵⁹ This mitochondrial dysfunction leads to insufficient ATP generation, which is required for energy-intensive processes critical for cytoplasmic maturation. These processes include the regulation of calcium ion oscillations, which are essential for signaling and activation post-fertilization, and the proper distribution of cortical granules, which are crucial for establishing the block to polyspermy. The study on ovine oocytes highlights that oxidative stress detected during extended meiotic arrest maintenance protocols can be detrimental, and that antioxidant supplementation is essential to improve oocyte developmental potential, underscoring the negative impact of ROS on cytoplasmic quality.⁶⁰ Furthermore, oxidative stress can disrupt other cytoplasmic components. For instance, PS-NPs were found to localize around the endoplasmic reticulum (ER) and disturb protein translation, a key aspect of cytoplasmic preparation.⁵⁸ The HGHL conditions also induced ER stress and poor organization of the actin cytoskeleton, which is vital for organelle positioning and cytokinesis.⁵⁹ The actin filament disorganization and aberrant cortical granule distribution observed under such conditions are direct manifestations of failed cytoplasmic maturation. Therefore, oxidative stress acts as a pervasive disruptor, targeting both the nuclear machinery for chromosome segregation and the cytoplasmic machinery for energy production, organelle function, and molecular synthesis. This dual assault ensures that even if an oocyte completes nuclear maturation, its cytoplasmic compartment remains inadequately prepared to support subsequent fertilization, embryo cleavage, and implantation, leading to overall poor developmental outcomes.

Leading to Abnormal Mitochondrial Structure and Function in Oocytes

Oxidative stress directly compromises oocyte quality by inducing structural and functional abnormalities in mitochondria, which are critical for oocyte competence. ROS directly attack mitochondrial components, leading to mitochondrial DNA (mtDNA) mutations and damage to membrane lipids. This damage manifests as a decline in mitochondrial membrane potential ($\Delta\Psi_m$) and morphological alterations such as swelling and cristae breakage.^{61–63} For instance, studies on post-ovulatory aging in mouse oocytes and hydrogen peroxide (H₂O₂)-induced stress in porcine oocytes demonstrate that oxidative stress causes mitochondrial dysfunction characterized by decreased $\Delta\Psi_m$ and ultrastructural damage.^{61,62} Similarly, vitrification of oocytes induces oxidative stress that damages mitochondrial structure, leading to blurred cristae and dysfunction.⁶³ Exposure to environmental toxicants like PBDE47, Sudan I, nivalenol, fumonisin B1, methylmercury chloride (MMC), rotenone, arsenic, cadmium, and juglone also triggers mitochondrial dysfunction in oocytes across species, evidenced by aberrant distribution, reduced $\Delta\Psi_m$, and morphological abnormalities.^{64–72} This structural damage is intrinsically linked to functional failure. Mitochondria with compromised integrity exhibit reduced oxidative phosphorylation capacity and metabolic activity, leading to decreased adenosine triphosphate (ATP) production.^{66–73} Crucially, these functionally impaired mitochondria become a source of further ROS generation, establishing a vicious cycle of escalating oxidative stress and mitochondrial decay.^{74,75} This self-perpetuating cycle is a core mechanism underpinning the decline in oocyte quality, as it severely diminishes the oocyte's bioenergetic capacity and metabolic homeostasis required for successful maturation, fertilization, and embryonic development.^{61,62,75} The central role of this mitochondrial-ROS vicious cycle is further highlighted by interventions targeting it. Antioxidants like melatonin, epigallocatechin-3-gallate (EGCG), Coenzyme Q10 (CoQ10), ubiquinol-10, Mito-TEMPO, L-carnitine, N-acetylcysteine (NAC), and glutathione (GSH) have been shown to mitigate oxidative stress, restore $\Delta\Psi_m$, improve mitochondrial ultrastructure, and enhance ATP production, thereby rescuing oocyte maturation and developmental competence.^{65–81} Furthermore, molecular regulators such as AMPK, DRP1, PKD, SIRT1, and GAS6 are implicated in maintaining mitochondrial function and preventing oxidative stress; their loss or inhibition leads to mitochondrial dysfunction, ROS accumulation, and oocyte quality defects.^{82–86} This pathological cascade is not limited to the oocyte itself but can have transgenerational consequences, as mitochondrial damage in oocytes can impair offspring health and mitochondrial function.^{61,87} Therefore, the direct assault by ROS on mitochondrial integrity, culminating in a self-amplifying loop of dysfunction and oxidative stress, represents a fundamental pathological pathway through which oxidative imbalance critically undermines oocyte quality and female fertility.

Impact on the Stability of Oocyte Epigenetic Modifications

Oxidative stress significantly compromises the stability of epigenetic modifications in oocytes, primarily by altering the activity of key enzymes responsible for DNA methylation and histone modifications. This disruption can lead to aberrant gene expression patterns that impair oocyte maturation and developmental competence. For instance, exposure to environmental toxicants like cadmium (Cd) or bisphenol F (BPF) induces severe oxidative stress and DNA damage in mouse oocytes, which is concurrently associated with altered histone modification levels, such as increased H3K27me3.⁸⁸ Similarly, studies on copper exposure in porcine oocytes demonstrate that oxidative stress induced by the metal leads to abnormalities in mitochondrial function and epigenetic modifications, including changes in histone acetylation (H3K9ac), ultimately reducing oocyte quality.⁸⁹ The direct link between reactive oxygen species (ROS) accumulation and epigenetic dysregulation is further evidenced in models of maternal obesity, where a high-fat diet increases ROS and DNA damage within oocytes, leading to significant abnormalities in DNA methylation and histone modification remodeling during subsequent zygotic genome activation.⁹⁰ This epigenetic instability is not merely a correlative finding; interventions that mitigate oxidative stress, such as supplementation with antioxidants like melatonin or *Nigella sativa* extract, consistently demonstrate a rescue of both oxidative parameters and epigenetic markers. For example, melatonin protects mouse oocytes from cadmium-induced meiosis defects by ameliorating oxidative stress and restoring altered epigenetic modifications like H3K9me2 and H3K4me2.⁹¹ Likewise, a hydro-alcoholic extract of *Nigella sativa* improved oocyte maturation in a polycystic ovary syndrome (PCOS) mouse model by modifying oxidative status and upregulating mRNA expression of epigenetic-related genes such as Dnmt1 and Hdac1.⁹² These findings collectively establish that oxidative stress acts as a potent disruptor of the enzymatic machinery governing the oocyte's epigenome, creating a vulnerable state that undermines its developmental potential.

The epigenetic alterations induced by oxidative stress in oocytes possess a profound transgenerational dimension, as these changes can be transmitted to the embryo and influence gene expression and long-term health in offspring, providing a mechanistic explanation for oxidative stress-mediated intergenerational effects. This concept is strongly supported by research showing that maternal exposure to stressors like cadmium or a high-fat diet leads to epigenetic modifications in oocytes that persist in the next generation. Maternal cadmium exposure during pregnancy in mice resulted in selective epigenetic alterations in offspring oocytes, including changes in H3K4me2, H4K12ac, and DNA methylation at the H19 locus, which were linked to decreased oocyte quality and impaired early embryonic development.⁹³ This study provides direct evidence for the transgenerational epigenetic inheritance of cadmium's reproductive toxicity. Similarly, maternal obesity in mice, driven by a high-fat diet, elevated RIF1 levels in oocytes, which mediated abnormal histone modification remodeling on the MuERV-L retrotransposon during zygotic genome activation in the embryo; this epigenetic dysregulation was associated with an increased metabolic risk in the offspring.⁹⁰ The transmission mechanism often involves the oocyte's compromised ability to maintain proper epigenetic marks under oxidative duress, which then sets an aberrant epigenetic landscape in the early embryo. For example, exposure of mouse oocytes to the insecticide rotenone, which generates oxidative stress, altered the expression of genes involved in histone methylation and acetylation modifications; these changes contributed to meiotic defects and were partially heritable, as melatonin treatment could rescue both the oxidative damage and the associated histone modification abnormalities.⁹⁴ Furthermore, oxidative stress induced by factors like vitrification or heat stress in bovine oocytes leads to reduced expression levels of various epigenetic modifications, including DNA methylation and multiple histone marks (eg, H1, H2A, H2B, H4), in both oocytes and resulting embryos, compromising their developmental resilience.^{95,96} The persistence of these oxidative stress-induced epigenetic errors into the blastocyst stage and beyond underscores their potential to program long-term phenotypic outcomes. This is exemplified by studies on perfluorohexane sulfonate (PFHxS), where exposure during bovine oocyte maturation not only decreased developmental competence but also induced transcriptomic and DNA methylation changes in the resulting blastocysts, enriching pathways related to oxidative stress response.⁹⁷ Thus, the oocyte serves as a critical vector for the intergenerational transmission of environmentally induced epigenetic disturbances, with oxidative stress being a key upstream driver that disrupts the stability of the epigenetic code, thereby influencing the developmental trajectory and health of subsequent generations.

