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Role of Dehydroepiandrosterone (DHEA) in the Pathophysiology and Clinical Manifestations of Polycystic Ovary Syndrome (PCOS)

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Abstract *— Polycystic ovary syndrome (PCOS) is a prevalent endocrinopathy with a complex etiology involving metabolic, reproductive, and psychological components. Dehydroepiandrosterone (DHEA), an adrenal androgen and stress biomarker, has been implicated in PCOS pathophysiology, yet its role remains controversial. To critically examine the contribution of DHEA to the development and clinical progression of PCOS, emphasizing its hormonal, metabolic, and neuroendocrine implications. This review synthesizes evidence from clinical, biochemical, and experimental studies evaluating DHEA levels and regulatory pathways in women with PCOS, including analyses of phenotypic variation, adrenal versus ovarian androgen production, and stress-axis dysregulation. Elevated DHEA and its sulfated form (DHEAS) are observed in a subset of women with PCOS, particularly those exhibiting hyperandrogenism. However, findings across studies remain inconsistent due to heterogeneity in diagnostic criteria, age-related hormonal variability, and methodological differences. DHEA has been shown to influence ovarian function, metabolic status, and neuropsychological symptoms, suggesting a multifactorial role in PCOS pathogenesis. DHEA contributes to the complex hormonal milieu of PCOS and may serve as both a biomarker and a mechanistic factor in its pathophysiology. Standardized measurement protocols and stratified phenotypic analyses are essential for elucidating its diagnostic and therapeutic relevance.*

Keywords *— **Polycystic ovary syndrome, DHEA, hyperandrogenism, HPA axis, metabolic dysfunction, adrenal androgens***

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder affecting approximately 5–15% of women of reproductive age worldwide. Initially characterized by Stein and Leventhal in 1935, PCOS is now recognized for its broad clinical spectrum, encompassing reproductive, metabolic, and psychological disturbances. The Rotterdam criteria, endorsed globally, define PCOS as the presence of at least two of the following: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) on ultrasonography. PCOS is associated with several comorbidities including insulin resistance, dyslipidemia, type 2 diabetes mellitus, obesity, cardiovascular risk, infertility, and mood disorders. The heterogeneous nature of PCOS complicates its diagnosis and management and suggests a multifactorial etiology that integrates genetic susceptibility, environmental exposure, and neuroendocrine dysregulation.

One hormone of growing interest in PCOS research is dehydroepiandrosterone (DHEA), a weak androgen

synthesized predominantly by the adrenal cortex. DHEA and its sulfated counterpart, DHEAS, serve as precursors for more potent sex steroids and are also key mediators of stress via the hypothalamic-pituitary-adrenal (HPA) axis. Elevated DHEA levels are often interpreted as markers of adrenal hyperactivity and have been variably reported in PCOS. This review explores the regulatory mechanisms of DHEA production, its physiological and pathological roles, and the implications of its dysregulation in PCOS development and phenotypic expression.

II. CLINICAL PRESENTATION AND SYMPTOMATOLOGY

PCOS manifests with a diverse and heterogeneous range of clinical symptoms that vary widely among individuals and may evolve over time. The most prevalent clinical hallmark is menstrual dysfunction, typically presenting as oligomenorrhea (menstrual cycles >35 days) or amenorrhea (absence of menstruation for ≥3 months). These disturbances stem from chronic anovulation driven by dysregulated gonadotropin and androgen levels. Hyperandrogenic symptoms represent another cardinal feature of PCOS. These include hirsutism, acne, and androgenic alopecia, all of which reflect the systemic effects of excess androgens. Hirsutism, defined as male-pattern terminal hair growth in females, is commonly quantified using the modified Ferriman-Gallwey scoring system. Acne and scalp hair thinning further contribute to the physical and psychosocial burden of the disorder.

Metabolic disturbances frequently accompany the reproductive and dermatological manifestations. Many women with PCOS exhibit central adiposity, insulin resistance, dyslipidemia, and an increased risk of type 2 diabetes mellitus. Obesity, particularly abdominal, exacerbates both the hormonal and metabolic components of the syndrome. PCOS is also increasingly recognized as a disorder with significant psychological and emotional ramifications. Women with PCOS experience higher rates of anxiety, depression, and impaired self-esteem, often exacerbated by cosmetic concerns and subfertility. These psychological stressors, in turn, may perpetuate hypothalamic-pituitary-adrenal axis dysregulation, compounding the endocrine imbalance. Importantly, the chronic anovulation associated with PCOS also elevates the risk of endometrial hyperplasia and carcinoma due to prolonged unopposed estrogen exposure. Collectively, these multifactorial symptoms underscore the complex, systemic nature of PCOS and highlight the need for multidisciplinary approaches to diagnosis and treatment.

