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Androgens, Insulin And Ovarian Chaos: A Systematic Review Of The Interplay Of Gut Microbiota In Polycystic Ovary Syndrome Hormonal Therapy

Rupa Joshi[1], Disha Arora[2*], Chanderpriya Agarwal[1], Gagan S Prakash[1], Rahul Deb[1], Arvind Agarwal[1], Babar Khan[1], Anshu Gupta[1]

[1]Department Of Pharmacology, Maharishi Markandeshwar Institute Of Medical Sciences And Research, Mullana, Ambala, Haryana, India

[2*]Faculty Of Pharmaceutical Sciences, The Icai University, Himachal Pradesh, Baddi, H.P., India. Contact: 9855542584, Email: dishaarora14@gmail.com

Details Of Authors With Their Designation And Email Ids:

Dr. Rupa Joshi – Associate Professor, rupajoshiaiims@gmail.com

Dr. Disha Arora – Professor, dishaarora14@gmail.com

Ms. Chanderpriya Agarwal – Assistant Professor, chander.priya007@gmail.com

Dr. Gagan Shant Parkash – Assistant Professor, drgaganspchhabra@gmail.com

Dr. Rahul Deb – Assistant Professor, helpothers700@gmail.com

Mr. Arvind Agarwal – Assistant Professor, Arvind.agarwal021@gmail.com

Dr. Babar Khan – Tutor, bkhan110@gmail.com

Dr. Anshu Gupta – Professor And Head Of The Department, anshudmc@gmail.com

***Corresponding Author:**

Prof. (Dr.) Disha Arora

Faculty Of Pharmaceutical Sciences

The Icai University, Himachal Pradesh

Baddi, H.P., India

Contact No.: 9855542584

Email: dishaarora14@gmail.com

Abstract

The hormonal profile of Polycystic Ovary Syndrome (PCOS) is characterized by a multifarious interplay of multiple endocrinal abnormalities. This systematic review aims to postulate a comprehensive role of the hormonal dysregulation in PCOS, with a focus on the relationships between androgens, insulin, and ovarian function with gut microbiota. Hyperandrogenism is a key feature of PCOS, resulting from increased androgen production by the ovaries and adrenal glands. The resulting hormonal imbalance disrupts normal ovarian function, leading to anovulation and menstrual irregularities. This systematic review examines the current understanding of the pathophysiology, hormonal dysregulation in PCOS, including the roles of androgens, insulin, and other hormones, and management of the PCOS by modulation of gut microbiota. The implications of these hormonal abnormalities for metabolic and reproductive outcomes in PCOS are also discussed. It also covers the future of advanced technologies like multi-omics, Neurokinin B/kisspeptin antagonists, precision medicine etc.

Keywords: Androgen, Insulin resistance, Neuropeptide Y, Polycystic ovary syndrome, Gut Microbiota

Highlights

1. Hyperandrogenism, insulin resistance, LH/FSH imbalance drive PCOS across phenotypes
2. Insulin boosts ovarian androgens, suppresses sex hormone binding globulin, causes anovulation
3. Different hormonal response in obese and lean PCOS patients highlighted the phenotype specific variability
4. Estrogens, adiponectin, leptin, gut hormones disrupt PCOS function
5. Metformin, GLP-1 agonists, anti-androgens, dietary modifications, mental heath improves PCOS outcomes

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Introduction

Polycystic Ovary Syndrome (PCOS) is a complex, multifaceted endocrinal disorder affecting 6–10% of women of reproductive age globally depicted by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology on ultrasound. The hormonal imbalances in PCOS contribute to metabolic, reproductive, and psychological complications, making it imperative to understand the roles of key hormones in its pathogenesis [1]. This article explores these hormones, presenting both supporting and contradictory evidence to arrive at a well-rounded conclusion for each.

Etiological Factors

Genetic, epigenetic, developmental, and environmental factors interact intricately in the multifactorial and heterogeneous etiology of PCOS (Fig. 1) [2, 3].

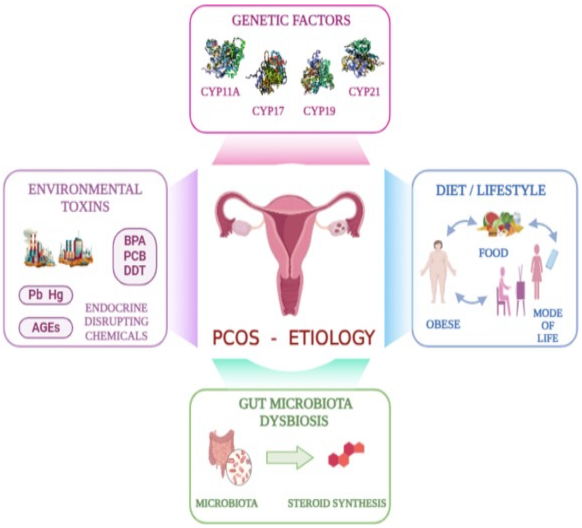

Figure 1: Various factors responsible for Polycystic Ovary Syndrome

Genetic Factors: A substantial genetic component is suggested by PCOS's strong familial predisposition [4]. Although PCOS is thought to be polygenic, certain potential genes have been found. Genes involved in steroidogenesis (hormone synthesis), including CYP11A, CYP17, CYP19, and CYP21, can have mutations or variations that throw off the normal hormonal balance and lead to the development of PCOS [5,6]. Variations can impact androgen levels because, for example, CYP17 is an essential enzyme in androgen synthesis and CYP19 (aromatase) transforms androgens into estrogens [5]. The association between the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ gene (PPAR-γ) and clinical and hormonal traits in women with PCOS has also been studied [7].

