Redox biology in PCOS: Biomarkers, mechanistic networks, and targeted interventions (Review)

YUENA QIU[1], XIAOJING GUO[2] and JIE AN[2]

[1]Department of Reproductive Medicine, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian 362000, P.R. China; [2]Department of Gynecology, Kunshan Hospital of Traditional Chinese Medicine Affiliated to Yangzhou University,Yangzhou University, Suzhou, Jiangsu 215300, P.R. China

Received November 23, 2025; Accepted July 16, 2026

DOI: 10.3892/ijmm.2026.5960

Abstract. Polycystic ovary syndrome (PCOS) is a lifelong endocrine-metabolic disorder affecting 11-13% of women worldwide. Beyond ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology, PCOS is tightly linked to insulin resistance, dyslipidemia, hypertension, and increased cardiometabolic risk. Converging evidence places oxidative stress at the core of PCOS pathophysiology, but current evidence should be interpreted in a phenotype-aware manner. Obese, hyperandrogenic, and Rotterdam phenotype A/B presentations generally carry a heavier systemic oxidant-inflammatory burden than phenotype D, whereas lean PCOS may still exhibit clinically relevant local ovarian redox abnormalities despite a milder metabolic background. Mitochondrial dysfunction, insulin resistance, and androgen excess amplify reactive oxygen species generation, while granulosa-cell mitochondrial depolarization, apoptotic signaling, and NF-κB-driven inflammation degrade follicular fluid quality, oocyte competence, and embryo development. However, the literature remains heterogeneous because assay platform, specimen type, cycle phase, adiposity, and treatment exposure all influence biomarker reproducibility and comparability. In addition, most human research supports association, whereas stronger causal support comes from interventional or mechanistic research showing that modulation of NADPH oxidase 4, antioxidant pathways, mitochondrial function, or sex hormone-binding globulin-related oxidative signaling can alter key reproductive and metabolic phenotypes. To improve translational value, the present review prioritizes a core biomarker panel spanning serum/plasma and follicular fluid, distinguishes systemic oxidative markers from local ovarian microenvironmental markers, and critically compares antioxidant and metabolic interventions by evidence level, sample size, endpoint type, and major limitations. Recent phenotype-oriented and multi-omics reearch is further integrated to propose a biomarker-guided framework for phenotype-stratified trials and precision management of PCOS.

Contents

1. Introduction

Polycystic ovary syndrome (PCOS) is a common, lifelong endocrine disorder in women. Its global prevalence is 11-13%, and population-based studies using the Rotterdam criteria report estimates of 14-19%, highlighting a substantial public health burden (1,2). Clinically, PCOS is characterized by ovulatory dysfunction leading to oligomenorrhea or amenorrhea, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology. Insulin resistance and hyperinsulinemia are frequent and are closely linked to early-onset type 2 diabetes (1,3,4). Prevalence varies by region and ethnicity; obesity aggravates endocrine disturbances and further increases prevalence, underscoring interactions between metabolic susceptibility and environmental factors (5-7). In addition, dyslipidemia, impaired glucose metabolism, and hypertension are more common in PCOS, with a consequent increase in cardiovascular events and related outcomes, emphasizing the need for early identification and management (8-10).

Oxidative stress is a state of disrupted homeostasis caused by an imbalance between the generation and clearance of reactive oxygen species (ROS). It results in oxidative damage to proteins, lipids, and DNA, along with dysregulation of cellular signaling networks (11). As a key pathophysiological node, oxidative stress is closely associated with numerous chronic

Correspondence to: Dr Jie An, Department of Gynecology, Kunshan Hospital of Traditional Chinese Medicine Affiliated to Yangzhou University,Yangzhou University, 388 Zuchongzhi South Road, Suzhou, Jiangsu 215300, P.R. China
E-mail: anjie8261137@163.com

Key words: polycystic ovary syndrome, biomarkers, redox biology

diseases, including metabolic disorders such as diabetes, and has therefore become a central focus for elucidating disease mechanisms and identifying therapeutic targets (11-13).

Recent evidence places oxidative stress at the core of female reproductive disorders and shows a tight link with the onset and progression of PCOS, offering a fresh perspective on its pathology (14,15). In PCOS, mitochondrial dysfunction and insulin resistance drive excessive ROS production and amplify inflammatory and stress signaling, further disrupting redox balance and creating a self-perpetuating pathological loop (16,17). Hyperandrogenism increases leukocyte sensitivity to hyperglycemia and promotes ROS accumulation, thereby intensifying systemic oxidative load and low-grade inflammation (18). Together, these changes damage the follicular microenvironment and oocyte quality, disturb ovulation and steroidogenesis, and ultimately worsen oligo-ovulation and infertility. These observations suggest that antioxidant therapy and metabolic correction may be key avenues for intervention (19).

Against this background, the present review not only synthesizes recent advances on oxidative stress in PCOS, but also extends prior narratives in four aspects. Redox features are compared across lean and obese PCOS, hyperandrogenic and non-hyperandrogenic states, and Rotterdam phenotypes A-D (20,21). Correlative clinical observations are further distinguished from pathways supported by experimental intervention, cell-based manipulation, or animal evidence (21). A prioritized translational biomarker panel is proposed, with consideration of specimen choice, assay limitations, and major sources of inter-study variability (20). Antioxidant and metabolic interventions are critically appraised with respect to evidence strength, endpoint hierarchy, and the remaining gaps in long-term and head-to-head evaluation. Recent phenotype-based biomarker studies and multi-omics analyses further strengthen the rationale for precision-oriented redox research in PCOS (22,23).

2. Pathophysiological foundations of PCOS

The pathophysiology of PCOS reflects the combined effects of hypothalamic-pituitary-ovarian (HPO) axis imbalance, insulin resistance, disruption of the local ovarian microenvironment, and chronic low-grade inflammation. These processes amplify one another and show heterogeneity across individuals and life stages (24,25).

Endocrine imbalance. Patients with PCOS commonly exhibit a remodeled HPO rhythm: An increased frequency of gonadotropin-releasing hormone (GnRH) pulses drives higher luteinizing hormone (LH) output with a relative deficiency of follicle-stimulating hormone (FSH), yielding the characteristic LH/FSH imbalance that underlies the ovarian phenotype (24,26) (Fig. 1). Elevated LH directly stimulates theca cells, enhancing steroidogenesis and upregulating androgen synthesis, the upstream driver of clinical hyperandrogenism and the polycystic ovarian morphology (27,28). Insulin acts together with LH in theca cells to promote androgen biosynthesis; in parallel, hepatic synthesis of sex hormone-binding globulin (SHBG) is suppressed, increasing free androgens and magnifying androgen exposure and actions in peripheral tissues (28,29). Anti-Müllerian hormone (AMH) from small antral follicles is often elevated, inhibiting granulosa-cell aromatase and FSH-dependent follicular progression, thereby reinforcing a pro-androgenic milieu and delaying follicle selection (30,31). During adolescence and early adulthood, relative resistance to progesterone negative feedback can sustain high-frequency GnRH/LH pulsatility, stabilizing the endocrine imbalance (24,32). Genetic susceptibility loci, such as DENN domain-containing 1A (DENNDIA), and dysregulated microRNAs have been linked to an intrinsic pro-androgenic program in the ovary, possibly through the upregulation of steroidogenic pathways that maintain androgen excess (27,33).

Within this axis framework, heightened excitability of arcuate kisspeptinergic neurons is considered to accelerate GnRH pulses and blunt progesterone-mediated negative feedback, maintaining elevated LH pulse frequency and amplitude and progressively uncoupling endocrine crosstalk between the theca and granulosa compartments (24,32). Persistent LH predominance limits granulosa cell aromatase capacity, constraining the conversion of testosterone to estradiol and deepening the androgenic environment; folliculogenesis stalls, and ovulatory dysfunction ensues (28,30). AMH elevation not only suppresses initial follicle recruitment within the ovary but may also act via hypothalamic receptors to modulate GnRH pulsatility, further amplifying the pro-androgen loop and compounding impaired feedback along the axis (30,31).

Hyperandrogenism, in turn, weakens estrogen- and progesterone-mediated feedback at the hypothalamus and pituitary, favors the accumulation of small antral follicles, and produces a polycystic morphology, thereby consolidating irregular ovulation and luteal insufficiency (26,28). Interacting with body-composition and metabolic cues, hyperinsulinemia both heightens theca-cell sensitivity to LH and suppresses hepatic SHBG synthesis, markedly raising the fraction of free androgens and amplifying receptor-mediated effects in skin/hair follicles, liver, and adipose tissue (27,29). In lean PCOS, the LH/FSH imbalance tends to be more pronounced, whereas in obese PCOS, hyperinsulinemia can sustain an androgen load even when the LH/FSH shift is modest, suggesting shared upstream drivers behind divergent phenotypes (26,29).

Ovarian stromal hyperplasia and heightened angiogenesis are linked to androgen-dependent activation of vascular endothelial growth factor (VEGF) signaling. This pattern aligns with the tendency toward exaggerated responses during ovulation induction and highlights constraints imposed by the vascular microenvironment on follicle growth (27,34). At the paracrine level, increased follistatin and reduced activin A reshape signaling between granulosa and theca cells, enforcing arrest at the small antral stage, lowering FSH sensitivity, and decreasing the likelihood of dominant-follicle emergence (30,35). During adolescence, physiologic increases in small antral follicles and AMH can occur; thus, clinical assessment should integrate menstrual history, evidence of hyperandrogenism, and metabolic status to avoid over-diagnosing transient physiologic changes (31,36). At the molecular genetic level, genome-wide studies highlight loci related to the gonadotropin axis and metabolic pathways; DENND1A variants, in particular, are associated with programmed activation of theca-cell steroidogenesis, mirroring clinical heterogeneity

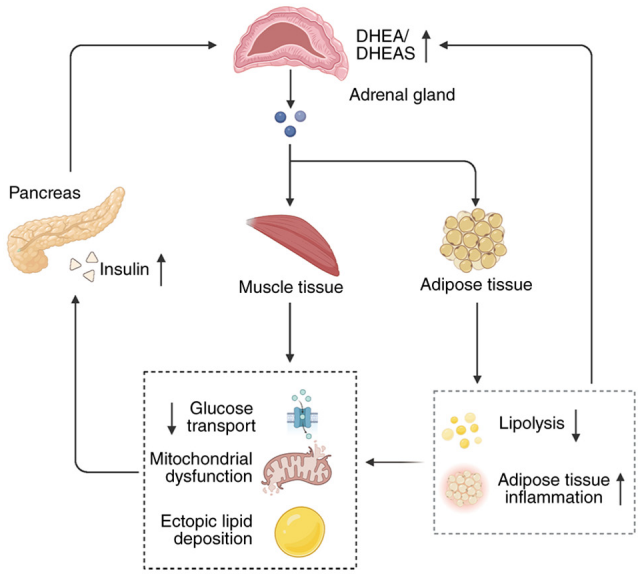

Figure 1. Remodeling of the HPO axis in PCOS. Elevated AMH acts on the hypothalamus to increase gonadotropin-releasing hormone GnRH, yielding preferential LH output with relatively reduced FSH. LH targets theca cells to enhance androgen (testosterone) production, while granulosa cells produce estradiol. Ovarian steroid feedback to the hypothalamus-pituitary is impaired. Hyperinsulinemia from the pancreatic islet augments androgen synthesis and the liver lowers SHBG, increasing bioavailable androgens. AMH is also elevated within the ovary. Together, increased GnRH/LH drive, insulin excess, and reduced SHBG sustain a pro-androgenic milieu and disrupt follicular function across the theca-granulosa unit. HPO, hypothalamic-pituitary-ovarian; PCOS, polycystic ovary syndrome; AMH, anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate.

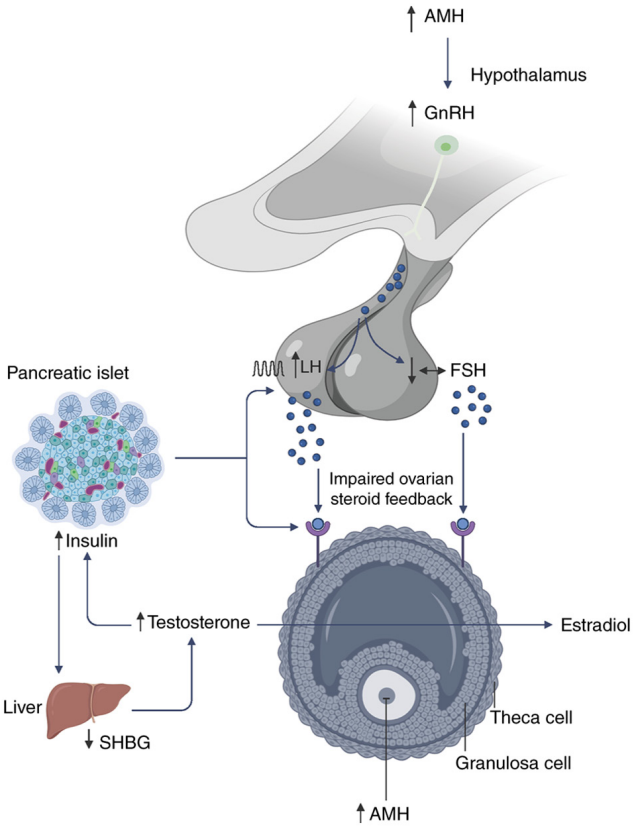

Figure 2. Insulin resistance and the metabolic-ovarian axis in PCOS. Insulin resistance induces compensatory hyperinsulinemia from the pancreatic islet. Insulin enhances theca-cell androgen (testosterone) production, while granulosa cells generate estradiol. In parallel, the liver decreases SHBG, increasing free androgens. These changes impair ovarian steroid feedback and maintain a pro-androgenic environment that disrupts follicular function. PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; AMH, anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

and indicating that genetic background confers vulnerability to endocrine disequilibrium (27,33).

From a systems perspective, neuroendocrine and metabolic signals couple through pro-androgenic and anti-estrogenic effects to establish a persistent disruption of ovarian homeostasis. Through increased free androgens and insulin signaling, this imbalance extends to peripheral tissues, forming a pathological loop with limited reversibility and marked inertia (26,29).

Insulin resistance and metabolic syndrome. Across ages and body sizes, insulin resistance is common in PCOS. It features a marked reduction in insulin-stimulated glucose uptake with compensatory hyperinsulinemia, which strengthens ovarian androgen production and promotes the accumulation of metabolic complications (37,38). Oxidative stress acts as a cross-system amplifier. Mitochondrial ROS and radicals generated by NADPH oxidase weaken insulin-receptor signaling and induce chronic low-grade inflammation, which further aggravates hyperinsulinemia and its pro-androgenic effects (39,40) (Fig. 2).

In skeletal muscle, insulin-signaling defects include abnormal serine phosphorylation of the insulin receptor and an imbalance in insulin receptor substrate (IRS)-linked pathways, directly impairing glucose transport and downstream metabolic actions (41,42). Mitochondrial dysfunction together with ectopic lipid deposition lowers the efficiency of oxidative phosphorylation and drives energy-metabolism reprogramming. The accompanying excess ROS then feeds back to suppress insulin signaling, forming a vicious cycle (39,43). Adipose-tissue secretion patterns shift, with higher leptin and follistatin and lower adiponectin, reducing whole-body insulin sensitivity and increasing cardiometabolic risk (38,44). When oxidative stress coexists with low adiponectin, adipose inflammation and insulin resistance intensify, adding to the metabolic burden (40).