III. DIAGNOSTIC CRITERIA AND CONSIDERATIONS

The diagnosis of PCOS remains a clinical challenge due to its heterogeneous presentation and overlapping features with other endocrine disorders. The Rotterdam criteria, established in 2003, serve as the most widely accepted diagnostic framework. These criteria require the presence of at least two of the following three features: (1) oligo- or anovulation, (2) clinical or biochemical signs of hyperandrogenism, and (3) polycystic ovarian morphology (PCOM) on ultrasound, after excluding other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, and thyroid dysfunction.

Menstrual irregularities, particularly oligomenorrhea and amenorrhea, indicate chronic anovulation. These are linked to dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis and elevated androgen levels that impair follicular maturation. Biochemical markers of hyperandrogenism include elevated serum concentrations of total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. Clinical manifestations include hirsutism, acne, and alopecia, which may also be quantified using standardized scoring systems.

PCOM is typically identified via transvaginal ultrasonography and is characterized by the presence of ≥12 antral follicles measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm^3). It is essential to interpret ultrasound findings within the context of clinical and biochemical evidence, particularly in adolescents and lean women where polycystic morphology may occur in the absence of PCOS.The phenotypic variability of PCOS has led to classification into four subtypes: Phenotype A (hyperandrogenism, ovulatory dysfunction, and PCOM), Phenotype B (hyperandrogenism and ovulatory dysfunction), Phenotype C

(hyperandrogenism and PCOM), and Phenotype D (ovulatory dysfunction and PCOM without hyperandrogenism). This subclassification has clinical relevance for prognosis and therapeutic strategy development. Accurate diagnosis also necessitates the exclusion of mimicking conditions such as hyperprolactinemia, Cushing's syndrome, thyroid disorders, and non-classic congenital adrenal hyperplasia. A comprehensive clinical assessment, combined with targeted laboratory and imaging evaluations, is essential for differential diagnosis and appropriate management planning.

IV. MANAGEMENT AND THERAPEUTIC STRATEGIES

The management of PCOS necessitates an individualized, multidisciplinary approach targeting both symptom relief and long-term health optimization. Clinical strategies encompass lifestyle interventions, pharmacological treatments, fertility management, and psychological support, each tailored to the patient's primary concerns—be it menstrual irregularity, hirsutism, infertility, metabolic risk, or emotional distress.

4.1 Lifestyle Modifications Lifestyle optimization is considered first-line therapy, particularly for overweight and obese patients. Evidence supports that a modest weight loss of 5–10% can restore ovulatory function, enhance insulin sensitivity, reduce androgen levels, and improve quality of life. Dietary interventions emphasize a low-glycemic index diet rich in fiber, lean proteins, and healthy fats. Regular physical activity, including both aerobic and resistance training, is recommended to address insulin resistance and cardiovascular risk factors.

4.2 Pharmacological Interventions Pharmacotherapy is often employed in conjunction with lifestyle measures. Combined oral contraceptives (COCs) remain the cornerstone for regulating menstrual cycles and managing hyperandrogenism. COCs reduce ovarian androgen production and increase sex hormone-binding globulin (SHBG), thereby lowering circulating free testosterone levels. Antiandrogens such as spironolactone, flutamide, and cyproterone acetate may be added to mitigate hirsutism and acne, though these require caution due to potential teratogenicity. Metformin, an insulin-sensitizing agent, is widely prescribed to manage insulin resistance, particularly in women with impaired glucose tolerance or metabolic syndrome. It has shown benefits in restoring ovulation and improving metabolic parameters. Inositols (myo-inositol and D-chiro-inositol), though less well studied, have also demonstrated promising effects on insulin signaling and ovarian function.

4.3 Fertility Management In women seeking fertility, ovulation induction is the primary therapeutic objective. Letrozole, an aromatase inhibitor, has emerged as the preferred first-line agent, superseding clomiphene citrate in efficacy. For clomiphene-resistant cases, gonadotropin therapy or laparoscopic ovarian drilling may be considered. In vitro fertilization (IVF) remains a viable option for refractory infertility, although it carries a higher risk of ovarian hyperstimulation syndrome (OHSS) in PCOS patients.

4.4 Management of Metabolic and Psychological Comorbidities Screening for and managing comorbidities such as type 2 diabetes mellitus, dyslipidemia, hypertension, and sleep apnea is essential. Statins may be prescribed for dyslipidemia, and antihypertensive agents are used as needed. Mental health support should be an integral component of care, given the elevated incidence of anxiety and depression in PCOS. Cognitive-behavioral therapy and, when indicated, pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) may be beneficial.

