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Comprehensive Signaling Network Dysregulation in Polycystic Ovary Syndrome: Integrating Genetic, Epigenetic, and Metabolic Pathways Toward Precision Medicine

Reshpal Kaur[1], Avijit Mazumder[1*], Saumya Das[1], Ankit Awasthi[2], Reenoo Jauhari[3]

[1]Department of Pharmacology, Noida Institute of Engineering and Technology (Pharmacy Institute),19 Knowledge Park-II, Greater Noida, 201306, Uttar Pradesh, India

[2]Chitkara College of Pharmacy, Chitkara University Rajpura, Punjab,140401, India

[3]School of Pharmacy, Graphic Era Hill University, Dehradun, India

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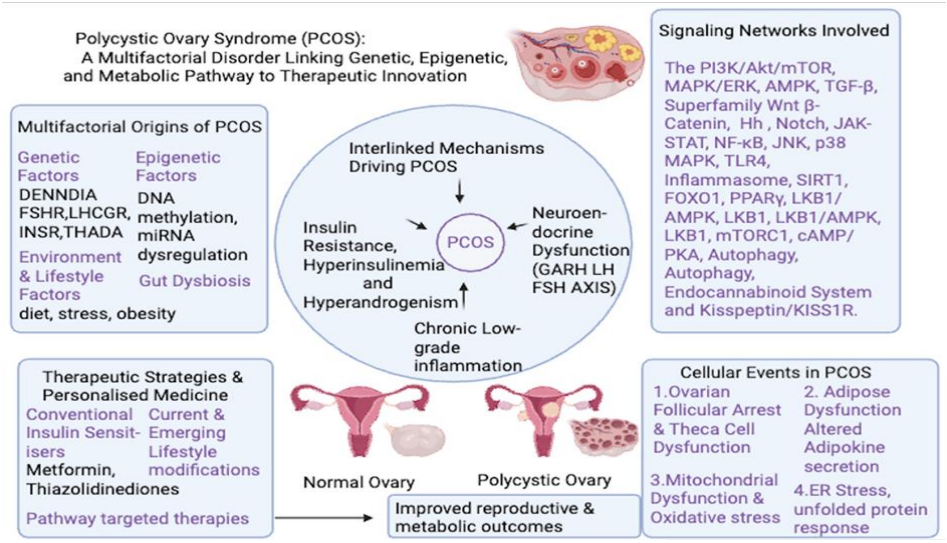
Polycystic Ovary Syndrome (PCOS), Insulin Resistance, Hyperandrogenism, signaling pathways, Epigenetics, Gut Dysbiosis, Clinical trials.

ABSTRACT:

Polycystic Ovary Syndrome (PCOS) is one of the metabolic disorders affecting females of reproductive age, with a complex, multifactorial etiology. This review aims to consolidate the current understanding of PCOS, delving into its heterogeneous pathophysiology, which is characterized by the interplay of genetic, epigenetic, environmental, and gut microbiome factors. We explore the core pathogenic pathways, including insulin resistance (IR) and hyperinsulinemia, hyperandrogenism, neuroendocrine dysfunction, and chronic low-grade inflammation. Numerous intricate signaling pathways, such as The PI3K/Akt/mTOR, MAPK/ERK, AMPK, TGF-β, Superfamily Wnt β-Catenin, Hh , Notch, JAK-STAT, NF-κB, JNK, p38 MAPK, TLR4, Inflammasome, SIRT1, FOXO1, PPARγ, LKB1/AMPK, LKB1, LKB1/AMPK, LKB1, mTORC1, cAMP/PKA, Autophagy, Autophagy, Endocannabinoid System and Kisspeptin/KISS1R are involved in these events. Furthermore, the review examines the role of epigenetics, specifically DNA methylation and miRNA dysregulation, in mediating the disease phenotype. We compiled clinically significant genes like the DENND1A, FSHR, LHCGR, INSR as well as THADA. and discuss their interactions. The proliferating field of gut dysbiosis and its bidirectional relationship with PCOS pathogenesis is also highlighted. Finally, we summarize current and emerging therapeutic strategies, from conventional insulin sensitizers and lifestyle modifications to novel targets informed by genetic and pathway analyses, concluding with future perspectives on personalized medicine for PCOS management.

Graphical Abstract:



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1. Introduction

Polycystic ovary syndrome or PCOS is a heterogeneous and multifaceted endocrine disorder that occurs mostly in women in their reproductive age. It is the most widespread cause of anovulatory infertility and one of the major contributors of metabolic and psychological morbidity in the whole world (Azziz et al., 2016). The syndrome is diagnostically defined as a complex of symptoms, and its definition has changed with time. The most popular modern diagnostic criteria are the Rotterdam Consensus Criteria, the presence of which requires the absence of other etiologies and the following three features: 1) oligo or anovulation, 2) clinical and or biochemical evidence of hyperandrogenism, and 3) polycystic ovarian morphology on ultrasound (Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group, 2004). It is an inclusive definition that recognizes the phenotypic variability of the syndrome and thus different phenotypes are identified.

The application of the Rotterdam criteria has given rise to four main PCOS phenotypes. Phenotype 1 (Classic PCOS): This phenotype, also known as the "full blown" syndrome, presents with all three Rotterdam criteria: hyperandrogenism, ovulatory dysfunction, and PCOM. Moran et al. (2010) discovered that it is often associated with the most severe metabolic disturbances, including significant insulin resistance and dyslipidaemia. Phenotype 2 (Hyperandrogenic PCOS): This group includes women with hyperandrogenism and ovulatory dysfunction but without evident PCOM on ultrasound. The metabolic implications of these phenotypes reveal critical insights into PCOS pathology. Phenotypes A and D share significant metabolic risks, a connection Diamanti-Kandarakis and Panidis (2007) attribute to the potent combination of hyperandrogenism and chronic anovulation as primary drivers of metabolic sequelae. In contrast, Phenotype C (Ovulatory PCOS) presents a more nuanced picture. Characterized by hyperandrogenism and PCOM alongside preserved ovulation, this group, as Li et al. (2012) demonstrated, confirms that androgen excess can exist independently of ovulatory dysfunction, though it often correlates with milder metabolic manifestations. The most contentious subgroup, Phenotype B (Non-hyperandrogenic PCOS), lacks clinical or biochemical androgen excess but features ovulatory dysfunction and PCOM. Despite often being classified as a milder form, Brennan et al. (2009) caution that these women may still face a heightened risk for metabolic complications compared to the general population, suggesting other pathophysiological pathways are at play.

For the millions of women living with Polycystic Ovary Syndrome (PCOS), the condition often feels like a puzzle with pieces scattered across their entire body. Its origins are deeply personal, woven from a complex tapestry of inherited traits and life experiences. A strong genetic predisposition runs in families, influencing how the body handles androgens, insulin, and egg development (Kahsar-Miller et al., 2001). Intriguingly, the stage may even be set before birth; Abbott et al. (2002) proposed that exposure to excess androgens in the womb could "program" a developing foetus, predisposing her to PCOS later in life. After birth, lifestyle becomes a powerful player. As Barber et al. (2019) demonstrated, factors like obesity and a sedentary diet can act as potent triggers, worsening the underlying genetic susceptibility by fueling insulin resistance.

The impact of this dysregulation is not confined to the ovaries. It manifests as a constellation of symptoms that can dominate a woman's daily life. These include the visible distress of irregular periods, unwanted hair growth (hirsutism), acne and hair thinning alongside the private heartache of subfertility. The skin may show dark, velvety patches (acanthosis nigricans), a visible sign of underlying insulin resistance. The reach of PCOS however, extends far beyond reproduction and appearance. As Dokras et al. (2018) reported, it casts a long shadow over metabolic and mental health, significantly increasing the risks for obesity, type 2 diabetes, cardiovascular problems, sleep apnea and the heavy burden of anxiety and depression. This is not a rare condition. It has a staggering global prevalence of 6 to 20% of women of reproductive age (Bozdag et al., 2016), PCOS represents a major public health crisis. The economic burden on healthcare systems is substantial, driven by the costs of fertility treatments, managing long term metabolic diseases, and providing essential psychiatric care (Azziz et al., 2005).

The significance of this review lies in its commitment to weaving these disparate threads into a coherent whole. We aim to move beyond a simple list of symptoms and risks to provide a holistic, in-depth synthesis of PCOS as a multi system disorder. By integrating the latest research

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from cellular signaling and genetics to the emerging roles of epigenetics and the gut-brain-ovary axis. This paper serves as a comprehensive resource. It seeks to bridge the critical gap between laboratory discoveries and the patient in the clinic thereby highlighting novel therapeutic targets and paving the way for personalized management. Furthermore, by uniquely compiling over 25 dysregulated signaling pathways and linking them directly to genetic and epigenetic findings. This review offers an unprecedented roadmap for understanding the intricate pathogenesis of this common and debilitating condition.

2. Pathogenesis of PCOS

The pathogenesis of PCOS is increasingly viewed as a multifactorial process, where no lone anomaly is sufficient to explain the syndrome. Instead, it arises from a complex, often self-reinforcing, interplay of numerous pathophysiological disturbances. These pathways form an autocytic cycle which is expressed as the clinical and biochemical symptoms of the syndrome. Insulin resistance and compensatory hyperinsulinemia, ovarian and adrenal hyperandrogenism, neuroendocrine dysfunction with gonadotropin releasing hormone (GnRH) pulsatility, and a condition of chronic low-grade inflammation are the key pillars of PCOS pathogenesis.

Insulin Resistance and Hyperinsulinemia are arguably the cornerstone metabolic disturbances in PCOS. Dunaif et al. (1989) discovered that a significant majority of women with PCOS, including those with normal body weight, exhibit insulin resistance, meaning their tissues have a blunted response to insulin. This defect is primarily post receptor, involving impairments in the insulin signaling cascade. The pancreas compensates for this resistance by secreting excessive amounts of insulin, leading to hyperinsulinemia. Nestler et al. (1998) demonstrated that this elevated insulin level exerts pathogenic effects on multiple organs, as in the ovary, insulin, through its own receptor and by cross talk with the IGF-1 system, acts synergistically with luteinizing hormone (LH) to enhance androgen production by theca cells. It also inhibits the production of sex hormone binding globulin (SHBG) in the liver, thus increasing the bioavailability of free androgens in the circulation. (Pugeat et al., 1991). Hyperinsulinemia contributes further to anovulation through inhibiting follicular development/follicular arrest, possibly through an alteration of intraovarian paracrine signaling. (Willis et al. 1998).

Hyperandrogenism is the clinical and biochemical hallmark of PCOS; the ovarian theca cell is the principal source of excess androgens, exhibiting intrinsic overactivity of steroidogenesis. According to Nelson et al. (1999), it is driven by an increased response to LH and insulin, which leads to increased expression of key enzymes of androgen biosynthesis such as CYP17A1.The adrenal gland also contributes to hyperandrogenemia in a subset of women, as evidenced by a heightened response to adrenocorticotropic hormone (ACTH) (Azziz et al., 1998). The androgens themselves further exacerbate insulin resistance, creating a vicious cycle. They also directly impact the ovary, disrupting folliculogenesis and promoting the formation of cystic follicles, and act on the pituitary to alter gonadotropin secretion.

Neuroendocrine Dysfunction also recognized as a prominent cause in PCOS. According to Waldstreicher et al. (1988), PCOS women were found to have increased rate of hypothalamic hypothalamus GnRH pulse generator activity. This modified pulsatility predisposes the secretion and production of LH compared to follicle stimulating hormone (FSH) by the anterior pituitary. Subsequent rise in LH:FSH ratio further activates theca cell production of androgens and relative FSH deficiency causes follicles to fade to maturing follicle and select a dominant follicle resulting in anovulation and many small antral follicles typical of PCOM. Dumesic et al. (2015) suggested that this neuroendocrine abnormality is programmable in the uterus by exposure to androgen, and furthermore, it is mediated by other agents including insulin and some neuropeptides such as kisspeptin.

Chronic low-Grade Inflammation is now recognized as a key player in PCOS. Gonzalez et al. (2006) found that women with the syndrome have elevated serum levels of pro inflammatory cytokines, including C reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). This inflammatory state, often exacerbated by obesity, contributes to development of insulin resistance in adipose tissue and liver. It also exerts local effects within the ovary, with inflammatory mediators disrupting the follicular microenvironment to cause impairment in oocyte quality and promoting hyperandrogenism through effects on theca cell function.