At the glucose-uptake step, reduced postreceptor expression of glucose transporter type 4 (GLUT4) limits insulin-mediated glucose entry into adipocytes and myocytes, worsening glucose intolerance and hyperinsulinemia (38,45). ROS can also inhibit GLUT4 translocation and diminish the expression and activity of multiple insulin-pathway components, thereby reinforcing the postreceptor defect (39,40). In the control of lipolysis, fewer β2-adrenergic receptors and insufficient activation of protein kinase A restrict phosphorylation of hormone-sensitive lipase, blunting basal and stimulated lipolysis and altering lipid turnover (46,47). The resulting lipid spillover causes hepatic and skeletal-muscle lipotoxicity. In concert with mitochondrial injury in muscle, this amplifies systemic insulin resistance and the metabolic-syndrome phenotype (43,48). Lipid peroxidation driven by lipotoxicity further increases ROS generation, creating a positive feedback

that maintains insulin resistance and oxidative stress at a high steady state (49). Upregulation of the androgen-activating enzyme aldo-keto reductase family 1 member C3 (AKR1C3) in adipose tissue has been shown to enhance local testosterone formation, establishing a self-reinforcing loop between metabolic dysfunction and hyperandrogenism that promotes ectopic fat deposition and escalates inflammation (50,51). In addition, androgen excess was found to heighten leukocyte oxidative reactivity to hyperglycemia, amplifying systemic inflammation and oxidative pressure and further damaging insulin signaling (52).

The adrenal contribution to PCOS is often underestimated. Under regulation by adrenocorticotropic hormone and insulin, the zona reticularis synthesizes dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Clinically, functional adrenal hyperandrogenism has been reported in 20 to 40% of patients, and DHEAS, owing to its long half-life, serves as a stable marker (53). Elevated DHEAS usually signals a higher systemic androgen load. In a subset of young women with phenotype A, however, it is accompanied by lower BMI and insulin levels, indicating age- and phenotype-dependent heterogeneity in adrenal androgen patterns and metabolic traits (53). Peripheral metabolism of DHEA and its sulfate was shown to couple with AKR1C3-driven local androgen activation, promoting lipid accumulation and worsening insulin resistance, which forms a feed-forward loop with lipotoxicity and inflammation (50,54). In the context of oxidative stress, DHEA-induced animal models demonstrated that NADPH oxidase 4 (NOX4) upregulation and ROS accumulation can trigger ovarian and systemic metabolic injury. Treatment with superoxide-dismutase mimetics or inhibition of NOX4 was found to improve ovulation and glucose homeostasis, pointing to a causal link between adrenal precursors and oxidative pathways (55,56).

Changes in the ovarian microenvironment. In PCOS, the number of antral follicles smaller than 9 mm is increased and AMH is highly expressed. These changes suppress FSH-dependent follicle recruitment and selection, causing numerous follicles to stall at early stages and reducing the chance of a dominant follicle, which directly lowers the probability of ovulation (30,36). Within the paracrine network of granulosa and theca cells, higher follistatin and lower activin A shift the balance of growth factors, block further growth to the preovulatory size, and weaken the normal response to the LH surge (30,35). During ovulation induction, this blockade can be partly overcome by exogenous FSH, indicating some plasticity of the granulosa cell response and providing a rationale for clinical intervention (30).

High AMH in small antral follicles, together with an ovarian androgenic milieu, delays maturation and cascade progression of FSH receptor pathways, further reduces aromatase efficiency, and expands the pool of early follicles (30,35). Estrogens and androgens may induce premature luteinization; early expression of the progesterone receptor disrupts the timing needed for follicle maturation, leading to asynchrony between ovulation triggering and follicle rupture and affecting luteal function and cycle stability (35,57). In parallel, ovarian stromal volume and angiogenic activity are broadly increased. This is associated with androgen-driven upregulation of VEGF signaling, matches the clinical tendency toward ovarian hyperresponse during ovulation induction, and suggests that the vascular microenvironment constrains follicle growth and nutrient supply (27,34).

It is important to note that during adolescence, especially in those without signs of hyperandrogenism, a physiologic rise in small antral follicles and AMH can occur. Evaluation of microenvironmental abnormalities should therefore integrate endocrine and metabolic context to reduce overdiagnosis of transient physiologic states (31,36). Follicular arrest and defects in the microenvironment together lower oocyte quality and maturity. By altering steroidogenesis and the timed response to the LH surge, they influence fertilization and early embryo development, producing linked adverse effects on reproductive outcomes (30,35).

3. Associations between oxidative stress and the clinical features of PCOS

As a shared pathological basis across metabolic and reproductive phenotypes, oxidative stress shows stable, measurable signals in the multidimensional presentation of PCOS and closely tracks with elevated circulating oxidative biomarkers (58,59). Reviews and meta-analyses indicate that these redox abnormalities are not driven solely by obesity; differences remain in weight-matched cohorts and often coexist with low-grade inflammation (59,60). The redox imbalance is associated with insulin resistance, ovulatory dysfunction, lipid disorders, and cardiovascular risk markers, underscoring a central role in shaping the multisystem phenotype (58,61).

Insulin resistance and dysglycemia/dyslipidemia. Clinically, oxidative-stress markers are commonly elevated in PCOS and related to reduced insulin sensitivity, an association that remains significant after adjusting for body weight (59,62). High glucose augments reactive oxygen production in peripheral monocytes and couples the phenotypes of insulin resistance and hyperandrogenism, suggesting that glucotoxicity and oxidative load amplify one another in the metabolic profile (63). Glucose-induced monocyte oxidative stress is linked to impaired β-cell function, pointing to a clinical connection between oxidative signaling and the secretion-sensitivity axis of insulin (17). Dietary saturated fat can rapidly raise leukocyte ROS and thiobarbituric acid-reactive substances; the magnitude of this rise was shown to be inversely correlated with insulin sensitivity from oral testing and does not depend on obesity status (64). Defects of mitochondrial complex I in leukocytes parallel systemic insulin resistance, supporting a link between immune-cell oxidative metabolism and clinical metabolic disturbance (65). A composite score integrating LDL, oxidative stress, and inflammatory indices can distinguish PCOS from controls and reflect metabolic load, offering a quantitative tool for risk stratification (66). Lower serum paraoxonase-1 (PON1) activity, together with reduced high-density lipoprotein (HDL) antioxidant capacity, indicates impairment of enzymatic defenses and a higher susceptibility to atherosclerosis in the setting of insulin resistance (67). Population studies also show that higher total cholesterol and LDL often coexist with elevated malondialdehyde (MDA) and reduced total

antioxidant capacity (TAC), illustrating the parallel course of dyslipidemia and oxidative stress (59,68).

Ovulatory dysfunction and reduced oocyte quality. With respect to reproductive outcomes, oxidative stress is strongly associated with disordered ovulation; diminished antioxidant capacity within the follicular microenvironment accompanies lower conception rates, indicating a clinical impact on ovarian function (58,69). In assisted-reproduction studies, higher MDA and lower TAC in follicular fluid were associated with poorer embryo quality and lower fertilization rates, showing a direct coupling between local oxidative status and oocyte competence (70). Advanced glycation end products (AGEs) are elevated systemically and in ovarian tissue in women with PCOS, and are associated with anovulation and abnormal follicle development, suggesting that dietary and endogenous AGEs may influence reproductive outcomes through oxidative-inflammatory pathways (71). As a therapeutic signal, antioxidant adjuncts such as N-acetylcysteine have been shown to improve ovulation and pregnancy rates in a subset of patients, supporting the feasibility of lowering oxidative load to enhance oocyte quality and ovulatory efficiency (72). Notably, oxidative stress, insulin resistance, and androgen excess can form a self-reinforcing reproductive-metabolic loop that sustains and recurs in ovulatory dysfunction (59,69).

Obesity and adipose-tissue oxidative stress. Adipose tissue in PCOS shows features of dysfunction. Even in non-obese individuals, adipocytes exhibit disturbed homeostasis and altered secretory profiles; oxidative stress and abnormal adipokine profiles together contribute to higher systemic metabolic risk (61). Oxidative load and low-grade inflammation in adipose tissue promote each other and align with markers of insulin resistance and atherogenic risk, highlighting the amplifier role of peripheral fat stores in whole-body redox imbalance (60,61). Clinically, lower PON1 activity is accompanied by an unfavorable lipoprotein-subclass pattern, while the adiponectin-to-leptin ratio serves as an index of adipose function that reflects insulin resistance and oxidative burden, providing actionable metrics for assessing adipose health in PCOS (67,73). Population data also show that elevations of MDA commonly coexist with higher LDL in PCOS, supporting the association between lipid abnormalities and oxidative injury (68). Multiple analyses further demonstrate that, even after excluding obesity, women with PCOS display a systemic oxidative-stress phenotype, indicating sources of oxidative load that are independent of excess adiposity (59).

Elevated cardiovascular risk. Quantitative assessments of endothelial function reveal significantly reduced flow-mediated dilation in PCOS, including in young and non-obese individuals, indicating early endothelial injury (74). Longitudinal and functional research show impaired endothelium-dependent vasodilation in young women with PCOS independent of obesity, suggesting an increased risk for early cardiovascular events (75). Oxidative stress has been shown to be associated with cardiovascular risk indices and subclinical atherosclerosis, such as greater carotid intima-media thickness, supporting a role for oxidative processes in vascular structural and functional abnormalities (76,77). Overall, a network centered on oxidative stress and low-grade inflammation, combined with insulin resistance and dyslipidemia, places numerous women with PCOS on a high cardiometabolic-risk trajectory during the reproductive years. These data support early, multidisciplinary assessment and timely intervention (58,60).

Phenotype-specific redox heterogeneity and clinical implications. An important translational issue is that oxidative stress is not distributed uniformly across PCOS phenotypes. Hyperandrogenic and more metabolically adverse phenotypes, particularly Rotterdam phenotypes A and B, generally show a higher burden of insulin resistance, dyslipidemia, and inflammatory activation, and therefore are more likely to exhibit stronger systemic oxidant signatures (20,21,78). Phenotype C usually retains androgen-related oxidative features but tends to show an intermediate metabolic burden, whereas phenotype D is often characterized by milder systemic metabolic disturbance and lower overall cardiometabolic risk. Obesity further amplifies these differences, but it does not fully explain them, because lean PCOS can still display redox abnormalities linked to hyperandrogenism, altered mitochondrial function, and impaired ovarian signaling (21,59).

At the biomarker level, this heterogeneity argues against interpreting all oxidative readouts as interchangeable. Serum or plasma markers such as MDA, total oxidant or antioxidant indices, antioxidant enzyme activities, and inflammatory mediators are more informative for the systemic metabolic-inflammatory burden, whereas follicular-fluid markers better reflect the local ovarian microenvironment and oocyte competence (22,79). This distinction is particularly relevant in lean PCOS and in *in vitro* fertilization (IVF) populations, in whom systemic metabolic impairment may be modest while follicular oxidative disturbance remains biologically important (70,80). Phenotype-stratified studies should therefore prespecify both clinical subgrouping and sample compartment, rather than pooling women with fundamentally different endocrine-metabolic backgrounds into a single oxidative-stress category (20,23).

4. Mechanisms of oxidative stress in PCOS

Oxidative stress is an imbalance between pro-oxidant and antioxidant forces. In PCOS, it can be profiled by multidimensional markers from body fluids and the ovarian microenvironment, and it has been repeatedly documented by evidence from multiple sources (14,81). The imbalance appears as higher levels of several reactive oxygen species and oxidative damage products, together with lower readouts of key antioxidant systems, with a consistent direction across platforms and specimen types (82,83).

Changes in oxidative-stress markers

Pro-oxidant markers. Focusing first on total ROS burden and species composition, including superoxide anion, hydroxyl radical, singlet oxygen, hydrogen peroxide, and peroxynitrite, multiple datasets show upward shifts, which indicate a stronger overall oxidative pressure with stable directionality (82,84). Coherent evidence around lipid peroxidation shows that MDA is persistently elevated and rises in parallel with ROS load. This pattern reflects increased vulnerability

of polyunsaturated fatty acids and membrane lipids and positions MDA as a core intensity marker (85,86). Within the same damage spectrum, protein carbonylation often increases alongside MDA, suggesting a coordinated accumulation of lipid and protein oxidative modifications that together outline the pro-oxidant injury phenotype (81,83). At the nucleic-acid level, 8-hydroxy-2'-deoxyguanosine (8-OHdG) is elevated in the same direction as the above indices, providing direct evidence of oxidative susceptibility of genetic material and adding molecular detail to the damage profile (81,87).

Composite measures, such as total oxidant status and related ratios, are generally higher than in controls, which supports the presence of systemic oxidative stress and allows relative ranking of overall burden (83,88). Regarding population heterogeneity, women with obesity or metabolic abnormalities show larger and directionally consistent pro-oxidant signals, which helps distinguish them from those with purely reproductive phenotypes and points to a higher oxidative background (89,90). Across physiological rhythms, ROS levels may fluctuate by stage, yet in PCOS they often remain on a higher plateau, implying an elevated baseline that may affect interpretation of cycle-related measures (91,92). In the ovary, oxidative species and their derivatives are also increased and move in parallel with systemic status, reflecting coupling between the local microenvironment and whole-body metabolic and endocrine states (19,93).

Compensatory changes are sometimes observed. Fat-soluble antioxidants such as α-tocopherol and retinol can show mild increases, but end products such as MDA remain high, indicating that such compensation is insufficient to offset chain peroxidation and should be interpreted together with pro-oxidant readouts (85,86). Phenotype-linked data show that hyperandrogenic subtypes usually carry higher pro-oxidant levels and more active damage markers, in line with clinical severity and supporting the logic of phenotype stratification (94,95). When metabolic risk factors are present, the upward shifts in pro-oxidant indices are more pronounced and uniform, which facilitates risk assessment and separation from isolated reproductive phenotypes (90,96). Findings from animal and *in vitro* studies add causal support. Nonspecific scavenging of reactive species was shown to alter several ovulation-related measures, indirectly confirming that pro-oxidant levels participate in key steps of reproductive physiology (97,98).

Antioxidant defenses. On the antioxidant side, both enzymatic and nonenzymatic defenses tend to decline. Activities of superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase are commonly reduced, which indicates weaker clearance and breakdown of peroxidative substrates and sets the stage for oxidative imbalance (99,100). For example, SOD activity was shown to be inversely related to MDA and other end products, suggesting insufficient superoxide clearance, substrate accumulation, and amplification of downstream damage, with continuity between upstream and downstream indices (68,86). Catalase and GSH peroxidase normally remove hydrogen peroxide and organic peroxides. Declines in their activity prolong the persistence of these substrates and are accompanied by higher pro-oxidant readouts, which strengthens the detectability and discriminative power of systemic oxidative stress (99,101).

Among nonenzymatic defenses, total GSH or the reduced fraction often decreases, in line with lower TAC and a stable direction across subgroups. This pattern reflects weaker intracellular-reducing buffers and a broad loss of resilience (100,102). As a composite measure, TAC is persistently low, while total oxidant status is high, creating a bidirectional shift that allows set-based quantification of imbalance and supports graded risk ranking (83,88). In the ovarian microenvironment, activities of antioxidant enzymes and levels of nonenzymatic components often decline together and mirror the rise in pro-oxidant species, indicating that reduced defenses and enhanced damage signals coexist and track with systemic status (19,93).

Observations related to luteal function add a functional link. Low SOD activity often coincides with higher oxidative pressure and shows observable associations with the duration and efficiency of progesterone production, which underscores the regulatory role of the antioxidant barrier in reproductive endocrine output (92,98). At the individual level, women with obesity or metabolic abnormalities display larger drops in antioxidant enzyme activity that match the rises in pro-oxidant end products. This combination can help identify those with high oxidative burden and supports tiered risk classification (89,90). It is noteworthy that fat-soluble vitamin antioxidants may rise slightly as compensation, but they rarely reverse the overall low capacity and should be interpreted alongside enzymatic readouts to avoid bias from single markers (85,86). When TAC is low, rises in DNA oxidation markers are more frequently observed. This provides a complementary dimension for DNA damage and cross-validates pro-oxidant measures, reinforcing internal consistency within the oxidative-stress marker set (103,104). In addition, antioxidant indices are sensitive to endocrine and environmental cues. Although their amplitudes vary with physiological states, the overall low pattern persists. In longitudinal tracking, these measures can be combined with pro-oxidant indices to depict both the magnitude and the trajectory of imbalance (86,91).

