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PSYCHONEUROENDOCRINE ASPECTS OF POLYCYSTIC OVARY SYNDROME: FROM MECHANISMS TO CLINICAL CONSEQUENCES - A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Purpose: Growing evidence conceptualizes Polycystic Ovary Syndrome (PCOS) as a complex psychoneuroendocrine condition whose consequences extend far beyond reproductive health. Research indicates that hyperandrogenism, insulin resistance, and chronic low-grade inflammation interact dynamically, affecting central nervous system functioning, stress responsiveness, and neurotransmitter regulation. These interrelated mechanisms contribute to a substantially increased vulnerability to depression, anxiety, disordered eating behaviors, and cognitive disturbances in women with PCOS. Dysregulation of both the hypothalamic-pituitary-ovarian (HPO) and hypothalamic-pituitary-adrenal (HPA) axes, together with adipokine imbalance and neuroinflammatory activity, provides a biologically coherent framework for understanding the heightened psychiatric burden associated with the syndrome.

Importantly, psychological manifestations of PCOS are heterogeneous. Symptom severity and presentation are influenced by phenotype, metabolic status, body composition, age, and exposure to psychosocial and environmental stressors. Interventions targeting metabolic and inflammatory dysfunction, including insulin-sensitizing agents, anti-inflammatory strategies, lifestyle modification, and psychologically informed therapies have shown beneficial effects on mental health and quality of life, though responses vary considerably. These observations highlight the need for individualized, integrative treatment approaches and underscore the importance of longitudinal, mechanism-driven research to improve clinical outcomes.

Methodology: A systematic review of the scientific literature was conducted, focusing on studies examining the psychoneuroendocrine mechanisms and mental health outcomes associated with Polycystic Ovary Syndrome (PCOS). The review primarily included clinical trials, observational studies, meta-analyses, and mechanistic research in human populations, with particular emphasis on endocrine, metabolic, neurobiological, and psychological outcomes.

Findings: PCOS is consistently associated with a significantly increased burden of depression, anxiety, disordered eating, and cognitive complaints, mediated by interconnected psychoneuroendocrine mechanisms. The reviewed evidence indicates that hyperandrogenism, insulin resistance, and chronic low-grade inflammation disrupt neurotransmitter systems, stress-axis regulation, and brain connectivity, collectively contributing to mood dysregulation and reward-processing deficits. Interventions that improve metabolic function such as insulin sensitizers, anti-inflammatory strategies, and lifestyle modification, appear to alleviate psychological symptoms and improve quality of life, although effects vary by PCOS phenotype, metabolic status, age and treatment modality.

Conclusions: Current evidence supports the role of Polycystic Ovary Syndrome as a condition with significant psychoneuroendocrine involvement, contributing to an increased risk of mood disorders, disordered eating, and cognitive dysfunction. However, further high-quality, longitudinal and mechanistically focused studies are required to elucidate the precise causal pathways linking endocrine and metabolic disturbances to brain function, and to determine optimal, personalized management strategies targeting both metabolic and mental health outcomes. These remain critical priorities for future research.

KEYWORDS

Polycystic Ovary Syndrome (PCOS), Psychoneuroendocrinology, Hyperandrogenism, Insulin Resistance, Mental Health Disorders, Inflammation

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1. Introduction

Polycystic Ovary Syndrome (PCOS) is currently recognized as the most prevalent endocrine disorder affecting women of reproductive age. While historically viewed primarily as a cause of anovulatory infertility, contemporary understanding defines PCOS as a complex, multisystem condition characterized by reproductive, metabolic, and psychological dysfunctions that persist throughout the lifespan (1).

Diagnostic Criteria

The diagnosis of PCOS remains a challenge due to its heterogeneous presentation and the use of varying criteria. The syndrome is primarily diagnosed based on the presence of at least two of the following three features, following the widely accepted Rotterdam criteria:

Oligo- or Anovulation (OA): Irregular menstrual cycles, defined by age-specific criteria (cycles <21 or >35 days, or <8 cycles per year for adults).

Clinical and/or Biochemical Hyperandrogenism (HA): Manifested by hirsutism, severe acne, or biochemical evidence of elevated androgen levels (e.g., testosterone, free androgen index).

Polycystic Ovary Morphology (PCOM): Identified by ultrasound (≥20 follicles per ovary or ovarian volume ≥10 cm3) or by elevated Anti-Müllerian hormone (AMH) levels (for adults only).

Prior criteria, such as the NIH criteria (1990), required both HA and OA. The Androgen Excess and PCOS Society (AE-PCOS) criteria (2006) emphasized HA as a mandatory component. The 2023 International Guidelines now recommend the modified Rotterdam criteria, with the exclusion of other relevant disorders (e.g., thyroid disorders, congenital adrenal hyperplasia, hyperprolactinemia) (1,2).

Epidemiology

The global prevalence of PCOS varies largely depending on the diagnostic criteria applied and the population studied. Estimates suggest that PCOS affects approximately 8% to 13% of reproductive-aged women under the Rotterdam criteria. Despite its high prevalence, a significant diagnostic gap persists, with up to 70% of affected individuals worldwide remaining undiagnosed (1). When applying the narrower NIH criteria, prevalence is lower, estimated at approximately 6% to 10% of reproductive-aged women (3).

Symptoms typically emerge in adolescence and early adulthood, but diagnosis is often delayed. Ethnic disparities play a significant role in the phenotypic expression and prevalence of the syndrome. Studies indicate a higher prevalence and greater metabolic severity (e.g., insulin resistance) in women of South Asian, Indigenous, and Middle Eastern descent compared to Caucasians. Conversely, East Asian women often present with a lower Body Mass Index (BMI) but comparable metabolic risks, highlighting the limitations of BMI as a universal screening tool (6,7). Association has been noted with genetic susceptibility, early life androgen exposure, prepubertal obesity, premature adrenarche and family history of PCOS (4,5).

Clinical Heterogeneity and Subtypes

PCOS is a highly heterogeneous disorder marked by a wide array of symptoms and varying degrees of reproductive and metabolic dysfunction. The variation in symptom combinations has led to the classification of four distinct phenotypes based on the Rotterdam criteria, which carry different implications for long-term health outcomes (8,2).