Journal of Chemical Health Risks
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The interrelationship between inflammation, insulin resistance, and hyperandrogenism constitutes another self-reinforcing cycle that maintains the PCOS phenotype.

In sum, pathogenesis in PCOS is interlinked through networks of dysregulation. Genetic susceptibility provides the backdrop against which environmental factors such as obesity provide not only a trigger but also an amplifier for these key pathogenic pathways including insulin resistance, hyperandrogenism, neuroendocrine dysfunction, and inflammation, which result in the varied clinical features of the syndrome.

The following diagram demonstrates the pathophysiology of PCOS.

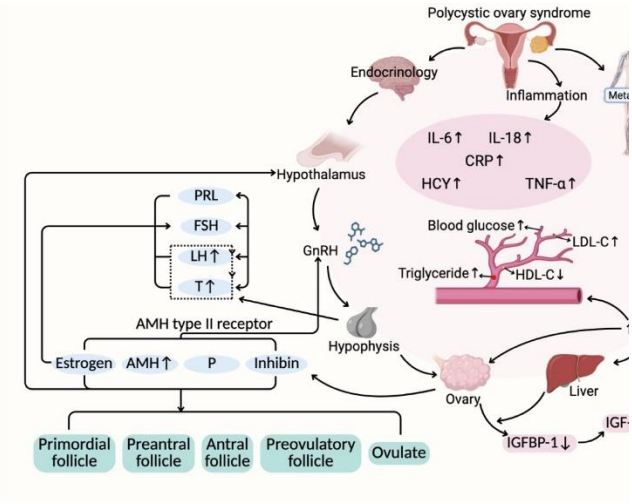

Fig.1.

Pathophysiology of PCOS

3. Cellular Events in PCOS

The clinical manifestations of PCOS result from a series of abnormal cellular events occurring in the ovary and adipose tissue, among other metabolic organs. A more detailed look into these cellular events provides a better understanding of the pathophysiology of the syndrome. The below shown representation demonstrates the central events leading to PCOS.

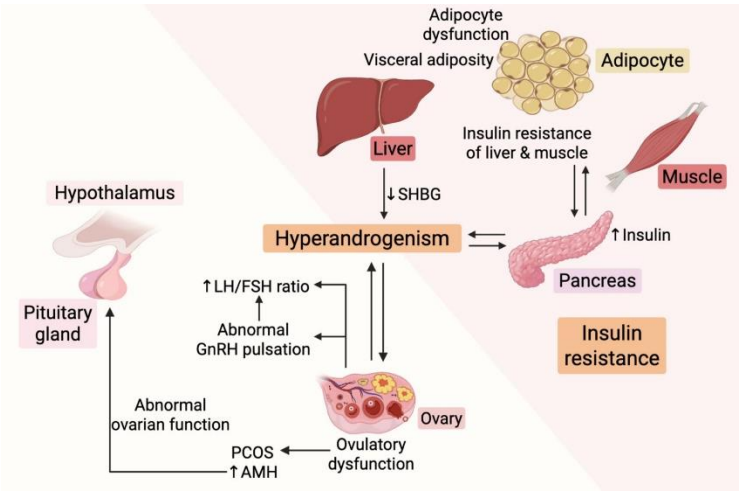

Fig.2. Central events leading to PCOS.

Ovarian Follicular Arrest and Theca Cell Dysfunction represent the central cellular pathology in PCOS. Normal folliculogenesis is a highly regulated process where a cohort of primordial follicles is recruited, and a single dominant follicle is selected for ovulation. Jonard & Dewailly (2004) described that in PCOS, this process is arrested at the early antral stage, leading to the accumulation of numerous small (2 to 9 mm) follicles, which gives the ovary its characteristic "polycystic" morphology on ultrasound. This arrest is multifactorial. Gilling Smith et al. (1997) discovered that intrinsic abnormalities in theca cells lead to their hyper responsiveness to LH and insulin signals, resulting in excessive production of androgens like androstenedione and testosterone. These high intraovarian androgen levels are detrimental to follicular development. Vendola et al. (1998) demonstrated that they impede granulosa cell proliferation, promote premature luteinization, and can induce granulosa cell apoptosis, thereby preventing the selection of a dominant follicle. Furthermore, granulosa cells from PCOS women, even in these small follicles, often exhibit a paradoxical profile of being both hyper proliferative and functionally compromised, with altered steroidogenic capacity, including impaired conversion of androgens to estrogens by aromatase (CYP19A1) (Jakimiuk et al., 2001). This altered follicular microenvironment, rich in androgens and potentially deficient in other paracrine factors like anti Müllerian hormone (AMH) which is itself significantly elevated in PCOS that creates a milieu that is inhibitory to follicular maturation (Pellatt et al., 2007). Recent evidence also points to abnormalities in the oocyte itself,

Journal of Chemical Health Risks
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JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

with Wood et al. (2007) suggesting that the quality of the oocyte may be compromised in PCOS, contributing to the reduced developmental competence of eggs and the lower fertility rates observed.

Adipocyte Dysfunction and Altered Adipokine Secretion play a pivotal role in the metabolic derangements of PCOS. Adipose tissue is not a simple passive repository of energy but an active endocrine organ. Corbould (2008) reported that in the context of PCOS, especially when associated with obesity, the adipocytes undergo hypertrophy and hyperplasia, leading to dysfunction in the adipose tissue. This is characterized by increased lipolysis leading to an enhanced flux of free fatty acids (FFA) into the circulation. Itani et al. (2002) have demonstrated that FFAs induce insulin resistance in the skeletal muscle and liver through activation of inflammatory pathways and impairment in insulin signaling. Further, dysfunctional adipose tissue in PCOS exhibits an altered secretory profile of adipokines. There is a well-documented reduction in the secretion of insulin sensitizing and anti-inflammatory adipokine adiponectin (Spranger et al., 2004). On the other hand, the secretion of proinflammatory adipokines such as leptin along with resistin, is often increased. Moschos et al. (2002) stated that leptin, while exerting effects on regulating satiety, may contribute to insulin resistance and can have possible direct effects on the hypothalamic pituitary ovarian axis and thus disturb the GnRH pulsatility. This dysregulation in the adipokine profile thus creates a systemic environment which promotes insulin resistance and inflammation which further exacerbating ovarian hyperandrogenism and metabolic complications.

Mitochondrial Dysfunction as well as Oxidative Stress are proving to be crucial cellular events in PCOS. Mitochondria are the cellular workhouses, and their functionality is essential in energy production and homeostasis of the cell. Victor et al. (2009) reported that PCOS women could possess innate malpractice of the mitochondria in an assortment of tissues, such as skeletal muscle, fat, and the ovary. The researcher proposed that in the ovary, mitochondrial dysfunction may impair the quality of oocytes, as well as define the functionality of granulosa cells, which can directly affect fertility (Ratchford et al., 2007). This mitochondrial damage is tightly connected with the escalation of oxidative stress, the state of imbalance between production of reactive oxygen species (ROS) and antioxidant defense mechanisms of the body. Gonzalez et al. (2006) demonstrated that PCOS women exhibit increased indicators of oxidative stress and low antioxidant potential. The surplus ROS may cause damage to lipids, proteins and DNA, which further reduce the functionality of cells. Gonzalez et al. (2006) also established that oxidative stress can cause inflammatory response such as NF-kB as well as to increase insulin resistance by disrupting insulin signaling cascades and to directly trigger ovarian androgen production. Accordingly, the mitochondrial dysfunction and subsequent oxidative stress is a vicious cycle that increases the core pathogenic characteristics of PCOS.

Endoplasmic Reticulum Stress and Unfolded Protein Response is another cellular pathology of PCOS. Protein folding and maturation is done by the endoplasmic reticulum (ER). Hotamisligil (2010) explained that inappropriate homeostasis of ER can be caused by nutrients overload, inflammatory actions and oxidative stress which causes the accumulation of misfolded proteins a process referred to as ER stress. This activates the unfolded protein response (UPR), an adaptive signaling pathway that is designed to restore the ER function. But chronic or severe stress in the ER may result in apoptosis. There has been an indication that ER stress is found in ovaries and metabolic tissues of women with PCOS. Yang et al. (2016) indicated that ER stress could be an element that leads to dysregulation of steroidogenic enzymes in theca cell, favoring hyperandrogenism. Ozcan et al. (2004) found that ER stress is also an involved cause of insulin resistance in insulin responsive tissues such as the liver and adipose tissue since it may inhibit the phosphorylation of key insulin signaling pathway components through the activities of c Jun N terminal kinase (JNK). Hence, ER stress is a molecular bridge between the metabolic insults prevalent in PCOS (such as hyperglycemia, hyperlipidemia) and the cellular dysfunction that is witnessed both in the reproductive and metabolic tissues.

In conclusion, pathophysiology of PCOS is driven by a cascade of interconnected cellular events. From the arrested follicular development in the ovary due to theca granulosa cell miscommunication, to the dysfunctional adipose tissue secreting an adverse adipokine profile, and the overarching cellular stress from mitochondrial dysfunction and ER stress, these events collectively underpin the clinical syndrome. Understanding these

Journal of Chemical Health Risks
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cellular mechanisms is paramount for developing targeted interventions that addresses root causes of PCOS.

4. Factors influencing PCOS

Development as well as expression of PCOS are influenced by wide array of factors, ranging from genetic predisposition to lifestyle along with environmental exposures. These factors interact in complex ways to determine an individual's risk and the severity of their symptoms.

The layer of predisposition to PCOS lies in Genetic Predisposition and Heritability. As observed by Vink et al. (2006) by using twin studies, PCOS is highly heritable, with a concordance rate being higher in monozygotic compared to dizygotic twins. The inheritance is complex and polygenic, i.e. several genes with a small effect cause the total risk. Hayes et al. (2015) found with large scale genome wide association studies (GWAS) that there were many susceptibility loci of PCOS. Genes involved in gonadotropin action (e.g., FSHR, LHCGR), androgen biosynthesis and metabolism (e.g., CYP11A1, CYP17A1, CYP19A1), insulin secretion and signaling (e.g., INSR, IRS1/ 2) and folliculogenesis (e.g., DENND1A, THADA, YAP1) are commonly implicated by these loci. As an example, McAllister et al. (2014) have found that a gene, DENND1A, taking part in the intracellular trafficking, possesses a variant that is overexpressed in theca cells in PCOS women, causing excessive androgen production. Nevertheless, the identified genetic variations are only a part of the heritability, which indicates that there are additional mechanisms, including epigenetics and interactions between genes and their surroundings that are key factors in determining the full progression of the disease.

Prenatal and Perinatal Programming is a compelling hypothesis that suggests the intrauterine environment can permanently "program" the foetal physiology, increasing the risk of developing PCOS in adult life. The most prominent theory is the foetal androgen exposure hypothesis. Abbott et al. (2002) showed in animal models, particularly in primates and sheep, that female offspring exposed to excess testosterone in utero develop a phenotype remarkably like human PCOS, including hyperandrogenism, oligo ovulation, and metabolic disturbances. In humans, the source of excess androgens could be the mother (e.g., from PCOS itself) or the foetus (due to genetic variants in steroidogenic pathways). Dumesic et al. (2015) proposed that this prenatal androgen excess is thought to alter the development of key tissues, including the hypothalamus, leading to the characteristic accelerated GnRH pulsatility; the pituitary, favoring LH secretion; and the ovary, predisposing theca cells to hyper secrete androgens. Other perinatal factors, such as low birth weight and prematurity, have also been associated with an increased risk of developing PCOS and its metabolic features, possibly through programming of the hypothalamic pituitary adrenal axis and insulin sensitivity (Ibañez et al., 1998).