Prioritized biomarker panel, assay constraints, and inter-study variability. Because dozens of oxidative markers have been reported with uneven reproducibility (105), a translational hierarchy is needed. For systemic evaluation, a practical core panel should prioritize one lipid peroxidation marker with relatively broad clinical use, for example MDA or 8-isoprostane, one composite antioxidant readout, such as TAC or ferric reducing antioxidant plasma (FRAP), and at least one enzymatic antioxidant component, for example SOD or GSH peroxidase, interpreted together with metabolic context such as homeostatic model assessment of insulin resistance (HOMA-IR), SHBG, and lipid parameters (106). For ovarian microenvironmental evaluation, follicular-fluid MDA or 8-OHdG, GSH-related indices, and HDL/PON1-associated antioxidant function may be more informative than serum markers alone, particularly in assisted reproductive technology (ART) settings (70,107). Direct measurement of short-lived ROS species is less suitable for routine clinical comparison because it is highly sensitive to sampling and analytical conditions (105).

Table I. Phenotype-stratified redox patterns and clinical implications in PCOS.

Phenotype/subgroup	Dominant redox-metabolic pattern	Most informative biomarkers	Clinical implication/ therapeutic emphasis
Phenotype A (HA + OA + PCOM)	Highest combined reproductive and metabolic burden; strong systemic oxidative-inflammatory signal often coexists with insulin resistance.	Serum/plasma MDA or 8-isoprostane; TAC/FRAP; SOD/GPx; HOMA-IR; SHBG; lipids.	Highest priority for combined lifestyle, insulin-sensitizing, and redox-directed strategies; monitor cardiometabolic risk early.
Phenotype B (HA + OA)	Marked androgen excess and anovulation with substantial systemic oxidative burden, often close to phenotype A.	Same systemic panel as phenotype A; consider SHBG and androgen panel as key contextual markers.	Likely to benefit from endocrine control plus metabolic/redox targeting; avoid relying on reproductive markers alone.
Phenotype C (HA + PCOM)	Intermediate metabolic burden; androgen-related oxidative features persist despite ovulatory status.	Systemic oxidative panel plus SHBG/androgen indices; local follicular markers if fertility treatment is planned.	Phenotype-specific risk may be underestimated if ovulation is used as a proxy for low metabolic risk.
Phenotype D (OA + PCOM)	Milder systemic metabolic-inflammatory profile on average, but oxidative disturbance is not necessarily absent.	Systemic markers may be less deranged; local ovarian markers become more informative when infertility is the dominant issue.	Do not assume redox quiescence from absence of hyperandrogenism; reproductive-context assessment is still needed.
Lean PCOS	Systemic metabolic impairment may be modest, while ovarian/ follicular oxidative abnormalities remain biologically relevant.	Follicular-fluid markers, targeted metabolomics, ovarian-function readouts, plus selected serum markers.	Useful reminder that obesity-independent oxidative mechanisms exist in PCOS.
Obese PCOS	Amplified systemic oxidative stress, inflammation, dyslipidemia, and insulin resistance.	Full systemic panel with cardiometabolic context; local follicular markers as secondary readouts.	Systemic biomarker monitoring is especially important for treatment tracking and long-term risk reduction.

PCOS, polycystic ovary syndrome; HA, hyperandrogenism; OA, oligo-anovulation; PCOM, polycystic ovarian morphology; MDA, malondialdehyde; TAC, total antioxidant capacity; FRAP, ferric reducing antioxidant power; SOD, superoxide dismutase; GPx, glutathione peroxidase; HOMA-IR, homeostatic model assessment of insulin resistance; SHBG, sex hormone-binding globulin.

Inter-study variability arises from several nontrivial sources. Sample type, serum vs. plasma vs. follicular fluid, menstrual phase, obesity status, androgen exposure, oral contraceptive use, storage duration, freeze-thaw cycles, and assay platform all influence oxidative readouts (105). Even when the same nominal marker is reported, different analytical methods may capture different chemical entities or time windows of oxidative injury (105). This is especially relevant for MDA, TAC, and enzyme-activity assays, which are often affected by preanalytical handling and laboratory standardization (105). Consequently, biomarker panels should be interpreted as patterned profiles rather than isolated absolute values, and future studies should report specimen handling, assay methodology, phenotype composition, and treatment exposure in a standardized manner (Table I).

Systemic and local markers should not be conflated. Serum or plasma biomarkers primarily reflect whole-body metabolic-inflammatory burden and are most useful for risk stratification and longitudinal monitoring (105), whereas follicular-fluid biomarkers capture the ovarian niche and are most relevant to oocyte competence and ART outcomes (70,106). Improvement in serum oxidative markers after oral supplementation does not by itself prove restoration of the follicular environment, because follicular penetration and local pharmacodynamic effects are rarely measured directly. This distinction should therefore be maintained throughout both observational and interventional studies.

Molecular and cellular mechanisms

Mitochondrial dysfunction. In ovarian and peripheral tissues relevant to PCOS, mitochondria show a combined pattern of inadequate energy metabolism and excessive oxidative pressure. The core features are lower efficiency of oxidative phosphorylation together with limits in radical-scavenging systems, creating a cellular milieu that is unfavorable for follicle growth and oocyte maturation (100,108). This metabolic phenotype rests on dual vulnerabilities in respiratory-chain

complexes and mitochondrial genome stability, accompanied by unstable membrane potential, collapsed cristae, and fragile mitochondrial (mt)DNA. These changes amplify ROS generation and suppress adenosine triphosphate (ATP) output, causing bioenergetics and redox homeostasis to deviate in parallel (109,110). Beyond the ovary, convergent evidence from blood and ovarian samples has shown that lower mtDNA copy number is inversely associated with insulin resistance and lipid abnormalities, indicating a shared direction between systemic energy imbalance and ovarian mitochondrial status in PCOS (104,108). In the setting of androgen excess and inflammatory cues, granulosa cells display reduced mitochondrial ATP content and complex proteins, along with vacuolated ultrastructures, which suggests that endocrine and immune signals jointly heighten mitochondrial fragility and oxidative injury (111,112). In granulosa cells, lower nicotinamide adenine dinucleotide (NAD) has been shown to weaken sirtuin-centered deacetylation and antioxidant responses, reduce respiratory efficiency, and promote ROS accumulation, contributing to a self-reinforcing loop of energy depletion (109,112). Across cohorts and cell models, complex I repeatedly emerges as a key target of oxidative injury, with reduced activity tracked by lower membrane potential, higher GSH oxidation, and higher tumor necrosis factor (TNF)-α, which links mitochondrial redox metabolism to low-grade inflammation in PCOS (65,113). In line with this, systematic reviews report cross-tissue mitochondrial changes that involve oxidative phosphorylation, the tricarboxylic acid cycle, and fatty-acid oxidation. Although skeletal muscle shows some heterogeneity, ovarian cells appear more sensitive to energy imbalance and oxidative pressure (114,115). Within the follicular microenvironment, oxidative markers in follicular fluid rise together with mitochondrial dysfunction in granulosa cells and correlate with lower oocyte maturity and poorer fertilization outcomes, indicating a direct clinical impact of local redox instability (116,117). Single-cell transcriptomics further reveals abnormal activation or timing shifts in mitochondrial gene modules as early as the germinal vesicle stage, suggesting early disruption of coupling between mitochondrial programs and meiosis (115,118). Notably, some cohorts show no clear fall in skeletal-muscle respiration, which points to tissue specificity and metabolic phenotype as determinants of mitochondrial readouts. Ovarian cells are more vulnerable and thus serve as early targets of systemic metabolic and endocrine imbalance (114,119).

At the granulosa-cell level, lower membrane potential, crista disruption, and reduced mtDNA copy number reinforce one another, creating a continuous chain from structure to function. Increased susceptibility of the permeability transition pore and unstable potential favor programmed cell death and suppress steroidogenesis (110). Disrupted mitochondrial dynamics run through this process. Excessive fission centered on dynamin-related protein 1 and insufficient fusion mediated by mitofusin 2 and optic atrophy 1 have been shown to convert the network from tubular to fragmented, lowering coupling efficiency, spare respiratory capacity, and stress tolerance (114,120). In androgen-driven models, this fission bias was found to occur together with lower complex protein expression and ultrastructural damage, implying that androgen signaling worsens dysfunction by altering both dynamics and electron transport (121). Mitochondria-endoplasmic reticulum (ER) coupling is also disturbed. Upregulated ER stress and disordered calcium handling increase ROS via mitochondria-associated membranes and trigger further crista remodeling and membrane permeability changes (108,122). Within the suirtin (SIRT)3-centered deacetylation network, PCOS granulosa cells exhibit downregulated SIRT3 signaling and abnormal expression of metabolic genes. The result is a weaker antioxidant shield, including SOD2, along with shifts in lipid metabolism and glycolysis that drag down oxidative phosphorylation (123). Electron leak from complexes I and III increases under this imbalance, with excess NADH and greater proton leak across the inner membrane. The combined outcome is inadequate ATP output and higher lipid oxidation, a coupled phenotype (65). Beyond the respiratory chain, NADPH oxidases also contribute to ovarian ROS. Evidence for NOX4 indicates important effects on granulosa-cell activity and apoptotic threshold, suggesting cooperation between mitochondrial and non-mitochondrial ROS sources (56,124). Antioxidant defenses in granulosa cells, including GSH systems and peroxiredoxins, tend to be downregulated, which weakens protection against lipid and protein oxidation and indirectly destabilizes membrane potential (104,109). As oxidative injury accumulates, mtDNA damage and copy-number shifts become more likely, together with lower mitochondrial transcription factor A and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), pointing to a broad weakening of mitochondrial quality control (113). Cross-tissue work suggests that some patients carry mitochondrial genome variants and show population-level changes in peripheral mtDNA copy number, which may underlie the vulnerability of ovarian energy economics (104). Oocytes are even more sensitive than somatic cells. As early as the germinal vesicle stage, timing of respiratory-chain subunits and ribosomal genes deviates from normal, implying premature or misplaced coupling of mitochondrial transcription and translation, which can disrupt meiosis and cytoplasmic maturation (115,118).

Mitochondrial energy defects also couple to rewiring of glucose and lipid metabolism in granulosa cells. In an oxidative milieu, insulin signaling is easily suppressed. Oxidative modifications at IRS and phosphoinositide 3-kinase (PI3K) nodes reduce Akt activation, limit glucose uptake and glycolytic flux, and promote accumulation of NADH and acyl-CoA, thereby increasing the likelihood of electron leak (108,113). In granulosa cells, uncoupling protein 2-related proton leak is associated with steroidogenesis, suggesting that when coupling efficiency falls, the balance between steroid production and energy allocation shifts and alters the endocrine features of the follicular niche (125,126). Redox and inflammatory signals intersect at thioredoxin-interacting protein (TXNIP) and NOD-like receptor family pyrin domain-containing 3 (NLRP3). These pathways translate redox imbalance into inflammasome activation and a pro-death tendency, connecting mitochondrial oxidative stress to chronic ovarian inflammation and lowering the apoptotic threshold (127,128). System-level data indicate that, although some skeletal-muscle studies do not show reduced respiration, numerous reports support cross-organ disruption of mitochondrial signaling in PCOS. Under metabolic stress or endocrine disturbance, ovarian cells show earlier and stronger loss of membrane potential

and respiratory efficiency (114,119). When these changes act during follicle development, lipid and DNA oxidation markers in follicular fluid are negatively associated with fertilization and early embryo events, emphasizing the decisive effect of mitochondrial status on oocyte quality and early embryo competence (116,117). Finer coupling between structure and dynamics is supported by links between androgen levels and fusion-promoting factors such as mitoguardin-2. Insufficient fusion together with excessive fission fragments the network, reduces sharing of genetic material and intermediates, and lowers overall respiratory capacity and stress margin. This trajectory from structure to function runs in step with NAD deficiency and inhibition of sirtuin pathways, which normally regulate antioxidant and metabolic enzymes by deacetylation. When NAD supply is limited, coupling between redox control and energy metabolism is broadly disruped (109,111,112,120).

Dysregulation of insulin signaling. Oxidative stress promotes abnormal serine phosphorylation of the insulin receptor and its substrates and suppresses activation at key tyrosine sites. Post-receptor signaling shifts from coupled to uncoupled and weakens the transmission of PI3K and Akt-mediated metabolic commands (41). In PCOS skeletal muscle and ovarian cells, aberrant phosphorylation at IRS1 Ser312 coincides with lower IRS1-associated PI3K activity. Glucose uptake and glycolytic flux fall, consistent with sustained suppression of the cascade by ROS-related modifications (129). Stress-kinase activation is a central mechanism. c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor-κB kinase phosphorylate serine residues near the phosphotyrosine-binding domain of IRS1, disrupt binding to the receptor, and block downstream signaling (130). At the protein level, oxidative stress drives site-specific IRS1 hyperphosphorylation with altered turnover. Different sites contribute variably to metabolic suppression, implying that the modification pattern sets the depth of signaling loss (131). Overactivation of noncanonical pathways also adds negative feedback. Higher ERK activity promotes IRS1 serine phosphorylation, weakens interaction with p85, and limits effective recruitment of PI3K to the membrane (42). Even when receptor autophosphorylation on tyrosine is not markedly impaired, post-receptor pathways become uncoupled because IRS adaptors are compromised and stress kinases intervene. The result is lower responsiveness of the metabolic branch and a shifted spatiotemporal profile of signaling (132).

Redox changes reshape signaling thresholds and duration through oxidative modification of phosphatases and lipid phosphatases. Hydrogen peroxide can reversibly oxidize catalytic cysteines and transiently inhibit protein tyrosine phosphatases, altering patterns of dephosphorylation in insulin signaling (133). On the lipid side, the PTEN catalytic cysteine Cys124 is highly redox sensitive. Oxidation reduces phosphatidylinositol (3,4,5)-trisphosphate dephosphorylation and shifts the balance of PI3K and Akt at the membrane, which distorts signal gain and feedback (134). Together with IRS serine modification, this phosphatase network disturbance yields an apparent paradox of erroneous amplification and sustained desensitization. The net outcome is functional suppression of the metabolic pathway and attenuated cellular responses to insulin (135).

External and internal stressors converge to suppress ovarian insulin signaling. Endocrine disruptors such as bisphenol A, acting through aryl hydrocarbon receptor pathways, lower GLUT4 in granulosa cells and induce disordered glucose metabolism, which indirectly raises redox pressure and weakens the PI3K-Akt axis (136). In insulin-responsive tissues such as the endometrium, GLUT4 expression declines under the influence of the insulin-androgen axis and metabolic status. This offers histological evidence for local insulin resistance in the reproductive tract and echoes transport limits in the ovary (137). Research in immune cells and skeletal muscle show that women with PCOS generate more ROS in response to high glucose, with corresponding declines in insulin sensitivity, supporting consistency between systemic oxidative load and local ovarian signaling defects (63). At the adaptor level, oxidative stress not only changes IRS1 phosphorylation, it also lowers IRS1 protein abundance and accelerates turnover. Fewer effective interactions with p85 further restrict signal flow (138). Nutrient-driven O-linked N-acetylglucosamine (O-GlcNAc)ylation adds another layer. Higher O-GlcNAc on IRS1 and Akt2 is associated with insulin resistance and interacts with stress-kinase pathways (139). In adipocytes, increased O-GlcNAc is associated with lower phosphorylation of Akt Thr308 and downstream glycogen synthase kinase 3β, indicating that nutrient sensing can rewrite cascade efficiency through glycosylation (140). O-GlcNAc cycling is also present in granulosa cells. Perturbing this cycle alters proliferation, glycolysis, and mitochondrial metabolism, and reduces responsiveness to insulin signaling (141).

Granulosa-cell apoptosis and decline in oocyte quality. Excess ROS triggers cytochrome *c* release and the caspase cascade via the mitochondrial pathway. Granulosa-cell survival and differentiation decline, with reduced steroidogenesis and weaker paracrine support to the oocyte (116,142). In PCOS and model systems, higher oxidative load in follicular fluid is associated with lower mitochondrial membrane potential, mitochondrial dysfunction, and increased early apoptosis in granulosa cells. These changes are negatively correlated with oocyte maturity and early embryo quality (109,116). Upstream oxidases amplify the signal. NOX-dependent ROS promotes Bax upregulation and cleavage of caspase-3 and caspase-9, which strengthens the apoptotic pathway (56,142). Stress-kinase networks that include JNK and p53 mediate death responses to hydrogen peroxide, highlighting their role as execution interfaces for apoptosis. Consistent human data show higher oxidative markers and apoptosis in PCOS granulosa cells together with lower fertilization and implantation, linking the oxidative milieu directly to reproductive outcomes (116,142) (Fig. 3).