Phenotype A (Classic PCOS): HA + OA + PCOM.

Phenotype B (Classic non-PCOM): HA + OA.

Phenotype C (Ovulatory PCOS): HA + PCOM.
Phenotype D (Non-hyperandrogenic PCOS): OA + PCOM.

Metabolic and Reproductive Features

Recent literature emphasizes that these phenotypes are not merely diagnostic labels but reflect underlying pathophysiological differences. Phenotype A is consistently associated with the most severe metabolic profile, including the highest rates of insulin resistance (IR), abdominal obesity, and dyslipidemia. In contrast, Phenotype D generally presents with the mildest endocrine and metabolic disturbances, though risks remain higher than in the healthy population. Accordingly, phenotypic stratification of patients with PCOS-associated infertility may facilitate more accurate prognostication regarding disease severity and fertility outcomes (10).

Furthermore, recent large-scale genome-wide association studies (GWAS) and cluster analyses have proposed a new paradigm of classifying PCOS into biologically driven subtypes rather than symptom-based phenotypes. For instance, a seminal study identified reproductive and metabolic subtypes, suggesting distinct genetic underpinnings where one group is driven by high LH and SHBG levels, while the other is driven by high BMI, glucose, and insulin levels (9).

Rationale for Exploring Psychoneuroendocrine Aspects

Despite the somatic focus of standard diagnostic criteria, PCOS is intrinsically linked to significant neuropsychological morbidity. The rationale for this review lies in the bidirectional relationship between the endocrine and nervous systems, often referred to as the psychoneuroendocrine (PNE) axis.

The burden of mental health disorders in PCOS is substantial. Meta-analyses indicate that women with PCOS have an approximately 3- to 4-fold increased odds of depression and a 3- to 5-fold increased odds of anxiety compared to controls, independent of BMI (11,12). Moreover, the prevalence of disordered eating and body dysmorphic concerns is significantly elevated (13).

The Hormonal-Neural Connection

This comorbidity cannot be explained solely by the psychosocial distress of infertility or cosmetic symptoms (hirsutism). Emerging evidence points to shared physiological mechanisms linking metabolic and reproductive hormones with brain function. Androgens and their metabolites can cross the blood-brain barrier, influencing neurotransmitter systems (GABA, serotonin) involved in mood regulation (14). Chronic low-grade inflammation and hyperinsulinemia are known to exert neurotoxic effects and alter hypothalamic-pituitary-adrenal (HPA) axis reactivity (15). Women with PCOS frequently exhibit an exaggerated cortisol response to stress, suggesting a fundamental maladaptation in the stress response system (16).

Therefore, understanding PCOS requires a shift from a purely gynecological perspective to a psychoneuroendocrine model. This review aims to synthesize current knowledge on these mechanisms to better inform holistic clinical management.

2. Methodology

This review was conducted through a structured search and critical appraisal of the scientific literature related to Psychoneuroendocrine Aspects of Polycystic Ovary Syndrome. Electronic databases including PubMed, Scopus and Google Scholar, were systematically queried to identify relevant peer-reviewed publications. Data synthesis followed the GRADE framework to assess evidence quality, consistent with international guideline development processes. The initial literature search identified a broad range of potentially relevant publications. These records were subsequently screened and filtered according to predefined inclusion criteria, which comprised original human studies, systematic reviews and meta-analyses, investigations addressing psychoneuroendocrine aspects of polycystic ovary syndrome (PCOS), articles published in the English language, and high-quality observational studies focusing on neuroendocrine markers, psychological outcomes, and integrated care models. Exclusion criteria included animal studies, non–peer-reviewed publications, and studies that did not clearly define PCOS as the primary condition of interest or lacked a relevant psychoneuroendocrine focus.

3. Pathophysiological Mechanisms Linking PCOS and Mental Health

The comorbidity of Polycystic Ovary Syndrome (PCOS) and psychiatric disorders (most notably depression, anxiety, and bipolar disorder) represents a complex interplay of neuroendocrine, metabolic, and inflammatory pathologies. The "dual diagnosis" is not merely coincidental but rooted in shared biological substrates. Current research posits that the central nervous system (CNS) in women with PCOS is subjected to a chronic, aberrant chemical environment characterized by hyperandrogenism, insulin resistance, and sterile inflammation (12,15,16).

Hormonal Dysregulation

The endocrine hallmarks of PCOS - hyperandrogenism and hypothalamic-pituitary-ovarian (HPO) axis dysfunction - exert profound effects on the structural and functional architecture of the brain. Steroid hormones are potent neuroplastic agents, their dysregulation during critical developmental windows or chronically in adulthood can fundamentally alter neurochemistry and emotional processing circuits (15,16).

Hyperandrogenism is the most defining feature of PCOS. Androgens, including testosterone (T), dihydrotestosterone (DHT), and androstenedione, are lipophilic molecules that readily traverse the blood-brain barrier (BBB). Once within the CNS, they act as "neurosteroids," influencing neuronal excitability, synaptic plasticity, and neurotransmitter turnover through both genomic (nuclear receptor) and non-genomic (membrane receptor) mechanisms (14,17).

The gamma-aminobutyric acid (GABA) system, the primary inhibitory neurotransmitter network in the brain, is a critical target of androgenic modulation. The GABA-A receptor is a ligand-gated ion channel that contains specific binding sites for neuroactive steroids. Under physiological conditions, progesterone metabolites, such as allopregnanolone, act as positive allosteric modulators of the GABA-A receptor, enhancing chloride influx and producing anxiolytic and sedative effects.In the context of PCOS, this homeostatic mechanism is disrupted. DHT is a potent androgen that can modulate the expression of GABA-A receptor subunits. Furthermore, women with PCOS often exhibit elevated baseline levels of allopregnanolone compared to healthy controls. This finding presents a paradox: despite higher levels of this potent anxiolytic neurosteroid, women with PCOS suffer from high rates of anxiety. This phenomenon is described as "neurosteroid resistance" or tolerance. It is hypothesized that chronic exposure to elevated neurosteroids induces a compensatory downregulation or desensitization of GABA-A receptors, rendering the brain less responsive to the buffering effects of GABAergic inhibition during stress (18,19,20).