Lifestyle and Environmental Factors are also considered to be an effective PCOS phenotype modulator. Obesity is the biggest environmental precipitant and Barber et al. (2019) discovered over fifty percent of women with PCOS were overweight or obese. Adiposity and more particularly visceral fat elevate insulin resistance and hyperinsulinemia, which eventually leads to rise of ovarian and adrenal androgen production. It is also the pro inflammatory condition associated with obesity that has contributed to the malfunction of the metabolism and reproductive system. It is also sensitive to dietary make up. Moran et al. (2013) developed this statement further to affirm that high refined carbohydrates and saturated fats diets could worsen the state of insulin resistance and inflammation, and that high fiber and monounsaturated fats with low glycemic index diets would serve in enhancing the metabolic parameters. These effects will be enhanced by exercise that will decrease the insulin sensitivity and weight gain. Besides diet and exercise, endocrine disrupting chemicals (EDCs) too have been reported to cause pathogenesis of PCOS. Kandaraki et al. (2011) had established that EDCs such as bisphenol A (BPA), which is contained in the plastics are capable of mimicking or interfering with the endogenous hormones and the women with PCOS are seen to have higher serum levels of BPA and this could be contributing to insulin resistance, hyperandrogenic and ovarian dysfunction when the material attaches to the estrogen and androgen receptors.

Psychosocial and Iatrogenic Factors are increasingly recognized for their impact on PCOS. Dokras et al. (2018) reported that the chronic nature of the condition, coupled with symptoms like hirsutism, infertility, and weight struggles leads to a high prevalence of

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

psychological distress, including anxiety, depression, and poor body image. Such psychological stress is not only a consequence but also a causative factor. Chronic stress stimulates the HPA axis, resulting in increased cortisol levels, which may contribute to exacerbating insulin resistance and possibly influence androgen metabolism. Certain drugs can also precipitate or unmask a PCOS like state. For instance, Isojärvi et al. (1993) have reported that valproate an anticonvulsant mood stabilizer can cause weight gain, insulin resistance, and hyperandrogenism in some women. Appreciation of these varied influencing factors requires a comprehensive approach to PCOS management, which must extend beyond pharmacological interventions to lifestyle modification, psychological support as well as environmental awareness.

5. Exploring the Signaling Pathways Associated with PCOS

The phenotypic expression of PCOS is orchestrated by the dysregulation of a multitude of intracellular signaling pathways. These pathways transduce extracellular signals such as hormones and nutrients into specific cellular responses controlling metabolism, steroidogenesis, and proliferation. Their detailed examination uncovers the molecular underpinnings of the syndrome.

5.1 The PI3K/Akt/mTOR Signaling Pathway

In PCOS, the PI3K/Akt/mTOR signaling pathway is the primary intracellular pathway for metabolic insulin signaling (Manning & Toker, 2017). Manning & Toker (2017) described that upon insulin binding to its receptor, insulin receptor substrates (IRS) are phosphorylated, recruiting and activating phosphatidylinositol 3-kinase (PI3K). PI3K generates phosphatidylinositol (3,4,5) trisphosphate (PIP3), which recruits Akt (Protein Kinase B) to the plasma membrane for activation (Manning & Toker, 2017). Akt then phosphorylates numerous downstream targets, including the mTOR complex and AS160, to promote glucose uptake via GLUT4 translocation, glycogen synthesis, and protein synthesis (Manning & Toker, 2017). Dunaif et al. (1995) discovered that in PCOS, this pathway is impaired in insulin responsive tissues like skeletal muscle and adipose tissue, with defects occurring at multiple levels, including reduced tyrosine phosphorylation of IRS-1 and increased serine phosphorylation, which inhibits its interaction with PI3K (Dunaif et al., 1995). This blunted PI3K/Akt signaling is a fundamental cause of insulin resistance in PCOS, leading to reduced glucose uptake and hyperinsulinemia (Dunaif et al., 1995). Interestingly, Wu et al. (2014) found that in the ovarian theca cell, insulin signaling may utilize alternative pathways or the PI3K/Akt pathway may remain relatively intact, allowing hyperinsulinemia to paradoxically drive excessive androgen production (Wu et al., 2014).

5.2 The MAPK/ERK Signaling Pathway

The MAPK/ERK pathway is considered an important limb of the insulin signaling pathway, separate from the metabolic PI3K/Akt pathway. While the PI3K/Akt pathway mediates most of insulin's metabolic actions, such as glucose uptake, insulin's growth promoting and mitogenic effects are generally thought to be mediated through the MAPK/ERK pathway. In general, this pathway represents a kinase cascade that is usually activated by growth factors, which include insulin and IGF-1, and this signal transduction involves activation of the small GTPase Ras, which then activates Raf (a MAPK kinase kinase), which phosphorylates and activates MEK (a MAPK kinase), which then phosphorylates and activates ERK (the MAPK). Once activated, ERK translocates to the nucleus, where it phosphorylates a multitude of transcription factors, including c-Fos and c-Myc, leading to the expression of genes that drive cell proliferation, differentiation, and survival. In PCOS, this pathway has been reported to be normally or even hypersensitive, which contrasts with the impaired PI3K/Akt pathway. This differential insulin signaling in terms of pathway utilization is considered one of the cornerstones in the pathophysiology of PCOS. According to Corbould et al. (2005), this hyperactive MAPK/ERK pathway persists despite the presence of insulin resistance at the metabolic level. It helps explain the clinical paradox observed in PCOS: hyperinsulinemia fails to adequately stimulate glucose uptake in muscle and adipose tissue due to impairment in the PI3K/Akt pathway but simultaneously and effectively promotes cellular growth through the unabated MAPK/ERK signaling. In the ovary, this heightened mitogenic signaling also contributes directly to the development of theca cell hyperplasia, an over proliferation of theca cells in ovarian follicles. These hyperplastic theca cells are a primary source of the excessive androgen production that characterizes PCOS,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

while the proliferative drive of the MAPK/ERK pathway is not confined to the ovary but is extended to other insulin responsive tissues such as the endometrium. Activation of MAPK/ERK via hyperinsulinemia in the lining of the uterus can result in excessive cellular proliferation, increasing the risk of endometrial hyperplasia and, eventually, endometrial cancer in women with PCOS (Corbould et al., 2005). This pathway thus represents a direct link between systemic hyperinsulinemia and the specific tissue pathologies that define the syndrome, ensuring that even in a state of metabolic resistance, the growth promoting signals of insulin remain potent and problematic (Corbould et al., 2005).

5.3 AMP Activated Protein Kinase (AMPK) Signaling Pathway

The AMP activated Protein Kinase (AMPK) signaling pathway functions as a fundamental cellular energy sensor, crucial for maintaining metabolic homeostasis (Hardie, 2007). It is activated under conditions of energy depletion, which is biochemically represented by an increase in the cellular AMP to ATP ratio (Hardie, 2007). As detailed by Hardie (2007), upon activation, AMPK orchestrates a metabolic switch that favors energy production over energy consumption (Hardie, 2007). It promotes catabolic processes that generate ATP, such as fatty acid oxidation in the mitochondria and glucose uptake in muscle tissue, while simultaneously inhibiting anabolic, energy consuming processes like lipogenesis, cholesterol synthesis, and protein synthesis (Hardie, 2007). This makes AMPK a master regulator of whole-body energy balance (Hardie, 2007). In states of nutrient excess and insulin resistance, such as PCOS, AMPK activity is often found to be downregulated. This suppression contributes significantly to the metabolic disturbances of the syndrome. Reduced AMPK activity in the liver diminishes its ability to inhibit gluconeogenesis, leading to excessive hepatic glucose output, a key contributor to fasting hyperglycemia. In skeletal muscle, impaired AMPK signaling reduces glucose uptake and fatty acid oxidation, exacerbating insulin resistance and lipid accumulation. The central role of AMPK in PCOS therapeutics is highlighted by the mechanism of metformin, a first line insulin sensitizing drug. Zhou et al. (2001) discovered that metformin's primary action is the activation of AMPK (Zhou et al., 2001). By activating AMPK in the liver, metformin potently suppresses gluconeogenesis, thereby reducing fasting blood glucose and insulin levels (Zhou et al., 2001). In peripheral tissues, AMPK activation by metformin enhances insulin receptor signaling and facilitates GLUT-4 mediated glucose uptake (Zhou et al., 2001). Beyond its metabolic effects, AMPK activation may also influence ovarian function. By improving systemic insulin sensitivity, metformin reduces the hyperinsulinemic drive on ovarian theca cells, thereby indirectly attenuating hyperandrogenism. There is also emerging evidence that AMPK may directly modulate steroidogenic enzymes within the ovary. Thus, the downregulation of the AMPK pathway in PCOS creates a state of perceived energy surplus that promotes anabolic processes and exacerbates metabolic and reproductive dysfunction, and its pharmacological activation remains a cornerstone of treatment (Zhou et al., 2001).

5.4 Transforming Growth Factor-β (TGF-β) Superfamily Signaling Pathway

The Transforming Growth Factor-β (TGF-β) superfamily contains many secreted cytokines important in growth, differentiation, apoptosis, and homeostasis. In the ovary, this pathway is critical for the regulation of folliculogenesis and steroidogenesis. Members of this superfamily important in PCOS include AMH and the growth differentiation factors, such as GDF-9 and BMP-15, and inhibins. Ligands signal via a specific pathway initiated by the association of type I and type II serine/threonine kinase receptors, which, upon activation, phosphorylate intracellular Smad proteins, primarily R-Smads. These R-Smads then bind a co-Smad, Smad4, and translocate to the nucleus to control target gene transcription. The TGF-β superfamily pathway is significantly disrupted in PCOS, with AMH being a very prominent biomarker. Pellatt et al. (2007) demonstrated that both serum and follicular fluid levels of AMH are dramatically raised in women with PCOS. This excess AMH has been thought to be pivotal in the characteristic arrest of follicular development. Through excessive suppression of follicle responsiveness to FSH, AMH prevents the selection of a dominant follicle, resulting in the accumulation of numerous small, arrested follicles seen on ultrasound. Moreover, the TGF-β pathway does not act in isolation; it is part of a complex interaction with both androgen and insulin signaling pathways within the ovarian microenvironment. It has

Journal of Chemical Health Risks
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JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

been shown that androgens can stimulate AMH production from granulosa cells, establishing a potential positive feedback loop to maintain follicular arrest. Meanwhile, elevated insulin levels may further perturb the expression of the TGF-β superfamily members and their receptors. This complex interplay between TGF-β, insulin, and androgen signaling forms a self-reinforcing cycle that disrupts the delicate balance between follicle growth and atresia and plays a critical role in the anovulatory phenotype seen in PCOS.

5.5 Wnt/β Catenin Signaling Pathway

The Wnt/β catenin pathway, also referred to as the canonical Wnt pathway, is a conserved signal transduction cascade crucial for embryonic development, cell fate determination, proliferation along with stem cell maintenance. In the absence of Wnt signaling, cytoplasmic β-catenin is continuously targeted for proteolytic degradation by a protein complex called the destruction complex. Binding of the Wnt ligand to its Frizzled receptor together with the co receptor LRP inactivates this destruction complex, allowing β-catenin to accumulate and upon translocation into the nucleus, to combine with TCF/LEF transcription factors to activate target gene expression essential for cellular proliferation as well as differentiation. This critical pathway has recently been associated with pathogenesis of PCOS. Accordingly, Wang et al. (2019) have proposed that dysregulated Wnt/β catenin signaling significantly contributes to both ovarian dysfunction and metabolic features of the syndrome. In ovary, normal Wnt signaling is required for classical folliculogenesis and steroidogenesis. Aberrant activation of this pathway may disrupt the highly orchestrated cross talk between theca and granulosa cells, leading to arrest of follicular growth typical of PCOS (Wang M et al., 2019). This pathway also has extensive cross talk with several other signaling networks reported to be disturbed in PCOS. For instance, it interacts with androgen receptor signaling and thus might modulate theca cell responses, contributing to hyperandrogenism. The Wnt pathway also interacts with insulin signaling; β-catenin can regulate insulin sensitivity, while insulin resistance modulates the components of the Wnt pathway. Such an interaction provides a plausible molecular link between the reproductive and metabolic manifestations of PCOS. Dysfunctional Wnt signaling in adipose tissue and the liver impairs adipogenesis and promotes hepatic glucose output, contributing to insulin resistance. Thus, the Wnt/β-catenin pathway acts as a node integrating developmental, reproductive, metabolic signals and its dysregulation in PCOS offers a unifying view on the syndromic nature of the condition.