Noncoding RNAs also regulate oxidative apoptosis. For example, miR-1224-5p and miR-484 have been shown to influence stress responses and mitochondrial stability and promote a pro-apoptotic tendency in the PCOS context (143,144). Inflammation and oxidation promote each other. Higher immunologic mediators in follicular fluid activate inflammatory programs inside granulosa cells, reduce proliferation, and increase apoptotic sensitivity, which weakens nutritional and metabolic support for the oocyte (116,145). Overall, oxidative stress drives granulosa cells toward programmed death through mitochondrial damage and inflammatory coupling,

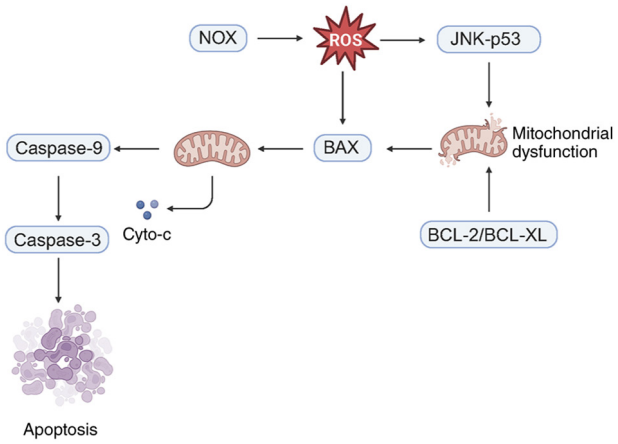

Figure 3. ROS-mediated mitochondrial apoptosis pathway. NOX generates ROS, which activates JNK-p53 and promotes BAX. JNK-p53 induces mitochondrial dysfunction; BAX targets mitochondria to trigger cyto-c release. Cyto-c activates caspase-9, leading to caspase-3 activation and apoptosis. Anti-apoptotic BCL-2/BCL-XL act at the mitochondria. Arrows indicate activating steps. ROS, reactive oxygen species; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; JNK, c-Jun N-terminal kinase; p53, tumor protein p53; BAX, BCL-2-associated X protein; cyto-c, cytochrome c; BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large.

and this process aligns with lower oocyte quality and restricted embryo potential (109,116).

Chronic inflammation and NF-κB activation. Sustained oxidative stress is observed systemically and within the ovarian microenvironment in PCOS. Oxidative products accumulate while antioxidant defenses are suppressed, and part of this signal is independent of obesity, implying that oxidative pressure is a basal driver of the disease phenotype (59). Reviews and quantitative summaries show broad increases in lipid, protein, and DNA oxidation, together with dysfunction of SOD and GSH systems, which indicates a lower antioxidant reservoir and inadequate radical clearance (146). A chronic, low-grade inflammatory network centered on NF-κB forms a reciprocal amplifier with oxidative stress. ROS act as second messengers to promote inhibitor of κB (IκB) degradation and nuclear translocation, while inflammatory pathways feed back to raise radical production, creating a key immune-metabolic intersection (147). In peripheral monocytes from women with PCOS, high-glucose stress was shown to produce higher nuclear NF-κB activity and lower IκB, showing that nutrient-driven oxidative load rapidly converts into amplified inflammatory signaling, even after controlling for obesity (148). Postprandial saturated-fat exposure was found to enhance NF-κB and downstream cytokines through Toll-like receptor 4-related pathways and is accompanied by lower insulin sensitivity and a shift toward androgen production, revealing two-way coupling between nutritional oxidative stress and endocrine imbalance (149) (Fig. 4).

In granulosa cells, increased oxidative stress coexists with mitochondrial dysfunction, observed as more ROS, unstable membrane potential, and restricted respiratory efficiency. Energy metabolism and oxidative injury are therefore jointly embedded in follicular ecology (150). Cells from immature follicles show limited glycolysis and inadequate ATP production. ROS accumulation intersects with substrate shortage and disrupts coordinated follicle growth (151). Antioxidant responses are compromised. The Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 (Nrf2) axis has been shown to be dysregulated in PCOS granulosa cells, lowering the oxidative threshold. Cells then become more vulnerable to damage more easily under androgen exposure, lipotoxicity, or hyperglycemia (152). At the molecular junction, the redox-sensitive adaptor TXNIP is upregulated and activates the NLRP3 inflammasome, providing a direct link between oxidative signals and pro-inflammatory cell-death programs in granulosa cells (127). TXNIP also reshapes glycolytic flux through effects on the IRS1-PI3K axis, establishing positive feedback between energy metabolism and oxidative pressure, with concurrent weakening of substrate supply and antioxidant capacity (153).

In the follicular-fluid niche, lipid peroxidation products such as 8-isoprostanes are elevated in PCOS and associated with lower embryo quality, implying that local oxidative pressure affects oocyte competence by altering lipids and apolipoprotein function (79). DNA oxidation is also higher. Follicular-fluid 8-OHdG is associated with lower fertilization and early embryo metrics, indicating a role for oxidative DNA damage in reducing developmental potential (70). Early research showed that accumulation of 8-OHdG within granulosa cells was negatively associated with oocyte and embryo quality, which supports a dose-response link between oxidative injury and reproductive outcome (154). Persistent ROS elevation aligns with activation of apoptotic pathways in granulosa cells and poorer IVF results, emphasizing that disruption of somatic-cell homeostasis around the oocyte directly shapes oocyte competence (116). A previous systematic review corroborated a consistent pattern of higher oxidative markers and altered antioxidant indices across PCOS phenotypes and weight strata, supporting oxidative stress as a shared pathological background (58).

HDL in follicular fluid has substantial antioxidant capacity and contributes most of the total. Changes in HDL antioxidant function is correlated with key steps in fertilization, showing that local lipoprotein networks are important carriers that modulate the oxidative microenvironment (107). Broader compositional and metabolomic assessments show consistent relationships among redox balance, lipid profiles in follicular fluid, and reproductive outcomes, suggesting that oxidative pressure influences oocyte maturation and early embryo development by shifting microenvironmental components (80).

From a signaling-network perspective, ROS and NF-κB form a loop in PCOS. Mitochondrial and NADPH oxidase sources of ROS directly promote NF-κB activation and enhance pattern-recognition receptor signaling, which further increases ROS and depletes antioxidant systems (147). Nutritional stimuli accelerate this loop. Postprandial surges in fats and glucose drive immediate NF-κB activation and raise inflammatory mediators in blood and the ovary. Repeated short-term bursts can consolidate into chronic immune-metabolic abnormalities (149). When antioxidant transcriptional programs are suppressed, granulosa cells respond to androgen exposure, lipotoxicity, and hyperglycemia by entering damage zones more readily. Membrane lipids and mtDNA undergo oxidation, steroidogenesis becomes less efficient, and cell-cycle timing is disturbed (152). TXNIP connects redox sensing to NLRP3 inflammasomes and to IRS1-PI3K signaling, creating

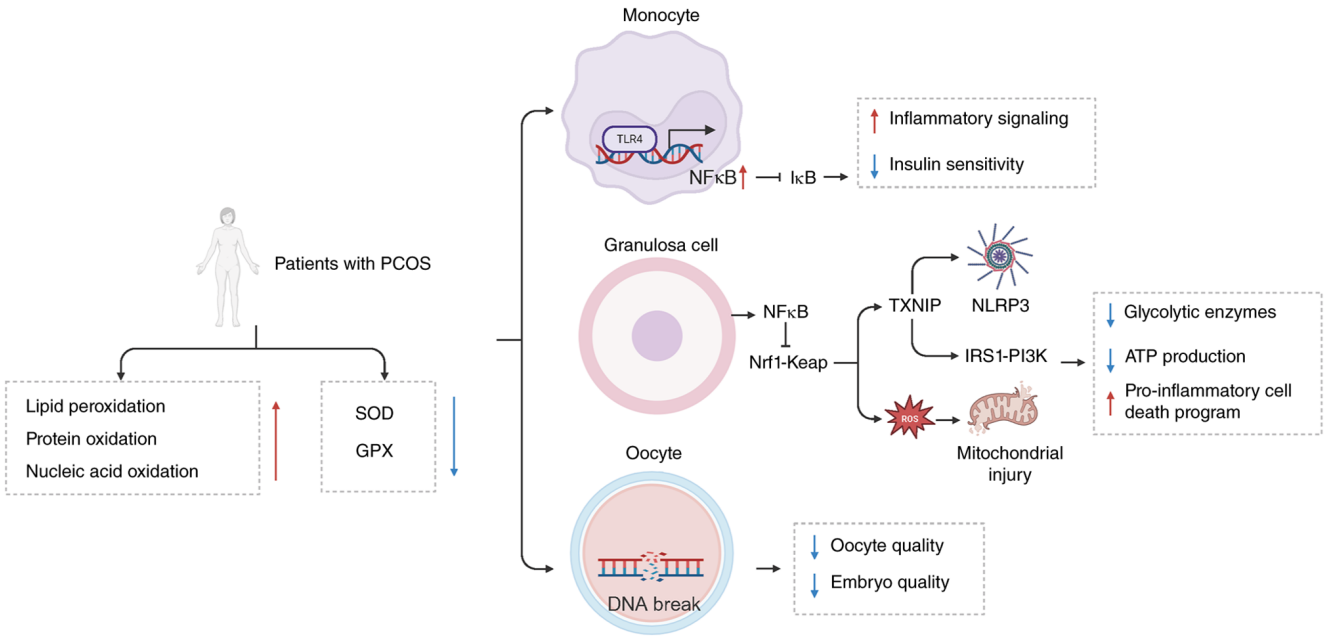

Figure 4. Chronic oxidative stress and NF-κB-mediated inflammation in PCOS. Patients show increased lipid, protein, and nucleic-acid oxidation with reduced antioxidant enzymes (SOD and GPX). In monocytes, TLR4 signaling activates NF-κB with IκB loss, heightening inflammatory signaling and lowering insulin sensitivity. In granulosa cells, NF-κB activation with downregulation of the Nrf1-Keap defense promotes ROS accumulation and mitochondrial injury. The redox adaptor TXNIP links to NLRP3 and IRS1-PI3K pathways, decreasing glycolytic enzymes, reducing ATP production, and promoting pro-inflammatory cell-death programs. Oocytes display DNA breaks with consequent declines in oocyte and embryo quality. Arrows indicate activation or direction of change. NF-κB, nuclear factor-κB; PCOS, polycystic ovary syndrome; SOD, superoxide dismutase; GPX, glutathione peroxidase; TLR4, Toll-like receptor 4; IκB, inhibitor of nuclear factor κB; Nrf1, nuclear factor erythroid 2-related factor 1; Keap, Kelch-like ECH-associated protein; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein; NLRP3, NOD-like receptor family pyrin domain-containing 3; IRS1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid.

a bottleneck in glycolysis and causing simultaneous deterioration of energy supply and redox balance. The result is a loss of metabolic resilience in the ovary (153). Follicular-fluid readouts of lipid and DNA oxidation integrate the metabolic state and stress history of oocytes and surrounding cells, and, by altering apolipoprotein function and membrane properties, influence the success of fertilization and early embryonic events (107).

Taken together, oxidative pressure in PCOS is not a bystander. By driving the NF-κB axis, altering energy flux, and degrading microenvironmental quality, it shapes multiple scales of the phenotype, including uncoupling of insulin signaling, arrest of follicle development, and declines in oocyte quality (59). Convergent human and cellular data support a pathway in which repeated nutritional and endocrine hits push transient oxidative surges beyond the buffering range of antioxidant systems. In response, inflammatory and metabolic channels are jointly rewired, and the ovarian ecosystem settles into an abnormal steady state (58). In this context, markers such as 8-isoprostanes and 8-OHdG are more than state readouts. They reflect the balance of radicals and defenses and show biologically plausible correlations with oocyte maturation and early embryo quality (70). When substrate limitation and low mitochondrial efficiency coincide with high oxidative load, granulosa cells experience a combined energy and redox stress. Steroidogenesis, membrane potential, and cell-cycle control are affected in a linked manner, which appears externally as lower fertilization rates and fewer high-quality embryos (116).

From association to causality: What is supported and what remains inferential. A clearer separation between correlation and causality is essential. Most human studies in PCOS show cross-sectional associations between oxidative indices and insulin resistance, androgen excess, ovulatory dysfunction, or adverse metabolic profiles. These data establish consistency, but they do not by themselves define directionality. Stronger causal inference emerges when oxidative pathways are experimentally perturbed. In DHEA- or letrozole-based models, pharmacologic inhibition of NOX4 or use of SOD mimetics was shown to reduce ROS accumulation, attenuate granulosa-cell apoptosis, and improve ovulatory or metabolic phenotypes, indicating that redox imbalance can function as an upstream driver rather than a passive by-product (51,52).

Human mechanistic support, although still limited, is also available. A clinical and cell-based study showed that oxidative stress is linked to lower circulating SHBG in PCOS, while oxidized lipoproteins directly suppressed SHBG and hepatocyte nuclear factor-4α expression in HepG2 cells, providing a plausible mechanistic route by which oxidative injury can intensify hyperandrogenemia (155). Human granulosa-cell data further showed that modulation of PI3K/Akt signaling can reduce ROS accumulation and apoptosis, supporting a direct link between redox imbalance and granulosa-cell dysfunction in PCOS (156). Even so, direct interventional evidence in phenotype-stratified human cohorts remains scarce. Accordingly, pathways involving mitochondrial dysfunction, NF-κB activation, TXNIP-NLRP3 signaling, and insulin-pathway disruption should be viewed on a spectrum ranging from well-supported mechanistic drivers in models to incompletely validated causal mediators in clinical PCOS (127,157).

Table II. Prioritized translational biomarker panel for redox assessment in PCOS.

Biomarker	Preferred sample	What it reflects	Main strengths	Key limitations/suggested use
MDA or 8-isoprostane	Serum/plasma (or FF in ART)	Lipid peroxidation burden.	Frequently reported; useful for directional comparison across studies.	Sensitive to preanalytical handling and assay platform; use as part of a panel, not as a stand-alone diagnostic marker.
TAC or FRAP	Serum/plasma	Global antioxidant capacity.	Simple composite readout; useful for follow-up.	Chemically nonspecific; values vary with method and supplementation status.
SOD/GPx/catalase	Serum/plasma or cellular assays	Enzymatic antioxidant defense.	Biologically interpretable and complements peroxidation markers.	Enzyme activity depends on specimen processing and laboratory standardization.
GSH-related indices	Serum/plasma or FF	Reducing-buffer capacity.	Mechanistically linked to NAC/ALA and redox homeostasis.	Less standardized clinically; affected by storage and oxidation during handling.
8-OHdG	Serum/urine/FF	Oxidative DNA damage.	Adds mechanistic depth beyond lipid peroxidation.	Matrix-specific interpretation required; best used when DNA oxidative injury is a major question.
PON1/HDL antioxidant function	Serum or FF	Lipoprotein-associated antioxidant protection.	Links oxidative stress to dyslipidemia and vascular or follicular function.	Less widely available; interpretation depends on lipid context and assay type.
Targeted FF metabolites	Follicular fluid	Local ovarian niche, oocyte competence, pathway-level disturbance.	Most informative for IVF/ART and local microenvironment studies.	Not interchangeable with serum markers; not practical for routine non-ART monitoring.

PCOS, polycystic ovary syndrome; FF, follicular fluid; ART, assisted reproductive technology; MDA, malondialdehyde; TAC, total antioxidant capacity; FRAP, ferric reducing antioxidant power; SOD, superoxide dismutase; GPx, glutathione peroxidase; GSH, glutathione; NAC, N-acetylcysteine; ALA, α-lipoic acid; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; DNA, deoxyribonucleic acid; PON1, paraoxonase 1; HDL, high-density lipoprotein; IVF, *in vitro* fertilization.

