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HORMONAL CHANGES IN POLYCYSTIC OVARY SYNDROME AND MODERN TREATMENT APPROACHES

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Abstract: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, with a prevalence of 5-20% worldwide. This condition is characterized by complex hormonal imbalances that affect multiple physiological systems. This article examines the pathophysiological mechanisms underlying hormonal changes in PCOS and reviews contemporary treatment modalities, including pharmacological interventions, lifestyle modifications, and emerging therapeutic strategies.

Introduction. Polycystic ovary syndrome represents a heterogeneous disorder characterized by reproductive, metabolic, and psychological manifestations. The syndrome was first described by Stein and Leventhal in 1935, but our understanding of its complex pathophysiology has evolved significantly over recent decades. According to the Rotterdam criteria established in 2003, PCOS diagnosis requires the presence of at least two of three features: oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination.

The condition affects not only reproductive health but also increases the risk of metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and endometrial cancer. Understanding the hormonal alterations in PCOS is essential for developing effective treatment strategies that address both immediate symptoms and long-term health consequences.

Hormonal Pathophysiology of PCOS

Hyperandrogenism constitutes the cardinal endocrine feature of PCOS. Approximately 60-80% of women with PCOS exhibit elevated levels of androgens, particularly testosterone and androstenedione. The excessive androgen production originates from both ovarian and adrenal sources. In the ovaries, increased luteinizing hormone (LH) stimulation of theca cells leads to enhanced androgen synthesis. Additionally, insulin resistance, present in up to 70% of PCOS patients, amplifies androgen production by directly stimulating ovarian theca cells and increasing the bioavailability of androgens through reduced sex hormone-binding globulin (SHBG) production in the liver.

The clinical manifestations of hyperandrogenism include hirsutism, acne, androgenic alopecia, and virilization in severe cases. These symptoms significantly impact quality of life and psychological well-being. At the molecular level, excessive androgens interfere with normal follicular development, contributing to the characteristic polycystic ovarian morphology.

Gonadotropin Dysregulation

Women with PCOS typically demonstrate abnormal gonadotropin secretion patterns, characterized by elevated LH levels and a disproportionately high LH to follicle-stimulating hormone (FSH) ratio, often exceeding 2:1 or 3:1. This altered ratio results from increased frequency and amplitude of gonadotropin-releasing hormone (GnRH) pulses. The elevated LH preferentially stimulates androgen production in ovarian theca cells while the relatively low FSH levels prove insufficient for normal follicular maturation and aromatase activity in granulosa cells.

This hormonal imbalance creates a vicious cycle: inadequate FSH prevents proper follicular development and estrogen production, leading to chronic anovulation, while excessive LH drives

continued androgen synthesis. The resulting hormonal milieu arrests follicles at various stages of development, producing the characteristic "string of pearls" appearance on ultrasound.

Insulin Resistance and Hyperinsulinemia

Insulin resistance represents a central feature in PCOS pathogenesis, affecting both obese and lean phenotypes, though more prevalent and severe in overweight patients. Hyperinsulinemia develops as a compensatory mechanism for peripheral insulin resistance. Insulin exerts multiple detrimental effects in PCOS: it directly stimulates ovarian androgen production, reduces hepatic SHBG synthesis thereby increasing free testosterone levels, and synergizes with LH to amplify theca cell androgen synthesis.

Furthermore, insulin resistance contributes to the metabolic complications associated with PCOS, including dyslipidemia, increased cardiovascular risk, and progression to type 2 diabetes. Studies indicate that women with PCOS have a four to seven-fold increased risk of developing diabetes compared to age-matched controls. The molecular mechanisms underlying insulin resistance in PCOS involve post-receptor signaling defects, including serine phosphorylation of the insulin receptor and insulin receptor substrate proteins.

Anti-Müllerian Hormone Elevation

Anti-Müllerian hormone (AMH), produced by granulosa cells of small antral follicles, demonstrates markedly elevated levels in PCOS patients, typically two to three times higher than in healthy women. Elevated AMH correlates with increased antral follicle count and may contribute to follicular arrest by inhibiting FSH-stimulated follicular development and aromatase activity. Recent research suggests AMH may also directly affect GnRH pulse frequency, potentially explaining the altered gonadotropin secretion patterns in PCOS.

Contemporary Treatment Approaches

Lifestyle intervention represents the first-line treatment for overweight and obese women with PCOS. Weight loss of just 5-10% of body weight can significantly improve hormonal profiles, restore ovulatory function, and reduce metabolic risk factors. Dietary modifications emphasizing reduced glycemic load, increased fiber intake, and balanced macronutrient distribution demonstrate beneficial effects on insulin sensitivity and androgen levels.

Exercise interventions, combining aerobic and resistance training, improve insulin sensitivity independent of weight loss and provide additional cardiovascular benefits. A meta-analysis of randomized controlled trials confirmed that lifestyle modifications produce comparable improvements in reproductive outcomes to pharmacological treatments in overweight PCOS patients, while simultaneously addressing metabolic dysfunction.

Insulin Sensitizers

Metformin, a biguanide insulin sensitizer, has become widely utilized in PCOS management despite not being officially approved for this indication in many countries. Metformin improves insulin sensitivity primarily by reducing hepatic glucose production and enhancing peripheral glucose uptake. In PCOS patients, metformin treatment reduces androgen levels, improves menstrual regularity, and may enhance ovulation rates. The typical dosage ranges from 1500 to 2000 mg daily, administered in divided doses to minimize gastrointestinal side effects.