5.6 Hedgehog (Hh) Signaling Pathway

The Hedgehog (Hh) signaling pathway represents another evolutionarily preserved mechanism that plays a vital role in embryonic organization, tissue orientation, and the maintenance of stem cells. In mature organisms, its function is primarily confined to the processes of tissue repair and regeneration. This pathway begins when a Hedgehog ligand (such as Sonic Hedgehog or Indian Hedgehog) attaches to its receptor, Patched (Ptch). This interaction alleviates the suppression that Ptch imposes on a different transmembrane protein known as Smoothened (Smo). Once activated, Smo initiates an intracellular signaling cascade that results in the activation and movement of Gli family transcription factors into the nucleus, which in turn modulate the expression of target genes associated with cell growth and differentiation. Within the scope of the adult ovary, Hh signaling has been recognized as a crucial regulator of the development and function of theca cells. Theca cells, which are vital for offering structural support to the developing follicle and for synthesizing androgens, originate from interstitial stem cells influenced by Hh signals coming from the oocyte and granulosa cells. Wang J et al. (2012) found that this pathway is altered in the ovaries of women with PCOS (Wang J et al., 2012). Specifically, there is evidence of upregulated Hh signaling, which may be a primary driver of theca cell hyperplasia that is the excessive proliferation of theca cells that is a hallmark of the PCOS ovary (Wang J et al., 2012). This hyperplastic growth provides a greater mass of steroidogenically active cells, which in turn leads to the overproduction of androgens, directly contributing to the hyperandrogenism that is central to the syndrome (Wang J et al., 2012). The sustained activation of the Hh pathway in PCOS suggests a reactivation of a developmental program in the adult ovary, leading to aberrant tissue growth and function (Wang J et al., 2012). This makes the Hh pathway a critical link between developmental signaling cascades and the adult pathophysiology of PCOS, highlighting how pathways crucial for building the ovary can, when dysregulated, contribute to its dysfunction (Wang J et al., 2012).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

5.7 Notch Signaling Pathway

The Notch signaling pathway is a highly conserved means of mediating direct cell to cell communication fundamental for the determination of cell fate, proliferation, differentiation, as well as apoptosis. Different from many signaling pathways that involve secreted ligands, the Notch pathway depends on membrane bound ligands, the most common ones being Delta and Jagged on one cell interacting with the Notch receptor on an adjacent cell. This interaction initiates a series of proteolytic cleavages of the Notch receptor, whereby the released Notch intracellular domain (NICD) translocates into the nucleus. There, it binds to a transcription factor CSL (RBP-Jκ) and co activators to initiate the expression of target genes, which include those of the Hairy/Enhancer of Split (Hes) family. Within the ovary, Notch signaling is active in both theca and granulosa cells. It intervenes in the regulation of follicle recruitment, growth, and selection. Its precise, spatiotemporal regulation is quite crucial to ensure that a single dominant follicle is selected for ovulation, while others undergo atresia. Zhang et al. (2018) reported that this careful balance is disrupted in PCOS, as evidenced by signs of Notch pathway dysregulation within the granulosa cells of affected women. Altered expression of Notch receptors, ligands, and target genes disrupts the critical communication between the oocyte and its surrounding granulosa cells, together with amongst the granulosa cells themselves. Such a breakdown in communication could lead to the failure of follicular maturation, contributing to the arrested growth and accumulation of small antral follicles. Furthermore, aberrant Notch signaling can impair luteinization and promote granulosa cell apoptosis, further compromising follicle health and ovulation. Thus, the dysregulation of the Notch pathway in PCOS granulosa cells should represent a fundamental defect in the local cellular dialogue necessary for normal ovarian function, providing a mechanistic basis for the follicular arrest which defines the syndrome.

5.8 JAK-STAT Signaling

The JAK-STAT pathway is a universal signaling cascade used by a wide array of cytokines, growth factors, and hormones. It represents a critical regulator of immune and inflammatory responses, cell growth, proliferation, and differentiation. The pathway is activated by the binding of a ligand to its matching cell surface receptor, which, through the auto or trans phosphorylation of associated JAK kinases, brings about receptor phosphorylation and thus creates docking sites for STAT proteins. Once recruited, STATs are phosphorylated by JAKs, leading to their dimerization and translocation into the nucleus, where they work as transcription factors for target genes. In PCOS, a state of low-grade chronic inflammation is now recognized as one of its salient features. As pointed out by Duleba & Dokras (2012), this inflammatory environment involves the activation of the JAK-STAT pathway promoted by pro-inflammatory cytokines such as IL-6 and leptin. Elevated levels of these cytokines in the serum and tissues of women with PCOS induce persistent JAK-STAT signaling. This chronic activation has been shown to have systemic repercussions, as it could induce insulin resistance through interference with IRS proteins. Local JAK-STAT activation within the ovarian tissue by inflammatory mediators disrupts the normal follicular microenvironment. It may affect granulosa cell proliferation and steroidogenesis and contribute to the premature luteinization of those cells, further contributing to defective ovulatory function. Therefore, the JAK-STAT pathway serves as a crucial conduit through which systemic inflammation is translated into both metabolic insulin resistance and local ovarian dysfunction, positioning it as a key player in the interplay between immune and reproductive pathology in PCOS.

5.9 NF-κB Signaling

NF-κB, also known as Nuclear Factor Kappa-B, is a protein complex that regulates inflammation and immune responses, cell survival as well as proliferation. In its inactive form, NF-κB, usually a p50-p65 heterodimer, resides in the cytoplasm, bound by inhibitory proteins called IκBs. A variety of stimuli, such as pro-inflammatory cytokines e.g., TNF-α, IL-1β), PAMPs, and oxidative stress may trigger the IκB kinase complex. The IκB kinase complex subsequently phosphorylates IκB, targeting it for degradation and the subsequent release of the NF-κB dimer, which translocate to the nucleus to initiate the transcription of numerous inflammatory genes. As identified by Gonzalez et al. (2006), the NF-κB pathway is a key driver of the chronic inflammatory state that characterizes PCOS (Gonzalez et al., 2006). The high levels of IKK are constantly activated by the continued presence of

Journal of Chemical Health Risks
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JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

oxidative stress and pro-inflammatory cytokines in PCOS and subsequently NF-κB Gonzalez et al. 2006. Once activated, NF-κB induces the expression of key Inflammatory mediators include TNF-α, IL-6, and C-Reactive Protein (CRP) (Gonzalez et al., 2006). This Creates a vicious, self-perpetuating cycle where TNF- and IL-6, not only reinforce this inflammatory state but also actively promote insulin resistance by serine-phosphorylating IRS proteins, which disrupt insulin signaling. Gonzalez et al. (2006) This cycle ensures a persistent, low grade inflammatory tone that contributes to the long term metabolic and cardiovascular complications associated with PCOS include type 2 diabetes and atherosclerosis. Gonzalez et al., 2006). The NF-κB pathway is thus positioned as the central inflammatory hub, integrating multiple pathogenic stimuli in PCOS and translate them into a sustained transcriptional program underlying the syndrome's chronic pathology (Gonzalez et al., 2006).

5.10 JNK Signaling

The c-Jun N-terminal Kinase (JNK) pathway is a member of the stress activated subgroup of the MAPK family. It is activated by a diverse range of cellular stressors, including inflammatory cytokines (e.g., TNF-α, IL-1β), endoplasmic reticulum (ER) stress, oxidative stress, and free fatty acids. Upon activation, a kinase cascade leads to the phosphorylation and activation of JNK, which then phosphorylates various substrates, including transcription factors like c-Jun, which form the Activator Protein-1 (AP-1) complex. The critical link between JNK activation and insulin resistance was decisively demonstrated by Hirosumi et al. (2002), who showed that JNK can directly phosphorylate Insulin Receptor Substrate-1 (IRS-1) on specific serine residues (e.g., Ser307) (Hirosumi et al., 2002). This serine phosphorylation inhibits the tyrosine phosphorylation of IRS-1 that is normally required for proper insulin signal transduction, thereby blunting the insulin response (Hirosumi et al., 2002). In PCOS, the chronic inflammatory environment and the presence of nutrient excess create ideal conditions for sustained JNK activation (Hirosumi et al., 2002). Elevated levels of inflammatory cytokines and free fatty acids provide a constant stimulus for JNK, leading to a persistent state of IRS-1 inhibition (Hirosumi et al., 2002). This mechanism forms a direct molecular link between the inflammatory/stress milieu of PCOS and the core defect of insulin resistance (Hirosumi et al., 2002). Furthermore, JNK activation can also promote apoptosis in various cell types, including ovarian cells, which may have implications for follicular atresia. Therefore, the JNK pathway acts as a critical sensor of metabolic and inflammatory stress, transducing these signals into a direct impairment of insulin action (Hirosumi et al., 2002).

5.11 p38 MAPK Signaling

The p38 MAPK pathway is another crucial stress sensitive kinase cascade, operating alongside JNK. It springs into action under similar stressful conditions, such as exposure to inflammatory cytokines, various cellular stresses, osmotic shock, and lipopolysaccharides (LPS). When activated, p38 MAPK sets off a chain reaction, phosphorylating a wide range of downstream targets, including other kinases and transcription factors. This influences key processes like inflammation, cell cycle arrest, differentiation, and cell death. Research by Chen et al. (2015) shows that this pathway is also active in PCOS (Chen et al., 2015). Its activation plays a part in the disease's development through several mechanisms (Chen et al., 2015). Much like JNK, p38 MAPK can phosphorylate IRS-1 on specific serine residues that block its function. This offers another route through which inflammation and stress disrupt insulin signaling, fueling systemic insulin resistance (Chen et al., 2015). Inside the ovary, faulty p38 MAPK signaling may interfere with granulosa cell function, potentially upsetting the balance of steroid hormone production and the development of follicles (Chen et al., 2015). It can also ramp up the production of inflammatory molecules, thereby intensifying both local and body wide inflammatory responses (Chen et al., 2015). The involvement of p38 MAPK in PCOS highlights that multiple stress kinase pathways are switched on at the same time, weaving a complex web of signaling events that together drive metabolic dysfunction and ovarian problems (Chen et al., 2015).

5.12 TLR4 Signaling

Toll like Receptor 4 (TLR4) is a primary sentinel of our innate immune system, famous for its role in spotting bacterial lipopolysaccharides (LPS). However, we now know that TLR4 can also be triggered by internal alarm signals, particularly saturated fatty acids, which are often high in obesity and metabolic syndrome. When activated

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

by these signals, TLR4 sets in motion a cascade that ultimately switches on transcription factors like NF-κB and AP-1. This leads to the production of pro-inflammatory cytokines such as TNF-α and IL-6. Tremellen & Pearce (2012) put forward the idea that TLR4 signaling is a major player in the chronic inflammation seen in PCOS, largely through the concept of "metabolic endotoxemia" (Tremellen & Pearce, 2012). Gut dysbiosis, common in PCOS, weakens the intestinal barrier, allowing bacterial LPS from the gut to leak into the bloodstream (Tremellen & Pearce, 2012). These elevated LPS levels, along with dietary saturated fats, act as powerful triggers for TLR4 (Tremellen & Pearce, 2012). The activation of TLR4 on immune cells and metabolic tissues (like fat and liver) drives the production of inflammatory cytokines, which then worsen insulin resistance (Tremellen & Pearce, 2012). This creates a vicious cycle: a poor diet and imbalanced gut flora activate TLR4, leading to inflammation and insulin resistance, which in turn further worsens the metabolic profile of PCOS (Tremellen & Pearce, 2012). The TLR4 pathway, therefore, directly connects the gut microbiome, our innate immune system, and the metabolic dysfunction of PCOS (Tremellen & Pearce, 2012).

5.13 Inflammasome Signaling

Inflammasomes are large, multi-protein complexes that sit at the heart of inflammatory responses. The most well studied is the NLRP3 inflammasome. It assembles in response to a wide range of "danger signals," including microbial molecules, ATP, uric acid crystals, and reactive oxygen species (ROS). Once assembled, the NLRP3 inflammasome activates the enzyme caspase-1. Active caspase-1 then cuts the inactive forms of the powerful inflammatory cytokine's interleukin-1β (IL-1β) and IL-18, turning them into their active, secreted forms. The role of the NLRP3 inflammasome in the "sterile" (non-infectious) inflammation of metabolic diseases is now well recognized. Brennan et al. (2019) discovered that the NLRP3 inflammasome is activated in PCOS (Brennan et al., 2019). The metabolic chaos characteristic of PCOS including high blood sugar, lipotoxicity, and oxidative stress provides the perfect danger signals to trigger NLRP3 (Brennan et al., 2019). The resulting production of mature IL-1β is especially significant, as this cytokine is a powerful driver of insulin resistance and systemic inflammation (Brennan et al., 2019). By activating IL-1β, the NLRP3 inflammasome acts as a molecular platform that translates metabolic problems into a potent inflammatory reaction (Brennan et al., 2019). This pathway elegantly connects the metabolic and immune pathologies of PCOS, positioning the inflammasome as a key converter of cellular stress into clinical inflammation (Brennan et al., 2019).