5. Advances in antioxidant therapies

Because therapeutic studies differ markedly in design, patient selection, and endpoint structure, the interventional literature should be interpreted cautiously rather than uniformly positively. Most studies are short-term, enroll relatively small and clinically heterogeneous populations, and rely mainly on surrogate outcomes such as HOMA-IR, MDA, TAC, C-reactive protein (CRP), or androgen levels rather than live birth, durable ovulation, long-term cardiometabolic outcomes, or sustained symptom improvement. In addition, serum or plasma oxidative markers and follicular-fluid markers should not be treated as equivalent endpoints: The former reflect systemic burden, whereas the latter reflect the local ovarian niche, and the extent to which oral antioxidants reach or normalize the follicular compartment is rarely measured directly. Accordingly, Table II presents a prioritized translational biomarker panel for redox assessment in PCOS, whereas the following sections summarize the available agents and Table III provides a comparative appraisal of evidence strength, effect direction, and major translational gaps.

Free radical scavengers and the GSH pathway

N-acetylcysteine (NAC). Common oral regimens are ~1.8 g per day, or 0.6 g two to three times daily. Used alone or with clomiphene, NAC has been shown to increase ovulation and clinical pregnancy rates and lower fasting insulin and HOMA-IR. These effects are consistent with cysteine replenishment, enhanced GSH synthesis, and direct ROS scavenging, which together improve insulin signaling and the ovarian microenvironment (158,159). In DHEA-induced PCOS mice, oral NAC at roughly 160 mg/kg/day was found to reduce intra-oocyte ROS, raise mitochondrial membrane potential, and normalize spindle structure, with upregulation of Nrf2 signaling and GSH-pathway enzymes, indicating cytoskeletal protection and mitochondrial stabilization during folliculogenesis (158). Meta-analytic data also showed lower MDA and higher TAC, matching improvements in ovulation and metabolic indices and supporting a GSH-centered scavenging strategy (159).

a-Lipoic acid (ALA). ALA is typically administered at 600 mg orally per day, alone or combined with inositol. Trials report lower fasting insulin and HOMA-IR and higher TAC.

Table III. Comparative appraisal of antioxidant and metabolic interventions in PCOS.

Intervention class	Representative agents	Typical evidence profile	Most consistent endpoints	Main gaps/caveats	Overall interpretation
GSH-supporting/ direct scavenging	N-acetylcysteine, and α-lipoic acid	Mostly small RCTs and meta-analyses; short treatment duration.	HOMA-IR, MDA/TAC, and ovulation-related outcomes.	Limited long-term data; mixed baseline phenotypes; surrogate endpoints dominate.	Promising for metabolic-redox correction, but evidence certainty remains moderate at best.
Mitochondrial modulators	CoQ10, L-carnitine, and acetyl-L-carnitine	Small RCTs plus supportive mechanistic studies.	Androgens, CRP, MDA/ TAC, insulin resistance, and menstrual regularity.	Head-to-head comparisons scarce; pregnancy and long-term outcomes limited.	Useful adjuncts, especially when mitochondrial dysfunction is clinically relevant.
Inositol pathway modulators	Myo-inositol, and D-chiro-inositol	Broad clinical use; evidence strongest for reproductive-metabolic endpoints.	Cycle regularity, insulin sensitivity, gonadotropin requirement, and oocyte/ embryo metrics.	Intra-ovarian ratio issues; oxidative readouts not consistently measured.	Clinically practical, but redox benefit is often inferred rather than directly quantified.
Vitamins/trace elements	Vitamin D, vitamin E, selenium, and chromium	Multiple small RCTs; frequent use in combinations.	Inflammatory and oxi-dative markers, fasting glucose, HOMA-IR, and lipids.	High heterogeneity in deficiency status, co-supplementation, and assay methods.	Potentially helpful in selected subgroups, not uniformly supported for routine universal use.
Polyphenols/ natural products	Resveratrol, curcumin, quercetin, and berberine	Mixture of small RCTs, meta-analyses, and preclinical studies.	Androgens, HOMA-IR, inflammatory markers, and oxidative markers.	Formulation and bioavaila-bility vary; numerous trials are short and small.	Mechanistically attractive, but comparative efficacy and durability remain uncertain.
Lipid-based anti-inflammatory supplements	Omega-3 fatty acids	RCTs and meta-analyses with moderate heterogeneity.	CRP, MDA/TAC, SHBG, testosterone, and lipids.	Dietary background and baseline inflammatory status influence effect size.	Reasonable adjunct for inflam-matory-metabolic phenotypes, but not a stand-alone solution.
Chronobiology/ mitochondrial antioxidant support	Melatonin	Small double-blind trials plus preclinical evidence.	TAC/GSH, CRP/cytokines, HOMA-IR, and androgen indices.	Long-term reproductive and cardiometabolic outcomes are not established.	Potentially valuable where sleep, circadian disruption, and mitochondrial stress coexist.

PCOS, polycystic ovary syndrome; GSH, glutathione; RCTs, randomized controlled trials; HOMA-IR, homeostatic model assessment of insulin resistance; MDA, malondialdehyde; TAC, total antioxidant capacity; CoQ10, coenzyme Q10; CRP, C-reactive protein; D-chiro-inositol, D-chiroinositol; SHBG, sex hormone-binding globulin.

Mechanisms include its role as a cofactor for the pyruvate dehydrogenase complex, regeneration of GSH and vitamin C, and direct radical chelation, thereby influencing the coupled metabolic-oxidative phenotype (160,161). In combination protocols, ALA plus inositol was further shown to improve menstrual cyclicity and insulin resistance, likely via optimization of follicular-fluid redox state and second-messenger signaling, suggesting utility alongside ovulation induction or metabolic therapy (160,161).

Mitochondrial and energy-metabolism modulators

Coenzyme Q10. Doses of Coenzyme Q10 at 100 to 200 mg per day for 8 to 12 weeks have been found to lower total testosterone and DHEAS, raise sex hormone-binding globulin and TAC, and reduce MDA and high-sensitivity CRP. These findings are consistent with stronger electron-transport chain function, less lipid peroxidation, and stabilization of the mitochondrial membrane, with protective effects on hyperandrogenism and low-grade inflammation (162). Network and conventional meta-analyses support benefits across glycemic control and oxidative-inflammatory indices, aligning with a mitochondria-protective route to metabolic and reproductive gains (162).

L-carnitine and acetyl-L-carnitine. L-carnitine is used at 250 mg per day up to 3 g per day for ~12 weeks. A trial revealed reductions in weight and waist circumference together with lower fasting glucose, insulin, and HOMA-IR, consistent with enhanced mitochondrial β-oxidation, lower electron leak, and reduced ROS generation (163). Overall, carnitines functioned beyond weight loss by improving mitochondrial lipid handling and antioxidant defenses, which lowered lipotoxicity and ROS burden and benefited insulin responses and ovarian inflammation (163).

Inositol second messengers and insulin sensitization

Myo-inositol. Myo-inositol is commonly administered at 2 g twice daily, either alone or as an adjunct to ovulation induction. Studies evaluating myo-inositol supplementation have demonstrated reduced gonadotropin requirements, shorter stimulation duration, improved oocyte and embryo quality, lower fasting insulin and HOMA-IR, and more regular menstrual cycles. Mechanistically, as a second messenger for insulin and FSH, myo-inositol improves glucose use in follicular fluid and relieves oxidative stress, thereby improving both reproductive and metabolic endpoints (164,165).

D-chiro-inositol. D-chiro-inositol is often adminstered at 300 to 600 mg per day. Early randomized trials in lean PCOS report lower insulin and androgens and improvements in blood pressure and triglycerides, consistent with stronger postreceptor insulin signaling via inositol-phosphate pathways and antioxidant-linked metabolic routes. Attention to the intra-ovarian myo- to D-chiro-inositol ratio is advisable to avoid unfavorable shifts in the follicular niche (164,165).

Fat-soluble vitamins and trace elements

Vitamin D. Vitamin D supplementation is commonly administered as 50,000 IU intermittently every two weeks or 3,200-4,000 IU daily, often in combination with metabolic nutrients or omega-3 fatty acids. Trials show reductions in fasting glucose and total cholesterol with improvements in inflammatory and oxidative markers. Effects likely involve vitamin D receptor-mediated induction of antioxidant enzymes and inhibition of NF-κB activity, producing both indirect and direct benefits on metabolic and endocrine outcomes (164,166). In vitamin D-deficient, overweight women with PCOS, adding calcium to vitamin D supplementation was shown to further improve inflammatory and oxidative indices, supporting combined management of metabolism and ovarian function (166,167).

Vitamin E. Vitamin E is commonly administered at 400 IU per day, alone or with minerals. Studies have reported lower MDA and higher TAC with improvements in glycemic and lipid markers and inflammation, consistent with lipophilic radical scavenging, inhibition of lipid peroxidation, and membrane protection. Benefits may be greater in insulin-resistant patients (162,164). The additive effect of vitamin E varies across combinations and may depend on baseline oxidative stress and dietary fat composition, underscoring individualized selection (162,164).

Selenium. Selenium is often administered at 200 μg per day, frequently in combination with probiotics for 8 to 12 weeks. Trials show higher TAC, lower MDA, and improvements in some metabolic indices, reflecting its role as an essential cofactor for GSH peroxidases and enhancement of endogenous antioxidant defenses, with downstream effects on the ovarian microenvironment and insulin sensitivity (168,169). Previous reviews have noted modest overall effects on several metabolic and hormonal endpoints, suggesting selective use for oxidative or follicular-quality indications rather than routine supplementation (168,169).

Chromium. Chromium is typically administered as chromium picolinate at 200 μg per day for 8 to 12 weeks. Randomized studies show reductions in fasting insulin and HOMA-IR with favorable changes in inflammatory gene expression, consistent with stronger PI3K-Akt signaling and improved insulin responses that are coupled with reduced oxidative stress. Effects on reproductive hormones are less consistent; therefore, selection based on metabolic phenotype is prudent (170,171).

Plant polyphenols and natural products

Resveratrol. At 1,500 mg per day for 3 months in double-blind trials, resveratrol was demonstrated to lower total testosterone and DHEAS, reduce fasting insulin, and increase insulin sensitivity. Proposed mechanisms include activation of SIRT1 and AMPK, inhibition of lipid peroxidation, and damping of inflammatory pathways (172). Systematic reviews show moderate reductions in androgen-axis indices, supporting a role as an adjunct to first-line therapies to secure more robust clinical gains (172). In DHEA- or letrozole-induced PCOS rats, 20 to 30 mg/kg/day was shown to improve ovarian histology, weight, and hormone profiles, lower TNF-α and LH, and influence follicle dynamics, indicating SIRT1-dependent deacetylation and antioxidant effects that directly improve ovarian function (173,174).

Curcumin. Doses of 500 to 1,500 mg of curcumin per day for 8 to 12 weeks were found to reduce weight, fasting glucose, and HOMA-IR, with higher PGC-1α expression and GSH peroxidase activity. These findings suggest promotion of mitochondrial biogenesis and stronger antioxidant defenses, lowering systemic oxidative stress and improving metabolic and endocrine outcomes (160,161). Previous reviews have reported consistent benefits on inflammatory markers and cardio-metabolic indices with a favorable safety profile, supporting use in PCOS with prominent metabolic and oxidative burdens (160,175).

Quercetin. Quercetin is often administered at 1,000 mg per day for 12 weeks. Trials of quercetin supplementation have shown reductions in testosterone and LH, improved insulin resistance, higher adiponectin, and reduced resistin. Mechanisms were found to center on AMPK and adiponectin-receptor pathways that suppress oxidative stress-linked inflammation and lipotoxicity. Weight loss was not the primary driver; the value lay in redox and inflammatory control and coordination of the gonadal-metabolic axis, supporting use with metabolic interventions or ovulation induction (176,177).

Berberine. Berberine is typically administered at 500 mg three times daily for 8 to 12 weeks. Trials of berberine showed improvements in insulin resistance and lipid profiles comparable to or better than metformin, and pre-ART use was demonstrated to improve endocrine indices and pregnancy rates. Mechanisms included AMPK activation, inhibition of NADPH oxidase, and reduced lipid peroxidation, yielding direct effects on metabolic and reproductive endpoints (178,179). Mechanistic reviews describe downregulation of inflammatory and oxidative pathways in ovarian and peripheral tissues, improved glucose and lipid handling, and restraint of excessive steroidogenesis, consistent with clinical reductions in HOMA-IR and androgens (179,180).

Lipid-based anti-inflammatory and antioxidant supplements

Omega-3 polyunsaturated fatty acids. Omega-3 polyunsaturated fatty acids are commonly administered at 2,000 mg per day for ~12 weeks, with or without vitamin D supplementation. Randomized and meta-analytic evidence revealed reductions in CRP and MDA, higher TAC, higher sex hormone-binding globulin, and lower total testosterone. These effects are compatible with membrane-lipid remodeling, resolution of inflammation, and less lipid peroxidation, which indirectly ease oxidative stress and improve hyperandrogenic and metabolic phenotypes (164). These findings suggest a potential role for omega-3 fatty acids in improving oxidative and inflammatory status, although the reported effects were observed in the context of combined supplementation with vitamin D (164).

Melatonin and the circadian-mitochondrial antioxidant network

Melatonin. Melatonin is typically administered at 3 mg nightly for 8 to 12 weeks. Double-blind trials reported decreased total testosterone and high-sensitivity CRP, reduced HOMA-IR, higher TAC and GSH, and lower expression of IL-1 and TNF-α. These outcomes are consistent with coupling of circadian and mitochondrial antioxidant networks, with direct effects on oxidative inflammation and mitochondrial function, and parallel improvements in reproductive and metabolic endpoints (181,182). Mechanistically, melatonin has been shown to stabilize mitochondrial membrane potential, enhance electron-transport efficiency, and induce antioxidant enzymes, decreasing ovarian ROS and improving oocyte quality, in step with improved psychological and metabolic scores clinically (181,182). In a letrozole model, intraperitoneal melatonin at 10 mg/kg/day improved ovarian morphology and hormone profiles and attenuated oxidative and inflammatory markers, consistent with relief of coupled mitochondrial-ER stress and activation of antioxidant enzymes that restore the follicular microenvironment (183).

Critical appraisal of current interventional evidence. Across intervention classes, the overall direction of effect is often favorable, but the certainty of evidence remains modest (184,185). Numerous randomized trials include <100 participants, last only 8-12 weeks, and pool women with different BMI categories, androgen status, infertility status, or background treatments (186). Combination regimens further complicate attribution of benefit to a single antioxidant or metabolic agent (186). Although meta-analyses can increase statistical power, they also inherit between-study heterogeneity in diagnostic criteria, supplement formulation, dose, comparator choice, and laboratory assays (184,185).

Another limitation is endpoint hierarchy. Improvements in MDA, TAC, CRP, fasting insulin, or HOMA-IR are useful proof-of-direction biomarkers, but they are not equivalent to improved live birth, long-term menstrual regularity, prevention of diabetes, or reduced cardiovascular risk (185). ART-related research is informative for the follicular microenvironment but represents a selected fertility-treatment population rather than the broader PCOS spectrum (79). Head-to-head trials between antioxidant strategies are scarce, long-term safety data are limited for several nutraceutical regimens, and phenotype-stratified trials remain the exception rather than the rule (186). Future studies should prespecify phenotype, specimen compartment, and clinically meaningful primary endpoints, while integrating mechanistic biomarkers with reproductive and cardiometabolic outcomes (79,184).

6. Conclusion

Evidence across human, cellular, and animal studies supports oxidative stress as a biologically relevant component of PCOS rather than a nonspecific epiphenomenon. However, the oxidative signature of PCOS is heterogeneous. Women with obesity, hyperandrogenism, and Rotterdam phenotypes A or B generally exhibit the greatest systemic metabolic-inflammatory burden, whereas phenotype D is often milder and lean PCOS may retain clinically relevant local ovarian oxidative abnormalities despite less marked systemic impairment.