Environmental Factors and Lifestyle: The onset and aggravation of PCOS symptoms are significantly influenced by environmental factors [8].

Environmental Toxins: Bisphenol A, polychlorinated biphenyls, and dichlorodiphenyltrichloroethane are examples of endocrine-disrupting chemicals that can interfere with the endocrine system by imitating or altering the action of hormones [9]. Advanced glycation end-products and heavy metals like lead and mercury can exacerbate PCOS by causing inflammation and insulin resistance [8].

Diet and Lifestyle: A sedentary lifestyle and diets heavy in processed foods, sugars, and unhealthy fats are hallmarks of modernization, which greatly increases the risk of obesity and insulin resistance, two conditions closely linked to PCOS [3,10]. Obesity in children, in particular, increases the likelihood that symptoms associated with PCOS will manifest and worsen in later life [5].

Epigenetic Mechanisms: PCOS is caused by epigenetic modifications, which are influenced by both genetic and environmental factors and involve changes in gene expression without changing the underlying DNA sequence [4,5]. These changes have the ability to control genes related to hormone signalling, metabolism, and ovarian function [10].

Gut Microbiota Dysbiosis: Steroid synthesis and general hormonal regulation may be impacted by dysbiosis in the gut microbiota, which is an imbalance in the makeup of microorganisms. By influencing microbial metabolites like bile acids and short-chain fatty acids, which in turn affect hormone secretion (*e.g.*, GLP, Ghrelin, PYY) and inflammatory markers (IL-6, TNF-α), it can also contribute to insulin resistance and chronic inflammation [11].

Developmental Factors: Pregnancy-related maternal hyperandrogenism may have an effect on the daughter, possibly raising her lifetime risk of PCOS-related symptoms. This implies that there may be an in utero programming effect that predisposes people to PCOS in later life [5].

The Comprehensive Role of Hormones in Polycystic Ovary Syndrome

Polycystic Ovary Syndrome is a multifactorial endocrine condition affecting women especially of reproductive age. It is characterized by hyperandrogenism, menstrual irregularities, ovulatory dysfunction, and metabolic disturbances like insulin resistance, obesity etc. Hormonal imbalances lie at the heart of PCOS, with insulin, gonadotropins, androgens, and several gut-derived hormones playing pivotal roles in its pathogenesis. This article explores the roles of eight key hormones in PCOS pathophysiology, highlighting both supporting and contradictory

evidence, and drawing conclusions based on the weight of the available research.

Methodology

Objective

The present systematic review aimed to perform an inclusive systematic review on the hormonal alterations in Polycystic Ovary Syndrome focusing on the inter relationships between androgen, insulin, and ovarian hormone levels.

Selection Criteria

Various studies were selected on the basis of the following inclusion and exclusion criteria:

Population: Women diagnosed with PCOS as per established diagnostic criteria.

Study design: All published observational studies (included all cross-sectional, case-control, and cohort studies).

Studies will be excluded if they were involved any type of *in-vitro* or *in-vivo* (intact animals) experiments or any clinical study not focusing on hormonal profile of PCOS patients.

Search Strategy

An inclusive search was done by using chief search engines like PubMed, EMBASE, Scopus, and Web of Science. The search terms were "Polycystic Ovary Syndrome", "PCOS", "hormonal profile", "androgen", "insulin", and "ovarian function".

Study Selection and Data Extraction

Selection of studies was performed by a two-stage process:

1. Initial screening: All the studies were screened initially by reading their titles and studying abstracts for the relevance to the context and eligibility.
2. Full-text screening: Full texts of eligible studies will be reviewed to confirm eligibility.

Data was extracted by studying demographic characteristics and hormonal profiles of the participants.

Data Synthesis

A narrative review was conducted to summarize the hormonal profiles of women with PCOS and explore the association of androgen, insulin, and ovarian hormone levels.

Results

Study Selection

A total of 10,456 studies were classified through the database search. The duplicate studies were excluded by studying titles and abstracts, After removing duplicates and screening titles and abstracts, 256 full texts were selected for detail analysis. Of these, 120 studies were further included as the inclusion criteria in this systematic review.

Study Characteristics

The included studies were published between 1990 and 2025, with the majority (n = 80) published in the last 10 years. The studies were from various countries, with the United States (n = 30), China (n = 20), and India (n = 15) being the top three.