Interference of Oxidative Stress with Ovarian Steroid Hormone Synthesis

Inhibition of Key Enzyme Activities for Estrogen Synthesis in Granulosa Cells

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, exerts a profound inhibitory effect on the activity and expression of aromatase (CYP19A1), the key enzyme responsible for converting androgens to estradiol in granulosa cells, thereby contributing to estrogen insufficiency. Multiple studies across different models demonstrate this consistent downregulation. In sow granulosa cells, oxidative stress downregulates the transcription of CYP19A1 and reduces 17 β -estradiol (E2) release via the FoxO1 and NORSF axis.⁹⁸ Similarly, in human KGN granulosa-like tumor cells, treatments that induce a hyperandrogenic, PCOS-like state, such as D-chiro-inositol and bacterial lipopolysaccharide (LPS), significantly downregulate both aromatase gene and protein expression, leading to reduced estradiol secretion.⁹⁹ This impairment is not limited to pathological models; even in the context of high glucose exposure mimicking diabetic conditions, mouse granulosa cells show decreased estradiol secretion and downregulation of Cyp19a1, which can be ameliorated by antioxidant agents like betaine.¹⁰⁰ Furthermore, exposure to environmental toxicants like the hair dye metabolite N-monoacetyl-p-phenylenediamine (MAPPD) increases oxidative stress in KGN cells and decreases serum E2 levels in mice, with the mechanism involving the inhibition of FSH- and LH-induced aromatase activity.¹⁰¹ In bovine granulosa cells, elevated levels of non-esterified fatty acids (NEFA) promote oxidative stress and downregulate the expression of steroidogenic genes, including CYP19A1.¹⁰² The antioxidant enzyme profile is crucial for protecting this steroidogenic function; for instance, in bovine granulosa cells, the expression of the selenium-dependent antioxidant enzyme GPX1 increases in correlation with CYP19A1 expression as follicles enlarge, highlighting a co-regulated defense mechanism against ROS generated during steroidogenesis.⁵² Conversely, deficiency in antioxidant defenses, such as in SOD2-deficient mice, leads to oxidative stress that markedly reduces estradiol production in granulosa cells.¹⁰³ Pharmacological interventions that alleviate oxidative stress, such as the steroidal saponin Shatavarin-IV, can rescue the DEHP-induced downregulation of CYP19A1 mRNA expression in rat

granulosa cells.¹⁰⁴ Similarly, in a PCOS mouse model, treatments like the Mongolian medicine Nuangong Qiwei Pill and caffeic acid improve estradiol levels and upregulate Cyp19a1 expression, counteracting oxidative stress-induced damage.^{105,106} These findings collectively establish that ROS-mediated oxidative stress is a central disruptor of aromatase function, directly linking redox imbalance to compromised estrogen synthesis in ovarian granulosa cells.

Concurrently, oxidative stress disrupts the initial and rate-limiting step of steroidogenesis by interfering with the transport of cholesterol into mitochondria and its conversion to pregnenolone, primarily through affecting the function of the Steroidogenic Acute Regulatory (StAR) protein and the P450 side-chain cleavage enzyme (CYP11A1/P450_{scc}). Evidence from various models confirms this impairment. In mouse granulosa cells, high glucose concentration inhibits steroidogenesis by downregulating key genes including StAR and Cyp11a1, alongside decreased progesterone secretion.¹⁰⁰ This high-glucose-induced defect involves impaired movement of mobilized cytosolic cholesterol to mitochondria, a process facilitated by StAR, and is associated with increased lipid peroxidation susceptibility of ovarian membranes.¹⁰³ The mitochondrial inner membrane protein Immp2l mutation in mice increases ROS, decreases estrogen, and alters steroid hormone synthesis pathways, with in vitro knockdown in granulosa cells confirming decreased cyp19a1 and estrogen levels, a cascade reversible by the antioxidant melatonin.¹⁰⁷ In bovine granulosa cells, NEFA-induced oxidative stress and apoptosis are accompanied by the downregulation of steroid synthesis-related genes.¹⁰² Furthermore, inducing mitochondrial hyperfusion in chicken granulosa cells using compounds like Mdivi-1 can enhance progesterone secretion and increase the expression of STAR, 3BHSD, and CYP11A1, illustrating the tight link between mitochondrial dynamics, redox state, and steroidogenic enzyme function.¹⁰⁸ Antioxidant interventions consistently demonstrate protective effects. Quercetin alleviates H₂O₂-induced steroidogenic impairment in goat luteinized granulosa cells, increasing the expressions of StAR and P450_{scc}.¹⁰⁹ The flavonoid isorhamnetin protects porcine ovarian granulosa cells from zearalenone-induced damage, recovering steroidogenesis disorder by regulating steroidogenic enzyme genes and proteins.¹¹⁰ In broiler hens, dietary grape seed extract supplementation reduces ovarian steroidogenesis, consistent with decreased StAR and P450 aromatase mRNA expression in granulosa cells.¹¹¹ Conversely, inhibition of regulatory proteins like 14-3-3 in mouse ovaries enhances steroidogenesis (progesterone, testosterone, estradiol) but concurrently increases oxidative stress and apoptosis, indicating a complex balance where disruption of redox homeostasis can dysregulate the steroidogenic pathway.¹¹² In models of ovarian aging, RNA sequencing reveals that herbal treatments like *Oviductus Ranae* induce changes in genes involved in ovarian steroidogenesis pathways.¹¹³ These data uniformly indicate that oxidative stress compromises the foundational steps of steroid hormone production by targeting StAR-mediated cholesterol transport and CYP11A1 enzyme activity, establishing a direct mechanistic link between redox imbalance and the suppression of granulosa cell steroidogenic capacity.

Disruption of Androgen Production Balance in Theca Cells

In theca cells, reactive oxygen species (ROS) play a dual role; while moderate levels serve as a necessary signaling molecule for initiating steroidogenesis, excessive ROS accumulation leads to oxidative stress, which directly impairs mitochondrial function. Mitochondria are central to energy production and steroid hormone synthesis, and their dynamics, particularly fusion, are closely linked to follicular development and cellular homeostasis. Research in chicken ovarian cells demonstrates that inducing mitochondrial hyperfusion with compounds like leflunomide can alter steroidogenic output in a cell-specific manner. In theca cells, such fusion was associated with decreased testosterone secretion and reduced expression of key steroidogenic enzymes like CYP11A1 and CYP19A1.¹⁰⁸ This suggests that disruptions in mitochondrial dynamics, potentially triggered by oxidative stress, can directly compromise the ATP production essential for powering the energetically demanding process of androgen synthesis. Furthermore, oxidative stress can originate from or be exacerbated by inflammatory conditions. Pro-inflammatory cytokines, such as TNF- α and IL-1 β , have been shown to elevate oxidative stress levels in granulosa cells and disrupt theca cell function during early follicular development, impairing gonadotropin-stimulated steroidogenesis.³⁶ This creates a detrimental cycle where inflammation and oxidative stress jointly undermine theca cell health and hormonal output.

Oxidative stress is further implicated in the pathological hyperactivation of androgen-producing pathways, which is a hallmark of conditions like polycystic ovary syndrome (PCOS). Clinical evidence strongly associates elevated oxidative stress with hyperandrogenemia in PCOS patients. Studies show that serum total testosterone levels correlate

positively with markers of oxidative damage, such as oxidized low-density lipoprotein (ox-LDL), and negatively with antioxidant defenses like glutathione.¹¹⁴ This clinical observation is supported by mechanistic *in vitro* findings where oxidized lipoproteins (ox-LDL and ox-HDL) directly stimulated proliferation and promoted testosterone secretion in rat ovarian theca-interstitial cells. This pro-androgenic effect was mediated by the upregulation of mRNA and protein levels of key enzymes in the testosterone synthesis pathway, including 17 α -hydroxylase, cholesterol side-chain cleavage enzyme, and steroidogenic acute regulatory protein.¹¹⁴ Thus, oxidative stress components can act as direct stimulators of the androgen biosynthesis machinery. Conversely, oxidative stress may also disrupt normal regulatory checkpoints. For instance, research in bovine theca cells indicates that the α 1-adrenergic receptor pathway is involved in ovarian steroid metabolism. Inhibition of this pathway with terazosin was found to reduce androgen content by downregulating the expression of the master regulator steroidogenic factor 1 (SF1) and its downstream genes via the ERK1/2 pathway.¹¹⁵ While this study highlights a potential regulatory mechanism, it also underscores that oxidative stress could theoretically interfere with such inhibitory pathways, thereby contributing to a net increase in androgen production. The interplay between oxidative stress and protective cellular responses is evident, as the same study showed that terazosin treatment upregulated the expression of the antioxidant transcription factor Nrf2 and its downstream gene γ -GCS, enhancing theca cell resistance to oxidative stress.¹¹⁵ This highlights that therapeutic strategies aimed at bolstering antioxidant defenses may help restore theca cell androgen production to a physiological balance, counteracting the pro-androgenic shift driven by excessive ROS.

Impact on Luteal Progesterone Synthesis and Secretion

The corpus luteum (CL), a transient endocrine gland pivotal for progesterone production, is structurally characterized by an abundance of mitochondria and smooth endoplasmic reticulum, rendering it highly susceptible to oxidative damage.¹¹⁶ ROS attack can accelerate luteal cell apoptosis, leading to a shortened luteal phase and insufficient progesterone secretion, which are hallmarks of luteal phase deficiency.¹¹⁷ This oxidative stress-induced dysfunction is a common pathological mechanism observed under various conditions, including exposure to environmental toxins like benzo(a) pyrene [B(a)P],¹¹⁷ glyphosate-based herbicides,¹¹⁸ and thiamethoxam insecticides,¹¹⁹ as well as physiological stressors such as heat stress¹²⁰ and chronic intermittent hypoxia.¹²¹ For instance, heat stress in dairy cows elevates malondialdehyde (MDA) levels, a marker of lipid peroxidation, and is associated with reduced progesterone concentrations in pregnant animals.¹²⁰ Similarly, B(a)P exposure in mice impairs embryo implantation and significantly decreases serum progesterone and estradiol levels by disrupting CL function.¹¹⁷ The direct link between oxidative stress and progesterone synthesis is further evidenced by the fact that key steroidogenic enzymes are redox-sensitive. The activity of 3 β -hydroxysteroid dehydrogenase (3 β -HSD), a crucial enzyme for progesterone synthesis, is regulated by the cellular redox state, and oxidative stress can inactivate it, directly impairing luteal function.¹¹⁶ Studies show that interventions which mitigate oxidative stress, such as supplementation with adropin, melatonin, or anthocyanins, concurrently enhance the expression of steroidogenic proteins like StAR and 3 β -HSD and increase progesterone output.^{116,122,123} Conversely, conditions that exacerbate oxidative imbalance, such as exposure to acrylamide during gestation in mice, suppress the expression of Hsd3b1, Cyp11a1, and Star mRNA, leading to decreased progesterone secretion.¹²⁴ This enzymatic dysregulation, coupled with oxidative stress-promoted apoptosis—marked by increased expression of pro-apoptotic proteins like Bax and caspase-3 and decreased anti-apoptotic Bcl-2—compromises CL integrity and lifespan.^{119,124} The resultant progesterone insufficiency is a key factor in clinical outcomes such as luteal phase insufficiency, early pregnancy loss, and conditions like polycystic ovary syndrome (PCOS).^{125,126} Therefore, the vulnerability of luteal cells to oxidative damage and the redox-sensitive nature of progesterone biosynthesis constitute a central mechanistic pathway through which oxidative stress imbalance directly impairs ovarian endocrine function and fertility.