For translation, a tiered biomarker strategy is more useful than long unranked marker lists. Serum or plasma panels centered on lipid peroxidation, global antioxidant capacity, and enzymatic antioxidant defenses are most suitable for evaluating systemic redox burden, especially when interpreted alongside insulin resistance, androgen

excess, adiposity, dyslipidemia, and low-grade inflammation. Markers such as MDA, 8-isoprostane, TAC, FRAP, SOD, GSH peroxidase, and related GSH indices may therefore be useful as part of a patterned systemic profile rather than as isolated diagnostic readouts. By contrast, follicular-fluid biomarkers are more appropriate for assessing the ovarian microenvironment, granulosa-cell function, oocyte competence, and ART-related outcomes, because they reflect local oxidative injury more directly than circulating markers. These compartments should not be merged analytically. A change in serum oxidative markers cannot be assumed to indicate parallel restoration of follicular redox homeostasis unless follicular penetration, local pharmacodynamic effects, or reproductive endpoints are directly assessed. Future studies should therefore standardize sample type, menstrual or stimulation phase, storage conditions, freeze-thaw history, assay platform, treatment exposure, obesity status, androgenic phenotype, and Rotterdam phenotype composition to improve reproducibility and clinical interpretability across cohorts.

The mechanistic literature also needs to be interpreted by level of evidence. Human clinical studies mainly support association, showing that oxidative indices are correlated with insulin resistance, hyperandrogenemia, ovulatory dysfunction, obesity-related metabolic disturbance, and inflammatory activation. These findings are biologically consistent, but they cannot establish whether oxidative stress is a primary driver, a downstream consequence, or part of a self-reinforcing endocrine-metabolic loop. Stronger causal support comes from mechanistic interventions in cell and animal models, where modulation of NOX4 activity, mitochondrial dysfunction, antioxidant pathways, granulosa-cell apoptosis, inflammatory signaling, or SHBG-related oxidative regulation can alter reproductive and metabolic phenotypes. Such evidence supports the concept that redox imbalance can participate actively in PCOS pathophysiology rather than merely reflecting disease severity. However, the translational threshold has not yet been reached for most oxidative biomarkers. Current evidence justifies continued redox-focused investigation and phenotype-stratified biomarker development, but it does not support treating all oxidative markers as validated clinical decision tools or using antioxidant response alone as proof of disease modification. Current antioxidant and metabolic interventions show encouraging but still incomplete translational value. Most trials report short-term improvements in surrogate metabolic, inflammatory, or oxidative endpoints, yet robust data on live birth, durable ovulatory recovery, long-term cardiometabolic protection, and head-to-head comparative efficacy remain limited. The next stage of the field should therefore move from descriptive supplementation studies to phenotype-stratified, adequately powered trials that integrate systemic biomarkers, local ovarian readouts, and clinically meaningful endpoints.

Finally, recent multi-omics studies suggest that future precision management of PCOS will depend on integrating redox biology with transcriptomic, proteomic, metabolomic, and follicular niche data. Such approaches may refine subtype definition, uncover novel redox-sensitive therapeutic targets, and distinguish patients in whom oxidative stress is a dominant driver from those in whom it is a secondary amplifier.

Acknowledgements

Not applicable.

Funding

The present study received funding from the Natural Science Foundation of Fujian Province (grant no. 2025J01825), the Kunshan High-level Health Talent Program Project (grant no. 2025KSKY08), the Natural Science Foundation Project of Nanjing University of Chinese Medicine (grant no. XZR2024194), the Suzhou Science and Technology Tackling Program (Healthcare Innovation) Project (grant no. SYWD2025056) and the Jiangsu Provincial Traditional Chinese Medicine Science and Technology Development Plan General Project (project no. MS202577).

Availability of data and materials

Not applicable.

Authors' contributions

YQ and JA designed the scope and structure of the review, performed the structured literature searches, and critically synthesized and interpreted the findings. YQ and JA drafted and edited the manuscript. XG critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, M Redman L, A Boyle J, *et al*: Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 120: 767-793, 2023.
2. March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ and Davies MJ: The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 25: 544-551, 2010.
3. Liu Q, Tang B, Zhu Z, Kraft P, Deng Q, Stener-Victorin E and Jiang X: A genome-wide cross-trait analysis identifies shared loci and causal relationships of type 2 diabetes and glycaemic traits with polycystic ovary syndrome. Diabetologia 65: 1483-1494, 2022.
4. Long C, Feng H, Duan W, Chen X, Zhao Y, Lan Y and Yue R: Prevalence of polycystic ovary syndrome in patients with type 2 diabetes: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 13: 980405, 2022.
5. Wu Q, Gao J, Bai D, Yang Z and Liao Q: The prevalence of polycystic ovarian syndrome in Chinese women: A meta-analysis. Ann Palliat Med 10: 74-87, 2021.

6. Moran C, Arriaga M, Rodriguez G and Moran S: Obesity differentially affects phenotypes of polycystic ovary syndrome. Int J Endocrinol 2012: 317241, 2012.
7. Kataoka J, Larsson I, Björkman S, Eliasson B, Schmidt J and Stener-Victorin E: Prevalence of polycystic ovary syndrome in women with severe obesity-effects of a structured weight loss programme. Clin Endocrinol (Oxf) 91: 750-758, 2019.
8. Cooney LG and Dokras A: Cardiometabolic risk in polycystic ovary syndrome: Current guidelines. Endocrinol Metab Clin North Am 50: 83-95, 2021.
9. Berni TR, Morgan CL and Rees DA: Women with polycystic ovary syndrome have an increased risk of major cardiovascular events: A population study. J Clin Endocrinol Metab 106: e3369-e3380, 2021.
10. van der Ham K, Koster MPH, Velthuis BK, Budde RPJ, Fauser BCJM, Laven JSE and Louwers YV: Change in androgenic status and cardiometabolic profile of middle-aged women with polycystic ovary syndrome. J Clin Med 12: 5226, 2023.
11. Chandra K, Salman AS, Mohd A, Sweety R and Ali KN: Protection against FCA induced oxidative stress induced DNA damage as a model of arthritis and in vitro anti-arthritic potential of Costus speciosus Rhizome extract. Int J Pharmacogn Phytochem Res 7: 383-389, 2015.
12. Boveris AA: Rebeca gerschman: A brilliant woman scientist in the fifties. Free Radic Biol Med 21: 5-6, 1996.
13. Abbasihormozi SH, Babapour V, Kouhkan A, Niasari Naslji A, Afraz K, Zolfaghary Z and Shahverdi AH: Stress hormone and oxidative stress biomarkers link obesity and diabetes with reduced fertility potential. Cell J 21: 307-313, 2019.
14. Christodoulakos G, Augoulea A, Lambrinoudaki I, Sioulas V and Creatsas G: Pathogenesis of endometriosis: The role of defective 'immunosurveillance'. Eur J Contracept Reprod Health Care 12: 194-202, 2007.
15. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A and Gupta S: The effects of oxidative stress on female reproduction: A review. Reprod Biol Endocrinol 10: 49, 2012.
16. Murphy MP: How mitochondria produce reactive oxygen species. Biochem J 417: 1-13, 2009.
17. Malin SK, Kirwan JP, Sia CL and González F: Glucose-stimulated oxidative stress in mononuclear cells is related to pancreatic beta-cell dysfunction in polycystic ovary syndrome. J Clin Endocrinol Metab 99: 322-329, 2014.
18. Shan H, Luo R, Guo X, Li R, Ye Z, Peng T, Liu F and Yang Z: Abnormal endometrial receptivity and oxidative stress in polycystic ovary syndrome. Front Pharmacol 13: 904942, 2022.
19. Yalçınkaya E, Cakıroğlu Y, Doğer E, Budak O, Cekmen M and Calışkan E: Effect of follicular fluid NO, MDA and GSH levels on in vitro fertilization outcomes. J Turk Ger Gynecol Assoc 14: 136-141, 2013.
20. Ma YC, Law KS, Wang WS and Chang HM: Phenotypic variations in polycystic ovary syndrome: Metabolic risks and emerging biomarkers. J Endocrinol 267: e250226, 2025.
21. Padder KA, Jahan N, Yousuf MA, Shah IA, Bhat GA, Khurshid R, Zargar MH and Ganie MA: Deciphering the interplay between oxidative stress and inflammation in polycystic ovary syndrome: Outcome of a case-control study. J Ovarian Res 18: 196, 2025.
22. Chen Y, Xie M, Wu S, Deng Z, Tang Y, Guan Y, Ye Y, He Q and Li L: Multi-omics approach to reveal follicular metabolic changes and their effects on oocyte competence in PCOS patients. Front Endocrinol (Lausanne) 15: 1426517, 2024.
23. Naqvi I, Bandyopadhyay A, Panda A and Hareramadas B: Polycystic ovarian syndrome: A review of multi-omics analyses. Reprod Sci 32: 618-646, 2025.
24. Patel B, Koysombat K, Mills EG, Tsoutsouki J, Comninos AN, Abbara A and Dhillo WS: The emerging therapeutic potential of kisspeptin and neurokinin B. Endocr Rev 45: 30-68, 2024.
25. Velez LM, Seldin M and Motta AB: Inflammation and reproductive function in women with polycystic ovary syndrome†. Biol Reprod 104: 1205-1217, 2021.
26. Burt Solorzano CM, Beller JP, Abshire MY, Collins JS, McCartney CR and Marshall JC: Neuroendocrine dysfunction in polycystic ovary syndrome. Steroids 77: 332-337, 2012.
27. Comim FV, Teerds K, Hardy K and Franks S: Increased protein expression of LHCG receptor and 17α-hydroxylase/17-20-lyase in human polycystic ovaries. Hum Reprod 28: 3086-3092, 2013.
28. Nisenblat V and Norman RJ: Androgens and polycystic ovary syndrome. Curr Opin Endocrinol Diabetes Obes 16: 224-231, 2009.
29. Baillargeon JP and Carpentier A: Role of insulin in the hyperandrogenemia of lean women with polycystic ovary syndrome and normal insulin sensitivity. Fertil Steril 88: 886-893, 2007.
30. di Clemente N, Racine C, Pierre A and Taieb J: Anti-mullerian hormone in female reproduction. Endocr Rev 42: 753-782, 2021.
31. Barbotin AL, Mimouni NEH, Kuchcinski G, Lopes R, Viard R, Rasika S, Mazur D, Silva MSB, Simon V, Boursier A, *et al*: Hypothalamic neuroglial plasticity is regulated by anti-Müllerian hormone and disrupted in polycystic ovary syndrome. EBioMedicine 90: 104535, 2023.
32. Blank SK, McCartney CR, Chhabra S, Helm KD, Eagleson CA, Chang RJ and Marshall JC: Modulation of gonadotropin-releasing hormone pulse generator sensitivity to progesterone inhibition in hyperandrogenic adolescent girls-implications for regulation of pubertal maturation. J Clin Endocrinol Metab 94: 2360-2366, 2009.
33. McAllister JM, Modi B, Miller BA, Biegler J, Bruggeman R, Legro RS and Strauss JF III: Overexpression of a DENND1A isoform produces a polycystic ovary syndrome theca phenotype. Proc Natl Acad Sci USA 111: E1519-E1527, 2014.
34. Tropea A, Lanzone A, Tiberi F, Romani F, Catino S and Apa R: Estrogens and androgens affect human luteal cell function. Fertil Steril 94: 2257-2263, 2010.
35. Norman RJ, Milner CR, Groome NP and Robertson DM: Circulating follistatin concentrations are higher and activin concentrations are lower in polycystic ovarian syndrome. Hum Reprod 16: 668-672, 2001.
36. Pea J, Bryan J, Wan C, Oldfield AL, Ganga K, Carter FE, Johnson LM and Lujan ME: Ultrasonographic criteria in the diagnosis of polycystic ovary syndrome: A systematic review and diagnostic meta-analysis. Hum Reprod Update 30: 109-130, 2024.
37. Dunaif A, Segal KR, Futterweit W and Dobrjansky A: Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 38: 1165-1174, 1989.
38. Mannerås-Holm L, Leonhardt H, Kullberg J, Jennische E, Odén A, Holm G, Hellström M, Lönn L, Olivecrona G, Stener-Victorin E and Lönn M: Adipose tissue has aberrant morphology and function in PCOS: Enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. J Clin Endocrinol Metab 96: E304-E311, 2011.
39. Hanna F, Wu P, Heald A and Fryer A: Diabetes detection in women with gestational diabetes and polycystic ovarian syndrome. BMJ 382: e071675, 2023.
40. Dapas M and Dunaif A: Deconstructing a syndrome: Genomic insights into PCOS causal mechanisms and classification. Endocr Rev 43: 927-965, 2022.
41. Dunaif A, Xia J, Book CB, Schenker E and Tang Z: Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest 96: 801-810, 1995.
42. Corbould A, Zhao H, Mirzoeva S, Aird F and Dunaif A: Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome. Diabetes 55: 751-759, 2006.
43. Skov V, Glintborg D, Knudsen S, Jensen T, Kruse TA, Tan Q, Brusgaard K, Beck-Nielsen H and Højlund K: Reduced expression of nuclear-encoded genes involved in mitochondrial oxidative metabolism in skeletal muscle of insulin-resistant women with polycystic ovary syndrome. Diabetes 56: 2349-2355, 2007.
44. Raeisi T, Rezaie H, Darand M, Taheri A, Garousi N, Razi B, Roever L, Mohseni R, Hussien Mohammed S and Alizadeh S: Circulating resistin and follistatin levels in obese and non-obese women with polycystic ovary syndrome: A systematic review and meta-analysis. PLoS One 16: e0246200, 2021.
45. Ezeh U, Chen IYD, Chen YH and Azziz R: Adipocyte expression of glucose transporter 1 and 4 in PCOS: Relationship to insulin-mediated and non-insulin-mediated whole-body glucose uptake. Clin Endocrinol (Oxf) 90: 542-552, 2019.
46. Arner P: Effects of testosterone on fat cell lipolysis. Species differences and possible role in polycystic ovarian syndrome. Biochimie 87: 39-43, 2005.
47. Ek I, Arner P, Rydén M, Holm C, Thörne A, Hoffstedt J and Wahrenberg H: A unique defect in the regulation of visceral fat cell lipolysis in the polycystic ovary syndrome as an early link to insulin resistance. Diabetes 51: 484-492, 2002.
48. Stener-Victorin E, Eriksson G, Mohan Shrestha M, Rodriguez Paris V, Lu H, Banks J, Samad M, Perian C, Jude B, Engman V, *et al*: Proteomic analysis shows decreased type I fibers and ectopic fat accumulation in skeletal muscle from women with PCOS. Elife 12: RP87592, 2024.
49. Stener-Victorin E, Teede H, Norman RJ, Legro R, Goodarzi MO, Dokras A, Laven J, Hoeger K and Piltonen TT: Polycystic ovary syndrome. Nat Rev Dis Primers 10: 27, 2024.