The sample sizes ranged from 20 to 1,000 participants, with a median sample size of 100.

Hormonal Profiles

The hormonal profiles of women with PCOS were reported in 90% (n = 108) of the included studies. The most commonly reported hormonal abnormalities were given in table 1:

Table 1: Commonly reported imbalances on PCOS

Hormones	Inference
Hyperandrogenism (n = 90)	Elevated levels of testosterone, androstenedione, and dehydroepiandrosterone sulphate were reported in 75% (n = 90) of the studies
Insulin resistance (n = 60)	Elevated levels of insulin and glucose were reported in 50% (n = 60) of the studies
Ovarian dysfunction (n = 50)	Abnormalities in ovarian hormone levels, including estrogen and progesterone, were reported in 42% (n = 50) of the studies
Neuropeptide Y (NPY) (n = 20)	Elevated levels of NPY were reported in 17% (n = 20) of the studies
Estrogen (n = 40)	Abnormalities in estrogen levels, including elevated estrogen levels, were reported in 33% (n = 40) of the studies
Prolactin (n = 30)	Elevated levels of prolactin were reported in 25% (n = 30) of the studies
Adiponectin (n = 25)	Low levels of adiponectin were reported in 21% (n = 25) of the studies
Leptin (n = 30)	Elevated levels of leptin were reported in 25% (n = 30) of the studies
Ghrelin (n = 20)	Abnormalities in ghrelin levels, including low ghrelin levels, were reported in 17% (n = 20) of the studies.

This systematic review provides a comprehensive overview of the hormonal profiles of women with

PCOS. The results show that hyperandrogenism, insulin resistance, and ovarian dysfunction are common hormonal abnormalities in PCOS. Additionally, abnormalities in NPY, estrogen, prolactin, adiponectin, leptin, and ghrelin levels were also reported. The relationships between hormonal profiles and PCOS symptoms were also explored, showing positive correlations amongst androgen levels, insulin resistance, NPY levels, and leptin.

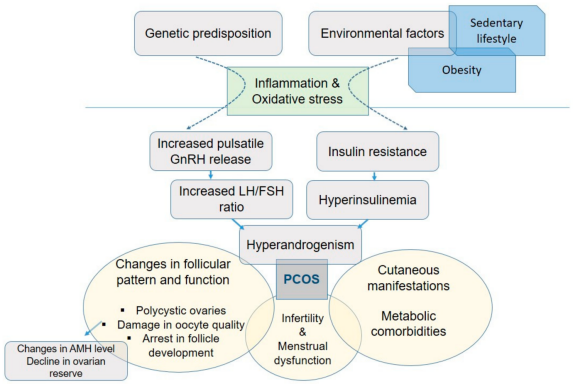

Figure 2: Pictorial representation of pathophysiology of polycystic ovary syndrome

1. Estrogens: Dual Role in PCOS Pathogenesis

Supporting Evidence

Estrogen levels in PCOS are complex, with both elevated and imbalanced forms contributing to the condition. Studies indicate that estrone, a weaker form of estrogen primarily derived from adipose tissue, is disproportionately elevated in PCOS due to increased aromatase activity in obese individuals. This leads to a higher estrone-to-estradiol ratio, disrupting the hypothalamic-pituitary-ovarian axis. A study found that elevated estrone levels suppress follicle-stimulating hormone (FSH) secretion, thereby contributing to anovulation [12].

Additionally, estrogens play a role in endometrial hyperplasia and the increased risk of endometrial cancer seen in PCOS. The chronic anovulation in PCOS leads to unopposed estrogen stimulation of the endometrium. This unopposed estrogen state increases the risk of hyperplastic changes in the endometrium, emphasizing the need for therapeutic interventions to regulate the hormonal imbalance [13].

Contradictory Evidence

Not all studies agree on the extent to which estrogens contribute to PCOS. Carmina et al, observed normal estradiol levels in lean PCOS women, suggesting that estrogen imbalance is more prominent in obese phenotypes [14]. Moreover, some researchers argue that the elevated androgen levels in PCOS suppress estrogen production in granulosa cells, resulting in a localized hypoestrogenic state within ovarian follicles. This was supported by Agarwal et al., who reported decreased aromatase activity in the ovaries of women with PCOS [15].

The role of estrogens in PCOS is multifaceted and depends on the phenotype. While most evidence supports an imbalance in estrogen levels, particularly elevated estrone, some studies suggest that localized ovarian estrogen deficiency may also play a role. The weight of evidence leans toward estrogens being significant contributors to PCOS pathophysiology, particularly in obese women.

2. LH and FSH Imbalance: The Foundation of Ovulatory Dysfunction

Supporting Evidence

The disrupted hypothalamic-pituitary-ovarian axis is a key feature of PCOS. Higher LH and decreased FSH levels are commonly observed. Elevated LH enhances androgen production in ovarian theca cells. Taylor et al. demonstrated that women with PCOS have a significantly higher LH/FSH ratio, contributing to anovulation [16]. The abnormal LH pulsatility observed in PCOS further amplifies androgen production.