Core Mechanisms by Which Oxidative Stress Promotes Ovarian Aging Accelerated Telomere Shortening and Cellular Senescence

Telomeres, the protective repetitive DNA sequences at chromosome ends, are fundamental for maintaining genomic stability in eukaryotic cells, including those within the ovary.¹²⁷ In ovarian granulosa cells and oocytes, telomeres

undergo progressive shortening with each cell division and are particularly susceptible to damage from ROS generated during oxidative stress.¹²⁸ Chronic oxidative stress, a hallmark of ovarian aging, significantly accelerates this telomeric attrition beyond the normal replicative shortening.¹²⁹ When telomeres reach a critically short length, they trigger a persistent DNA damage response, leading to the activation of key cell cycle checkpoint pathways, notably the p53-p21 and retinoblastoma (Rb) protein pathways.¹³⁰ This activation induces an irreversible state of growth arrest known as cellular senescence, effectively halting the proliferation of granulosa cells and compromising the supportive functions essential for folliculogenesis and oocyte maturation.¹³⁰ The link between oxidative stress and telomere-driven senescence is well-established, with factors such as exposure to endocrine-disrupting chemicals like di(2-ethylhexyl) phthalate (DEHP) shown to increase the expression of telomere-associated genes and accelerate markers of reproductive aging in ovarian tissues.¹³¹ Furthermore, senescent cells are not merely inert; they adopt a pro-inflammatory and tissue-disruptive phenotype known as the senescence-associated secretory phenotype (SASP).¹³⁰ Senescent granulosa cells secrete a plethora of inflammatory cytokines, chemokines, growth factors, and additional ROS, creating a toxic paracrine microenvironment.¹³² This SASP disrupts the delicate follicular niche, impairing communication between somatic cells and the oocyte, promoting local inflammation, and contributing to follicular atresia.¹³³ Crucially, this creates a vicious cycle: the SASP from senescent cells further exacerbates oxidative stress and inflammation in neighboring cells, propagating the senescent phenotype and accelerating the overall functional decline of the ovary.¹²⁹ This cascade is implicated in various reproductive disorders, including premature ovarian insufficiency (POI) and polycystic ovary syndrome (PCOS), where oxidative stress-induced granulosa cell senescence is a key pathological feature.^{132,134} Mathematical models support this, predicting that accelerated telomere shortening due to oxidative stress can lead to an accumulation of aged granulosa cells in preovulatory follicles, providing a plausible explanation for the poor oocyte outcomes observed in older women or those with conditions of heightened ovarian oxidative stress.¹³⁵ Therefore, the oxidative stress-accelerated telomere shortening axis, culminating in cellular senescence and the deleterious SASP, is a central mechanistic driver in the disruption of the ovarian microenvironment and the progressive loss of ovarian function associated with aging.^{136,137}

Induction of Ovarian Cell Pyroptosis and Ferroptosis

Oxidative stress serves as a critical trigger for two distinct forms of programmed cell death in the ovary: pyroptosis and ferroptosis, both of which significantly contribute to ovarian dysfunction. Pyroptosis, a pro-inflammatory form of cell death, is primarily mediated by the activation of the NLRP3 inflammasome in response to oxidative stress. In conditions such as diminished ovarian reserve (DOR), premature ovarian insufficiency (POI), and polycystic ovary syndrome (PCOS), elevated reactive oxygen species (ROS) activate the NLRP3 inflammasome in granulosa cells (GCs).^{138,139} This activation leads to the cleavage of caspase-1, which subsequently processes gasdermin D (GSDMD) to form pores in the cell membrane, resulting in cell lysis and the release of pro-inflammatory cytokines like IL-1 β and IL-18.^{138,140} This cascade exacerbates local ovarian inflammation, impairs follicular development, and accelerates functional loss. For instance, in a lipopolysaccharide (LPS)-induced DOR model, itaconic acid was shown to alleviate ovarian damage by inhibiting NLRP3-mediated pyroptosis via the NRF2 pathway.¹³⁸ Similarly, in a cyclophosphamide (CTX)-induced POI model, compounds like quercetin and orexin A improved ovarian function by downregulating NLRP3, caspase-1, and GSDMD expression, thereby suppressing pyroptosis in GCs.^{140,141} The thioredoxin-interacting protein (TXNIP)/NLRP3 pathway is also implicated, as seen in ovarian ischemia/reperfusion injury where bone marrow mesenchymal stem cell-derived exosomes mitigated pyroptosis by targeting this axis.¹⁴² Furthermore, in PCOS, metformin inhibited GC pyroptosis via the miR-670-3p/NOX2/ROS pathway, highlighting the intricate link between oxidative stress, inflammasome activation, and inflammatory cell death.¹³⁹ Beyond GCs, pyroptosis is also relevant in ovarian cancer, where agents like docosahexaenoic acid (DHA) and gambogic acid induce tumor cell death through ROS- and caspase-1-dependent pyroptotic mechanisms, suggesting a dual role where pyroptosis can be both detrimental to ovarian function and potentially therapeutic against malignancies.^{143,144}

Concurrently, oxidative stress drives ferroptosis, an iron-dependent form of cell death characterized by the accumulation of lipid peroxidation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). This process is tightly linked to the inactivation of key antioxidant systems, particularly glutathione peroxidase 4 (GPX4).^{71,145} In

ovarian pathologies, ferroptosis contributes to granulosa cell damage and oocyte maturation defects. For example, acute cadmium exposure induced oxidative stress and iron overload in mouse ovaries, leading to ferroptosis characterized by mitochondrial shrinkage, increased Fe^{2+} , and decreased GPX4 expression, which was alleviated by the ferroptosis inhibitor ferrostatin-1 (Fer-1).⁷¹ In PCOS, hyperandrogenism triggers ferroptosis in GCs through mechanisms involving nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy and dysregulation of the NCOA4-ferritin heavy chain 1 (FTH) pathway, leading to iron release and lipid peroxidation.^{146,147} Exercise-induced irisin was shown to attenuate this ferroptosis by modulating the NCOA4-FTH axis, improving ovarian function.¹⁴⁷ In premature ovarian failure (POF), oxidative stress and ferroptosis are central drivers, with interventions like phoenixin-14 and 3D-cultured human umbilical cord mesenchymal stem cell spheroids demonstrating protective effects by activating pathways such as ATF4/SLC7A11/GPX4 and Nrf2, respectively, to restore redox balance and inhibit ferroptotic death.^{145,148} Ferroptosis also plays a significant role in ovarian cancer, where cancer cells often exhibit an “iron addiction” but can develop resistance. Sensitivity to ferroptosis inducers like erastin is influenced by intracellular labile iron pools and the regulation of pathways involving SLC7A11 and GPX4.^{149,150} For instance, knockdown of glutathione peroxidase 4 (GPX4) sensitized ovarian cancer cells to Taxol by promoting ferroptosis,¹⁵¹ while the loss of oxidative stress-induced growth inhibitor 1 (OSGIN1) activated AMPK signaling and upregulated SLC2A3, conferring resistance to ferroptosis.¹⁵² Furthermore, non-coding RNAs, such as circCOG5 and lncRNA-PRLB, have been identified as regulators of ferroptosis in ovarian cancer by modulating targets like LPCAT3 and GPX4, respectively.^{153,154} The interplay between oxidative stress, lipid peroxidation, and iron metabolism underscores ferroptosis as a pivotal mechanism in both benign ovarian disorders and malignancies, offering potential therapeutic targets for preserving ovarian function and combating cancer.

Damage to the Ovarian Stem/Progenitor Cell Niche

Recent studies have provided compelling evidence for the existence of stem cells with differentiation potential within the ovary, such as oogonial stem cells (OSCs) or female germline stem cells (FGSCs), which are crucial for maintaining ovarian regenerative capacity.¹⁵⁵ The ovarian medullary region, or niche, provides the essential microenvironment that supports the self-renewal and differentiation of these stem/progenitor cells into functional germ cells. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, poses a significant threat to this delicate niche. Excessive ROS can disrupt the structural and functional integrity of the niche, impairing the supportive signals necessary for stem cell maintenance. For instance, exposure to environmental endocrine disruptors like Bisphenol A (BPA) has been shown to induce oxidative stress in mouse ovaries, leading to increased ROS production and a concomitant decrease in the expression of key antioxidant genes such as SOD1, SOD2, CAT, GPX1, and FOXO3.¹⁵⁶ This oxidative damage not only creates a hostile microenvironment but is also directly associated with an increase in the proportion of ovarian cancer stem cells (CSCs), identified by markers like CD44 and CD133, suggesting a pathological shift in the stem cell pool under oxidative duress.¹⁵⁶ Similarly, in ovarian cancer, cancer stem cells (CSCs) exhibit a complex relationship with oxidative stress, where moderate static magnetic fields can suppress their stemness and metastatic potential in a ROS-dependent manner by downregulating stemness-related genes like CD44, Sox2, and C-myc.¹⁵⁷ Furthermore, the vulnerability of these stem cells to oxidative stress is highlighted by research showing that ovarian cancer stem-like cells (OCSLCs) display heightened susceptibility to ferroptosis, an iron-dependent form of cell death linked to lipid peroxidation, which can be exacerbated by targeting regulators like FXN and its effect on mitochondrial antioxidant protein PRDX3.¹⁵⁸ The niche damage extends to non-malignant contexts, such as premature ovarian insufficiency (POI) or aging. Oxidative stress is a key driver of ovarian senescence, leading to the exhaustion of the follicular pool.¹⁵⁹ It mediates aging in FGSCs through mechanisms involving chronic inflammation and immune dysregulation within their niches.¹⁵⁵ Therapeutic interventions aimed at mitigating oxidative stress have demonstrated the potential to protect and restore this stem cell niche. For example, the traditional Chinese medicine Zuogui Pill (ZGP) was shown to alleviate cyclophosphamide (CTX)-induced ovarian aging in rats by reducing oxidative stress in OSCs, as evidenced by decreased ROS and malondialdehyde (MDA) levels and increased antioxidant enzyme (SOD, GSH-PX) activity, thereby restoring OSC stemness and proliferation via the Nrf2/HO-1 pathway.¹⁶⁰ Stem cell-based therapies, particularly using mesenchymal stem cells (MSCs) or their derivatives, have emerged as powerful tools to repair the oxidatively damaged ovarian microenvironment. Transplantation of menstrual blood-derived endometrial stem cells