50. O'Reilly MW, Kempegowda P, Walsh M, Taylor AE, Manolopoulos KN, Allwood JW, Semple RK, Hebenstreit D, Dunn WB, Tomlinson JW and Arlt W: AKR1C3-mediated adipose androgen generation drives lipotoxicity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 102: 3327-3339, 2017.
51. Huang ZH, Manickam B, Ryvkin V, Zhou XJ, Fantuzzi G, Mazzone T and Sam S: PCOS is associated with increased CD11c expression and crown-like structures in adipose tissue and increased central abdominal fat depots independent of obesity. J Clin Endocrinol Metab 98: E17-E24, 2013.
52. Leinonen JT, Mars N, Lehtonen LE, Ahola-Olli A, Ruotsalainen S, Lehtimäki T, Kähönen M, Raitakari O; FinnGen Consortium; Piltonen T, *et al*: Genetic analyses implicate complex links between adult testosterone levels and health and disease. Commun Med (Lond) 3: 4, 2023.
53. Carmina E and Longo RA: Increased prevalence of elevated DHEAS in PCOS women with non-classic (B or C) phenotypes: A retrospective analysis in patients aged 20 to 29 years. Cells 11: 3255, 2022.
54. Amer SA, Alzanati NG, Warren A, Tarbox R and Khan R: Excess androgen production in subcutaneous adipose tissue of women with polycystic ovarian syndrome is not related to insulin or LH. J Endocrinol 241: 99-109, 2019.
55. Li T, Zhang T, Gao H, Liu R, Gu M, Yang Y, Cui T, Lu Z and Yin C: Tempol ameliorates polycystic ovary syndrome through attenuating intestinal oxidative stress and modulating of gut microbiota composition-serum metabolites interaction. Redox Biol 41: 101886, 2021.
56. Li Y, Xu J, Li L, Bai L, Wang Y, Zhang J and Wang H: Inhibition of Nicotinamide adenine dinucleotide phosphate oxidase 4 attenuates cell apoptosis and oxidative stress in a rat model of polycystic ovary syndrome through the activation of Nrf-2/HO-1 signaling pathway. Mol Cell Endocrinol 550: 111645, 2022.
57. Walters KA, Allan CM and Handelsman DJ: Androgen actions and the ovary. Biol Reprod 78: 380-389, 2008.
58. Mohammadi M: Oxidative stress and polycystic ovary syndrome: A brief review. Int J Prev Med 10: 86, 2019.
59. Murri M, Luque-Ramirez M, Insenser M, Ojeda-Ojeda M and Escobar-Morreale HF: Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): A systematic review and meta-analysis. Hum Reprod Update 19: 268-288, 2013.
60. Mancini A, Bruno C, Vergani E, d'Abate C, Giacchi E and Silvestrini A: Oxidative stress and low-grade inflammation in polycystic ovary syndrome: Controversies and new insights. Int J Mol Sci 22: 1667, 2021.
61. Bril F, Ezeh U, Amiri M, Hatoum S, Pace L, Chen YH, Bertrand F, Gower B and Azziz R: Adipose tissue dysfunction in polycystic ovary syndrome. J Clin Endocrinol Metab 109: 10-24, 2023.
62. Bannigida DM, Nayak BS and Vijayaraghavan R: Insulin resistance and oxidative marker in women with PCOS. Arch Physiol Biochem 126: 183-186, 2020.
63. González F, Rote NS, Minium J and Kirwan JP: Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab 91: 336-340, 2006.
64. González F, Considine RV, Abdelhadi OA and Acton AJ: Oxidative stress in response to saturated fat ingestion is linked to insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab 104: 5360-5371, 2019.
65. Victor VM, Rocha M, Bañuls C, Sanchez-Serrano M, Sola E, Gomez M and Hernandez-Mijares A: Mitochondrial complex I impairment in leukocytes from polycystic ovary syndrome patients with insulin resistance. J Clin Endocrinol Metab 94: 3505-3512, 2009.
66. Blagojević IP, Ignjatović S, Macut D, Kotur-Stevuljević J, Božić-Antić I, Vekić J, Bjekić-Macut J, Kastratović-Kotlica B, Andrić Z and Ilić D: Evaluation of a summary score for dyslipidemia, oxidative stress and inflammation (the doi score) in women with polycystic ovary syndrome and its relationship with obesity. J Med Biochem 37: 476-485, 2018.
67. Mohamadin AM, Habib FA and Elahi TF: Serum paraoxonase 1 activity and oxidant/antioxidant status in Saudi women with polycystic ovary syndrome. Pathophysiology 17: 189-196, 2010.
68. Enechukwu CI, Onuegbu AJ, Olisekodiaka MJ, Eleje GU, Ikechebelu JI, Ugboaja JO, Amah UK, Okwara JE and Igwegbe AO: Oxidative stress markers and lipid profiles of patients with polycystic ovary syndrome in a Nigerian tertiary hospital. Obstet Gynecol Sci 62: 335-343, 2019.
69. Rudnicka E, Duszewska AM, Kucharski M, Tyczyński P and Smolarczyk R: Oxidative stress and reproductive function: Oxidative stress in polycystic ovary syndrome. Reproduction 164: F145-F154, 2022.
70. Liu Y, Yu Z, Zhao S, Cheng L, Man Y, Gao X and Zhao H: Oxidative stress markers in the follicular fluid of patients with polycystic ovary syndrome correlate with a decrease in embryo quality. J Assist Reprod Genet 38: 471-477, 2021.
71. Garg D and Merhi Z: Advanced glycation end products: Link between diet and ovulatory dysfunction in PCOS? Nutrients 7: 10129-10144, 2015.
72. Sandhu JK, Waqar A, Jain A, Joseph C, Srivastava K, Ochuba O, Alkayyali T, Ruo SW and Poudel S: Oxidative stress in polycystic ovarian syndrome and the effect of antioxidant N-acetylcysteine on ovulation and pregnancy rate. Cureus 13: e17887, 2021.
73. Xita N, Papassotiriou I, Georgiou I, Vounatsou M, Margeli A and Tsatsoulis A: The adiponectin-to-leptin ratio in women with polycystic ovary syndrome: Relation to insulin resistance and proinflammatory markers. Metabolism 56: 766-771, 2007.
74. Sprung VS, Atkinson G, Cuthbertson DJ, Pugh CJ, Aziz N, Green DJ, Cable NT and Jones H: Endothelial function measured using flow-mediated dilation in polycystic ovary syndrome: A meta-analysis of the observational studies. Clin Endocrinol (Oxf) 78: 438-446, 2013.
75. Kravariti M, Naka KK, Kalantaridou SN, Kazakos N, Katsouras CS, Makrigiannakis A, Paraskevaidis EA, Chrousos GP, Tsatsoulis A and Michalis LK: Predictors of endothelial dysfunction in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 90: 5088-5095, 2005.
76. Hyderali BN and Mala K: Oxidative stress and cardiovascular complications in polycystic ovarian syndrome. Eur J Obstet Gynecol Reprod Biol 191: 15-22, 2015.
77. Meyer ML, Malek AM, Wild RA, Korytkowski MT and Talbott EO: Carotid artery intima-media thickness in polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update 18: 112-126, 2012.
78. Wen X, Wang L and Bai E: Metabolic characteristics of different phenotypes in reproductive-aged women with polycystic ovary syndrome. Front Endocrinol (Lausanne) 15: 1370578, 2024.
79. Gongadashetti K, Gupta P, Dada R and Malhotra N: Follicular fluid oxidative stress biomarkers and ART outcomes in PCOS women undergoing in vitro fertilization: A cross-sectional study. Int J Reprod Biomed 19: 449-456, 2021.
80. Moreira MV, Vale-Fernandes E, Albergaria IC, Alves MG and Monteiro MP: Follicular fluid composition and reproductive outcomes of women with polycystic ovary syndrome undergoing in vitro fertilization: A systematic review. Rev Endocr Metab Disord 24: 1045-1073, 2023.
81. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D and Bitto A: Oxidative stress: Harms and benefits for human health. Oxid Med Cell Longev 2017: 8416763, 2017.
82. Lubrano V, Pingitore A, Traghella I, Storti S, Parri S, Berti S, Ndreu R, Andrenelli A, Palmieri C, Iervasi G, *et al*: Emerging biomarkers of oxidative stress in acute and stable coronary artery disease: Levels and determinants. Antioxidants (Basel) 8: 115, 2019.
83. Sabuncu T, Vural H, Harma M and Harma M: Oxidative stress in polycystic ovary syndrome and its contribution to the risk of cardiovascular disease. Clin Biochem 34: 407-413, 2001.
84. Yang B, Chen Y and Shi J: Reactive oxygen species (ROS)-based nanomedicine. Chem Rev 119: 4881-4985, 2019.
85. Ayala A, Muñoz MF and Argüelles S: Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev 2014: 360438, 2014.
86. Kolesnikova LI, Kolesnikov SI, Darenskaya MA, Grebenkina LA, Nikitina OA, Lazareva LM, Suturina LV, Danusevich IN, Druzhinina EB and Semendyaev AA: Activity of LPO processes in women with polycystic ovarian syndrome and infertility. Bull Exp Biol Med 162: 320-322, 2017.
87. Kaltsas A, Zikopoulos A, Moustakli E, Zachariou A, Tsirka G, Tsiampali C, Palapela N, Sofikitis N and Dimitriadis F: The silent threat to women's fertility: Uncovering the devastating effects of oxidative stress. Antioxidants (Basel) 12: 1490, 2023.
88. Uyanikoglu H, Sabuncu T, Dursun H, Sezen H and Aksoy N: Circulating levels of apoptotic markers and oxidative stress parameters in women with polycystic ovary syndrome: A case-controlled descriptive study. Biomarkers 22: 643-647, 2017.

89. Yilmaz M, Bukan N, Ayvaz G, Karakoç A, Törüner F, Cakir N and Arslan M: The effects of rosiglitazone and metformin on oxidative stress and homocysteine levels in lean patients with polycystic ovary syndrome. Hum Reprod 20: 3333-3340, 2005.
90. Reddy TV, Govatati S, Deenadayal M, Sisinthy S and Bhanoori M: Impact of mitochondrial DNA copy number and displacement loop alterations on polycystic ovary syndrome risk in south Indian women. Mitochondrion 44: 35-40, 2019.
91. Kicińska AM, Maksym RB, Zabielska-Kaczorowska MA, Stachowska A and Babińska A: Immunological and metabolic causes of infertility in polycystic ovary syndrome. Biomedicines 11: 1567, 2023.
92. Yan F, Zhao Q, Li Y, Zheng Z, Kong X, Shu C, Liu Y and Shi Y: The role of oxidative stress in ovarian aging: A review. J Ovarian Res 15: 100, 2022.
93. Nuñez-Calonge R, Cortés S, Gutierrez Gonzalez LM, Kireev R, Vara E, Ortega L, Caballero P, Rancan L and Tresguerres J: Oxidative stress in follicular fluid of young women with low response compared with fertile oocyte donors. Reprod Biomed Online 32: 446-456, 2016.
94. Siti HN, Kamisah Y and Kamsiah J: The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascul Pharmacol 71: 40-56, 2015.
95. Rosenfield RL and Ehrmann DA: The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 37: 467-520, 2016.
96. Mahalingaiah S and Diamanti-Kandarakis E: Targets to treat metabolic syndrome in polycystic ovary syndrome. Expert Opin Ther Targets 19: 1561-1574, 2015.
97. Shkolnik K, Tadmor A, Ben-Dor S, Nevo N, Galiani D and Dekel N: Reactive oxygen species are indispensable in ovulation. Proc Natl Acad Sci USA 108: 1462-1467, 2011.
98. Takiguchi S, Sugino N, Kashida S, Yamagata Y, Nakamura Y and Kato H: Rescue of the corpus luteum and an increase in luteal superoxide dismutase expression induced by placental luteotropins in the rat: Action of testosterone without conversion to estrogen. Biol Reprod 62: 398-403, 2000.
99. Ighodaro OM and Akinloye OA: First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alex J Med 54: 287-293, 2018.
100. Gao Y, Zou Y, Wu G and Zheng L: Oxidative stress and mitochondrial dysfunction of granulosa cells in polycystic ovarian syndrome. Front Med (Lausanne) 10: 1193749, 2023.
101. Gusti AMT, Qusti SY, Alshammari EM, Toraih EA and Fawzy MS: Antioxidants-related superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: A preliminary case-control study. Antioxidants (Basel) 10: 595, 2021.
102. Sulaiman MA, Al-Farsi YM, Al-Khaduri MM, Saleh J and Waly MI: Polycystic ovarian syndrome is linked to increased oxidative stress in Omani women. Int J Womens Health 10: 763-771, 2018.
103. Asally R, Markham R and Manconi F: Mitochondrial DNA haplogroup H association with endometriosis and possible role in inflammation and pain. J Endometr Pelvic Pain Disord 12: 158-164, 2020.
104. Lee SH, Chung DJ, Lee HS, Kim TJ, Kim MH, Jeong HJ, Im JA, Lee DC and Lee JW: Mitochondrial DNA copy number in peripheral blood in polycystic ovary syndrome. Metabolism 60: 1677-1682, 2011.
105. Aguilar Diaz De Leon J and Borges CR: Evaluation of oxidative stress in biological samples using the thiobarbituric acid reactive substances assay. J Vis Exp: 10.3791/61122, 2020.
106. Uckan K, Demir H, Turan K, Sarikaya E and Demir C: Role of oxidative stress in obese and nonobese PCOS patients. Int J Clin Pract 2022: 4579831, 2022.
107. Nagy RA, van Montfoort APA, Groen H, Homminga I, Andrei D, Mistry RH, Anderson JLC, Hoek A and Tietge UJF: Anti-oxidative function of follicular fluid HDL and outcomes of modified natural cycle-IVF. Sci Rep 9: 12817, 2019.
108. Yan H, Wang L, Zhang G, Li N, Zhao Y, Liu J, Jiang M, Du X, Zeng Q, Xiong D, *et al*: Oxidative stress and energy metabolism abnormalities in polycystic ovary syndrome: From mechanisms to therapeutic strategies. Reprod Biol Endocrinol 22: 159, 2024.
109. Zhang Q, Ren J, Wang F, Pan M, Cui L, Li M and Qu F: Mitochondrial and glucose metabolic dysfunctions in granulosa cells induce impaired oocytes of polycystic ovary syndrome through Sirtuin 3. Free Radic Biol Med 187: 1-16, 2022.
110. Xie C, Lu H, Zhang X, An Z, Chen T, Yu W, Wang S, Shang D and Wang X: Mitochondrial abnormality in ovarian granulosa cells of patients with polycystic ovary syndrome. Mol Med Rep 29: 27, 2024.
111. Song L, Yu J, Zhang D, Li X, Chen L, Cai Z and Yu C: Androgen excess induced mitochondrial abnormality in ovarian granulosa cells in a rat model of polycystic ovary syndrome. Front Endocrinol (Lausanne) 13: 789008, 2022.
112. Wang Y, Yang Q, Wang H, Zhu J, Cong L, Li H and Sun Y: NAD+ deficiency and mitochondrial dysfunction in granulosa cells of women with polycystic ovary syndrome‡. Biol Reprod 105: 371-380, 2021.
113. Zhang J, Bao Y, Zhou X and Zheng L: Polycystic ovary syndrome and mitochondrial dysfunction. Reprod Biol Endocrinol 17: 67, 2019.
114. Malamouli M, Levinger I, McAinch AJ, Trewin AJ, Rodgers RJ and Moreno-Asso A: The mitochondrial profile in women with polycystic ovary syndrome: Impact of exercise. J Mol Endocrinol 68: R11-R23, 2022.
115. Siemers KM, Klein AK and Baack ML: Mitochondrial dysfunction in PCOS: Insights into reproductive organ pathophysiology. Int J Mol Sci 24: 13123, 2023.
116. Lai Q, Xiang W, Li Q, Zhang H, Li Y, Zhu G, Xiong C and Jin L: Oxidative stress in granulosa cells contributes to poor oocyte quality and IVF-ET outcomes in women with polycystic ovary syndrome. Front Med 12: 518-524, 2018.
117. Sreerangaraja Urs DB, Wu WH, Komrskova K, Postlerova P, Lin YF, Tzeng CR and Kao SH: Mitochondrial function in modulating human granulosa cell steroidogenesis and female fertility. Int J Mol Sci 21: 3592, 2020.
118. Qi L, Liu B, Chen X, Liu Q, Li W, Lv B, Xu X, Wang L, Zeng Q, Xue J and Xue Z: Single-cell transcriptomic analysis reveals mitochondrial dynamics in oocytes of patients with polycystic ovary syndrome. Front Genet 11: 396, 2020.
119. Rabøl R, Svendsen PF, Skovbro M, Boushel R, Schjerling P, Nilas L, Madsbad S and Dela F: Skeletal muscle mitochondrial function in polycystic ovarian syndrome. Eur J Endocrinol 165: 631-637, 2011.
120. Yan MQ, Wang Y, Wang Z, Liu XH, Yang YM, Duan XY, Sun H and Liu XM: Mitoguardin2 is associated with hyperandrogenism and regulates steroidogenesis in human ovarian granulosa cells. J Endocr Soc 7: bvad034, 2023.
121. Chappell NR, Zhou B, Schutt AK, Gibbons WE and Blesson CS: Prenatal androgen induced lean PCOS impairs mitochondria and mRNA profiles in oocytes. Endocr Connect 9: 261-270, 2020.
122. Takahashi N, Harada M, Hirota Y, Nose E, Azhary JM, Koike H, Kunitomi C, Yoshino O, Izumi G, Hirata T, *et al*: Activation of endoplasmic reticulum stress in granulosa cells from patients with polycystic ovary syndrome contributes to ovarian fibrosis. Sci Rep 7: 10824, 2017.
123. Pang X, Cheng J, Wu T and Sun L: SIRT3 ameliorates polycystic ovary syndrome through FOXO1/PGC-1α signaling pathway. Endocrine 80: 201-211, 2023.
124. Yu N, Wu L and Xing X: NOX4 deficiency improves the impaired viability, inhibited the apoptosis and suppressed autophagy of DHEA-treated ovarian granulosa cells through inhibiting endoplasmic reticulum stress via inactivating PERK/ATF4 pathway. Tissue Cell 92: 102640, 2025.
125. Liu Y, Jiang H, Xing FQ, Huang WJ, Mao LH and He LY: Uncoupling protein 2 expression affects androgen synthesis in polycystic ovary syndrome. Endocrine 43: 714-723, 2013.
126. Liu Y, Jiang H, He LY, Huang WJ, He XY and Xing FQ: Abnormal expression of uncoupling protein-2 correlates with CYP11A1 expression in polycystic ovary syndrome. Reprod Fertil Dev 23: 520-526, 2011.
127. Wang Y, Yang J, Wang Y, Chen Y, Wang Y, Kuang H and Feng X: Upregulation of TXNIP contributes to granulosa cell dysfunction in polycystic ovary syndrome via activation of the NLRP3 inflammasome. Mol Cell Endocrinol 561: 111824, 2023.
128. Wang B, Shi M, Yu C, Pan H, Shen H, Du Y, Zhang Y, Liu B, Xi D, Sheng J, *et al*: NLRP3 inflammasome-dependent pathway is involved in the pathogenesis of polycystic ovary syndrome. Reprod Sci 31: 1017-1027, 2024.
129. Corbould A, Kim YB, Youngren JF, Pender C, Kahn BB, Lee A and Dunaif A: Insulin resistance in the skeletal muscle of women with PCOS involves intrinsic and acquired defects in insulin signaling. Am J Physiol Endocrinol Metab 288: E1047-E1054, 2005.