5.14 SIRT1 Signaling

Sirtuin 1 (SIRT1) is a NAD+ dependent enzyme that acts as a critical sensor of the cell's energy status. Its activity is directly tied to the NAD+/NADH ratio, meaning it is more active during states of energy scarcity, like fasting or exercise. SIRT1 modifies a wide array of protein targets, regulating key processes including glucose and lipid metabolism, mitochondrial biogenesis, inflammation, and resistance to oxidative stress. Ruderman et al. (2010) found that SIRT1 activates pivotal metabolic regulators (Ruderman et al., 2010). For instance, it activates PGC-1α, a master controller of mitochondrial creation and fatty acid burning, and FOXO1, a transcription factor that promotes stress resistance and regulates glucose production (Ruderman et al., 2010). Reduced SIRT1 activity has been observed in insulin resistant states, including PCOS (Ruderman et al., 2010). This downregulation may be due to nutrient excess, which lowers the NAD+/NADH ratio (Ruderman et al., 2010). Impaired SIRT1 function leads to decreased fatty acid oxidation, increased oxidative stress, and dysregulated glucose metabolism (Ruderman et al., 2010). The loss of SIRT1's protective, energy sensing actions contributes significantly to the mitochondrial dysfunction and metabolic inflexibility seen in PCOS (Ruderman et al., 2010). Therefore, SIRT1 signaling represents a crucial link between cellular energy status and metabolic health, the weakening of which is a key feature of the syndrome (Ruderman et al., 2010).

5.15 FOXO1 Signaling

Forkhead box protein O1 (FOXO1) is a transcription factor that plays a central role in regulating metabolism, particularly in the liver. Its activity is primarily controlled by the PI3K/Akt pathway. When insulin signaling is working properly and Akt is active, it directly phosphorylates FOXO1. This phosphorylation tags FOXO1 for export from the nucleus to the cytoplasm, where it can't act on DNA. As described by Nakae et al. (2001), in insulin resistant states like PCOS, where Akt

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

signaling is faulty, this control system breaks down (Nakae et al., 2001). FOXO1 remains largely unphosphorylated and active in the nucleus (Nakae et al., 2001). Once in the nucleus, FOXO1 binds to the promoters of key genes involved in glucose production, such as Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase), and ramps up their expression (Nakae et al., 2001). This increased liver glucose output is a major contributor to high fasting blood sugar and the overall problem with blood sugar control in PCOS (Nakae et al., 2001). Thus, the dysregulation of FOXO1 provides a direct molecular explanation for the excessive glucose production that occurs when insulin loses its ability to suppress this process due to impaired PI3K/Akt signaling (Nakae et al., 2001).

5.16 PPARγ Signaling

Peroxisome Proliferator Activated Receptor Gamma (PPARγ) is a nuclear hormone receptor that acts as a master regulator of fat cell differentiation, lipid storage, and glucose metabolism. It is highly expressed in adipose tissue. When activated by its ligands, which include natural fatty acid derivatives and synthetic diabetes drugs like thiazolidinediones (TZDs), PPARγ partners with the Retinoid X Receptor (RXR) and binds to DNA to control gene expression. As stated by Yki Järvinen (2004), the insulin sensitizing effects of TZDs in PCOS and type 2 diabetes work through their activation of PPARγ (Yki Järvinen, 2004). Activating PPARγ encourages preadipocytes to mature into small, insulin sensitive fat cells (Yki Järvinen, 2004). This improves the capacity for fat storage in subcutaneous adipose tissue, reducing the harmful deposition of fat in liver and muscle that drives insulin resistance (Yki Järvinen, 2004). Furthermore, PPARγ activation changes the cocktail of signals released by fat tissue, reducing pro-inflammatory cytokines like TNF-α and increasing the secretion of adiponectin, an insulin sensitizing hormone (Yki Järvinen, 2004). Through these mechanisms helps improving fat cell function, redirecting fat storage, and reducing inflammation. PPARγ signaling improves systemic insulin resistance, making it a critical therapeutic target in PCOS (Yki Järvinen, 2004).

5.17 LKB1/AMPK Signaling

The Liver Kinase B1 (LKB1)/AMPK axis is a fundamental cellular energy sensing pathway. LKB1 is a constitutively active kinase that acts as a primary switch for AMPK. In response to an increase in the AMP/ATP ratio (a sign of low energy), LKB1 phosphorylates and activates AMPK. Once activated, AMPK, as previously described, turns on energy producing processes and turns off energy consuming ones to restore balance. The discovery by Shaw et al. (2005) that metformin's activation of AMPK is partly dependent on LKB1 solidified the importance of this axis in metabolic medicine (Shaw et al., 2005). Dysregulation of the LKB1-AMPK pathway can deeply contribute to the metabolic defects in PCOS (Shaw et al., 2005). If LKB1 activity is compromised, the cell's ability to sense energy stress and activate AMPK is dulled (Shaw et al., 2005). This would lead to reduced fatty acid oxidation, continued fat and glucose production, and impaired glucose uptake—all hallmarks of PCOS (Shaw et al., 2005). Therefore, the proper functioning of the LKB1-AMPK axis is essential for maintaining metabolic flexibility, and its impairment represents a key upstream event in the development of insulin resistance in the syndrome (Shaw et al., 2005).

5.18 mTORC1 Signaling

The mechanistic Target of Rapamycin Complex 1 (mTORC1) is a kinase complex that integrates signals from growth factors, nutrients, and cellular energy status to control cell growth, proliferation, and metabolism. It is a key downstream target of both the Akt and AMPK pathways. Akt activates mTORC1, while AMPK, as an energy sensor, puts the brakes on it. As reported by Kayampilly & Menon (2009), mTORC1 signaling is hyperactive in PCOS (Kayampilly & Menon, 2009). This overactivity is likely driven by the chronic high insulin levels, which provide a constant growth signal through Akt (Kayampilly & Menon, 2009). Within the ovarian theca cells, hyperactive mTORC1 signaling can stimulate excessive cell proliferation, contributing to theca cell hyperplasia (Kayampilly & Menon, 2009). Furthermore, mTORC1 is a potent regulator of protein synthesis and can enhance the production of proteins involved in steroid hormone creation, thereby promoting the overproduction of androgens (Kayampilly & Menon, 2009). The hyperactive mTORC1 pathway in PCOS thus represents a point of convergence where growth factor signaling (insulin) drives both the structural (hyperplasia) and functional (hyperandrogenism) abnormalities of the ovary (Kayampilly & Menon, 2009).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

5.19 cAMP/PKA Signaling

The cyclic AMP (cAMP)/Protein Kinase A (PKA) pathway is a common intracellular signaling cascade activated by many hormones, including Luteinizing Hormone (LH). When LH binds to its receptor on theca cells, it activates an enzyme that produces cAMP. The rise in cAMP leads to the activation of PKA. Activated PKA then phosphorylates and turns on key steroidogenic enzymes, including StAR protein, which shuttles cholesterol into the mitochondria, and CYP17A1, a critical enzyme in androgen synthesis. The work of Nelson et al. (1999) elucidated this pathway in the ovary (Nelson et al., 1999). In PCOS, theca cells show an intrinsic and heightened responsiveness to cAMP signaling (Nelson et al., 1999). Even at normal levels of LH, the cAMP/PKA pathway in PCOS theca cells is overactive, leading to an exaggerated activation of StAR and CYP17A1 (Nelson et al., 1999). This results in the increased production of androgens that is a hallmark of the syndrome (Nelson et al., 1999). This intrinsic dysregulation of the cAMP/PKA pathway is considered a fundamental defect in PCOS theca cells, making them inherently prone to overproduce androgens (Nelson et al., 1999).

5.20 Calcium Signaling

Calcium ions (Ca2+) function as versatile intracellular messengers, regulating a diverse array of cellular processes including muscle contraction, neurotransmission, and hormone secretion. In steroid producing cells like ovarian theca cells, Ca2+ signaling is particularly important for the rapid control of steroid hormone synthesis. Fluctuations in intracellular Ca2+ can activate calcium/calmodulin dependent kinases (CaMKs) which, in turn, can phosphorylate and activate steroidogenic enzymes like StAR. As reported by Wang L et al. (2017), changes in intracellular calcium handling and signaling have been found in theca cells from women with PCOS (Wang L et al., 2017). These changes may include differences in the channels that allow Ca2+ entry into the cell or the receptors that release Ca2+ from internal stores (Wang L et al., 2017). This dysregulated calcium signaling could lead to abnormal activation of the steroid making machinery, contributing to the intrinsic overproduction of androgens on its own, or by working together with the cAMP/PKA pathway (Wang L et al., 2017). Thus, calcium signaling represents another layer of control that, when disturbed, adds to the hyperandrogenic phenotype of PCOS (Wang L et al., 2017).

5.21 Autophagy Signaling

Autophagy is an essential cellular "clean up" process that involves the breakdown and recycling of damaged organelles and proteins. It is crucial for maintaining cellular health, especially under stress. In the ovary, autophagy plays a vital role in follicular development, atresia, and egg quality by removing damaged components and providing energy during metabolic stress. The discovery by Choi et al. (2020) that autophagy is dysregulated in the granulosa cells of PCOS patients highlights a new aspect of the syndrome's pathophysiology (Choi et al., 2020). In PCOS, autophagy is often found to be suppressed or not working correctly (Choi et al., 2020). This dysregulation can lead to a buildup of damaged proteins and organelles, increasing oxidative stress within the follicle (Choi et al., 2020). Impaired autophagy in granulosa cells may disrupt their function and survival, contributing to the abnormal follicular development and stalled growth (Choi et al., 2020). Furthermore, since egg quality heavily depends on the health of its surrounding granulosa cells, defective autophagy in these cells can impair egg maturation and competence, adding to the fertility problems seen in PCOS (Choi et al., 2020).

5.22 Apoptosis Signaling

Apoptosis, or programmed cell death, is a tightly regulated process essential for tissue maintenance. In the ovary, the balance between cell survival and death is critical for the cyclical process of follicular recruitment, selection, and degeneration. Most follicles undergo atresia via apoptosis, and only a select few are chosen to ovulate. As found by Das et al. (2008), this delicate balance is upset in PCOS (Das et al., 2008). The arrested follicles characteristic of PCOS often show abnormal patterns of cell death (Das et al., 2008). In some cases, there may be a reduction in apoptosis within the granulosa cell layer, which could help explain why these small, non-ovulatory follicles persist (Das et al., 2008). In other contexts, inappropriate or increased cell death may contribute to the follicle's degeneration (Das et al., 2008). The failure of follicles to either mature properly or die off in a timely manner suggests a fundamental problem in the apoptotic signaling pathways that decide

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

a follicle's fate (Das et al., 2008). This disruption is a key factor in the development of the polycystic ovary morphology (Das et al., 2008).

5.23 Nrf2/ARE Signaling

The Nuclear factor erythroid 2 related factor 2 (Nrf2)/Antioxidant Response Element (ARE) pathway is the cell's main defense system against oxidative stress. Under normal conditions, Nrf2 is held captive by its repressor, Keap1, and marked for destruction. Upon exposure to oxidative stress, this interaction is broken, allowing Nrf2 to build up and move to the nucleus. There, it binds to the ARE in the promoter regions of genes encoding a wide array of antioxidant and protective enzymes. As suggested by Mihanfar et al. (2021), Nrf2 signaling is impaired in PCOS (Mihanfar et al., 2021). This impairment could be due to several factors, including the inflammatory environment or other modifications that hinder Nrf2's activity (Mihanfar et al., 2021). With compromised Nrf2 function, the cell's ability to launch an effective antioxidant defense is weakened (Mihanfar et al., 2021). This leads to an accumulation of reactive oxygen species (ROS), resulting in the heightened oxidative stress that is consistently seen in PCOS (Mihanfar et al., 2021). This oxidative stress, in turn, can damage lipids, proteins, and DNA, and can activate inflammatory pathways like NF-κB, creating a vicious cycle that worsens both metabolic and reproductive dysfunction (Mihanfar et al., 2021).