Beyond neurotransmission, hyperandrogenism appears to influence the macro-structural connectivity of the brain. Diffusion Tensor Imaging (DTI) and functional MRI (fMRI) studies have revealed that women with PCOS exhibit altered white matter integrity and functional connectivity in pathways associated with emotional regulation (22).

Specifically, elevated testosterone levels have been positively correlated with increased functional connectivity between the Left Middle Frontal Gyrus (MFG) and the Left Inferior Frontal Gyrus (IFG). The MFG is a critical hub for executive control and emotion regulation. The strengthening of this connectivity in hyperandrogenic states may reflect a compensatory neural effort to downregulate hyperactivity in limbic regions. Conversely, reduced white matter integrity (lower fractional anisotropy) has been observed in the corpus callosum and superior longitudinal fasciculus in patients with high free testosterone. These tracts are essential for inter-hemispheric communication and the integration of cognitive and emotional information. The disruption of these pathways suggests that androgens may exert a neurotoxic or anti-myelinating effect on specific fiber tracts, contributing to the emotional lability frequently reported by patients (22,23).

The amygdala, the brain's "fear center," is highly sensitive to steroid hormones. fMRI studies utilizing emotional tasks have demonstrated that women with PCOS show hyperactivation of the right amygdala in response to negative stimuli. This limbic hyperactivity is not merely an artifact of the disorder but is significantly correlated with circulating androgen levels and insulin resistance. The mechanism involves the androgen receptor (AR) density in the amygdala. Overstimulation of these receptors may lower the threshold for threat detection, creating a state of hypervigilance and anxiety. Interestingly, treatment with insulin-sensitizing agents like metformin has been shown to normalize this amygdala hyperactivity, suggesting that the "androgenic" effect may be partially mediated or exacerbated by concurrent hyperinsulinemia (24).

In PCOS, there is a persistent acceleration of GnRH pulse frequency. This rapid pulsatility favors the synthesis and secretion of LH over FSH, leading to the characteristic high LH:FSH ratio. The neurobiological driver of this acceleration lies in the KNDy neurons (Kisspeptin, Neurokinin B, Dynorphin) located in the arcuate nucleus of the hypothalamus. Kisspeptin is the most potent activator of GnRH neurons. Women with PCOS exhibit elevated serum and hypothalamic kisspeptin levels. This excessive excitatory drive forces the

GnRH neurons into a state of rapid firing. Under normal conditions, progesterone suppresses the GnRH pulse generator (slowing it down) by acting on KNDy neurons. In PCOS, this progesterone-mediated negative feedback is impaired, allowing the rapid pulse frequency to persist unchecked (25).

The consequences of elevated LH extend beyond the ovary. LH receptors are expressed in limbic structures of the brain, including the hippocampus and cerebral cortex. While their function in the CNS is not fully elucidated, evidence suggests that high levels of LH may have neuro-modulatory effects (26). More critically, the rapid GnRH pulsatility is associated with reduced levels of central inhibitory neurotransmitters, including serotonin (5-HT) and endogenous opioids (beta-endorphins). The reduction in central opioid tone (which normally restrains the GnRH pulse generator) may contribute to a heightened perception of pain and stress, as well as mood dysphoria (27).

Women with PCOS display an exaggeratedthe Hypothalamic-Pituitary-Adrenal (HPA) axis response to physiological and psychological stressors. This manifests as elevated production of adrenal androgens (DHEA-S) and cortisol.The relationship is bidirectional.

Chronic stress increases Hypothalamic Corticotropin-Releasing Hormone (CRH), which can inhibit GnRH directly (causing amenorrhea) or, in specific contexts like PCOS, dysregulate the pulse generator.

The state of hyperandrogenism and inflammation acts as a chronic physiological stressor. Elevated cortisol levels have neurotoxic effects on the hippocampus, a region rich in glucocorticoid receptors and critical for memory and mood regulation. Chronic hypercortisolism promotes dendritic atrophy in the hippocampus, a structural change strongly associated with Major Depressive Disorder (27).

Insulin Resistance and Metabolic Factors

Metabolic dysfunction is a core component of PCOS, with insulin resistance (IR) affecting 50–70% of patients, largely independent of obesity. While traditionally viewed as a peripheral metabolic issue, insulin resistance has profound implications for brain function, linking the metabolic syndrome of PCOS to neurodegenerative and psychiatric risks (27).

The brain is a highly metabolically active organ, consuming 20% of the body's glucose despite representing only 2% of its weight. Insulin is critical for glucose uptake in specific brain regions (like the hippocampus) and acts as a neuromodulator influencing synaptic plasticity, neurotransmitter turnover, and neuronal survival.

At the molecular level, the impact of insulin resistance on mental health is mediated through the disruption of the phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) signaling pathway. In a healthy neuronal state, insulin binds to its receptor (IR), triggering the autophosphorylation of Insulin Receptor Substrate 1 (IRS-1) and activating PI3K. This activates Akt, which subsequently phosphorylates and inhibits Glycogen Synthase Kinase.

In PCOS the insulin signaling cascade is blunted, often due to serine phosphorylation of IRS-1 (inhibitory) rather than tyrosine phosphorylation.

The failure to activate Akt leads to the disinhibition of GSK3β. Overactive GSK3β is a known pathogenic factor in mood disorders. In the PCOS brain, elevated GSK3β activity promotes neuronal apoptosis, inhibits neurogenesis, and facilitates the hyperphosphorylation of Tau protein (a marker of Alzheimer's disease).

The PI3K/Akt pathway is essential for Long-Term Potentiation (LTP), the cellular mechanism of learning and memory. Its impairment contributes to cognitive deficits for women with PCOS (28,29).

Dopaminergic Dysregulation and Reward Deficits

Insulin functions as a satiety signal in the CNS, interacting with the dopaminergic reward circuitry to regulate feeding behavior and motivation. Insulin receptors are expressed on dopaminergic neurons in the Ventral Tegmental Area (VTA) and Substantia Nigra.

In insulin-resistant states, this regulation is lost. Positron Emission Tomography (PET) studies have indicated that insulin resistance is associated with reduced Dopamine D2 Receptor availability in the striatum. Reduced D2R availability is a hallmark of the reward deficiency syndrome. Clinically, this manifests as anhedonia, a core symptom of depression (30,31).