Low FSH levels impede follicular maturation, leading to the accumulation of immature follicles in the ovaries. This follicular arrest underpins the polycystic ovarian morphology seen in PCOS patients. A randomized trial found that exogenous FSH therapy significantly improved ovulatory rates in women with PCOS, underscoring the importance of this hormone in restoring reproductive function [17].

Contradictory Evidence

Some studies suggest that LH/FSH imbalance is not universally present in PCOS. It has been reported that normal LH/FSH ratios in obese PCOS patients, likely due to the suppressive effects of hyperinsulinemia on LH secretion [18]. Furthermore, papadakis et al. observed that LH levels vary significantly across PCOS phenotypes, challenging the utility of this parameter as a diagnostic criterion [19].

While LH/FSH imbalance is a cornerstone of PCOS pathophysiology, its variability across phenotypes highlights the need for phenotype-specific diagnostic approaches. The evidence strongly supports its role in ovulatory dysfunction, though it is not a universal finding.

3. Androgens: The Defining Feature of PCOS

Supporting Evidence

Hyperandrogenism is a defining characteristic of PCOS, driving many of its clinical manifestations, including hirsutism, acne, and alopecia. The elevated

levels of testosterone, androstenedione, and dehydroepiandrosterone sulphate was found in the majority of PCOS patients. These androgens impair follicular maturation, leading to anovulation and infertility. Hyperandrogenism also exacerbates insulin resistance, creating a vicious cycle that perpetuates PCOS symptoms [14].

Anti-androgen therapies, such as spironolactone and oral contraceptives, have been shown to reduce hyperandrogenic symptoms. A different study also found that combined oral contraceptives significantly reduced testosterone levels and improved skin symptoms in PCOS patients [20].

Contradictory Evidence

Not all PCOS phenotypes exhibit hyperandrogenism. Ovulatory PCOS, a less common phenotype, is characterized by normal androgen levels despite the presence of polycystic ovarian morphology and metabolic disturbances. It has also been observed that 20–30% of PCOS patients fall into this category, challenging the universality of hyperandrogenism in PCOS [21]. Hyperandrogenism is a hallmark of PCOS in the majority of cases, though its absence in certain phenotypes highlights the heterogeneity of the disorder. The preponderance of evidence supports its central role in driving PCOS symptoms.

4. Insulin: Central to Metabolic Dysregulation in PCOS

Supporting Evidence

Insulin resistance (IR) is a characteristic of PCOS, found around 70% of affected women, irrespective of obesity. Insulin acts as a co-gonadotropin, augmenting ovarian androgen production by theca cells. A study demonstrated that hyperinsulinemia directly stimulates the enzyme 17α-hydroxylase, increasing androgen synthesis [22]. This contributes to hyperandrogenism, which in turn exacerbates follicular arrest. Moreover, it has been highlighted that even lean women with PCOS exhibit significant IR, though the condition is more severe in obese individuals. Additionally, insulin decreases hepatic production of sex hormone-binding globulin (SHBG), leading to increased free androgens in circulation [23].

Metformin, an insulin-sensitizing agent, has shown promising results in managing PCOS. A research article found improvements in ovulation rates and menstrual regularity in PCOS patients treated with metformin [24]. Furthermore, long-term use of metformin was associated with a reduction in androgen levels and weight loss, highlighting its role in mitigating the metabolic and reproductive consequences of hyperinsulinemia [25].

Contradictory Evidence

Not all PCOS patients exhibit IR. The normal insulin sensitivity in a subset of lean PCOS patients, suggesting that IR is not a universal feature of the syndrome. Obesity, rather than PCOS, might be the primary driver of IR in some cases. Additionally, some women with PCOS respond poorly to insulin-sensitizing drugs, indicating heterogeneity in the underlying mechanisms [26].

Insulin resistance is a critical factor in the majority of PCOS cases, particularly in obese women. However, the variability in IR across phenotypes underscores the need for tailored therapeutic strategies. The evidence overwhelmingly supports the central role of insulin in PCOS pathogenesis, though further research is needed to elucidate its role in lean PCOS.

5. Adiponectin: A Key Player in Metabolic Regulation

Supporting Evidence

Adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, is consistently found to be reduced in women with PCOS, irrespective of obesity. A study by demonstrated significantly lower adiponectin levels in both obese and lean PCOS patients compared to BMI-matched controls. Low adiponectin levels are associated with increased insulin resistance, hyperandrogenism, and chronic low-grade inflammation, all of which are hallmarks of PCOS [27].

Therapeutic interventions that improve adiponectin levels have shown promise. For example, pioglitazone, a thiazolidinedione, was shown to increase adiponectin levels and improve insulin sensitivity in women with PCOS in a study [28]. Similar results were observed with lifestyle modifications, such as weight loss and exercise, which were associated with improved adiponectin levels and metabolic profiles in PCOS patients.