5.24 Endocannabinoid System Signaling

The Endocannabinoid System (ECS) is a complex signaling network comprising endogenous cannabinoids (e.g., anandamide, 2-AG), their receptors (primarily CB1 and CB2), and the enzymes that make and break them down. The ECS plays a key role in regulating energy balance, appetite, lipid and glucose metabolism, and reward pathways. As reported by Bari et al. (2020), an overactive ECS, particularly through CB1 receptor activation, has been strongly linked to obesity and insulin resistance (Bari et al., 2020). There is growing evidence that the ECS is out of balance in PCOS (Bari et al., 2020). An overactive ECS, driven by increased endocannabinoid levels, could promote weight gain and central fat accumulation by stimulating appetite and fat creation (Bari et al., 2020). It can also directly contribute to insulin resistance in liver and adipose tissue (Bari et al., 2020). Furthermore, given the presence of cannabinoid receptors in the ovary, dysregulation of the ECS may have local effects on follicle development and steroid production, potentially influencing ovarian function (Bari et al., 2020). The ECS thus represents a link between the brain, metabolism, and the ovary in PCOS (Bari et al., 2020).

5.25 Kisspeptin/KISS1R Signaling

The Kisspeptin/KISS1R (also known as GPR54) signaling system is now recognized as the most potent stimulator of Gonadotropin Releasing Hormone (GnRH) neurons, making it a critical gatekeeper of the reproductive axis. Kisspeptin neurons in the hypothalamus release kisspeptin, which binds to KISS1R on GnRH neurons, triggering GnRH secretion. This, in turn, stimulates the pituitary release of LH and FSH. As stated by Romero Ruiz et al. (2019), alterations in the kisspeptin system are heavily implicated in the neuroendocrine dysfunction of PCOS (Romero Ruiz et al., 2019). It is proposed that there is an increased kisspeptin drive from one part of the hypothalamus, which leads to the increased GnRH pulsatility characteristic of PCOS (Romero Ruiz et al., 2019). This elevated GnRH pulse frequency preferentially stimulates pituitary LH production over FSH, resulting in the elevated LH/FSH ratio commonly seen in the syndrome (Romero Ruiz et al., 2019). The high LH levels then excessively stimulate theca cells in the ovary, driving the overproduction of androgens (Romero Ruiz et al., 2019). Thus, dysregulation of kisspeptin signaling sits at the very top of the reproductive axis, acting as a primary driver of the neuroendocrine abnormalities that perpetuate the high androgen state in PCOS (Romero Ruiz et al., 2019).

6. Network Pharmacology of PCOS: The Interconnected Web of Signaling Pathways.

It is not possible to reduce the pathophysiology of PCOS to a single defective pathway; rather, the pathophysiology emanates from a complex and dysregulated network of interconnected signaling cascades. A network pharmacology perspective reveals how these pathways cross talk to engage in a self-reinforcing system that drives both metabolic and reproductive manifestations of the syndrome. At the hub of this network are the PI3K/Akt and MAPK/ERK pathways, which represent the divergent arms of insulin

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

signaling, and the mTORC1 pathway, which acts as a critical integrator of nutrient and growth factor signals.

6.1. The Core Metabolic Defect: PI3K/Akt/FOXO1 and AMPK/SIRT1 Axis

A hallmark of systemic insulin resistance in PCOS is impairment of the PI3K/Akt pathway. Binding of insulin to its receptor fails to appropriately activate the PI3K/Akt cascade, with resultant reduced glucose uptake both in skeletal muscle and adipose tissue. One critical downstream consequence of this involves dysregulation of FOXO1. Nakae et al. described that in states of impaired Akt signaling, FOXO1 remains active in the nucleus and promotes the expression of genes for gluconeogenesis, such as PEPCK and G6Pase, directly contributing to fasting hyperglycemia and compounding hyperinsulinemia.

This metabolic dysfunction is exacerbated by the parallel downregulation of the AMPK and SIRT1 energy sensing pathways. Hardie stated that AMPK, activated by an increase in the AMP/ATP ratio, promotes catabolic processes to generate ATP while inhibiting anabolic processes. Its activity is often suppressed in the nutrient excess environment of PCOS. Similarly, Ruderman et al. found that SIRT1, a NAD+ dependent deacetylase, is also downregulated, reducing its ability to activate key metabolic regulators like PGC-1α. The LKB1/AMPK axis, identified by Shaw et al. as a critical energy sensing pathway, is thus compromised. Metformin, a first line therapy, directly targets this node; Zhou et al. discovered that Metformin is known to activate AMPK, thereby reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity. The activation of AMPK also inhibits the anabolic mTORC1 pathway, creating a direct link between cellular energy status and growth signaling.

6.2. The Mitogenic and Proliferative Hub: Hyperinsulinemia, MAPK/ERK, and mTORC1

Whereas the metabolic PI3K/Akt arm is impaired, insulin signaling through the mitogenic MAPK/ERK arm remains exquisitely sensitive. Corbould et al. reported that, in contrast with the impaired PI3K/Akt pathway, the MAPK pathway appears to be normally sensitive or even enhanced in PCOS. This differential insulin signaling represents a basic paradox. The resultant hyperactive MAPK/ERK pathway, due to hyperinsulinemia, drives cellular proliferation. This effect is a principal driver of theca cell hyperplasia in the ovary and predisposes to endometrial hyperplasia.

It is a proliferative signal that is powerfully amplified by the mTORC1 pathway. mTORC1 is a key integrator, receiving activating signals from the impaired but still active Akt and inhibitory signals from AMPK. Hyperactive mTORC1 signaling, possibly because of hyperinsulinemia, has been implicated in excessive theca cell growth and steroidogenesis by Kayampilly & Menon. Thus, the combined signal from hyperinsulinemia via Akt, along with nutrient excess via suppressed AMPK, forms a powerfully synergistic activation of mTORC1, driving excessive ovarian cell growth and steroid hormone production.

6.3. The Androgen Production Network: cAMP/PKA, Calcium, and Hh Signaling

Intrinsic ovarian defects, which are amplified by systemic signals, feed forward to promote the hyperandrogenism that defines PCOS. The cAMP/PKA pathway represents a key regulator of theca cell steroidogenesis. Thus, Nelson et al. demonstrated that binding of LH to its receptor on theca cells stimulates adenylate cyclase, increasing cellular levels of cAMP, which in turn activate PKA by phosphorylation. Activation of PKA leads to phosphorylation and activation of steroidogenic enzymes, including StAR and CYP17A1. Theca cells of women with PCOS exhibit an exaggerated responsiveness to this pathway.

This is complemented by altered calcium signaling. Wang et al. reported that alterations in intracellular calcium homeostasis and signaling have been reported in PCOS theca cells, which could contribute to the intrinsic overproduction of androgens. Furthermore, the Hedgehog (Hh) pathway contributes to the cellular mass capable of producing androgens. Wang et al. found that altered Hh signaling has been observed in PCOS ovaries and may contribute to theca cell hyperplasia and the associated hyperandrogenism. The proliferative signals from MAPK/ERK and mTORC1 expand the pool of theca cells, while the enhanced cAMP/PKA and calcium signaling hyper activate the steroidogenic machinery within each cell.

6.4. The Follicular Arrest Nexus: TGF-β, Notch, and Apoptosis/Autophagy

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

Another characteristic feature that is a part of PCOS pathology is the arrest in follicular development, which is the result of an interplay of pathways acting on the critical balance between follicle growth and atresia. The TGF-β superfamily, particularly AMH, plays a key role. Pellatt et al. reported that AMH is significantly higher in PCOS and contributes to the arrest of follicular development by reducing follicle sensitivity to FSH. This is further compounded by dysregulation in the Notch pathway. Zhang et al. reported that dysregulation in the Notch pathway has been shown in the granulosa cells from PCOS patients, which may be one of the contributing factors to the arrested growth and abnormal follicular development.

Thus, the fate of arrested follicles is shaped by the balance between apoptosis and autophagy. Das et al. documented a disturbance in the normal patterns of apoptosis in arrested follicles from PCOS, which could be an important factor for their failure to either mature or undergo timely atresia. Moreover, autophagy, a cellular self-renewal process, is also disturbed. Choi et al. observed abnormal autophagy to occur in the granulosa cells of patients with PCOS, which might be associated with follicular atresia, oxidative stress, and oocyte quality impairment. Wang et al. suggested that the Wnt/β-catenin pathway also contributes to such dysregulation because it is involved in cell fate decisions, and its dysregulation has been implicated in PCOS, thereby contributing to ovarian dysfunction and follicular arrest.

6.5. The Inflammatory & Stress Core: JNK, p38, NF-κB, TLR4, and Inflammasomes

The state of chronic, low-grade inflammation in PCOS is underpinned by a tightly interwoven network of immune and stress pathways that drive the inflammation. Examples of such pathways are the inflammatory cytokine and cellular stress induced JNK and p38 MAPK pathways. JNK phosphorylates IRS-1 on serine residues, inhibiting its function and contributing to insulin resistance. Chen et al. reported that p38 MAPK activation has been implicated in PCOS and has been postulated to contribute to insulin resistance and ovarian dysfunction.

These stress kinases are major activators of the master inflammatory regulator, NF-κB. Gonzalez et al. found that it is activated by many kinds of stimuli, including oxidative stress and pro-inflammatory cytokines, which are increased in PCOS. Activated NF-κB undergoes nuclear translocation and induces the transcription of genes encoding pro-inflammatory molecules such as TNF-α and IL-6. This inflammatory response is further fueled by innate immune pathways. Tremellen & Pearce proposed that TLR4 signaling, activated by gut derived LPS due to dysbiosis, leads to the activation of NF-κB and the production of pro-inflammatory cytokines. This "metabolic endotoxemia" is a key link between the gut and systemic inflammation in PCOS. Finally, the inflammasome complex translates this cellular stress into mature inflammation. Brennan et al. discovered that the NLRP3 inflammasome is activated by various danger signals and has been implicated in the sterile inflammation of PCOS, linking metabolic dysregulation to immune activation. The cytokines produced (e.g., IL-1β, IL-6, TNF-α) then activate the JAK-STAT pathway. Duleba & Dokras stated that chronic low-grade inflammation in PCOS involves the activation of the JAK-STAT pathway by pro-inflammatory cytokines like IL-6, which can contribute to insulin resistance.

6.6. The Neuroendocrine and Systemic Modulators

The Kisspeptin system sits at the top of the HPG axis. Romero Ruiz et al. stated that alterations in the kisspeptin system have been implicated in the neuroendocrine dysfunction of PCOS, potentially contributing to the increased GnRH pulsatility and elevated LH levels. This elevated LH then further stimulates the cAMP/PKA pathway in theca cells, exacerbating hyperandrogenism.

Systemic metabolic dysregulation is also influenced by the Endocannabinoid System and PPARγ. Bari et al. reported that an overactive endocannabinoid system has been linked to obesity and insulin resistance, and some studies suggest its dysregulation in PCOS. Conversely, the PPARγ pathway is a target for therapy. Yki Järvinen stated that thiazolidinediones, insulin sensitizing drugs used in PCOS, are agonists of PPARγ, which promotes adipocyte differentiation and reduces inflammation.

6.7. The Consequences of a Stressed System: Oxidative Stress and Nrf2

Heightened oxidative stress is the cumulative effect of metabolic and inflammatory stress. The major defense mechanism of the cell against this is the Nrf2/ARE

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

pathway. According to Mihanfar et al., impaired Nrf2 signaling has been suggested in PCOS and contributes to increased oxidative stress. This serves as a strong activator for the JNK, p38, NF-κB, and inflammasome pathways in a vicious cycle, perpetuating the entire pathological network.