To compensate for this low dopaminergic tone, individuals may engage in reward-seeking behaviors, such as the consumption of high-fat and high-sugar foods. This creates a biological drive for the binge-eating behaviors frequently observed in PCOS, distinct from simple hunger (32).

A recent study employing Mendelian Randomization identified that the inflammatory chemokine CCL11 causally influences PCOS risk by altering the ratio of dopamine sulfate isomers (dopamine 4-sulfate

to dopamine 3-O-sulfate), providing a direct genetic-metabolic link between inflammation, dopamine dysregulation, and the PCOS (33).

Role of Adipokines and Low-Grade Inflammation

Adipose tissue acts as a dynamic endocrine organ, secreting bioactive peptides called adipokines. In PCOS, particularly in the presence of visceral obesity, the secretion profile of adipokines is skewed towards a pro-inflammatory state (34).

Leptin is primarily known for regulating appetite, but it is also a potent neurotrophic factor with antidepressant-like properties. Leptin receptors are densely expressed in the hippocampus. Binding of leptin initiates the JAK2/STAT3 signaling pathway, which promotes the expression of Brain-Derived Neurotrophic Factor (BDNF) and supports synaptic plasticity.

Women with PCOS often exhibit hyperleptinemia, indicating a state of leptin resistance. Mechanisms include the saturation of leptin transporters at the BBB preventing leptin from entering the brain and the upregulation of SOCS3 (Suppressor of Cytokine Signaling 3), which inhibits STAT3 signaling. Consequently, despite high circulating levels, the brain perceives a state of leptin deficiency. This results in a loss of leptin's neuroprotective and antidepressant effects (35,36,37,38).

In contrast to leptin, adiponectin levels are typically reduced in women with PCOS. Adiponectin acts as an insulin sensitizer and has anti-inflammatory properties. In the brain, it promotes neurogenesis and protects against stress-induced neuronal injury. The reduction in adiponectin removes a critical buffer against neuroinflammation, rendering the PCOS brain more susceptible to the toxic effects of stress and cytokines. The imbalance of high leptin and low adiponectin creates a neurochemical milieu that favors depression and cognitive impairment (34,35).

Neurotransmitter and Neuroinflammatory Changes

The transition from physiological stress to clinical psychiatric disorder in PCOS is mediated by specific alterations in neurotransmitter metabolism, driven largely by the syndrome's chronic inflammatory state.

Women with PCOS exhibit a chronic, sterile, low-grade inflammation, evidenced by elevated circulating levels of C-Reactive Protein (CRP), Interleukin-1β (IL-1β), IL-6, and Tumor Necrosis Factor-α (TNF-α). These peripheral cytokines can cross the BBB or signal through the vagus nerve to activate microglia (the brain's immune cells), initiating a cascade of neurochemical disruptions (39).

The most established mechanism linking inflammation to depression involves the metabolism of Tryptophan (TRP). Under normal conditions, a portion of dietary tryptophan is converted into Serotonin (5-HT) by the enzyme Tryptophan Hydroxylase (TPH). However, the majority is metabolized via the Kynurenine Pathway (KP).In PCOS, pro-inflammatory cytokines potently induce the expression of the extrahepatic enzyme Indoleamine 2,3-dioxygenase (IDO). IDO upregulation accelerates the degradation of tryptophan into Kynurenine (KYN). This depletes the pool of tryptophan available for serotonin synthesis. The resulting reduction in central serotonin availability is a direct precipitate of depressive mood states (40,41).

Clinical studies confirm that women with PCOS exhibit an elevated Kynurenine/Tryptophan ratio (reflecting IDO activity)This neurotoxic shift provides a tangible biochemical explanation for the resistance to standard SSRI antidepressants (42).

Beyond the Kynurenine pathway, inflammatory cytokines (IL-1β) can directly inhibit the release of dopamine in the basal ganglia. This suppression of dopaminergic signaling contributes to the symptoms of fatigue, psychomotor retardation, and lack of motivation. The interplay between insulin-resistance-mediated D2 receptor reduction and cytokine-mediated dopamine suppression creates a double hit on the reward system (43).

Inflammation also suppresses the expression of Glutamate Decarboxylase (GAD), the enzyme responsible for converting glutamate to GABA. Lower GABA levels reduce the brain's inhibitory tone, exacerbating anxiety. It creates a state of cortical hyperexcitability, which is associated with anxiety, insomnia, and an increased risk of seizures (44).

4. Clinical and Psychological Consequences of Polycystic Ovary Syndrome

Depression and Anxiety

The epidemiological data unequivocally establishes a significantly elevated risk of psychiatric morbidity in women with PCOS compared to the general female population. Comprehensive meta-analyses and systematic reviews have sought to quantify this burden, revealing that the prevalence of depression and anxiety is consistently high across diverse geographical and cultural contexts.

A seminal meta-analysis encompassing 4 002 patients across 19 studies determined a mean prevalence of depression of 31% (95% CI: 22–41%) in women with PCOS, with a standardized mean difference (SMD) in depression scores of 0.421 compared to healthy controls. More critically, the odds of experiencing moderate to severe depressive symptoms are approximately 4.18 times higher (95% CI: 2.68–6.52) in this population. Regional variations are notable, for instance, studies conducted in conflict-affected regions such as Syria and Jordan report depression prevalence rates exceeding 65%, suggesting that environmental stressors may interact synergistically with the biological vulnerability inherent in PCOS (11,45,48).

Anxiety disorders appear to be even more ubiquitous than depression in the PCOS phenotype. Recent data indicates an average anxiety prevalence of 48% ($I2=97\%$; $p<0.001$), with mean anxiety scores significantly higher than those of controls (SMD=0.274). The overall probability of an anxiety diagnosis in women with PCOS is nearly double that of healthy women (RR: 1.91; 95% CI: 1.52–2.38). When severity is considered, the disparity widens: women with PCOS have a 6.55-fold increased odds of exhibiting moderate to severe anxiety symptoms (95% CI: 2.87–14.93) (11,46).