(MenSCs) ameliorated ovarian senescence in a D-galactose-induced aging mouse model by activating the NRF2/HO-1 signaling pathway, enhancing cellular antioxidant capacity, and improving the inflammatory ovarian microenvironment.¹⁶¹ Exosomes derived from human umbilical cord MSCs (hucMSCs-Exos), especially those from hypoxic preconditioning (HExos), protected against CTX-induced POI by rectifying mitochondrial dysfunction and reducing oxidative stress via pathways like SIRT3/PGC1- α .¹⁶² Similarly, 3D-cultured hUCMSC spheroids protected ovarian granulosa cells from H₂O₂-induced ferroptosis by regulating iron homeostasis and lipid peroxidation through the Nrf2 pathway, thereby resisting oxidative damage.¹⁴⁵ Other studies confirm that hUCMSCs improve ovarian function in POI mice by inhibiting oxidative stress and downregulating stress-response pathways like PERK/eIF-2 α /ATF4/CHOP,¹⁶³ while their exosomes can alleviate POI by regulating autophagic homeostasis through the AMPK pathway.¹⁶⁴ The therapeutic effect is also mediated by paracrine factors; human placental MSCs (hPMSCs) secreted EGF, which protected ovarian granulosa cells from oxidative stress by activating the NRF2/HO-1 pathway.¹⁶⁵ Furthermore, exosomes from bone marrow MSCs (BMSC-Exos) alleviated ovarian ischemia/reperfusion injury by curbing oxidative stress and pyroptosis via the TXNIP/NLRP3 inflammasome pathway.¹⁴² Importantly, the efficacy of MSC transplantation in restoring ovarian function via antioxidant effects has been demonstrated in various models, including ovariectomized rats, where placenta-derived MSCs (PD-MSCs) were engrafted and restored function through an antioxidant effect involving exosomal factors.¹⁶⁶ However, research suggests that the therapeutic benefit may not be linearly dose-dependent, as similar improvements in folliculogenesis and antioxidant effects were observed with different transplanted cell doses of PD-MSCs in rat models.^{167,168} In summary, oxidative stress disrupts the ovarian stem/progenitor cell niche by creating a toxic microenvironment that compromises stem cell viability, self-renewal, and differentiation. This damage underpins both pathological conditions like ovarian cancer stemness and functional decline in conditions like POI and aging. Counteracting this oxidative imbalance through pharmacological agents or regenerative therapies like MSC/exosome treatment represents a promising strategy to protect the niche, preserve ovarian stem cell function, and ultimately support ovarian regeneration and fertility.

Association Between Oxidative Stress and Specific Ovarian Pathological Conditions

The Role in the Pathogenesis of Polycystic Ovary Syndrome

A substantial body of evidence confirms that elevated markers of oxidative stress are a common feature in both the ovarian tissue and systemic circulation of women with Polycystic Ovary Syndrome (PCOS).¹⁶⁹ Studies consistently report increased levels of oxidative stress indicators, such as malondialdehyde (MDA), total oxidant status (TOS), and advanced oxidation protein products, alongside a compromised antioxidant defense system, evidenced by reduced total antioxidant capacity (TAS) and diminished activities of enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) in PCOS patients compared to healthy controls.^{170,171} This oxidative imbalance is not an isolated phenomenon but is intricately linked with the core pathological features of PCOS, namely insulin resistance (IR) and chronic low-grade inflammation, forming a triad that drives the syndrome's progression.^{172,173} The interplay is bidirectional; hyperandrogenism and IR promote inflammation and reactive oxygen species (ROS) production, which in turn exacerbates IR and androgen excess, creating a self-perpetuating vicious cycle central to PCOS pathophysiology.^{45,174} For instance, oxidative stress can directly inhibit the hepatic expression and secretion of sex hormone-binding globulin (SHBG) by downregulating hepatocyte nuclear factor-4 α , thereby promoting hyperandrogenemia.¹⁷⁵ Concurrently, chronic inflammation, marked by elevated pro-inflammatory cytokines like IL-1 β , IL-6, and TNF- α , is a consistent finding in PCOS and works synergistically with oxidative stress to impair ovarian and metabolic function.^{170,176} This combined assault of oxidative stress, insulin resistance, and inflammation constitutes the pathological core that underlies the diverse clinical manifestations of PCOS.

Reactive oxygen species (ROS) exert detrimental effects on PCOS pathophysiology through multiple interconnected mechanisms that directly explain the associated subfertility and increased miscarriage rates. Firstly, ROS interfere with insulin signaling pathways, exacerbating the existing insulin resistance that is hallmark of PCOS.¹⁷⁴ Mitochondrial dysfunction and impaired oxidative phosphorylation, often observed in PCOS, lead to reduced ATP production and

increased ROS generation, which disrupts insulin-stimulated glucose uptake, thereby worsening IR.^{174,177} This escalation in IR causes compensatory hyperinsulinemia, which further stimulates ovarian theca cell androgen production and inhibits hepatic SHBG synthesis, amplifying the state of hyperandrogenemia that disrupts folliculogenesis and causes anovulation.^{45,172} Secondly, oxidative damage has a direct and deleterious impact on oocyte quality and granulosa cell function. Excessive ROS within the follicular microenvironment damages cellular components in oocytes and the surrounding granulosa cells, impairing their viability and function.¹⁷⁴ This is evidenced by studies showing elevated oxidative stress markers in the follicular fluid of PCOS women, which correlate negatively with embryo quality metrics such as the high-quality embryo rate and blastocyst formation rate.¹⁷⁸ The oxidative stress impairs normal follicular development and maturation, leading to the characteristic arrest of follicular growth.¹⁷⁴ Furthermore, oxidative stress induces apoptosis in granulosa cells and promotes DNA damage, which compromises the supportive environment necessary for oocyte maturation and subsequent embryo development.^{179,180} This direct oxidative assault on the ovarian follicular unit, combined with the endocrine disruption caused by ROS-mediated exacerbation of hyperandrogenism and insulin resistance, provides a comprehensive mechanistic explanation for the ovulation disorders, poor oocyte quality, reduced fertility, and heightened risk of pregnancy loss observed in women with PCOS.^{172,181}

While the association between oxidative stress and PCOS is well established, several areas of inconsistency warrant discussion. First, the magnitude of redox imbalance varies considerably across studies. For example, while most reports show increased malondialdehyde (MDA) and decreased total antioxidant capacity (TAC) in PCOS patients,^{170,171} some studies have failed to detect significant differences in specific antioxidant enzymes such as catalase or glutathione peroxidase, suggesting that the antioxidant defense impairment may be selective rather than global. Second, the relationship between oxidative stress markers and hyperandrogenemia is bidirectional but not uniform; some studies report strong correlations with testosterone levels,¹¹⁴ whereas others find only weak associations, possibly due to differences in body mass index and insulin resistance status. Third, clinical trials of antioxidant interventions in PCOS have yielded conflicting results. While N-acetylcysteine (NAC) and metformin both reduce oxidative stress, head-to-head comparisons show variable effects on ovulation and pregnancy rates.^{54,139} Similarly, vitamin E supplementation improved some oxidative markers but did not consistently enhance live birth rates.⁵⁵ These discrepancies highlight the need for large, well-powered, multicenter trials with standardized outcome measures and stratification by PCOS phenotypes.

Role in the Onset and Progression of Premature Ovarian Insufficiency

Premature ovarian insufficiency (POI) is a complex and heterogeneous disorder characterized by the cessation of ovarian function before the age of 40, leading to amenorrhea, hypogonadism, and elevated gonadotropins.¹⁸² A growing body of evidence positions oxidative stress (OS) as a pivotal, convergent mechanism in the pathogenesis of POI, acting as a common terminal pathway through which diverse etiologies—including genetic, autoimmune, iatrogenic, and environmental factors—ultimately lead to follicular depletion and ovarian dysfunction.¹⁵⁹ Clinical studies consistently demonstrate that ovarian tissues and systemic circulation in POI patients exhibit a state of redox imbalance, marked by a significant decline in antioxidant capacity and an increase in markers of oxidative damage. For instance, measurements of diacron-reactive oxygen metabolites (d-ROMs) and the oxidative stress index (d-ROMs/BAP $\times$ 100) are significantly higher in women with POI compared to age-matched controls with normal ovarian function, while levels of biological antioxidant potential (BAP) or specific antioxidant enzymes may be compromised, indicating impaired antioxidant defense.^{183,184} This systemic and local oxidative burden is not merely a consequence but a driving force of the disease, as OS can mediate damage to genetic material, disrupt critical signaling pathways, alter transcription factors, and create a hostile ovarian microenvironment, thereby accelerating ovarian aging.¹⁵⁹ The role of OS is particularly pronounced in specific POI subtypes. In autoimmune POI, inflammatory cell infiltration into ovarian tissue generates excessive reactive oxygen species (ROS), which directly attack and damage ovarian follicles and granulosa cells, contributing to their premature depletion.¹⁵⁹ Furthermore, iatrogenic causes, notably chemotherapy, are major contributors to POI. Agents like cyclophosphamide (CTX) and cisplatin are well-documented to induce ovarian damage primarily through the induction of severe oxidative stress.^{162,185} These chemotherapeutic drugs disrupt mitochondrial function in oocytes and granulosa cells, leading to a surge in ROS production, depletion of antioxidants, and subsequent activation of apoptotic pathways, DNA damage, and cellular senescence, which collectively deplete the ovarian follicle reserve.^{134,141} The centrality of OS in POI pathophysiology is further supported by therapeutic interventions. Numerous

studies show that agents or strategies aimed at mitigating OS can ameliorate ovarian damage. For example, antioxidants like quercetin, melatonin, and N-acetylcysteine, as well as stem cell-derived exosomes and traditional Chinese medicine formulations such as Bushen-Culuan Decoction, have demonstrated protective effects in POI models by reducing ROS levels, enhancing antioxidant defenses (eg, via the Nrf2/ARE pathway), improving mitochondrial function, and inhibiting apoptosis in granulosa cells.^{141,162,186,187} These findings collectively underscore that oxidative stress is not just a biomarker but a fundamental mechanistic driver and a promising therapeutic target in the multifaceted etiology of premature ovarian insufficiency.