Thiazolidinediones, such as pioglitazone, represent another class of insulin sensitizers that activate peroxisome proliferator-activated receptor gamma (PPAR-γ). These agents demonstrate potent effects on insulin sensitivity and androgen reduction but carry concerns regarding weight gain and potential cardiovascular risks, limiting their widespread use. Recent guidelines generally reserve thiazolidinediones for selected cases with severe insulin resistance.

Inositol supplements, particularly myo-inositol and D-chiro-inositol, have emerged as promising insulin-sensitizing agents with favorable safety profiles. These naturally occurring compounds function as second messengers in insulin signaling pathways. Clinical trials demonstrate

improvements in metabolic parameters, menstrual regularity, and ovulation rates with inositol supplementation, though larger studies are needed to establish optimal dosing and long-term efficacy.

Ovulation Induction

For women with PCOS seeking pregnancy, ovulation induction represents a critical therapeutic intervention. Letrozole, an aromatase inhibitor, has emerged as the first-line pharmacological treatment for ovulation induction in PCOS, surpassing traditional clomiphene citrate in efficacy. Letrozole reduces estrogen production, thereby releasing negative feedback on the hypothalamic-pituitary axis and increasing FSH secretion. Clinical trials demonstrate higher live birth rates with letrozole compared to clomiphene citrate in PCOS patients.

Clomiphene citrate, a selective estrogen receptor modulator, remains widely used despite being relegated to second-line status. The typical protocol involves initiating treatment at 50 mg daily for five days, with dose escalation in non-responders. However, clomiphene's anti-estrogenic effects on the endometrium and cervical mucus may limit its effectiveness in some patients.

For women resistant to oral agents, gonadotropin therapy with recombinant FSH or human menopausal gonadotropin provides an effective alternative, though requiring careful monitoring to prevent ovarian hyperstimulation syndrome and multiple pregnancies. Low-dose step-up protocols minimize these risks while maintaining acceptable pregnancy rates.

Androgen-Blocking Therapies

Combined oral contraceptives (COCs) constitute the primary treatment for managing hyperandrogenic symptoms in women not seeking pregnancy. COCs suppress gonadotropin secretion, thereby reducing ovarian androgen production, while simultaneously increasing SHBG synthesis, which decreases free testosterone levels. Formulations containing anti-androgenic progestins, such as drospirenone, cyproterone acetate, or dienogest, provide additional benefits for hirsutism and acne management.

Anti-androgen medications offer targeted therapy for hirsutism and other androgen-excess symptoms. Spironolactone, an aldosterone antagonist with anti-androgenic properties, effectively reduces hirsutism scores at doses of 50-200 mg daily. The medication competitively inhibits androgen receptors and reduces testosterone synthesis. Finasteride, a 5-alpha-reductase inhibitor that blocks conversion of testosterone to the more potent dihydrotestosterone, represents an alternative option, though teratogenic concerns necessitate effective contraception in women of reproductive age.

Emerging Therapeutic Strategies

Recent advances in understanding PCOS pathophysiology have led to novel therapeutic approaches. GLP-1 receptor agonists, such as liraglutide and exenatide, originally developed for diabetes management, demonstrate promise in PCOS treatment. These agents improve insulin sensitivity, promote weight loss, and may directly affect ovarian function. Clinical studies show improvements in metabolic parameters, menstrual cyclicity, and androgen levels with GLP-1 agonist therapy.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors represent another class of anti-diabetic medications under investigation for PCOS. By promoting urinary glucose excretion, these agents induce weight loss and improve insulin sensitivity without stimulating insulin secretion. Preliminary studies suggest beneficial effects on metabolic and reproductive parameters in PCOS patients.

Targeting the endocannabinoid system has emerged as a novel therapeutic avenue. The endocannabinoid system plays roles in energy metabolism, inflammation, and reproductive function. Rimonabant, a cannabinoid receptor antagonist, showed promise in improving

metabolic parameters in PCOS but was withdrawn from the market due to psychiatric side effects. Research continues into safer compounds targeting this system.

Personalized Treatment Approaches

Contemporary PCOS management increasingly emphasizes phenotype-specific treatment strategies. The identification of distinct PCOS phenotypes—including reproductive, metabolic, and combined phenotypes—enables more targeted interventions. Women with predominantly reproductive symptoms may benefit most from ovulation induction and anti-androgen therapies, while those with significant metabolic dysfunction require aggressive insulin-sensitizing treatments and cardiovascular risk factor management.

Genetic and molecular profiling may eventually enable precision medicine approaches in PCOS. Polymorphisms in genes involved in steroid biosynthesis, insulin signaling, and gonadotropin action influence treatment responses. As our understanding of PCOS genetics advances, pharmacogenomic testing may guide medication selection and dosing.

Conclusion

Polycystic ovary syndrome represents a complex endocrine disorder characterized by multifaceted hormonal disturbances affecting reproductive, metabolic, and psychological health. The interplay between hyperandrogenism, gonadotropin dysregulation, insulin resistance, and elevated AMH creates a self-perpetuating cycle of dysfunction. Modern treatment approaches must address this complexity through individualized, comprehensive strategies combining lifestyle modifications, insulin sensitizers, ovulation induction agents, and anti-androgenic therapies as appropriate for each patient's presentation and goals.

Emerging therapeutic options, including GLP-1 receptor agonists and targeted molecular interventions, offer promising additions to the therapeutic armamentarium. Future research should focus on identifying biomarkers for treatment response, developing novel therapies targeting specific pathophysiological mechanisms, and implementing personalized medicine approaches based on phenotypic and genetic profiling. Through continued research and clinical innovation, we can improve outcomes and quality of life for the millions of women affected by this common yet challenging syndrome.

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