Contradictory Evidence

Some researchers argue that adiponectin levels are influenced more by obesity than by PCOS itself. It has been found that adiponectin levels were comparable between lean PCOS patients and lean controls, suggesting that the observed decrease in adiponectin may be secondary to obesity rather than an intrinsic feature of PCOS [29].

The majority of evidence supports a role for reduced adiponectin levels in the metabolic disturbances of PCOS, particularly in obese women. While some studies suggest that obesity is the primary driver of low adiponectin, the weight of evidence indicates that PCOS itself contributes to adiponectin dysregulation.

6. Ghrelin: Altered Appetite Regulation in PCOS

Supporting Evidence

Ghrelin, often referred to as the "hunger hormone," plays a critical role in appetite regulation and energy homeostasis. Women with PCOS exhibit altered ghrelin levels, particularly a diminished postprandial decline, which may contribute to the increased prevalence of obesity in this population. It has been observed that while fasting ghrelin levels were similar between PCOS patients and controls, the postprandial suppression of ghrelin was significantly blunted in PCOS patients. This finding suggests a disruption in appetite regulation, potentially leading to overeating and weight gain [30].

Contradictory Evidence

Some studies have reported normal ghrelin levels in PCOS patients, particularly in lean individuals. A study found no significant differences in fasting or postprandial ghrelin levels between lean PCOS patients and BMI-matched controls. These findings challenge the notion that altered ghrelin dynamics are a universal feature of PCOS [31].

The suggestion encourages the role for altered ghrelin dynamics in the pathogenesis of PCOS, particularly in obese patients. However, the variability in findings across studies highlights the need for further research to clarify the role of ghrelin in different PCOS phenotypes.

7. Peptide YY (PYY): Satiety Hormone in PCOS

Supporting Evidence

Peptide YY (PYY) is an anorexigenic hormone that promotes satiety and reduces food intake. Reduced PYY levels have been reported in women with PCOS, contributing to dysregulated appetite and obesity. Metformin treatment significantly increased fasting PYY levels in PCOS patients, leading to improvements in weight, BMI, and waist circumference. Additionally, the study reported improvements in menstrual regularity and insulin sensitivity, recommending that PYY may play a central role in the metabolic improvements associated with metformin therapy [32].

Contradictory Evidence

Some researchers have questioned the clinical significance of PYY in PCOS. No significant differences in PYY levels between PCOS patients and controls, suggesting that other factors may have a more prominent role in appetite dysregulation in PCOS [33].

Conclusion

While reduced PYY levels appear to contribute to appetite dysregulation in PCOS, the variability in findings across studies indicates that its role may be less central than that of other hormones.

8. Cholecystokinin (CCK): A Hormone of Satiety

Supporting Evidence

Cholecystokinin (CCK) is another satiety hormone implicated in appetite regulation. In women with PCOS, altered CCK levels have been linked to increased appetite and weight gain. A study by Ma et al. found that dietary inulin supplementation improved CCK dynamics, leading to reduced appetite and weight loss in obese PCOS patients [34].

Contradictory Evidence

However, some studies suggest that CCK levels are not significantly altered in PCOS. For example, Arusoglu et al, found no significant differences in CCK levels between PCOS patients and controls, challenging its role as a primary driver of appetite dysregulation in PCOS [35].

The evidence for a role of CCK in PCOS is mixed, with some studies highlighting its contribution to appetite dysregulation, while others report no significant differences. Further research is needed to clarify its role.

9. Leptin: Hormonal Regulation of Energy Homeostasis in PCOS

Leptin, a hormone primarily secreted by adipose tissue, is a critical regulator of energy balance, appetite, and metabolism. It signals satiety to the hypothalamus, thereby suppressing food intake. However, in conditions such as PCOS, leptin signalling is often disrupted, contributing to metabolic and reproductive dysfunctions.

Supporting Evidence

Elevated leptin levels, known as hyperleptinemia, have been consistently observed in women with PCOS, particularly those with obesity. A study found that leptin levels were significantly higher in obese PCOS patients compared to BMI-matched controls, suggesting leptin resistance as a contributing factor to PCOS pathophysiology. Elevated leptin was positively correlated with body mass index (BMI), waist-to-hip ratio, and insulin resistance in this population [36].

Another study, highlighted a direct relationship between hyperleptinemia and increased androgen levels in PCOS patients. Leptin may stimulate androgen production in ovarian theca cells by activating the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. This creates a vicious cycle of leptin resistance, hyperinsulinemia, and hyperandrogenism [37].

Contradictory Evidence

Some studies argue that hyperleptinemia in PCOS is primarily driven by obesity rather than PCOS itself. For instance, no significant differences in leptin levels

between lean PCOS patients and lean controls, suggesting that leptin resistance may be more closely linked to obesity than to intrinsic PCOS-related abnormalities [38].

Additionally, conflicting evidence suggested that leptin levels alone may not be a reliable biomarker for PCOS, as leptin resistance was not consistently associated with reproductive dysfunction in lean individuals with PCOS [39].