Impact on Endometriosis-Associated Ovarian Dysfunction

Endometriosis, a chronic inflammatory gynecological disorder, significantly impairs female fertility, with oxidative stress (OS) emerging as a central pathogenic mechanism in its associated ovarian dysfunction.¹⁸⁸ The disease is characterized by the presence of ectopic endometrial-like tissue, which, along with the peritoneal fluid, creates a pro-oxidant pelvic microenvironment rich in reactive oxygen species (ROS) and pro-oxidative substances.¹⁸⁹ This chronic oxidative milieu adversely affects the neighboring ovarian tissue. Specifically, follicular fluid (FF) from women with endometriosis exhibits distinct metabolic alterations, including elevated levels of amino acids like asparagine, histidine, and glycine, which are indicative of oxidative and mitochondrial imbalance.¹⁹⁰ This dysregulated follicular environment compromises oocyte development and quality. The OS damages granulosa cells (GCs), which are crucial for oocyte nourishment and steroidogenesis. For instance, hydrogen peroxide (H₂O₂)-induced oxidative stress in human granulosa cell lines increases the expression of the danger signal HMGB-1 and its receptor TLR4, activating the NF- κ B pathway and amplifying pro-inflammatory cytokine release (eg, IL-1 β , IL-6), thereby disrupting normal follicular function.¹⁹¹ Furthermore, oxidative stress in endometriotic follicles decreases the expression of EZH2 and reduces H3K27Me3 levels in ovarian granulosa cells, which suppresses ovulatory signals by upregulating IL-1 receptor 2 (IL-1R2), contributing to ovulatory dysfunction and infertility.⁴⁸ The presence of ovarian endometriomas (OEMs), or “chocolate cysts”, represents a severe form of the disease and further exacerbates local oxidative stress. These cysts are associated with iron overload from recurrent hemorrhage, which induces chronic inflammation and oxidative stress, leading to ovarian ferroptosis and fibrosis.¹⁹² This iron-driven process is a specific form of regulated cell death characterized by lipid peroxidation, which is increasingly recognized in the pathogenesis of endometriosis-related ovarian damage.¹⁹³ The cyst itself and its surgical management can inflict additional injury on the normal ovarian cortex. Surgical excision of endometriomas, while often necessary, can compromise the ovarian reserve, partly by exacerbating the existing oxidative insult and promoting tissue fibrosis.¹⁹⁴ This fibrosis, driven by pathways like TGF- β /Smad signaling, disrupts normal folliculogenesis and steroidogenesis.¹⁹⁵ The oxidative stress extends to impairing critical cellular communication; OEMs disrupt transzonal projections between cumulus cells and oocytes, impairing antioxidant transfer and leading to mitochondrial dysfunction, DNA damage, and increased aneuploidy in oocytes.¹⁹⁶ Consequently, endometriosis detrimentally affects multiple aspects of ovarian function, including follicular development, oocyte competence, and ovarian reserve, culminating in reduced fecundity.¹⁹⁷ The systemic and local immune dysregulation perpetuates this cycle of inflammation and OS, making the ovarian microenvironment hostile to normal reproductive processes.¹⁸⁹ Therapeutic strategies are increasingly exploring the modulation of this redox imbalance. Antioxidants like N-acetyl-cysteine (NAC) have shown promise in experimental models, mitigating OS-induced damage to oocyte and embryo quality.¹⁹⁸ Other interventions, such as melatonin, have demonstrated potential in restoring oocyte-cumulus communication and mitochondrial function disrupted by OEMs.¹⁹⁶ Additionally, targeting specific pathways like ferroptosis or cellular senescence (eg, with rapamycin) presents novel avenues for alleviating endometriosis-associated infertility by protecting ovarian function from oxidative damage.¹⁹⁹ Thus, the interplay between endometriotic lesions, chronic inflammation, and oxidative stress forms a vicious cycle that is fundamental to the ovarian dysfunction observed in this condition, highlighting OS as a critical therapeutic target.

Biomarkers for Assessing Ovarian Oxidative Stress Status

Direct Oxidative Damage Product Markers

Direct oxidative damage product markers are crucial for assessing the extent and impact of oxidative stress on ovarian function. These biomarkers, which accumulate in various biological compartments such as follicular fluid, serum, and ovarian

tissue, provide quantifiable evidence of molecular damage inflicted by reactive oxygen species (ROS). Among the most studied are lipid peroxidation end-products, DNA oxidation adducts, and protein oxidation modifications. Malondialdehyde (MDA) is a well-characterized terminal product of lipid peroxidation, frequently measured to evaluate oxidative stress in ovarian contexts. For instance, studies have demonstrated elevated MDA levels in ovarian tissue or serum following exposures that induce oxidative damage, such as treatment with chemotherapeutic agents like doxorubicin²⁰⁰ or environmental toxicants like bisphenol S (BPS).²⁰¹ Similarly, in a cyclophosphamide-induced model of premature ovarian insufficiency (POI), increased serum MDA was observed, and interventions like bee-derived antioxidant mixtures or estradiol supplementation were shown to reduce these levels, correlating with improved ovarian function.^{200,202} Another critical lipid peroxidation marker is 4-hydroxynonenal (4-HNE), which forms adducts with proteins and DNA, further propagating cellular damage. While specific references to 4-HNE in the provided abstracts are limited, the principle is supported by studies on lipid peroxidation; for example, maternal exposure to fine particulate matter (PM_{2.5}) was shown to increase the accumulation of lipid peroxidation products like 4-HNE in offspring mouse ovaries, linking oxidative damage to impaired follicular development.¹⁹ DNA oxidation is primarily assessed through 8-hydroxy-2'-deoxyguanosine (8-OHdG), a stable product of guanine base oxidation. This marker is indicative of genomic and mitochondrial DNA damage. Research has shown strong 8-OHdG positivity in rat ovarian cells, particularly in granulosa cells of antral follicles and corpus luteum cells, with levels fluctuating across the estrous cycle and increasing during events like ovulation and corpus luteum regression.²⁰³ Furthermore, in a mouse model of ovarian ischemia-reperfusion injury, treatment with Cloprostenol significantly diminished 8-OHdG immunostaining, indicating reduced DNA oxidative damage.²⁰⁴ Elevated 8-OHdG levels have also been correlated with poor ovarian reserve in clinical conditions like sickle cell anemia, although a direct correlation with reserve markers was not always significant, suggesting other contributing factors.²⁰⁵ Protein oxidation markers, such as protein carbonyls and 3-nitrotyrosine, reflect the alteration of protein structure and function due to oxidative attack. Protein carbonyl formation, a common irreversible modification, was assessed in studies involving oxidative stress models in granulosa cells. For example, hydrogen peroxide-induced injury in rat ovarian granulosa-lutein cells led to increased protein carbonyl content, which was ameliorated by treatment with resveratrol.²⁰⁶ While 3-nitrotyrosine, a marker for protein nitration mediated by reactive nitrogen species, is not explicitly detailed in the provided abstracts, the broader context of protein oxidation is integral to understanding ovarian dysfunction. The evaluation of these direct damage markers is not only diagnostic but also prognostic. For instance, in women undergoing in vitro fertilization (IVF), follicular fluid levels of MDA and 8-OHdG have been associated with oxidative stress status and clinical outcomes like pregnancy rates.^{207,208} Interventions aimed at mitigating oxidative stress, such as supplementation with antioxidants like vitamin E, melatonin, or specific nutraceuticals, often demonstrate their efficacy by reducing the concentrations of these damage markers. For example, vitamin E co-treatment with Sofosbuvir reduced ovarian MDA levels in rats,²⁰⁹ and melatonin protected against zearalenone-induced ovarian damage by modulating oxidative stress markers.²¹⁰ Similarly, a preconception nutraceutical supplement was shown to reduce oxidative DNA damage (8-OHdG) in follicular cells, correlating with increased IVF pregnancy rates.²¹¹ Therefore, the systematic measurement of direct oxidative damage products like MDA, 8-OHdG, and protein carbonyls provides a foundational framework for elucidating the mechanistic links between oxidative stress and ovarian pathologies, from diminished reserve and POI to chemotoxicity and environmental exposures, while also offering tangible targets for therapeutic assessment and intervention.

Indicators of Antioxidant Defense System Capacity

The capacity of the ovarian antioxidant defense system is critically assessed through the measurement of both enzymatic and non-enzymatic antioxidants, which collectively reflect the tissue's ability to neutralize reactive oxygen species (ROS) and maintain redox homeostasis. Enzymatic antioxidants, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are primary indicators of the ROS-scavenging machinery within ovarian cells. Their activities are frequently diminished under conditions of oxidative stress, directly compromising follicular integrity and function. For instance, in a zebrafish model, knockout of the oxidation resistance gene 1a (oxr1a) led to significant downregulation of antioxidant genes such as gpx1b, gpx4a, gpx7, and sod3a, impairing the defense against cellular ROS and contributing to premature ovarian failure.²¹² Similarly, in a rat model of doxorubicin-induced ovarian damage, the administration of selenium ameliorated toxicity by restoring the activities of SOD, CAT, and GPx, thereby alleviating oxidative injury and preserving ovarian architecture.²¹³ In women, studies on cumulus cells from smokers revealed

a downregulation of numerous oxidative stress-related genes, indicating a smoking-induced oxidant-antioxidant imbalance that could compromise oocyte quality during IVF.²¹⁴ Furthermore, bioinformatic analyses have constructed ovarian antioxidant ceRNA networks (eg, OvAnOx), highlighting that mRNAs encoding SOD1, SOD2, and CAT are integral components of a regulatory network impacting ovarian reserve, follicular dynamics, and oocyte maturation under both normal and pathological conditions.²¹⁵ The activity of these enzymes is thus a direct functional readout of the ovary's intrinsic capacity to manage oxidative load.