Beyond generalized anxiety, specific anxiety subtypes such as Adult Separation Anxiety (ASA) have been identified as prevalent comorbidities. A cross-sectional study revealed that 28.9% of women with PCOS exhibited ASA symptoms above the clinical cutoff. This manifestation of anxiety is characterized by excessive fear of rejection and separation from attachment figures, which may be exacerbated by the social stigma and interpersonal insecurities associated with PCOS symptoms like hirsutism and infertility (47).

While biological factors provide the substrate, psychosocial stressors act as triggers. The visible phenotype of PCOS (hirsutism, acne, and obesity) deviates from societal beauty standards, leading to body image distress and lower self-esteem.

Many women experience a significant diagnostic delay, often involving multiple physician visits before confirmation. This period of uncertainty fosters anxiety and a sense of lack of control over one's health (45,49,50).

Body Image and Eating Disorders

The relationship between PCOS and eating disorders (EDs) is pervasive, and clinically dangerous. Women with PCOS are at a 3- to 6-fold increased risk of developing an eating disorder compared to the general population. The landscape of eating disorders in PCOS is dominated by binge-spectrum behaviors rather than restrictive phenotypes like anorexia nervosa.

The prevalence of any eating disorder in women with PCOS ranges widely but can reach as high as 62% in some cohorts. The odds of having an abnormal score on eating disorders screening tools are approximately 3.05 times higher (95% CI: 1.33–6.99) in women with PCOS compared to controls (51,52).

Binge Eating Disorder (BED) is the most common ED in this population, occurring in approximately 42% of patients. The odds of BED are roughly 3-fold higher in PCOS women compared to controls (51,53).

Bulimia Nervosa (BN) is observed in approximately 12% of women with PCOS. The cycle of bingeing followed by compensatory behaviors (purging, excessive exercise) is often driven by the intense pressure to lose weight combined with biologically driven hunger (53).

Interestingly, anorexia nervosa is rarely diagnosed in the PCOS population. This may be due to the potent orexigenic drive of hyperinsulinemia, which makes sustained caloric restriction physiologically difficult, or because the metabolic phenotype of PCOS masks restrictive tendencies (53).

A prospective cohort study of adolescents revealed that girls who reported binge eating more than monthly had significantly higher odds of developing PCOS (aOR: 1.59; 95% CI: 1.09–2.33). This suggests that disordered eating may not only be a consequence but potentially a risk factor or early marker for the metabolic dysregulation of PCOS (54).

Endocrine Drivers of Binge Eating

Hyperinsulinemia is a potent appetite stimulant. High circulating insulin facilitates rapid glucose uptake into adipose tissue, often leading to reactive hypoglycemia or "neuroglycopenia" shortly after meals. This physiological state triggers an intense, primal signal to the brain to consume high-density energy sources (sugar

and fat), manifesting as a binge episode. Insulin resistance drives a cycle where high insulin promotes weight gain and hunger, while the resulting obesity further exacerbates insulin resistance (13).

Ghrelin known as the hunger hormone, is typically suppressed after food intake. In PCOS, this suppression is often blunted, meaning patients may not feel satisfied even after a calorically adequate meal. Paradoxically, some studies show lower fasting ghrelin in obese PCOS patients, a pattern also seen in Binge Eating Disorder, suggesting a downregulated sensitivity that requires larger food volumes to trigger satiety signals (53).

PCOS is associated with elevated leptin levels independent of BMI. However, the brain becomes resistant to leptin's anorexigenic (satiety) signal. This leptin resistance, combined with insulin resistance, leaves the patient in a state of perceived starvation, driving the binge-eating cycle (53).

Elevated levels of kisspeptin in PCOS patients have been linked to hormonal dysregulation and increased susceptibility to bulimia and binge eating. Kisspeptin influences the limbic system and glucose metabolism, potentially bridging the gap between reproductive function and appetite control (53).

A deficiency in central serotonin is a critical link between mood and eating behaviors. Serotonin regulates both mood and satiety. The established deficit in PCOS lowers the threshold for impulsive behavior (bingeing) and increases carbohydrate cravings, as carbohydrate consumption temporarily boosts tryptophan availability for serotonin synthesis (53).

Cognitive Dysfunctions

While mood disorders are well-documented, cognitive dysfunction in PCOS is an emerging area of concern. The mechanisms driving cognitive dysfunction in PCOS parallel those observed in metabolic syndrome and neurodegenerative diseases. Patients frequently report brain fog, memory lapses, and difficulty concentrating. Research utilizing standardized assessments such as the Montreal Cognitive Assessment (MoCA) has demonstrated quantifiable deficits in women with PCOS. A controlled study found that cognitive impairment (defined as MoCA < 26) occurred in 34.16% of PCOS patients, compared to a significantly lower rate in healthy controls (55).

The cognitive deficits are not uniform. While memory-related domains are often relatively preserved, significant impairments are observed in executive function, attention, verbal fluency, and visuospatial skills (55). Studies indicate slower reaction times and reduced processing speed, which correlates with the subjective experience of mental sluggishness or fog reported by patients (56).

Quality of Life

The convergence of physical symptoms, psychological distress, and cognitive impairment results in a substantial degradation of Quality of Life for women with PCOS. This impact is pervasive, affecting social relationships, professional productivity, and sexual intimacy. Women with PCOS consistently score lower on the World Health Organization Quality of Life (WHOQOL-BREF) scale across physical, psychological, and social domains compared to healthy controls (57).

The impact on QoL is phenotype-dependent. Women with visible symptoms (hirsutism and severe acne) report significantly lower social functioning scores due to stigma and withdrawal. Those with the metabolic phenotype (obesity, IR) report lower physical health scores due to fatigue, pain, and comorbidities (58).

The burden of PCOS also extends to the workplace. A survey of 1,105 women revealed that 50.4% reported missing work due to PCOS symptoms, and 72% felt the condition impacted the quality of their work (59).

Sexual Function

Female Sexual Dysfunction (FSD) is a prevalent comorbidity, with 50-60% of women with PCOS meeting the criteria for dysfunction based on the Female Sexual Function Index (FSFI). Domains of Dysfunction PCOS patients report reduced scores in sexual desire, arousal, and satisfaction, alongside increased pain (dyspareunia). While some studies show no difference in total FSFI scores between fertile and infertile PCOS women, others indicate that the combination of PCOS and infertility creates a synergistic negative effect on sexual function (60,61).