Taken together, PCOS is a systems biology disease wherein dysfunction in one pathway invariably perturbs many others. Hyperinsulinemia, driven by PI3K/Akt/FOXO1 impairment and AMPK/SIRT1 downregulation, simultaneously activates both MAPK/ERK and mTORC1 to drive proliferation. This intersects with intrinsic ovarian defects in cAMP/PKA, Hh, and Calcium signaling to cause androgen excess, while dysregulation of the TGF-β, Notch, Apoptosis, and Autophagy pathways contributes to follicular arrest. A core inflammatory module comprising JNK/p38, NF-κB, TLR4, Inflammasome, and JAK-STAT signaling both causes and is fueled by insulin resistance and oxidative stress compounded by a deficient Nrf2 response. Such an intricate network underpins clinical synergy of the PCOS phenotypes and explains why therapeutic strategies that simultaneously target multiple nodes, such as lifestyle intervention (improving AMPK, SIRT1, reducing inflammation) in combination with metformin (AMPK) or inositols insulin signaling yield most benefits.

7. Epigenetics in PCOS

Epigenetics encompasses heritable changes in gene expression not mediated by an alteration in the underlying DNA sequence. These mechanisms include DNA methylation, histone modifications, and noncoding RNAs and have emerged as an essential link between genetic predisposition, environmental exposure, and the phenotypic expression of complex diseases such as PCOS. Evidence accumulated recently indicates that epigenetic modifications are one of the key mechanisms underlying the pathogenesis and transgenerational transmission of PCOS traits.

DNA Methylation is the most extensively studied epigenetic mechanism in PCOS. It involves the addition of a methyl group to cytosine bases in CpG dinucleotides, typically leading to gene silencing. Xu et al. (2021) revealed through genome wide DNA methylation studies distinct methylation patterns in various tissues from women with PCOS compared to controls, including blood, adipose tissue, and ovarian cells. For instance, Wang et al. (2015) discovered that key genes involved in steroidogenesis, such as CYP19A1 (aromatase), have been found to be hypermethylated in granulosa cells of PCOS women, which could explain the impaired conversion of androgens to estrogens and contribute to the hyperandrogenic milieu. Conversely, Sagvekar et al. (2019) found that genes involved in inflammation and immune response often show hypomethylation, potentially contributing to the chronic low grade inflammatory state. Importantly, these epigenetic marks can be influenced by the environment. Xu et al. (2011) showed in animal models that prenatal exposure to excess androgens has been shown to induce lasting changes in the DNA methylome of foetal tissues, programming for a PCOS like phenotype in adulthood. Moreover, postnatal factors, such as diet and obesity, may further modify the epigenetic landscape, possibly promoting the disease.

Histone Modifications constitute another layer of epigenetic regulation. Histones are proteins around which DNA is wound to form chromatin. Post translational modifications to histone tails—such as acetylation, methylation, and phosphorylation—alter chromatin structure and accessibility, thereby regulating gene expression. Histone acetylation, generally associated with gene activation, is regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Qu et al. (2012) reported that studies have begun to uncover alterations in histone modifications in PCOS, for example, in PCOS theca cells, there is evidence of altered histone methylation at the promoters of androgen biosynthesis genes, which may contribute to their increased expression. The balance between HAT and HDAC activity can be influenced by metabolic signals, providing a potential mechanism by which hyperinsulinemia and nutrient excess in PCOS can directly alter the transcriptional program of genes involved in metabolism and steroidogenesis.

Non-Coding RNAs (ncRNAs), particularly microRNAs (miRNAs), are core post transcriptional regulators of gene expression. MiRNAs are small RNA molecules that bind with complementary sequences on target mRNAs, bringing about their degradation or translational repression. Sorensen et al. (2014) discovered that circulating and tissue specific miRNA profiles are significantly altered in PCOS. For example, miR-93,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

miR-223, and miR-21 have been consistently reported to be dysregulated in the serum and follicular fluid of PCOS women. These miRNAs target genes involved in insulin signaling, such as IRS1; steroid hormone receptors; and pathways that control follicular development and ovulation. Dysregulation of these miRNAs could thus disrupt both metabolic and reproductive functions. Li et al. (2020) suggested that exosomes are extracellular vesicles carrying miRNAs and other cargo that are emerging as important mediators of intercellular communication in PCOS, and it has been hypothesized that exosomal miRNAs secreted from one cell type (e.g., an insulin resistant adipocyte) can be taken up by another cell type (e.g., an ovarian theca cell), thereby transmitting the dysfunctional metabolic signal and contributing to ovarian hyperandrogenism.

In summary, epigenetics offers a dynamic, integrative platform by which to appreciate how genetic susceptibility, in conjunction with environmental factors, culminates in the manifestation of PCOS. The reversible nature of epigenetic marks also carries exciting therapeutic potential. "Epidrugs," such as HDAC inhibitors or drugs targeting specific miRNAs, are currently under investigation in other diseases and could represent a future direction of personalized PCOS therapy that aims at resetting the dysregulated epigenetic landscape.

8. Clinically Verified Genes for PCOS

While PCOS is polygenic, several candidate genes are consistently associated with the syndrome by large scale genetic studies (Hayes et al., 2015). These genes often cluster in biological pathways related to gonadotropin action, androgen biosynthesis, insulin signaling, and folliculogenesis, providing molecular validation for the key pathogenic hypotheses (Hayes et al., 2015). The following chart tends to show pathway of PCOS using genetics to target solutions.

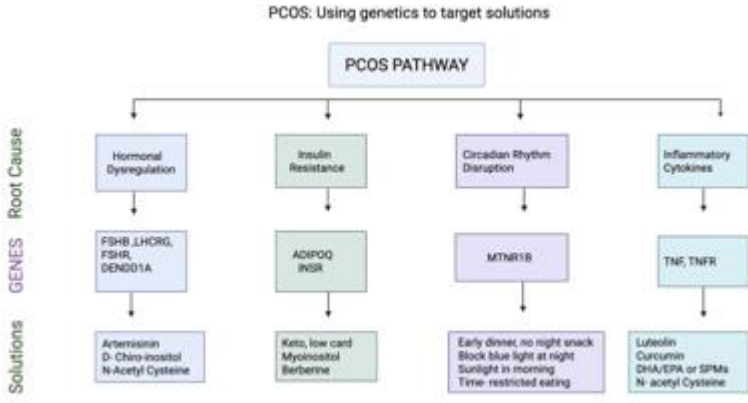

Fig.3. PCOS: Using genetics to target solutions

8.1 DENND1A (DENN/MADD Domain Containing 1A)

Among the most robustly replicated PCOS susceptibility genes identified by GWAS, DENND1A (McAllister et al., 2014) may be of interest. The gene DENND1A encodes the protein connecdem 1 involved in clathrin mediated endocytosis and intracellular trafficking. McAllister et al. (2014) identified an overexpressed splice variant, DENND1A.V2, only in theca cells of women with PCOS. Given its overexpression, this might improve the capacity of the cell to increase androgen production. While the exact mechanism is still being deciphered, McAllister et al. (2014) suggest that DENND1A.V2 influences trafficking of receptors or enzymes critical for androgen biosynthesis, exemplified by the LDL receptor necessary for cholesterol uptake or CYP17A1, thereby increasing androgen output following LH and insulin stimulation. Subsequent work has shown that the forced expression of the DENND1A.V2 isoform in normal human theca cells is sufficient to recapitulate a PCOS like phenotype, including the increased synthesis of testosterone and other androgens. This discovery of DENND1A underlines an intracellular membrane trafficking pathway hitherto unsuspected in the pathogenesis of ovarian hyperandrogenism and opens new avenues for targeted intervention.

8.2 FSHR (Follicle Stimulating Hormone Receptor)

FSHR is a gene of obvious relevance to ovarian function (Simoni et al., 1999). The FSHR is expressed on granulosa cells, and FSH binding is essential for

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

follicular growth, aromatase activity, and estrogen production (Simoni et al., 1999). Simoni et al. (1999) described that several polymorphisms in the FSHR gene have been investigated for their association with PCOS, with the most studied being the p. Asn680Ser (N680S) polymorphism (Simoni et al., 1999). The Ser680 variant has been associated with a less active receptor form, requiring higher levels of FSH to achieve the same biological effect (Simoni et al., 1999). In vitro functional studies have shown that the Ser680 variant is associated with decreased cAMP production in response to FSH stimulation, indicating reduced receptor efficiency (Simoni et al., 1999). In the context of PCOS, where FSH levels are often relatively low, possessing the Ser680 variant could contribute to impaired follicular development and anovulation (Simoni et al., 1999). This genetic variant may explain, in part, the heterogeneity in follicular response among women with PCOS and could have implications for predicting response to ovulation induction therapies (Simoni et al., 1999). Specifically, women with PCOS who are homozygous for the Ser680 allele may require higher doses of exogenous FSH for successful ovarian stimulation during in vitro fertilization (IVF) treatments (Simoni et al., 1999).

8.3 LHCGR (Luteinizing Hormone/Choriogonadotropin Receptor)

Raja Khan et al. (2011) stated that LHCGR codes for the receptor for both LH and hCG. It is highly expressed on theca cells and mature granulosa cells. Given the central role of LH in stimulating theca cell androgen production, LHCGR represents a strong candidate gene. Raja Khan et al. (2011) noted that specific polymorphisms of the LHCGR gene have been associated with an increased risk of developing PCOS. One SNP, rs13405728, in a genomic region containing LHCGR and other genes, has shown consistent replication across different ethnicities in several GWAS. Such variants may result in a hyperresponsive receptor or altered expression of the receptor, making theca cells more responsive to LH stimulation, with resultant excessive androgen synthesis. This concept is supported by the interaction of the LHCGR polymorphisms with the hyperinsulinemic environment, creating a potent stimulus for hyperandrogenism. Insulin has been demonstrated to synergize with LH in amplifying androgen production from theca cells, especially in the presence of genetic variants that increase the sensitivity or signaling of LHCGR (Raja Khan et al., 2011).

8.4 INSR (Insulin Receptor)

INSR gene variants have been sought as logical candidates for the insulin resistance in PCOS (Corbould et al., 2006). While no common INSR mutation is responsible for most cases, certain polymorphisms have been associated with PCOS risk (Corbould et al., 2006). More importantly, Corbould et al. (2006) discovered a specific mechanism of impaired insulin receptor function, identifying a disproportionate increase in the expression of the alternatively spliced dominant negative isoform of the insulin receptor, INSR-A (lacking exon 11), relative to the metabolic isoform INSR-B, in PCOS tissues (Corbould et al., 2006). This altered INSR-A: INSR-B ratio could contribute to the tissue specific insulin resistance observed in PCOS, where metabolic signaling is impaired but mitogenic signaling may be preserved or enhanced (Corbould et al., 2006). The INSR-A isoform, which binds insulin and IGF-2 with high affinity, is more associated with growth and mitogenic effects, while the INSR-B isoform is primarily responsible for metabolic actions (Corbould et al., 2006). The shift towards INSR-A expression in adipocytes and possibly other tissues of women with PCOS provides a molecular mechanism for the selective resistance to insulin's metabolic effects while its growth promoting actions remain intact (Corbould et al., 2006). This post transcriptional dysregulation of INSR splicing represents a key epigenetic link between genetic predisposition and the metabolic phenotype of PCOS (Corbould et al., 2006).

8.5 THADA (Thyroid Adenoma Associated)

THADA is another gene identified through GWAS that is strongly associated with PCOS risk. Although its function is less well understood, the THADA protein is implicated in pathways related to apoptosis and cellular stress responses. Variants in THADA also have been reported to confer an increased risk of type 2 diabetes, thereby supporting the shared genetic architecture between the two traits. Thus, genetic variations affecting THADA may alter β-cell function and insulin secretion or affect apoptosis within the ovarian follicle, influencing follicular arrest and development. A proposed function of THADA has been its role in regulation of calcium homeostasis in the endoplasmic

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

reticulum (ER). Its dysregulation has been known to induce ER stress, a key player in both insulin resistance and impaired pancreatic β-cell function. Moreover, within the ovary, altered apoptosis is a hallmark of the aberrant folliculogenesis seen in PCOS, and it is plausible that the THADA variants contribute to the disrupted balance between follicle survival and atresia, leading to the accumulation of small antral follicles. The strong genetic link between THADA, PCOS, and type 2 diabetes further underscores the central role of metabolic derangements in the etiology of the syndrome.