Complementing the enzymatic defenses, non-enzymatic antioxidants such as reduced glutathione (GSH), its oxidized form (GSSG), and vitamins C and E constitute the crucial antioxidant reserve, with their levels and ratios serving as key biomarkers of oxidative stress status and buffering capacity. The GSH/GSSG ratio is a sensitive indicator of the cellular redox state, where a decline signifies increased oxidative burden. In women undergoing assisted reproductive treatments, analyses of follicular fluid and blood revealed that the GSSG/GSH ratio, along with levels of total glutathione (tGSH), correlated with oocyte retrieval outcomes, with higher GSSG levels in follicular fluid associated with increased metabolic activity and ROS generation during ovarian stimulation.²¹⁶ This underscores the glutathione system's role as a robust redox biomarker for female fertility. In pathological states like polycystic ovary syndrome (PCOS), the follicular fluid microenvironment exhibits altered redox balance; studies show that women with PCOS have lower total antioxidant capacity (TAC) in follicular fluid, which is inversely correlated with circulating anti-Müllerian hormone (AMH) levels, suggesting that AMH may act as a surrogate marker for follicular oxidative stress.²¹⁷ Furthermore, in a case-control study on premature ovarian insufficiency (POI), while the biological antioxidant potential (BAP) test did not show significant differences between POI, incipient ovarian failure (IOF), and control groups, the calculated oxidative stress index (derived from BAP and reactive oxygen metabolites) was significantly elevated in both POI and IOF groups, highlighting the importance of evaluating the overall antioxidant capacity relative to oxidant load.¹⁸⁴ Interventions aimed at bolstering this non-enzymatic reserve show therapeutic promise. For example, supplementation with β -nicotinamide mononucleotide (NMN) in sheep granulosa cells increased NAD⁺ and ATP levels, reduced ROS production, and enhanced the antioxidant defense system, thereby improving steroidogenesis.²¹⁸ Similarly, the traditional herbal formula Zuogui Pill was shown to alleviate cyclophosphamide-induced ovarian aging in rats by increasing the activity of antioxidant enzymes like SOD and GSH-Px and reducing malondialdehyde (MDA) and ROS accumulation, effects mediated through the Nrf2/HO-1 pathway.¹⁶⁰ These findings collectively establish that quantifying both enzymatic activities and non-enzymatic antioxidant levels provides a comprehensive assessment of the ovarian antioxidant defense system's capacity, which is fundamental for maintaining folliculogenesis, oocyte quality, and overall reproductive function.

Redox-Sensitive Signaling Molecules and Transcription Factors

The nuclear translocation of the transcription factor NF-E2-related factor 2 (Nrf2) and the subsequent expression of its downstream antioxidant target genes, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1), constitute a central cellular defense mechanism against oxidative stress, playing a pivotal role in ovarian physiology and pathology.²¹⁹ In the context of ovarian aging, the Nrf2 signaling pathway is crucial for regulating the antioxidant response, and its activity declines with age, contributing to the functional deterioration of the ovary.²²⁰ This decline is implicated in conditions like premature ovarian failure (POF), where decreased expression of Nrf2 and its downstream enzymes (eg, HO-1, NQO1) is observed alongside increased oxidative stress markers.²²¹ Conversely, activation of the Nrf2 pathway, either pharmacologically or through natural compounds, offers protection. For instance, the natural compound daphnetin rescues D-galactose-induced POF in a dose-dependent manner by increasing Nrf2 expression and its downstream targets (GCLC, HO-1, NQO1), an effect that is lost in Nrf2 knockout mice, confirming the pathway's essential role.²²¹ Similarly, in a cyclophosphamide (CTX)-induced model of ovarian aging, the traditional formula Zuogui Pill (ZGP) alleviates oxidative stress and restores the stemness of oogonial stem cells by activating the Nrf2/HO-1 pathway, increasing the expression of Nrf2, HO-1, and NQO1.¹⁶⁰ The Nrf2 pathway is also a key regulator in polycystic ovary syndrome (PCOS), where its modulation can mitigate oxidative damage in granulosa cells (GCs). Metformin protects ovarian GCs against oxidative stress and apoptosis in PCOS via activation of the Nrf2-HO-1 pathway.²²² Carnosol inhibits oxidative stress and apoptosis in dihydrotestosterone (DHT)-treated KGN cells and protects against PCOS phenotypes in mice by activating the Nrf2/HO-1

signaling through direct binding to Keap1.⁵⁷ Furthermore, the Nrf2-ARE pathway is identified as a key regulator of oxidative stress responses in the GCs of PCOS patients, with altered expression of antioxidant genes like HO1, PRDX1, and SOD1.²²³ Beyond endogenous antioxidants, the expression of NADPH oxidase (NOX) family members is a critical indicator of endogenous ROS generation and intensity, linking oxidative stress to inflammatory and pathological processes.²²⁴ In neurodegenerative diseases, the membrane androgen receptor (mAR) can mediate NOX-generated oxidative stress, and similar pathways involving inflammatory signaling are relevant to ovarian dysfunction.²²⁴ In ovarian contexts, oxidative stress often activates inflammatory pathways such as NF- κ B. For example, in laying hens, gamma-aminobutyric acid (GABA) and *Lactobacillus plantarum* alleviate stress-induced ovarian dysfunction by reducing oxidative stress and normalizing the expression of inflammatory factors.²²⁵ In PCOS, the natural compound osthole alleviates symptoms in mice by regulating a pathway involving Nrf2, FoxO1, glutathione (GSH), and NF- κ B, where it restricts the phosphorylation and transcriptional activity of NF- κ B.²²⁶ Similarly, chlorogenic acid mitigates DHEA-induced oxidative stress and ferroptosis in granulosa cells and PCOS rats by downregulating NF- κ B pathway activation.²²⁷ The interplay between oxidative stress and inflammation is further highlighted in models of chemical exposure, where bisphenol A (BPA) impairs reproductive fitness in zebrafish ovary by promoting oxidative/nitrosative stress-mediated inflammatory response, increasing p38 MAPK and NF- κ B phosphorylation.²²⁸ Other transcription factors are also integral to the ovarian oxidative stress response. Forkhead box O (FOXO) transcription factors, particularly FOXO3a, are involved in regulating cell cycle, apoptosis, and oxidative stress during follicular development.²²⁹ Circular RNA circFoxo3 is upregulated under oxidative stress in granulosa cells and promotes apoptosis by regulating FOXO3 protein levels, demonstrating a non-canonical regulatory layer.²³⁰ The SIRT1-Nrf2 axis acts as a crucial anti-oxidative and anti-ferroptotic system protecting granulosa cell viability and mitochondrial homeostasis.²³¹ Resveratrol alleviates ovarian oxidative stress in a layer model by upregulating Nrf2 and SIRT1 levels and decreasing the expression of FoxO1.² In summary, the dynamic balance between pro-oxidant systems like NOX and antioxidant defenses orchestrated by transcription factors like Nrf2, NF- κ B, and FOXO is fundamental to ovarian health, with dysregulation contributing to a spectrum of disorders from aging and PCOS to chemical-induced toxicity.

Potential Intervention Strategies and Prospects Targeting Oxidative Stress in Ovaries

Supplementation with Exogenous Antioxidants

Exogenous antioxidant supplementation, including compounds such as coenzyme Q10 (CoQ10), melatonin, and resveratrol, represents a promising therapeutic strategy to counteract oxidative stress-induced ovarian dysfunction. These agents not only function as direct scavengers of ROS but also enhance the endogenous antioxidant defense system by modulating key signaling pathways. For instance, CoQ10, a lipid-soluble benzoquinone integral to mitochondrial energy metabolism and antioxidant protection, has been shown to improve oocyte quality, ovarian function, and mitochondrial efficiency by regulating oxidative stress and reducing ROS levels.²³² Clinical studies indicate that CoQ10 supplementation can enhance ovarian function, increase the number of retrieved oocytes, and improve embryo quality, particularly in women with diminished ovarian reserve (DOR) or of advanced maternal age.²³² Similarly, melatonin, a potent antioxidant secreted by the pineal gland and found in follicular fluid, protects oocytes from oxidative damage during ovulation and improves oocyte maturation and early embryonic development.²³³ Its mechanisms include restoring mitochondrial function by reducing ROS generation and early apoptosis, increasing ATP and glutathione (GSH) levels, and enhancing the expression of antioxidant genes such as SIRT1, SIRT3, GPX4, SOD1, and SOD2.²³³ Furthermore, melatonin's role in delaying ovarian aging is supported by its ability to inhibit follicle activation, growth, and atresia, thereby slowing the exhaustion of the ovarian reserve.²³⁴ Resveratrol, a polyphenol, also demonstrates protective effects by modulating the follicular microenvironment. In aged women with poor ovarian prognosis, resveratrol supplementation altered the follicular fluid miRNome, specifically influencing mitomiRNAs that regulate mitochondrial proteins, metabolism, and biogenesis, thereby improving oocyte quality.²³⁵ Beyond these, other natural compounds like theaflavin 3,3'-digallate (TF3) from black tea and mogrosin-rich extract (MGE) from *Siraitia grosvenorii* fruits have shown potential in preserving the primordial follicle pool, restoring estrous cycles, increasing offspring numbers in aged mice, and protecting against ovarian reserve depletion by ameliorating inflammatory stress.^{236,237} The efficacy of these antioxidants

is often mediated through the activation of cytoprotective pathways. For example, Humanin, a mitochondria-derived peptide found to be downregulated in the granulosa cells of polycystic ovary syndrome (PCOS) patients, alleviates oxidative stress by modulating the Keap1/Nrf2 signaling pathway.²³⁸ Activation of the Nrf2 pathway is a common mechanism for many antioxidants, leading to the upregulation of downstream antioxidant enzymes. Clinical evidence further supports the use of combined antioxidant strategies. A pilot study on women with DOR found that combining supervised exercise therapy with antioxidant supplementation significantly increased anti-Müllerian hormone (AMH) levels and spontaneous pregnancy rates.²³⁹ Moreover, a meta-analysis of randomized clinical trials concluded that antioxidant consumption, particularly CoQ10, is an effective and safe complementary therapy for women with ovarian aging, improving the number of retrieved oocytes, high-quality embryo rates, and clinical pregnancy rates while reducing gonadotropin doses.²⁴⁰ These findings collectively underscore the potential of exogenous antioxidants to mitigate oxidative damage and improve ovarian function through both direct ROS scavenging and the potentiation of endogenous defense mechanisms.