Biologically, testosterone drives libido. One might expect hyperandrogenic women to have increased sexual desire. However, studies show no correlation, suggesting that the psychological distress of hyperandrogenism overrides the biological drive of the hormone (61). Structural equation modeling identifies body image as a primary mediator of FSD. The Body Exposure during Sexual Activities Questionnaire (BESAQ) scores are strong predictors of sexual function. Women self-conscious about excess hair or central adiposity engage in avoidance behaviors during intimacy, preventing arousal (61,62).

5. Clinical Implications and Management Strategies

Screening and Assessment of Mental Health in PCOS

The clinical management of Polycystic Ovary Syndrome (PCOS) has undergone a significant paradigm shift in the last decade, moving from a purely reproductive or metabolic focus to a comprehensive psychoneuroendocrine model. This transition acknowledges that the psychiatric morbidity associated with PCOS, specifically depression, anxiety, and disordered eating is not merely a secondary reaction to physical symptoms but stems from shared pathophysiological pathways involving insulin resistance, chronic low-grade inflammation, and hyperandrogenism. The 2023 International Evidence-based Guideline for the Assessment and Management of PCOS emphasizes that mental health screening and management are no longer adjunctive but are fundamental components of the standard of care (1).

The intersection of endocrine dysregulation and psychological distress in PCOS necessitates a robust, multi-tiered screening approach. Consequently, clinical assessment must transcend the traditional evaluation of oligomenorrhea and hirsutism to include validated psychometric surveillance (45).

The 2023 International Evidence-based Guideline, in alignment with the Endocrine Society and the United States Preventive Services Task Force (USPSTF), recommends screening all women with PCOS for anxiety and depression at the time of diagnosis and during routine follow-up (1,71).

The Patient Health Questionnaire (PHQ-9) remains the gold standard for screening Major Depressive Disorder (MDD) in this population. It assesses the nine DSM-5 criteria for depression, providing both a diagnostic probability and a severity score. The PHQ-9 helps distinguish clinical depression from metabolic fatigue. Evidence indicates that women with PCOS have a seven-fold higher probability of suicidal thoughts compared to controls (45,71).

Given that anxiety disorders, including Generalized Anxiety Disorder (GAD), Social Anxiety Disorder, and Panic Disorder—affect up to 40% of women with PCOS, the GAD-7 is the recommended screening tool which is effective in isolating pathological anxiety from the baseline stress associated with chronic disease management (71).

Sexual dysfunction (FSD) in PCOS is a complex phenomenon driven by a triad of hormonal imbalance (hyperandrogenism), physical symptoms (obesity, hirsutism), and psychological distress (poor body image). Despite its prevalence, it is frequently overlooked in routine endocrine care. The Female Sexual Function Index (FSFI) The FSFI is the validated instrument endorsed for assessing sexual function in this demographic. It comprises 19 items across six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. A total score of ≤ 26.55 is generally indicative of sexual dysfunction (72,73).

The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ) is the disease-specific tool designed to capture the unique distress associated with the syndrome. Unlike generic tools, the PCOSQ includes specific domains for Body Hair, Weight, Infertility, Menstrual Problems, and Emotions. Studies consistently show that the "Body Hair" and "Weight" domains score the lowest (indicating worst quality of life) in women with PCOS (74).

The integration of these tools into routine care requires a structured workflow. The 2023 Guidelines and Alberta Clinical Pathways suggest system where positive screens on the PHQ-9 or GAD-7, or severe distress on the PCOSQ, trigger immediate referral to appropriate providers. While endocrinologists and gynecologists are responsible for the initial screening, the management of positive screens necessitates a multidisciplinary approach that ensures patients actually receive treatment (71,75).

Pharmacological Interventions

Pharmacological management in PCOS has traditionally focused on restoring ovulation (Clomiphene, Letrozole) and managing insulin resistance (Metformin). However, emerging evidence highlights that many metabolic agents possess significant neuroprotective and antidepressant properties. Conversely, psychotropic medications prescribed for mood disorders can have profound metabolic consequences.

Metformin is the first-line pharmacological intervention for the metabolic features of PCOS. Beyond its glucose-lowering effects, Metformin is increasingly recognized for its pleiotropic effects on the central nervous system. Metformin is capable of crossing the blood-brain barrier (BBB) and exerts neuroprotective effects primarily through the activation of AMP-activated protein kinase (AMPK). In the brain, AMPK activation enhances neuronal glucose uptake and mitochondrial function. Cerebral insulin resistance is hypothesized to contribute to neurocognitive dysfunction and depression. By sensitizing central insulin receptors, Metformin may reverse these deficits (76,77,78). Metformin also inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, thereby reducing the production of pro-inflammatory cytokines (IL-6, TNF-α). Metformin's anti-inflammatory properties may directly ameliorate depressive symptoms (79).

Studies indicate that Metformin treatment is associated with reductions in depressive symptom scores. This improvement is likely multifactorial, resulting from direct neurochemical effects as well as the psychological relief associated with weight stabilization (79,80).

For women with comorbid depression and metabolic syndrome, adding Metformin to antidepressant regimens (particularly SSRIs) can mitigate the weight gain associated with psychotropic medication (70,78).

The 2023 Guidelines support the use of Metformin for metabolic indications and acknowledge its potential secondary benefits for quality of life, although it is not yet labeled as a monotherapy for depression itself (1).

Inositols, particularly Myo-inositol (MI) and D-chiro-inositol (DCI), have emerged as compelling in PCOS management. They function as insulin sensitizers and, crucially, as precursors to second messengers in neurotransmitter signaling systems. Inositol phosphoglycans (IPGs) act as second messengers for insulin. MI facilitates the translocation of glucose transporter 4 (GLUT4) to the cell membrane, while DCI promotes glycogen synthesis (81).

Supplementation with the 40:1 MI/DCI ratio has been shown to significantly reduce fasting insulin and HOMA-IR, while increasing Sex Hormone Binding Globulin (SHBG). By lowering insulin, the drive for ovarian androgen production is reduced, alleviating the physical symptoms that fuel body image distress (81).