4.5 Long-Term Monitoring and Preventive Care Regular follow-up is crucial to assess treatment efficacy, monitor metabolic health, and adjust therapeutic regimens. Proactive endometrial protection is necessary in women with prolonged amenorrhea to mitigate the risk of endometrial hyperplasia and carcinoma. This may involve cyclic progestin therapy or continuous COC use.

Comprehensive PCOS care should integrate endocrinological, gynecological, dermatological, and psychological perspectives. Shared decision-making and patient education are key to fostering adherence and optimizing long-term outcomes.

V. BIOLOGICAL OVERVIEW OF DEHYDROEPIANDROSTERONE (DHEA)

Dehydroepiandrosterone (DHEA) is a multifunctional steroid hormone synthesized primarily in the adrenal zona reticularis and, to a lesser extent, by the gonads and central nervous system. As a precursor to potent androgens and estrogens, DHEA plays a vital role in maintaining endocrine homeostasis. Circulating primarily in its sulfated form—dehydroepiandrosterone sulfate (DHEAS)—it exhibits age-dependent variations, with peak secretion in early adulthood followed by a gradual decline, termed adrenopause. DHEAS is more stable in circulation due to its longer half-life and is frequently used as a biomarker for adrenal androgen status. In addition to its endocrine functions, DHEA exerts neurosteroidal effects, modulating neuronal excitability, synaptic plasticity, and mood regulation. DHEA also influences immune responses and metabolic processes, suggesting a broader physiological role in stress adaptation, glucose metabolism, and vascular health.

VI. REGULATORY MECHANISMS OF DHEA AND DHEAS

DHEA synthesis is principally regulated by adrenocorticotropic hormone (ACTH), which binds to melanocortin 2 receptors (MC2R) in the adrenal cortex, activating the cAMP-PKA signaling pathway and stimulating steroidogenesis. DHEA is subsequently sulfated to DHEAS via the action of the enzyme SULT2A1. Several co-regulators influence this pathway:

- **Prolactin:** Enhances ACTH responsiveness by upregulating steroidogenic enzymes and amplifying cAMP signaling.
- **Insulin-like Growth Factor-I (IGF-I):** Promotes adrenal cell proliferation and augments steroid synthesis via the PI3K/Akt pathway.
- **Estrogens:** Increase the expression of SULT2A1 and modulate HPA axis activity, contributing to sex-specific differences in DHEAS levels.
- **Zona Reticularis Morphology:** Structural integrity of this zone affects steroidogenic capacity, with age-related atrophy contributing to the decline in DHEA secretion.

Understanding these complex regulatory networks is essential for interpreting DHEA fluctuations across physiological and pathological contexts.

VII. DHEA IN PCOS: ENDOCRINE AND CLINICAL CORRELATIONS

Adrenal hyperandrogenism, characterized by elevated DHEAS levels, is observed in approximately one-third of women with hyperandrogenic PCOS. This elevation may coexist with increased ovarian androgen production, complicating etiological attribution. Age plays a critical role in DHEA interpretation, as adrenal androgen secretion declines significantly after the third decade of life. Studies limited to younger PCOS populations (ages 20–29) have reported elevated DHEAS in about 33% of cases. These individuals often demonstrate concurrent elevations in serum testosterone and androstenedione, indicating a systemic androgenic upregulation. Notably, phenotypic variations influence the pattern of adrenal involvement. Phenotypes B and C appear more likely to exhibit adrenal hyperandrogenism than the classic phenotype A, suggesting differential tissue contributions. Metabolic factors further modulate this relationship. In phenotype A, elevated DHEAS is paradoxically associated with lower body mass index and reduced insulin levels, whereas in phenotypes B and C, it correlates with higher BMI and insulin resistance. These findings highlight the heterogeneity of PCOS and the necessity of considering both phenotypic and metabolic stratification in clinical evaluations.

VIII. CONCLUSION

PCOS represents a multifactorial endocrine disorder with reproductive, metabolic, and psychological implications. DHEA, as a key adrenal androgen and neurosteroid, contributes to the pathophysiology of PCOS by influencing androgen excess, stress responses, and metabolic dysfunction. Although evidence supports a contributory role of DHEA in specific PCOS phenotypes, inconsistencies in study findings underscore the need for standardized

measurement protocols, age-specific analyses, and integrative diagnostic models.

Future research should aim to delineate the causative versus reactive nature of DHEA dysregulation in PCOS. The incorporation of stress modulation strategies and adrenal-targeted therapies may offer novel avenues for personalized intervention. A deeper mechanistic understanding of DHEA's role could enhance diagnostic precision and therapeutic outcomes for women with PCOS.

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