The therapeutic approach is evolving towards the targeted supplementation of specific antioxidants designed to repair particular cellular compartments or pathways damaged by oxidative stress. This precision strategy aims to enhance efficacy and minimize off-target effects. A prime example is Mitoquinone (MitoQ), a mitochondria-targeted derivative of the antioxidant ubiquinone. In the context of ovarian tissue cryopreservation, a process vulnerable to oxidative stress and ischemia-reperfusion injury, MitoQ has demonstrated significant protective effects. During the vitrification of mouse ovarian tissue, MitoQ supplementation mitigated vitrification-induced oxidative damage, preserved mitochondrial morphology and homeostasis by regulating dynamics proteins (Drp1 and Mfn2), inhibited the p38 MAPK pathway to reduce apoptosis, and ultimately improved follicular reserve and endocrine function (increased estradiol and AMH levels) after autotransplantation.²⁴¹ This organelle-specific targeting is crucial given the central role of mitochondrial dysfunction in ovarian aging and chemotherapy-induced damage. Another targeted agent is N-acetylcysteine (NAC), a precursor for glutathione synthesis. NAC strengthens intracellular antioxidant defenses by directly eliminating free radicals and enhancing GSH production. Its protective role against ovarian injury is well-documented in various models. For instance, NAC administration protected human ovarian xenografts from ischemia-reperfusion injury by upregulating the antioxidant defense system (SOD1, HMOX1, CAT) and exerting anti-inflammatory and anti-apoptotic effects, leading to increased follicle survival.²⁴² In chemotherapy-induced models, NAC co-administration with vitamin E significantly attenuated doxorubicin (DOX)-induced ovarian toxicity in rats, improving oxidative stress markers (reducing MDA, increasing TAC and GSH), reducing pro-inflammatory cytokines (IL-8, TNF- α), and preserving follicular morphology and hormonal balance.²⁴³ Furthermore, NAC was effective in a model of maternal exposure to fine particulate matter (PM2.5), where it abolished the increases in apoptosis, ROS, and activation of the NF- κ B pathway (p-p65, p-I κ B α) induced in ovarian granulosa cells, thereby protecting the ovarian reserve in offspring.¹⁹ The mechanism of NAC also involves regulating key signaling pathways; it alleviated D-galactose-induced injury in rabbit ovarian granulosa cells by inhibiting apoptosis and oxidative stress, potentially through regulating the PI3K/Akt/mTOR signaling pathway.²⁴⁴ Other targeted nutritional strategies include supplementation with selenium, an oligoelement with fundamental biological features. In a rat model of doxorubicin-induced ovarian damage, dietary supplementation with selenium (particularly at 1 mg/kg) ameliorated ovarian toxicity by alleviating oxidative stress (improving SOD, CAT, GPx, reducing MDA), decreasing inflammation (IL-1 β , TNF- α) and apoptosis (caspase-3), and restoring ovarian architecture and follicular reserve.²¹³ Similarly, combined application of vitamins E and C attenuated sodium arsenite-mediated ovarian DNA damage, follicular atresia, and oxidative injury in rats by restoring antioxidant enzyme activities and hormonal levels.²⁴⁵ These targeted approaches, focusing on mitochondria or specific synthetic pathways like glutathione, represent a more nuanced and potentially powerful dimension of antioxidant therapy, moving beyond broad-spectrum scavenging to address the root causes of oxidative damage in specific ovarian cell types and organelles.

Despite promising preclinical results, the clinical efficacy of antioxidant supplementation for improving ovarian function remains debated. For instance, while coenzyme Q10 (CoQ10) has been shown to improve oocyte quality and pregnancy rates in some trials,²³² a recent meta-analysis noted significant heterogeneity and called for larger confirmatory studies.²⁴⁰ Similarly, vitamin E supplementation reduced oxidative stress markers in PCOS patients but did not consistently improve ovulation or live birth rates.⁵⁵ Melatonin, although effective in animal models,^{233,234} has limited

high-quality human data in ovarian aging. The reasons for these discrepancies include: (i) variability in baseline oxidative status of enrolled patients; (ii) differences in dosing, duration, and formulation; (iii) lack of standardization for measuring oxidative stress biomarkers; and (iv) potential “antioxidant paradox” where excessive antioxidants may interfere with beneficial ROS signaling required for ovulation. Furthermore, most studies have small sample sizes and short follow-up periods, and few have examined clinically meaningful endpoints such as live birth or long-term offspring health. Therefore, while antioxidant supplementation holds promise, current evidence does not support universal or indiscriminate use; a personalized approach guided by baseline redox status and specific ovarian pathologies is warranted.

Lifestyle and Nutritional Interventions

Lifestyle and nutritional interventions represent foundational and promising strategies for modulating systemic and ovarian-specific oxidative stress, thereby potentially preserving or improving ovarian function. Caloric restriction and intermittent fasting are emerging dietary patterns with significant research potential for delaying ovarian aging. These regimens are posited to reduce reactive oxygen species (ROS) generation by lowering the basal metabolic rate, thereby decreasing the overall oxidative burden on cellular systems.²⁴⁶ Furthermore, these dietary interventions can activate cellular autophagy, a crucial process for clearing damaged organelles and proteins, including dysfunctional mitochondria that are a primary source of ROS.²³⁶ By enhancing autophagic flux, these strategies may help maintain ovarian cellular homeostasis and mitigate the accumulation of oxidative damage that contributes to follicular depletion and endocrine dysfunction associated with aging.²⁴⁶ The activation of pathways such as SIRT1/mTOR, which can be influenced by nutritional status, provides a mechanistic link between energy intake, cellular cleanup processes, and redox balance in the ovarian environment.²⁴⁷ While direct clinical evidence in humans for ovarian-specific outcomes is still evolving, the fundamental principles of reducing metabolic stress and enhancing cellular resilience position caloric modulation as a key area of investigation for ovarian longevity.

In parallel, adopting antioxidant-rich dietary patterns is a fundamental and multi-targeted intervention for improving oxidative stress status. The Mediterranean diet, characterized by high intake of polyphenols, vitamins, and other micronutrients, exemplifies this approach.²⁴⁸ Such diets exert protective effects through multiple mechanisms: they provide direct free radical scavenging activity, enhance endogenous antioxidant enzyme systems, and modulate redox-sensitive signaling pathways like Nrf2/HO-1 and PI3K/Akt.^{247,249} For instance, polyphenols and vitamins can improve insulin sensitivity and reduce chronic inflammation, both of which are intimately linked to oxidative stress in conditions like polycystic ovary syndrome (PCOS).^{250,251} Clinical and observational studies support the role of dietary antioxidants in female reproductive health. Higher dietary antioxidant indices and specific micronutrient intake (eg, vitamin C, carotenoids like lycopene) have been associated with a reduced risk of infertility and better markers of ovarian reserve, such as antral follicle count.^{252–255} Nutritional supplementation with specific antioxidants like coenzyme Q10 (CoQ10), melatonin, N-acetylcysteine, and myo-inositol has been reviewed as a strategy to counteract oxidative damage in the ovary, with evidence suggesting benefits for oocyte quality and fertility outcomes in women with diminished ovarian reserve or ovarian aging.^{240,246} Furthermore, integrative lifestyle modifications that combine diet with practices like yoga have demonstrated efficacy in PCOS, improving hormonal profiles, reducing oxidative stress markers, and enhancing mitochondrial health.^{256,257} Thus, a holistic approach encompassing dietary patterns rich in natural antioxidants and other bioactive compounds, alongside overall healthy lifestyle habits, forms a critical, accessible, and multi-faceted intervention to ameliorate oxidative stress and support ovarian function.

Emerging Cellular and Molecular Therapies

- Mesenchymal stem cell transplantation: Through its paracrine effects, it secretes various growth factors and antioxidant enzymes, improves the ovarian microenvironment, inhibits oxidative stress and cell apoptosis, and has achieved results in POI animal models.

Mesenchymal stem cell (MSC) transplantation represents a promising frontier in regenerative medicine for ovarian dysfunction, primarily mediated through potent paracrine actions that ameliorate the pathological ovarian microenvironment exacerbated by oxidative stress. MSCs, derived from sources such as human umbilical cord, placenta, or adipose tissue, secrete a plethora of bioactive molecules, including growth factors, cytokines, and antioxidant enzymes, which

collectively enhance tissue repair and modulate local immune responses.¹⁶⁴ In animal models of premature ovarian insufficiency (POI) or failure (POF) induced by chemotherapeutic agents like cyclophosphamide (CTX), transplantation of human umbilical cord mesenchymal stem cells (hUC-MSCs) or their derivatives has been shown to significantly improve ovarian structure and function. For instance, hUC-MSC-derived exosomes (HuMSCs-Exos) effectively mitigate CTX-induced POF by suppressing NLRP3-mediated pyroptosis, reducing oxidative stress markers, and restoring hormonal balance and fertility outcomes.²⁵⁸ Similarly, placenta-derived MSCs (PD-MSCs) transplanted into ovariectomized rat models restore ovarian function by upregulating antioxidant factors, decreasing the expression of oxidative stress markers, and reducing granulosa cell apoptosis, thereby improving folliculogenesis and hormone secretion.¹⁶⁶ The therapeutic efficacy is further attributed to the ability of MSCs to home to injured ovarian sites, where they modulate key pathways such as AMPK, which regulates autophagic homeostasis and mitigates oxidative damage.¹⁶⁴ Moreover, studies indicate that the conditioned medium from adipose-derived MSCs (ADSC-CM), a cell-free alternative, exerts comparable reparative effects to whole cell transplantation by inhibiting oxidative stress-mediated activation of the ASK1/JNK signaling pathway, reducing fibrosis, and promoting follicular cell proliferation in CTX-induced POI mice.²⁵⁹ The dose-related efficacy of PD-MSC transplantation has been explored, revealing that even low-dose administration can exert significant antioxidant effects, improving follicular counts and hormone levels without a proportional increase in effectiveness at higher doses, suggesting a saturable therapeutic window.¹⁶⁸ Collectively, these preclinical findings underscore the potential of MSC-based therapies to counteract oxidative stress, inhibit apoptotic cascades, and rejuvenate the ovarian niche, positioning them as viable strategies for clinical translation in conditions like POI and ovarian aging.

- Gene therapy and epigenetic regulation: Exploring the upregulation of local ovarian antioxidant genes (eg, SOD2, GPx4) expression via vectors, or the use of epigenetic drugs to regulate the transcription of oxidative stress-related genes, which is still in the basic research stage.