Clinical trials suggest that MI supplementation reduces anxiety and depressive scores in PCOS. Meta-analyses indicate that MI is non-inferior to Metformin in improving metabolic profiles but possesses a significantly better safety profile, with fewer gastrointestinal side effects. This makes it a preferable option for adolescents or those intolerant to Metformin, potentially improving long-term adherence and mental well-being (82,83,84).

The 2023 International Guidelines have codified a decisive shift, recommending Letrozole as the first-line pharmacological therapy for ovulation induction in PCOS, displacing Clomiphene (1).

Letrozole is a third-generation aromatase inhibitor (AI). Its mechanism of action involves the inhibition of the aromatase enzyme, which converts androgens to estrogens. This blockade lowers circulating estrogen levels, releasing the hypothalamus from negative feedback and triggering a compensatory surge in Follicle Stimulating Hormone (FSH). Unlike Clomiphene, Letrozole has a short half-life and does not deplete estrogen receptors in peripheral tissues. A critical safety advantage of Letrozole is its tendency to promote mono-follicular growth (development of a single dominant follicle) in 77–80% of cycles. Clomiphene, due to its prolonged receptor blockade, frequently recruits multiple follicles, increasing the risk of multiple gestations (twins/triplets) and Ovarian Hyperstimulation Syndrome (OHSS) (93,94).

The most common adverse effects associated with Letrozole are fatigue and dizziness, reported in approximately 20–30% of users. While fatigue can be significant, it is distinct from the intense mood swings associated with Clomiphene. The absence of anti-estrogenic CNS effects makes Letrozole a quieter drug psychologically (95,96).

Combined Oral Contraceptives (COCPs) remain the first-line pharmacological management for menstrual irregularity and hyperandrogenism in PCOS.

Large-scale register studies have identified a correlation between hormonal contraceptive use and the subsequent diagnosis of depression or antidepressant prescription. The data suggests that OCPs do not cause depression in the majority of users but may trigger it in a biologically susceptible subgroup. The proposed mechanism involves the modulation of GABA-ergic and serotonergic systems by synthetic progestins, which may induce a dysphoric state in susceptible individuals (85,86).

Conversely, for many women with PCOS, OCPs provide profound psychological relief by controlling the very symptoms that cause distress: hirsutism and acne. By suppressing ovarian androgen production (via LH suppression and SHBG elevation), OCPs can significantly improve body image and quality of life (86).

Anti-androgens are positioned as second-line agents, recommended only when COCPs are contraindicated, poorly tolerated, or have failed to yield satisfactory cosmetic improvement (1).

Spironolactone, a synthetic 17-lactone steroid, acts primarily as a non-selective mineralocorticoid receptor antagonist but possesses potent anti-androgenic properties. It functions through two distinct mechanisms: competitive inhibition of the androgen receptor (AR) in the hair follicle and sebaceous gland, and the inhibition of 17α-hydroxylase/17,20-lyase enzymes, which reduces overall androgen biosynthesis. Spironolactone is widely regarded as the standard of care among anti-androgens for PCOS. Systematic reviews and meta-analyses indicate that Spironolactone (typically dosed at 50–100 mg daily) significantly reduces Ferriman-Gallwey (FG) scores in women with idiopathic hirsutism and PCOS compared to placebo. In comparative effectiveness research, Spironolactone (100 mg/day) has demonstrated a significant reduction in

FG scores compared to Finasteride and Cyproterone Acetate, although some data suggests equipotency with flutamide. However, unlike metformin, Spironolactone monotherapy does not significantly improve metabolic parameters such as BMI, HOMA-IR (insulin resistance), or lipid profiles. It is primarily a cosmetic and dermatological intervention rather than a metabolic one, although combination therapy (with Metformin) may offer synergistic benefits for insulin sensitivity (89).

A significant drawback of Spironolactone monotherapy is menstrual irregularity (metrorrhagia), which occurs in 15–30% of women due to its progestogenic effects on the endometrium. This unpredictability can be a source of significant anxiety for women with PCOS who are already sensitive to reproductive dysfunction. Consequently, it is most often prescribed in conjunction with a COCP to ensure cycle stability and provide contraception (90).

Cyproterone Acetate is a potent synthetic progestogen with strong anti-androgenic activity. It exerts its effect by blocking androgen receptors and suppressing gonadotropin (LH) secretion via negative feedback on the pituitary, thereby inhibiting ovarian androgen production.

CPA is highly effective for severe hirsutism and acne. Comparative trials suggest that regimens containing CPA (often combined with ethinyl estradiol) are equipotent to or slightly more effective than Spironolactone in reducing acne scores and free androgen (91).

The use of CPA is complicated by its association with mood disturbances. Randomized controlled trials comparing CPA-Spironolactone combinations against insulin-sensitizers (Pioglitazone, Metformin) found that the CPA group exhibited increased serum levels of inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and complement components C3 and C4. Elevated CRP is a robust biomarker associated with depression and fatigue. This suggests that while CPA effectively treats the external signs of PCOS, it may exacerbate the underlying systemic inflammation that contributes to the syndrome's psychological burden (92).

When lifestyle and metabolic interventions are insufficient, antidepressants are indicated. The choice of agent in PCOS must account for the metabolic liability of psychotropic drugs. Many SSRIs (e.g. Paroxetine) and Tricyclic Antidepressants (TCAs) are associated with weight gain and worsening insulin resistance, which can exacerbate the underlying PCOS pathology. Long-term use of SSRIs (>1 year) poses a higher risk of metabolic disruption than short-term use, likely due to histamine (H1) receptor antagonism and 5-HT2C receptor downregulation leading to increased appetite (87).

Randomized controlled trials (RCTs) have shown Sertraline (50mg/day) to be effective in reducing depression severity in women with PCOS without significantly altering prolactin levels or exacerbating metabolic profiles. It is considered a well-tolerated first-line option (88).

As a norepinephrine-dopamine reuptake inhibitor (NDRI), Bupropion is unique in being weight-neutral or associated with modest weight loss. It is highlighted as a favorable option for women with PCOS who struggle with obesity and lethargic depression, as it avoids the sedation and weight gain common with SSRIs (87).

While pharmacotherapy addresses specific symptoms, the 2023 guidelines and emerging literature emphasize the role of supportive supplementation in addressing the underlying metabolic and inflammatory drivers of PCOS.