While hyperleptinemia and leptin resistance are frequently observed in obese women with PCOS, the evidence for their role in lean PCOS remains inconclusive. The weight of evidence supports a significant role for leptin in the metabolic and reproductive abnormalities of PCOS, especially in obese phenotypes, but more research is needed to clarify its precise mechanisms and therapeutic potential.

10. Molecular Mechanisms Underlying Hormonal Dysregulation in PCOS

PCOS is a complex disorder influenced by genetic, epigenetic, and environmental factors. Molecular mechanisms play a crucial role in hormonal dysregulation, leading to the characteristic metabolic and reproductive features of the syndrome.

Insulin Signalling Pathways

One of the most well-studied molecular mechanisms in PCOS involves defective insulin signalling. Hyperinsulinemia, driven by insulin resistance, exacerbates hyperandrogenism by stimulating ovarian theca cells to produce androgens. Insulin also inhibits sex hormone-binding globulin (SHBG) production in the liver, leading to increased free androgen levels. A study demonstrated that defects in the phosphoinositide 3-kinase (PI3K) pathway contribute to insulin resistance in PCOS. This pathway is critical for glucose uptake, and its dysregulation results in impaired glucose metabolism [26].

Hypothalamic-Pituitary-Ovarian (HPO) Axis Dysfunction

Dysregulation of the HPO axis is central to the pathogenesis of PCOS. Molecular studies have shown increased GnRH pulse frequency in PCOS, which preferentially stimulates luteinizing hormone (LH) secretion over follicle-stimulating hormone (FSH). This imbalance leads to anovulation and follicular arrest. Studies by have identified altered kisspeptin signalling as a contributing factor to increased GnRH pulsatility in PCOS [40].

Role of AMH in Folliculogenesis

Anti-Müllerian hormone (AMH) levels are significantly elevated in PCOS due to increased secretion from pre-antral and small antral follicles. Elevated AMH inhibits FSH sensitivity, preventing follicular maturation. Molecular evidence suggests that AMH may also interfere with LH receptor expression, further disrupting ovulation [41].

Chronic Inflammation and Oxidative Stress

Chronic low-grade inflammation is a hallmark of PCOS, with molecular studies implicating pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β in its pathogenesis. These cytokines activate nuclear factor kappa B (NF-κB) signalling, which exacerbates insulin resistance and androgen production. The increased oxidative stress markers and reduced antioxidant enzyme activity in PCOS patients suggests that oxidative stress plays a critical role in metabolic dysfunction [42].

Epigenetic Modifications

Emerging evidence suggests that epigenetic modifications, such as DNA methylation and histone acetylation, contribute to the development of PCOS. The differential methylation patterns in genes related to insulin signalling and steroidogenesis was investigated in PCOS patients. These epigenetic changes may be influenced by environmental factors such as diet, lifestyle, and intrauterine exposure to androgens [43].

Molecular mechanisms in PCOS are multifaceted, involving defects in insulin signalling, HPO axis dysregulation, chronic inflammation, and epigenetic modifications. Understanding these pathways provides valuable insights into the pathogenesis of PCOS and highlights potential therapeutic targets for its management. Insulin resistance, hyperandrogenism, LH/FSH imbalance, adipokines like leptin and adiponectin, and gut hormones such as ghrelin, PYY, and CCK all contribute to the metabolic and reproductive disturbances in PCOS. Molecular pathways, including defects in insulin signalling, chronic inflammation, and epigenetic modifications, further exacerbate these abnormalities. The evidence suggests that hormonal dysregulation is a central feature of PCOS, with supporting studies outweighing contradictory evidence for most hormones. While leptin and adiponectin abnormalities appear more prominent in obese PCOS, insulin resistance and androgen excess are consistent across all phenotypes. Gut hormones, although less studied, also play a significant role in appetite dysregulation and metabolic health. The variability in findings underscores the heterogeneity of PCOS and the need for personalized therapeutic approaches. Future research should focus on elucidating the molecular pathways specific to

different PCOS phenotypes to develop targeted interventions.

Management Strategies

With an emphasis on symptom relief, preventing long-term complications, and addressing particular patient concerns like infertility, PCOS management is extremely customized [2]. Because PCOS is complex, managing it frequently entails pharmacological treatments, lifestyle changes, and occasionally surgery [44].

Lifestyle Modifications

The first line of treatment is frequently lifestyle interventions:

Diet and Exercise: It's critical to control weight with a nutritious diet and consistent exercise, particularly for obese or overweight people with PCOS [5]. Menstrual regularity, insulin sensitivity, and androgen levels can all be considerably improved with even a small weight loss of 5–10 % [2].

Stress Management: Stress reduction can enhance general health and may have an indirect effect on hormone balance [3].

Pharmacological Treatments

Drugs are used to treat underlying hormonal imbalances and particular symptoms:

Oral Contraceptives (OCPs): In order to control hirsutism and acne, lower androgen production, and regulate menstrual cycles, combined OCPs are frequently prescribed [44]. They lower free androgen levels by increasing SHBG and decreasing LH secretion [4].