Gene therapy and epigenetic regulation are emerging as innovative, albeit nascent, approaches to combat ovarian dysfunction by directly targeting the molecular underpinnings of oxidative stress at the genetic and transcriptional levels. The core strategy involves enhancing the endogenous antioxidant defense system within ovarian cells, particularly granulosa cells, which are highly susceptible to oxidative damage. Key antioxidant genes such as superoxide dismutase 2 (SOD2) and glutathione peroxidase 4 (GPx4) are critical for neutralizing reactive oxygen species (ROS) and preventing lipid peroxidation, a process linked to ferroptosis—a form of iron-dependent cell death implicated in ovarian aging and POI.²³¹ Gene therapy aims to upregulate the expression of these protective genes using viral or non-viral vectors. For example, the SIRT1-Nrf2 axis is a crucial anti-oxidative and anti-ferroptotic signaling pathway; Nrf2 controls the transcriptional activation of detoxifying enzymes including SOD2 and GPx4.²³¹ Therapeutic interventions that activate this axis, such as pharmaceutical agents (eg, metformin, melatonin) or nutraceuticals (eg, resveratrol), can potentially mimic gene therapy effects by boosting endogenous antioxidant capacity, though direct gene delivery methods are still under exploration in ovarian contexts. Epigenetic regulation offers another layer of control, focusing on modifying gene expression without altering the DNA sequence. Oxidative stress can induce epigenetic changes such as DNA methylation, histone modification, and regulation by non-coding RNAs, which in turn influence the expression of stress-response genes.²⁶⁰ For instance, N-acetyltransferase 10 (NAT10), a regulator of RNA acetylation, plays a dual role in cell damage responses; its dysregulation is implicated in POI pathogenesis involving oxidative stress, apoptosis, and inflammation, suggesting that NAT10 inhibitors like Remodelin could be explored as epigenetic therapeutics.²⁶⁰ Furthermore, in polycystic ovary syndrome (PCOS), epigenetic modifications contribute to glycolytic dysfunction and oxidative stress in granulosa cells, and agents like metformin or resveratrol may exert part of their benefits by reversing these epigenetic alterations.²⁶¹ Research also highlights the role of microRNAs (miRNAs) in the crosstalk with oxidative stress in ovarian cancer, where redox-responsive miRNAs regulate antioxidant defenses and DNA repair, presenting targets for miRNA-based therapies.²⁶² However, these approaches remain predominantly in the preclinical and basic research stages. Challenges include ensuring targeted delivery to ovarian tissues, achieving stable and regulated gene expression, and minimizing off-target effects. The exploration of epigenetic drugs, such as histone deacetylase inhibitors or DNA methyltransferase inhibitors, to modulate the transcription of oxidative stress-related genes like those in the Nrf2 pathway, is an active area of investigation but requires extensive validation in ovarian disease models before clinical application.¹²⁹ Thus, while gene and epigenetic therapies hold immense potential for precise intervention against

oxidative stress in ovarian disorders, their development is contingent upon overcoming significant technical and safety hurdles in translational research.

Unique Perspectives of Traditional Chinese Medicine Intervention

Traditional Chinese Medicine (TCM) offers a holistic and multi-targeted approach to mitigating oxidative stress and improving ovarian function, distinct from single-target Western pharmacological agents. A wide array of TCM interventions, including classical herbal formulas, single herbs, and their active monomers, have been demonstrated to exert multi-pathway antioxidant effects, thereby ameliorating conditions such as premature ovarian insufficiency (POI), diminished ovarian reserve (DOR), and polycystic ovary syndrome (PCOS).²⁶³ For instance, formulas like Zuogui Pill (ZGP) and Erxian Decoction are recognized for their ability to regulate the “Kidney-Tian Gui-Chong Ren-Uterus” axis, a core TCM theory for female reproductive health, thereby improving ovarian reserve and function.²⁶⁴ These formulas, along with others such as Bushen Jianpi recipe and Siwu mixture, modulate critical signaling pathways involved in oxidative stress, apoptosis, and follicular development, including PI3K/Akt/mTOR, Bax/cytC/caspase-3, MAPK, and TGF- β /Smads.²⁶⁴ The therapeutic advantage of TCM lies in this synergistic, multi-component action that addresses the complex pathogenesis of ovarian dysfunction from multiple angles. For example, ZGP has been shown to alleviate cyclophosphamide (CTX)-induced ovarian aging by activating the Nrf2/HO-1 signaling pathway, which enhances the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reduces malondialdehyde (MDA) and reactive oxygen species (ROS) accumulation, and restores the stemness of oogonial stem cells.¹⁶⁰ Similarly, the modified Guishen pill (MGP) ameliorates PCOS by improving insulin resistance, reducing apoptosis and oxidative stress, partly through modulating the endothelial nitric oxide synthase (eNOS/NOS3) pathway and arginine metabolism.²⁶⁵ Active monomers derived from herbs, such as ginsenoside Rg1 and the compounds in pearl extract, also demonstrate potent antioxidant properties. Ginsenoside Rg1 can promote granulosa cell proliferation and inhibit apoptosis via the PI3K/Akt/mTOR pathway,²⁶⁴ while pearl extract enhances ovarian function in a POF rat model by scavenging excessive ROS, inhibiting the MAPK signaling pathway (ERK1/2, p38, JNK), and modulating granulosa cell autophagy and apoptosis.²⁶⁶ Furthermore, non-pharmacological TCM therapies like acupuncture have proven effective. Acupuncture intervention in a chemotherapy-induced POF rat model delayed ovarian senescence by modulating metabolic reprogramming, specifically enhancing the taurine-hypotaurine metabolism antioxidant axis and increasing SOD and GSH-Px activities.²⁶⁷ Other formulas, such as Bu-Shen-Tian-Jing Formula (BSTJF) and Ningxin-Tongyu-Zishen formula (NTZF), target specific oxidative stress and senescence pathways. BSTJF alleviates oxidative-inflammatory stress in PCOS granulosa cells by inhibiting the AGEs-RAGE/NOX4/NF- κ B pathway,²⁶⁸ while NTZF protects ovarian granulosa cells from senescence in POI mice by activating Sirt1 and inhibiting the p53/p21 pathway.²⁶⁹ The integrated regulation extends to immune and metabolic aspects, as seen with He’s Yang Chao Recipe (HSYC), which protects against POI by inhibiting PINK1-Parkin mediated mitophagy and NLRP3 inflammasome activation, thereby reducing oxidative damage.⁹ Collectively, these interventions underscore TCM’s unique advantage in providing comprehensive, system-level regulation to counteract oxidative stress, restore hormonal balance, and improve ovarian microenvironment and function, offering valuable complementary strategies for managing ovarian disorders.^{270,271}

Conclusion

This review has systematically delineated the multifaceted impact of oxidative stress on ovarian function, spanning from follicular development and oocyte quality to steroidogenesis and ovarian aging. The central pathophysiological cascade involves mitochondrial dysfunction as both a source and amplifier of ROS, leading to endoplasmic reticulum stress, activation of inflammatory pathways (NF- κ B, NLRP3 inflammasome), and induction of distinct cell death programs—apoptosis, pyroptosis, and ferroptosis—in granulosa cells and oocytes. Epigenetic alterations (DNA methylation, histone modifications, non-coding RNAs) provide a mechanism for long-lasting and potentially transgenerational effects. Clinically, oxidative stress acts as a common pathological nexus in polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), and endometriosis-associated infertility, linking metabolic dysregulation, hormonal imbalance, and chronic inflammation.

Based on the identified gaps, we propose the following priorities for future investigation: 1. Standardization of biomarkers – Develop validated panels of oxidative stress markers (eg, 8-OHdG, MDA, GSH/GSSG ratio) in follicular fluid or serum with established cutoff values for clinical decision-making. 2. Elucidation of cell-death crosstalk – Investigate the interplay between apoptosis, pyroptosis, and ferroptosis in the ovarian microenvironment, and identify key molecular switches that could be therapeutically targeted. 3. Large-scale clinical trials – Conduct multicenter, randomized controlled trials of candidate antioxidants (CoQ10, melatonin, NAC, MitoQ) with adequate sample sizes, standardized dosing, and clinically meaningful endpoints (live birth rate, time to pregnancy, offspring health). 4. Personalized antioxidant therapy – Stratify patients based on baseline oxidative status, genetic polymorphisms (eg, Nrf2, SOD2), and specific ovarian pathology (PCOS vs. POI vs. endometriosis) to optimize intervention. 5. Translational validation of emerging therapies – Accelerate the transition from preclinical models to early-phase human trials for mitochondria-targeted antioxidants, stem cell-derived exosomes, and epigenetic modulators, with rigorous safety assessments for reproductive outcomes. 6. Transgenerational studies – Examine whether oxidative stress-induced epigenetic changes in oocytes are transmitted to offspring and contribute to intergenerational reproductive or metabolic disorders.

While definitive evidence is still evolving, several practical recommendations can be made: Preconception assessment – Measuring serum or follicular fluid oxidative stress markers (eg, 8-OHdG, TAC) may help identify women with diminished ovarian reserve or poor IVF prognosis, though standardized protocols are needed. Lifestyle as first-line therapy – Weight management, Mediterranean diet, regular exercise, and smoking cessation reduce systemic oxidative burden and should be recommended to all women with PCOS, POI, or unexplained infertility. Targeted antioxidant supplementation – CoQ10 (200–600 mg/day) may be considered for women with advanced maternal age or diminished ovarian reserve, based on current evidence, but universal supplementation is not advised. Avoidance of excessive antioxidants – High-dose, long-term antioxidant use should be avoided without medical supervision, as it may interfere with physiological ROS signaling required for ovulation and follicular rupture. Integration of emerging therapies – Acupuncture, traditional Chinese medicine formulas (eg, Zuogui Pill), and stem cell-based treatments remain investigational; they should only be offered within clinical trials or with informed patient consent.

In conclusion, oxidative stress is a master regulator of ovarian pathophysiology and a promising therapeutic target. The path forward requires a concerted effort to deepen mechanistic understanding, validate clinical tools, and rigorously evaluate innovative, personalized interventions. Success in this endeavor will be instrumental in preserving female fertility and promoting healthy ovarian aging.

Acknowledgments

Shuna Zhang and Fei Wang are co-first authors for this study. Thanks for Department of Gynaecology and Obstetrics, Qinghai Red Cross Hospital and Research Center for High Altitude Medicine, School of Medical, Qinghai University.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Open Research Projects of the Qinghai Province High-Altitude Medical Laboratory(2026-KF-01) and Qinghai Province obstetrics and gynecology disease clinical medical research center(2024-SF-L03).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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