130. Gao Z, Hwang D, Bataille F, Lefevre M, York D, Quon MJ and Ye J: Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex. J Biol Chem 277: 48115-48121, 2002.
131. Bloch-Damti A, Potashnik R, Gual P, Le Marchand-Brustel Y, Tanti JF, Rudich A and Bashan N: Differential effects of IRS1 phosphorylated on Ser307 or Ser632 in the induction of insulin resistance by oxidative stress. Diabetologia 49: 2463-2473, 2006.
132. Venkatesan AM, Dunaif A and Corbould A: Insulin resistance in polycystic ovary syndrome: Progress and paradoxes. Recent Prog Horm Res 56: 295-308, 2001.
133. Meng TC, Fukada T and Tonks NK: Reversible oxidation and inactivation of protein tyrosine phosphatases in vivo. Mol Cell 9: 387-399, 2002.
134. Kim JH, Choi TG, Park S, Yun HR, Nguyen NNY, Jo YH, Jang M, Kim J, Kim J, Kang I, *et al*: Mitochondrial ROS-derived PTEN oxidation activates PI3K pathway for mTOR-induced myogenic autophagy. Cell Death Differ 25: 1921-1937, 2018.
135. Saltiel AR: Insulin signaling in health and disease. J Clin Invest 131: e142241, 2021.
136. Shi J, Hu KL, Li XX, Ge YM, Yu XJ and Zhao J: Bisphenol a downregulates GLUT4 expression by activating aryl hydrocarbon receptor to exacerbate polycystic ovary syndrome. Cell Commun Signal 22: 28, 2024.
137. Li X, Cui P, Jiang HY, Guo YR, Pishdari B, Hu M, Feng Y, Billig H and Shao R: Reversing the reduced level of endometrial GLUT4 expression in polycystic ovary syndrome: A mechanistic study of metformin action. Am J Transl Res 7: 574-586, 2015.
138. Potashnik R, Bloch-Damti A, Bashan N and Rudich A: IRS1 degradation and increased serine phosphorylation cannot predict the degree of metabolic insulin resistance induced by oxidative stress. Diabetologia 46: 639-648, 2003.
139. Park SY, Ryu J and Lee W: O-GlcNAc modification on IRS-1 and Akt2 by PUGNAc inhibits their phosphorylation and induces insulin resistance in rat primary adipocytes. Exp Mol Med 37: 220-229, 2005.
140. Vosseller K, Wells L, Lane MD and Hart GW: Elevated nucleocytoplasmic glycosylation by O-GlcNAc results in insulin resistance associated with defects in Akt activation in 3T3-L1 adipocytes. Proc Natl Acad Sci USA 99: 5313-5318, 2002.
141. Wang TF, Feng ZQ, Sun YW, Zhao SJ, Zou HY, Hao HS, Du WH, Zhao XM, Zhu HB and Pang YW: Disruption of O-GlcNAcylation homeostasis induced ovarian granulosa cell injury in bovine. Int J Mol Sci 23: 7815, 2022.
142. Wei JH, Yuan XY, Zhang JM and Wei JQ: Caspase activity and oxidative stress of granulosa cells are associated with the viability and developmental potential of vitrified immature oocytes. Eur J Obstet Gynecol Reprod Biol 198: 22-26, 2016.
143. Li Y, Yao N, Gao Y, Wang Y, Bai L, Xu J and Wang H: MiR-1224-5p attenuates polycystic ovary syndrome through inhibiting NOD-like receptor protein 3 inflammasome activation via targeting Forkhead box O 1. Bioengineered 12: 8555-8569, 2021.
144. Jaklic J and Prelovsek P: Universal charge and spin response in optimally doped antiferromagnets. Phys Rev Lett 75: 1340-1343, 1995.
145. Liu Y, Liu H, Li Z, Fan H, Yan X, Liu X, Xuan J, Feng D and Wei X: The release of peripheral immune inflammatory cytokines promote an inflammatory cascade in PCOS patients via altering the follicular microenvironment. Front Immunol 12: 685724, 2021.
146. Bahreiny SS, Ahangarpour A, Saki N, Dabbagh MR, Ebrahimi R, Mahdizade AH, Ghorbani H and Aghaei M: Association of free radical product and polycystic ovary syndrome: A systematic review and meta-analysis. Reprod Sci 31: 1486-1495, 2024.
147. Tan W, Zhang J, Dai F, Yang D, Gu R, Tang L, Liu H and Cheng YX: Insights on the NF-κB system in polycystic ovary syndrome, attractive therapeutic targets. Mol Cell Biochem 479: 467-486, 2024.
148. González F, Rote NS, Minium J and Kirwan JP: Increased activation of nuclear factor kappaB triggers inflammation and insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 91: 1508-1512, 2006.
149. González F, Considine RV, Abdelhadi OA and Acton AJ: Saturated fat ingestion promotes lipopolysaccharide-mediated inflammation and insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 104: 934-946, 2019.
150. McKelvey RS, Webb JA, Baldassar LV, Robinson SM and Riley G: Sex knowledge and sexual attitudes among medical and nursing students. Aust N Z J Psychiatry 33: 260-266, 1999.
151. Mazloomi S, Farimani MS, Tavilani H, Karimi J, Amiri I, Abbasi E and Khodadadi I: Granulosa cells from immature follicles exhibit restricted glycolysis and reduced energy production: A dominant problem in polycystic ovary syndrome. J Assist Reprod Genet 40: 343-359, 2023.
152. Wang Y, Li N, Zeng Z, Tang L, Zhao S, Zhou F, Zhou L, Xia W, Zhu C and Rao M: Humanin regulates oxidative stress in the ovaries of polycystic ovary syndrome patients via the Keap1/Nrf2 pathway. Mol Hum Reprod 27: gaaa081, 2021.
153. Zhu R, Yang L and Li Y: TXNIP participates in the pathogenesis of PCOS by regulating glycolysis in granulosa cells. Biochem Biophys Res Commun 775: 152149, 2025.
154. Seino T, Saito H, Kaneko T, Takahashi T, Kawachiya S and Kurachi H: Eight-hydroxy-2'-deoxyguanosine in granulosa cells is correlated with the quality of oocytes and embryos in an in vitro fertilization-embryo transfer program. Fertil Steril 77: 1184-1190, 2002.
155. Sun Y, Li S, Liu H, Bai H, Hu K, Zhang R, Liu Q and Fan P: Oxidative stress promotes hyperandrogenism by reducing sex hormone-binding globulin in polycystic ovary syndrome. Fertil Steril 116: 1641-1650, 2021.
156. Gong Y, Luo S, Fan P, Zhu H, Li Y and Huang W: Growth hormone activates PI3K/Akt signaling and inhibits ROS accumulation and apoptosis in granulosa cells of patients with polycystic ovary syndrome. Reprod Biol Endocrinol 18: 121, 2020.
157. Yao Q, Zou X, Liu S, Wu H, Shen Q and Kang J: Oxidative stress as a contributor to insulin resistance in the skeletal muscles of mice with polycystic ovary syndrome. Int J Mol Sci 23: 11384, 2022.
158. Fang YQ, Ding H, Li T, Zhao XJ, Luo D, Liu Y and Li Y: N-acetylcysteine supplementation improves endocrine-metabolism profiles and ovulation induction efficacy in polycystic ovary syndrome. J Ovarian Res 17: 205, 2024.
159. Wang YC, Qi ZP, Liu ZZ, Li T, Cui HX, Wang BQ and Chi N: Therapeutic effects and mechanisms of Opuntia dillenii Haw on atherosclerosis of rats. Yao Xue Xue Bao 50: 453-458, 2015 (In Chinese).
160. Jamilian M, Foroozanfard F, Kavossian E, Aghadavod E, Shafabakhsh R, Hoseini A and Asemi Z: Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clin Nutr ESPEN 36: 128-133, 2020.
161. Heshmati J, Golab F, Morvaridzadeh M, Potter E, Akbari-Fakhrabadi M, Farsi F, Tanbakooei S and Shidfar F: The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. Diabetes Metab Syndr 14: 77-82, 2020.
162. Karamali M and Gholizadeh M: The effects of coenzyme Q10 supplementation on metabolic profiles and parameters of mental health in women with polycystic ovary syndrome. Gynecol Endocrinol 38: 45-49, 2022.
163. Samimi M, Jamilian M, Ebrahimi FA, Rahimi M, Tajbakhsh B and Asemi Z: Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf) 84: 851-857, 2016.
164. Jamilian M, Samimi M, Mirhosseini N, Afshar Ebrahimi F, Aghadavod E, Talaee R, Jafarnejad S, Hashemi Dizaji S and Asemi Z: The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome. J Affect Disord 238: 32-38, 2018.
165. Showell MG, Mackenzie-Proctor R, Jordan V, Hodgson R and Farquhar C: Inositol for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev 12: CD012378, 2018.
166. Foroozanfard F, Jamilian M, Bahmani F, Talaee R, Talaee N, Hashemi T, Nasri K, Asemi Z and Esmaillzadeh A: Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. Clin Endocrinol (Oxf) 83: 888-894, 2015.
167. Razavi M, Jamilian M, Karamali M, Bahmani F, Aghadavod E and Asemi Z: The effects of vitamin D-K-calcium co-supplementation on endocrine, inflammation, and oxidative stress biomarkers in vitamin D-deficient women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Horm Metab Res 48: 446-451, 2016.

168. Jamilian M, Mansury S, Bahmani F, Heidar Z, Amirani E and Asemi Z: The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. J Ovarian Res 11: 80, 2018.
169. Zhao J, Dong L, Lin Z, Sui X, Wang Y, Li L, Liu T and Liu J: Effects of selenium supplementation on polycystic ovarian syndrome: A systematic review and meta-analysis on randomized clinical trials. BMC Endocr Disord 23: 33, 2023.
170. Ashoush S, Abou-Gamrah A, Bayoumy H and Othman N: Chromium picolinate reduces insulin resistance in polycystic ovary syndrome: Randomized controlled trial. J Obstet Gynaecol Res 42: 279-285, 2016.
171. Jamilian M, Bahmani F, Siavashani MA, Mazloomi M, Asemi Z and Esmaillzadeh A: The effects of chromium supplementation on endocrine profiles, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 172: 72-78, 2016.
172. Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L and Duleba AJ: Effects of resveratrol on polycystic ovary syndrome: A double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 101: 4322-4328, 2016.
173. Michalski AH and Winter PM: Surgical technique in experimental venous admixture. J Appl Physiol 22: 1020-1021, 1967.
174. Lancioni GE, Gigante A, O'Reilly MF, Oliva D and Montironi L: Indoor travel and simple tasks as physical exercise for people with profound multiple disabilities. Percept Mot Skills 91: 211-216, 2000.
175. Monvall E: Maximum 10-h workday or more free holidays? Length of work schedule and breaks discussed by professional representatives. Tidskr Sver Sjukskot 43: 4-5, 1976 (In Swedish).
176. Khorshidi M, Moini A, Alipoor E, Rezvan N, Gorgani-Firuzjaee S, Yaseri M and Hosseinzadeh-Attar MJ: The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. Phytother Res 32: 2282-2289, 2018.
177. Yim AP, Landreneau RJ, Izzat MB, Fung AL and Wan S: Is video-assisted thoracoscopic lobectomy a unified approach? Ann Thorac Surg 66: 1155-1158, 1998.
178. Mishra N, Verma R and Jadaun P: Study on the effect of berberine, myoinositol, and metformin in women with polycystic ovary syndrome: A prospective randomised study. Cureus 14: e21781, 2022.
179. Rondanelli M, Riva A, Petrangolini G, Allegrini P, Giacosa A, Fazia T, Bernardinelli L, Gasparri C, Peroni G and Perna S: Berberine phospholipid is an effective insulin sensitizer and improves metabolic and hormonal disorders in women with polycystic ovary syndrome: A one-group pretest-post-test explanatory study. Nutrients 13: 3665, 2021.
180. He S, Li H, Zhang Q, Zhao W, Li W, Dai C, Li B, Cheng J, Wu S, Zhou Z, *et al*: Berberine alleviates inflammation in polycystic ovary syndrome by inhibiting hyaluronan synthase 2 expression. Phytomedicine 128: 155456, 2024.
181. Jamilian M, Foroozanfard F, Mirhosseini N, Kavossian E, Aghadavod E, Bahmani F, Ostadmohammadi V, Kia M, Eftekhar T, Ayati E, *et al*: Effects of melatonin supplementation on hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome. Front Endocrinol (Lausanne) 10: 273, 2019.
182. Shabani A, Foroozanfard F, Kavossian E, Aghadavod E, Ostadmohammadi V, Reiter RJ, Eftekhar T and Asemi Z: Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. J Affect Disord 250: 51-56, 2019.
183. Meléndez-Marmolejo J, Díaz de León-Martínez L, Galván-Romero V, Villarreal-Lucio S, Ocampo-Pérez R, Medellín-Castillo NA, Padilla-Ortega E, Rodríguez-Torres I and Flores-Ramírez R: Design and application of molecularly imprinted polymers for adsorption and environmental assessment of anti-inflammatory drugs in wastewater samples. Environ Sci Pollut Res Int 29: 45885-45902, 2022.
184. Zhao J, Sui X, Shi Q, Su D and Lin Z: Effects of antioxidant intervention in patients with polycystic ovarian syndrome: A systematic review and meta-analysis. Medicine (Baltimore) 101: e30006, 2022.
185. He J, Deng R, Wei Y, Zhang S, Su M, Tang M, Wang J, Nong W and Lei X: Efficacy of antioxidant supplementation in improving endocrine, hormonal, inflammatory, and metabolic statuses of PCOS: A meta-analysis and systematic review. Food Funct 15: 1779-1802, 2024.
186. Alesi S, Ee C, Moran LJ, Rao V and Mousa A: Nutritional supplements and complementary therapies in polycystic ovary syndrome. Adv Nutr 13: 1243-1266, 2022.