Vitamin D deficiency is pervasive in PCOS, affecting 60–85% of women. Beyond its role in calcium homeostasis, Vitamin D functions as a neurosteroid with receptors in the hippocampus and other brain regions regulating mood (98).

A 2025 study on women with PCOS established a robust negative correlation between serum Vitamin D levels and scores for anxiety ($r = -0.79$) and depression ($r = -0.56$). The data indicated that women with Vitamin D deficiency were 8.5 times more likely to experience anxiety and 7 times more likely to suffer from depression compared to those with sufficient levels (98).

Omega-3 polyunsaturated fatty acids (PUFAs), particularly EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), act as potent anti-inflammatory agents. Omega-3 supplementation significantly reduces symptoms of anxiety and depression. The efficacy is notably dose-dependent: dosages of >1g/day of EPA are most effective for depression, while dosages around 2g/day show the greatest benefit for anxiety symptoms (99).

In addition to mood support, Omega-3s significantly reduce serum triglycerides, C-reactive protein (CRP), and insulin resistance in PCOS cohorts. This aligns with the 2023 guideline focus on reducing cardiovascular risk factors (100).

N-Acetylcysteine (NAC) is a precursor to glutathione, the body's master antioxidant. Systematic reviews indicate that NAC significantly improves ovulation rates, pregnancy rates, and endometrial thickness compared to placebo. It improves insulin sensitivity and reduces circulating testosterone, making it a viable adjunct to Letrozole or Metformin (101,102).

Lifestyle and Psychological Interventions

Lifestyle modification is the first-line therapy for PCOS, yet its implementation is often hindered by the mental health conditions it aims to treat. Depression reduces motivation, and anxiety can manifest as avoidance of physical activity. Therefore, interventions must be psychologically informed, moving beyond simple diet and exercise advice to comprehensive behavioral medicine.

Cognitive Behavioral Therapy (CBT)

CBT demonstrates obvious advantages in alleviating anxiety (SMD = –1.12) and improving quality of life related to hirsutism. However, its effect on depressive symptoms in PCOS was less robust in some analyses (SMD = –1.11, not statistically significant), potentially because standard CBT does not address the neuroendocrine drivers of depression as effectively as it addresses the cognitive drivers of anxiety (63). Crucially, CBT has been shown to improve compliance with lifestyle interventions, dietary and physical activity recommendations, indirectly improving metabolic outcomes (63).

A seminal 2025 Randomized Controlled Trial on the P-Milife intervention combining Mindfulness-integrated CBT (MiCBT) with lifestyle advice proved that this therapy significantly reduced both anxiety (Mean Difference = -3.41) and depression (Mean Difference = -4.17) and decreased the odds of concurrent anxiety/depression (OR = 0.210) (64). MiCBT works by reducing cortisol reactivity and improving emotional regulation. The 2025 study also found significant improvements in subjective well-being and body image distress, suggesting that mindfulness helps patients "uncouple" their self-esteem from their physical symptoms (64).

Anti-Inflammatory and Glycemic-Control Diets in PCOS

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet combines the anti-inflammatory properties of the Mediterranean diet with the blood-pressure-lowering benefits of the DASH diet. A 2024 RCT demonstrated that an 8-week MIND diet intervention significantly reduced depression and anxiety scores in women with PCOS compared to a control diet. It also improved the hirsutism domain of the PCOS, likely by reducing the inflammatory load that exacerbates hyperandrogenism (65).

Mediterranean Diet rich in omega-3 fatty acids, polyphenols, and fiber, this diet addresses the low-grade chronic inflammation (elevated CRP, TNF-α) seen in PCOS. Adherence is inversely associated with central adiposity and depressive symptoms. Pilot studies show it is a feasible and acceptable intervention that improves insulin sensitivity without the rigid calorie counting that can trigger disordered eating (66).

By preventing postprandial hyperglycemic spikes, low-GI diets stabilize insulin levels. Since insulin fluctuations can trigger mood lability and brain fog, glycemic stabilization acts as a psychiatric intervention. Meta-analyses confirm that low-GI diets reduce total testosterone and fasting insulin, correlating with improved mood scores (67).

Physical activity is a potent modulator of the HPA axis and increases the expression of Brain-Derived Neurotrophic Factor (BDNF), which is often low in depression. Compelling evidence demonstrates that physical activity significantly attenuates cardiovascular disease risk factors in women with PCOS. These cardioprotective effects are primarily mediated through the amelioration of insulin resistance and the reduction of hyperinsulinemia. Furthermore, exercise has been shown to enhance psychological well-being, a benefit inextricably linked to these physiological improvements. The Guidelines recommend 150 minutes of moderate-intensity activity per week. However, for mental health benefits and long-term adherence, consistency is considered more critical than the specific intensity or type of exercise (68,69).

6. Conclusions

The expanding body of evidence characterizes Polycystic Ovary Syndrome as a multifaceted psychoneuroendocrine disorder whose clinical impact extends well beyond reproductive dysfunction. Current data indicate that hyperandrogenism, insulin resistance, and chronic low-grade inflammation interact synergistically to influence central nervous system function, stress reactivity, and neurotransmitter homeostasis, thereby markedly increasing susceptibility to depression, anxiety disorders, disordered eating behaviors, and cognitive impairment. Dysregulation of the HPO and HPA axes, in conjunction with adipokine imbalance and neuroinflammatory processes, constitutes a biologically plausible and integrative framework explaining the elevated psychiatric burden observed in women with PCOS.

Importantly, psychoneuroendocrine outcomes in PCOS are heterogeneous rather than uniform. The magnitude and clinical expression of psychological symptoms appear to be shaped by PCOS phenotype, metabolic profile, body composition, age, and exposure to environmental and psychosocial stressors. Interventions targeting metabolic and inflammatory dysfunction - such as insulin-sensitizing therapies, anti-inflammatory approaches, structured lifestyle modification, and psychologically informed treatments - have demonstrated beneficial effects on mental health and quality of life. However, treatment responses are variable and highly context dependent. Taken together, these findings underscore the necessity of integrated, individualized management models and highlight the need for longitudinal, mechanism-based research to delineate causal relationships, refine therapeutic stratification, and improve long-term psychological and metabolic outcomes in women with PCOS.

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