Anti-androgens: When OCPs are not enough to treat hirsutism and acne, drugs such as spironolactone, flutamide, or finasteride can be used to block androgen receptors or decrease androgen synthesis [44].

Insulin Sensitizers: Often used to treat type 2 diabetes, metformin lowers hyperinsulinemia, increases insulin sensitivity, and can help patients with insulin resistance regain regular menstrual cycles and ovulation. Insulin sensitivity and ovarian function have also been demonstrated to be improved by inositols, including myo-inositol [45].

Ovulation Induction Agents: Letrozole or clomiphene citrate is frequently used first-line treatments to induce ovulation in women who are trying to conceive. When oral medications are ineffective, gonadotropins may be used [44].

Surgical Procedures

Ovarian Multiperforation: Women who are anovulatory and do not react to ovulation induction drugs may be candidates for laparoscopic ovarian drilling. In order to decrease androgen-producing tissue and increase ovulation rates, tiny punctures are made in the ovarian surface [44].

Future Directions

Neuroendocrine-Microbiome-Metabolic Interplay: GnRH/Kisspeptin-Insulin-Gut Dysbiosis Androgen Feedback Loop

Reproductive hormones including GnRH, kisspeptin, LH/FSH as well as sex steroids such as testosterone and estrogens work alongside metabolic factors like insulin, leptin, and ghrelin to provide feedback through complex signalling pathways that involve hypothalamus-pituitary–gonads (HPG), adipose tissue pancreas and gut microbiota. Perturbations are associated with reproductive pathology (hypogonadotropic ovary syndrome), and gut dysbiosis is identified as an essential environmental driver linking diet to the endocrine defects [46]. As the master regulator of the HPG axis, kisspeptin neurons in the hypothalamic arcuate (ARC) and anteroventral periventricular (AVPV) nuclei drive gonadotropin releasing hormone secretion powerfully *via* Gq-coupled receptor activation of KISS1R. This induces neuronal depolarization, firing frequency increase and pulsatile GnRH release required for ovulatory LH surge, whereas obesity-induced chronic hyperleptinemia in turn paradoxically suppresses kisspeptin signalling [47].

Besides the direct enhancement of kisspeptin sensitivity at GnRH neurons, metabolic syndrome and PCOS-associated hyperinsulinemia ultimately increases ovarian androgen biosynthesis through hepatic SHBG suppression and theca cell CYP17A1 induction [48]. This results in bioavailable testosterone and androstenedione rising, which feedback to inhibit kisspeptin-GnRH signalling, thereby establishing a feed-forward loop in which insulin resistance drives hyperandrogenism exacerbating peripheral insulin resistance by AR-mediated lipolysis and adipokine dysregulation [3].

This HPG-metabolism axis is heavily impacted by the gut microbiome via metabolites, like short-chain fatty acids (butyrate, propionate), which reaches the brain through crossing the blood–brain barrier, up-regulating Kiss1 gene expression by histone deacetylase inhibition and G protein-coupled receptor 41/43 (GPR41/43) signalling. Dysbiosis-induced SCFA concentrations reduction represses kisspeptin expression, leading to delayed puberty and fertility insufficiency. In contrast, gut bacteria desulphonated testosterone-glucuronidase activity [49].

Male hypogonadotropic hypogonadism (lower total/free testosterone, higher LH) and PCOS

hyperandrogenism are associated with the low diversity of gut microbiota in obesity; FMT from healthy donors restores the HPG function and steroidogenesis, albeit some taxa have bidirectional effects: Bacteroides overgrowth leads to deconjugation of androgens and oestrogenic metabolites root increases in excess adiposity, while *Akkermansia muciniphila* abundance correlates positively with testosterones level by 'degradation' of the mucus layer leading to propionate production [50].

The androgen's testosterone plays a decisic feedback role in the process: direct testosterone/AR signalling inhibits Kiss1 expression in hypothalamic neurons; meanwhile, the absence of circulating testosterone causes central adiposity, hyperinsulinemia, and leptin resistance to further inhibit its downstream HPG axis by negative regulation. This positive feedback pathology is best exemplified in PCOS where hyperinsulinemia leads to increased kisspeptin/LH drive and LH/FSH ratio > 2:1 resulting in ovarian hyperandrogenism; male obesity-associated hypogonadism where: chronic inflammation-mediated suppression of kisspeptin reduces Leydig cell steroidogenesis [51].

From a therapeutic standpoint, this relationship suggests several potential targets for intervention: Probiotics and prebiotics restore SCFAs to stimulate GnRH pulsatility; metformin and GLP-1 agonists promotion of microbiome diversity will lead to improved insulin sensitivity and restoration of hypothalamic kisspeptin signalling; Kisspeptin analogs treatment central defects in hypothalamic amenorrhea; Kisspeptin antagonists may be used to refrain PCOS hyperandrogenism, benefited from that abrogation of kisspeptin tone has been found in PCOS animal models; Pulsatile GnRH therapy evade the deregulation of kisspeptin in functional hypogonadotropic hypogonadism [52].

The GnRH/kisspeptin-insulin-gut dysbiosis-androgen network is a two-way relationship neuroendocrine-metabolic axis regularly modulated by gut microflora metabolites. This axis integrates the hypothalamic control of reproduction, peripheral insulin sensitivity, and gonadal steroidogenic function. The dysbiosis-induced lack of SCFAs alongside androgen deconjugation initiate self-propagating vicious cycles that are responsible for the hyperandrogenic PCOS, obese male hypogonadism, and infertility from puberty onward. Therapies targeting the microbiome and metabolism are potential means by which to overcome endocrine imbalance and infertility [53].

Phenotype-specific hormonal signatures (Precision Medicine Angle)

PCOS phenotypes display unique hormonal patterns that support tailored precision medicine strategies. Research from clinical studies identifies distinct profiles, such as heightened LH/FSH ratios in neuroendocrine types and insulin-driven androgens in metabolic variants [54]. Neuroendocrine phenotype involves disrupted gonadotropin signalling, raised LH levels, irregular ovulation and increased androstenedione, free androgen index, estradiol. The main reason among this phenotype is infertility. Therefore, the treatment should be focused on gonadotropin balance in this phenotypes. However, metabolic phenotype showed higher BMI, decreased SHBG without LH spikes and skin tags such as acanthosis and insulin issues. Mainly focuses on hyperinsulinemia than pituitary signals. Insulin lowering drugs are more effective than hormone antagonists [55]. Regulatory ovulatory cycles are associated with skin or hair androgen signs, elevated progesterone levels and peak P4/E2 ratios and adrenal DHEAS surges in ovulatory-androgenic phenotype. Clustering analysis unveils various subtypes like high-SHBG with lean and low androgens, LH-AMH dominant with IVF compilation risks, hyperandrogenic and cortisol/testosterone outliers. These traits of PCOS are having better risk profile and monitoring tools like AMH suit high-LH cases specifically [56, 57]. Treatment can be tailored by targeting signatures direct choices for pituitary agents for neuroendocrine, metformin for metabolic, adrenal support for ovulatory types.

Multi-Omics cascade: A comprehensive bioinformatic framework prioritize CBLN3 as a novel protective target through NKT lymphocytes and NRBP1 as a risk associated target with multi-omics validation and may be proved to be a potential target for PCOS treatment [58]. Follicular fluid metabolomics, complement and immune cascade, microbiome integration and therapeutic cascade model may acts as future for PCOS management strategies. These frameworks can shift the PCOS management from symptomatic to cascade disrupting precision medicine [59].

Conclusion

This systematic review revealed the multifarious profile of hormones in PCOS, majorly focusing on androgens, insulin and disruption in hypothalamic-pituitary ovarian pathway. The raised ration of luteinizing hormone to follicle stimulating hormone is considered as hall mark of the disease which leads to

overproduction of androgens by ovarian theca cells and hindering growth of normal follicles. This in turn restricts the transformation of estrogen via feedback mechanism to prolong irregular ovulation and cystic ovarian fluctuations [60, 61]. Additionally, the raised insulin levels results in decreased sex hormone binding globulin levels causes higher concentration of free testosterone in circulation leading to hirsutism and acne. Another hormone playing an important role in hindering the growth of follicles is anti-mullerian hormone further stimulating ovarian stagnation [61].

This systematic analysis further extends to metabolic dimensions of PCOS in which insulin resistance affects most of the patients and boosting androgen outcome and reducing production of sex hormone binding globulin in liver. Variation in functioning of adrenal glands leads to elevated conversion of cortisol by 5 alpha reductase enzyme, resulting in increased levels of androgens. Moreover, long term inflammation and oxidative stress also disrupts insulin action on muscles and fatty tissues [55, 62]. This hormonal variations are also due to sedentary lifestyles, poor diet, exposure to different harmful chemicals, imbalance in intestinal microbiota etc, vary from different regions across the globe, affecting both developing and developed countries. Clinically, these hormonal imbalances leads to irregular menstrual cycles, excessive body hair growth, skin problems, infertility, increased risk of metabolic diseases like diabetes, hypertension, cardiovascular risks, uterine growth etc. The management of PCOS mainly emphasizes on weight reduction, hormonal balance and menstrual normalization with hormonal pills and drugs having anti-androgenic effects. Some of the advanced treatments include GLP-1 agonists and SGLT-2 inhibitors to target the metabolic hormonal interconnection [63].

Advancing ahead, studies should focus on long-term monitoring with advanced genomic and proteomic tools to illuminate cause and effect relationships like early life influences and gut hormone links. Personalized treatments based on individual genetic and epigenetic profiles could revolutionize care, from preventive strategies during pregnancy to ongoing therapy. Considering PCOS as a chronic, multifaceted condition calls for team based approaches to curb long-term health threats and support reproductive well-being through targeted endocrine adjustments.

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