These genes, along with several other variants, provide a genetic template for PCOS, confirming the involvement of gonadotropin action (FSHR, LHCGR), androgen biosynthesis regulation (DENND1A), and insulin signaling/metabolism (INSR, THADA) (Hayes et al., 2015). However, each gene variant confers only a small increase in risk, and their combined effect, along with epigenetic and environmental modifiers, ultimately determines an individual's phenotype (Hayes et al., 2015).

9. Gut Dysbiosis and its Association with PCOS

Human gut microbiota, the vast community of microorganisms residing in gastrointestinal tract, is now recognized as a major controller of host metabolism, immunity, as well as endocrine function. A disruption in composition along with function of this microbial community, known as gut dysbiosis, has emerged as significant factor in pathogenesis of PCOS, creating “gut-brain-ovary" axis that contributes to the syndrome's features.

The State of Gut Dysbiosis in PCOS has been characterized in multiple studies comparing gut microbiota of females with PCOS to healthy controls. Liu et al. (2017) found that there is one consistent finding: reduced overall microbial diversity, generally associated with poorer metabolic health. At the phylum level, there is often a reduced ratio of Bacteroidetes to Firmicutes, a pattern also observed in obesity. More specifically, Torres et al. (2018) found that PCOS women show changes at the genus and species levels, including a reduction in beneficial bacteria, such as Akkermansia muciniphila, which improves gut barrier integrity and insulin sensitivity, and Lactobacillus species, together with an increase in potentially inflammatory bacteria. This dysbiotic profile is associated with clinical markers of PCOS, including hyperandrogenism and insulin resistance, independent of body mass index a direct link between the gut microbiota and the core pathophysiology of the syndrome.

The mechanisms behind the association between gut dysbiosis and PCOS pathogenesis are multifaceted. First, there is Increased Intestinal Permeability and Endotoxemia: Tremellen & Pearce (2012) suggested that dysbiosis can lead to integrity impairment of the intestinal epithelial barrier, leading to "leaky gut." This allows bacterial components, especially lipopolysaccharide (LPS) originating in Gram negative bacteria, to translocate into systemic circulation a condition known as metabolic endotoxemia. LPS induces a chronic low grade inflammatory response by triggering immune cells through the TLR4 signaling pathway, which results in the production of pro inflammatory cytokines such as TNF α and IL-6 that are known to induce insulin resistance in peripheral tissues. A subsequent factor involves Short Chain Fatty Acid (SCFA) Deficiency: den Besten et al. (2013) described that beneficial gut bacteria ferment dietary fiber to produce SCFAs, such as acetate, propionate, as well as butyrate, which have numerous beneficial effects: they serve as an energy source for colonocytes, strengthen the gut barrier, exert anti-inflammatory effects, as well as improve insulin sensitivity. Reduced abundance of SCFA producing bacteria in PCOS leads to a deficiency of these metabolites, thereby removing their protective effects on metabolism and inflammation. Additionally, Bile Acid Metabolism Alterations: Gut microbiota plays crucial role in modifying primary bile acids into secondary bile acids. Qi et al. (2021) discovered that dysbiosis can alter the bile acid pool, which in turn affects the signaling through the farnesoid X receptor (FXR) and Takeda G protein coupled receptor 5 (TGR5). These receptors are important regulators of glucose, lipid, along with energy metabolism, and disrupted bile acid signaling due to dysbiosis may therefore contribute to the metabolic disturbances in PCOS. Finally, an often-overlooked dimension is regulation of Androgen Levels: Emerging evidence suggests direct role for gut microbiome in regulating steroid hormone metabolism. Kwa et al. (2016) reported that certain gut bacteria possess enzymes, such as β-glucuronidase, that can deconjugate and reactivate estrogen and androgen metabolites that have been glucuronidated by the liver for

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

excretion. An altered microbiota with enhanced capacity for deconjugation could potentially increase the reabsorption and recirculation of androgens, contributing to systemic hyperandrogenemia.

Bidirectional Interaction with PCOS Genes: The relationship between gut dysbiosis & PCOS is likely bidirectional. While dysbiosis be competent to drive pathology, the genetic background of the host with PCOS may also shape the gut microbiota. Genes contributing to PCOS involved in steroidogenesis. For example, DENND1A and insulin signaling for example, INSR could generate an internal hormonal and metabolic environment that favors the growth of some microbial communities over others. For instance, Kelley et al. 2016 demonstrated in animal models that hyperandrogenism itself could be a cause for change in the gut microbiome composition as was indicated in studies in which androgen treatment induces dysbiosis. This forms a vicious circle: genetic predisposition leads to hormonal and metabolic changes promoting dysbiosis, which in its turn exacerbates hormonal and metabolic disturbances, amplifying the phenotype of PCOS.

In summary, gut dysbiosis is an integral part of the pathophysiology involved in PCOS. It contributes to insulin resistance, chronic inflammation, and probably hyperandrogenism through many interrelated mechanisms. This understanding opens new therapeutic perspectives by using prebiotics, probiotics, synbiotics, along with faecal microbiota transplantation as tools to restore a healthy gut microbiome to improve symptoms of PCOS. The following tables demonstrates the summary of Preclinical Studies on Gene Therapy for PCOS along with the other table representing Clinical Trials Investigating Genetic Associations and Interventions in PCOS.

Table 1: Summary of Preclinical Studies on Gene Therapy for PCOS

Target Gene/Pathway	Therapeutic Approach	Model Used	Key Findings	Reference
Androgen Receptor (AR)	siRNA against AR	DHEA induced PCOS rat model	Reduced ovarian androgen receptor expression, improved estrous cyclicity, decreased cystic follicles, and lowered serum testosterone.	(Cheng et al., 2019)
CYP17A1	shRNA targeting CYP17A1	Letrozole induced PCOS rat model	Suppressed ovarian CYP17A1 expression, leading to a significant lowering in serum androstenedione and testosterone levels, and restoration of ovarian morphology.	(Wang et al., 2020)
INSR Signaling	Adenovirus mediated expression of a constitutively active Akt	PCOS like mouse model	Improved systemic insulin sensitivity and glucose tolerance; ovarian effects not fully elucidated.	(Wu et al., 2014)
Adiponectin	Recombinant adiponectin or adenoviral delivery	DHEA induced PCOS mouse model	Ameliorated hyperandrogenism, improved estrous cyclicity, and reduced insulin resistance.	(Comim et al., 2013)
Kisspeptin	Antagonism of Kiss1r	Prenatally androgenized sheep model	Normalized LH pulse frequency and amplitude, reducing hyperandrogenism.	(Silveira et al., 2020)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

Table 2: Clinical Trials Investigating Genetic Associations and Interventions in PCOS

Trial Focus / Intervention	Genetic Target / Mechanism	Phase / Status	Key Outcomes / Objectives	Reference (ClinicalTrials.gov Identifier)
Metformin vs. Oral Contraceptive Pill	Analysis of genetic variants (e.g., STK11, INSR) in response to treatment.	Completed	To identify genetic predictors of metabolic and endocrine response to first line PCOS therapies.	NCT00704912
Vitamin D Supplementation	Interaction between Vitamin D receptor (VDR) gene polymorphisms along with treatment response.	Completed	To assess if VDR genotype influences the improvement in insulin sensitivity and hyperandrogenism with Vitamin D.	NCT01240213
Probiotic Supplementation	Modulating gut microbiome along with its impact on metabolic as well as hormonal parameters.	Various, Completed/Recruiting	Multiple trials aiming to see if probiotic induced changes in gut microbiota improve insulin resistance and reduce testosterone in PCOS.	e.g., NCT03409393
GLP-1 Receptor Agonists (Liraglutide)	Targeting insulin resistance and weight loss, potentially influenced by genetic background.	Phase 4, Completed	Demonstrated superior weight loss and metabolic improvement compared to placebo; genetic analyses may be ongoing.	NCT01568658
Myo-inositol Supplementation	Inositol pathways involved in insulin signaling; potential epigenetic effects.	Multiple, Completed	Many trials show improvement in insulin sensitivity, ovulation rates, along with reduction in androgens;	e.g., NCT02052271

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

			considered a nutraceutical intervention.	

10. Conclusion and Future Perspectives

PCOS is a very complex disorder that results from an eclectic interplay between genetic susceptibility, epigenetic modification, environmental factors, and a dysregulated gut microbiome. We have synthesized a large body of knowledge that has emphasized the central roles of insulin resistance, hyperandrogenism, neuroendocrine dysfunction, and inflammation in its pathogenesis. We have described the disrupted cellular signaling pathways from the metabolic PI3K/Akt, to the inflammatory NF-κB and the developmental Wnt and Hedgehog pathways that illustrate the fact that PCOS is a systemic disorder affecting multiple organs. The identification of important susceptibility genes, such as DENND1A and THADA, provides a genetic basis for these dysregulations, while epigenetic mechanisms provide a dynamic explanation of how environmental triggers can lock in the disease phenotype. The emerging role of gut dysbiosis further supports the connection between the gut ecosystem and systemic metabolism and ovarian function.

The future management of PCOS must move towards a more personalized and precision-based approach. Some specific areas where further research is warranted include the following: Integrative Multi Omics: The development of predictive models for disease risk, progression, and treatment response through the integration of genomics, epigenomics, transcriptomics, proteomics, and metabolomics data from large, well phenotyped cohorts, Targeted Therapeutics: Development of drugs directed against key pathogenic nodes, for example, DENND1A.V2 in theca cells, specific inflammatory pathways (e.g., NLRP3 inflammasome), or gut microbiome derived molecules, moving beyond metformin and oral contraceptives, Microbiome based Interventions: Large scale clinical trials are mandated to establish the efficacy of specific probiotic strains, prebiotics, and even fecal microbiota transplantation as adjuvant therapies for PCOS, Epi Therapies: Exploration of the potential of dietary and pharmacological agents that can reverse deleterious epigenetic marks associated with PCOS, and Focus on Mental Health and Quality of Life: Incorporation of routine psychological screening and support as a standard component of PCOS management and the development of interventions that address the psychological burden of the condition.

Though PCOS will remain a challenging syndrome, the unprecedented growth in our understanding of its underlying biology holds much promise. By deconstructing its complexity, we are paving the way for a future where PCOS can be managed with tailored strategies that address the root causes for each individual, ultimately improving reproductive, metabolic, along with psychological health of the millions of females affected worldwide.

Below is the list of abbreviations that were used in the manuscript.

Abbreviation	**Full Form**
ACTH	Adrenocorticotropic Hormone
AMH	Anti-Müllerian Hormone
AMP	Adenosine Monophosphate
AMPK	AMP-activated Protein Kinase
AP-1	Activator Protein-1
ARE	Antioxidant Response Element
AR	Androgen Receptor
ATP	Adenosine Triphosphate
BMP-15	Bone Morphogenetic Protein 15
BPA	Bisphenol A
CaMKs	Calcium/Calmodulin-dependent Kinases
cAMP	Cyclic Adenosine Monophosphate
CB1/CB2	Cannabinoid Receptor 1/2

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

CRP	C-reactive Protein
CYP11A1	Cytochrome P450 Family 11 Subfamily A Member 1
CYP17A1	Cytochrome P450 Family 17 Subfamily A Member 1
CYP19A1	Cytochrome P450 Family 19 Subfamily A Member 1
DENND1A	DENN/MADD Domain Containing 1A
DNA	Deoxyribonucleic Acid
ECS	Endocannabinoid System
EDCs	Endocrine Disrupting Chemicals
ER	Endoplasmic Reticulum
ERK	Extracellular Signal-regulated Kinase
ESHRE/ASRM	European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine
FFA	Free Fatty Acids
FOXO1	Forkhead box protein O1
FSH	Follicle Stimulating Hormone
FSHR	Follicle Stimulating Hormone Receptor
FXR	Farnesoid X Receptor
G6Pase	Glucose-6-Phosphatase
GDF-9	Growth Differentiation Factor 9
GLP-1	Glucagon-like Peptide-1
GLUT4	Glucose Transporter Type 4
GnRH	Gonadotropin-Releasing Hormone
GWAS	Genome-Wide Association Study/Studies

HATs	Histone Acetyltransferases
HDACs	Histone Deacetylases
Hh	Hedgehog
HPG axis	Hypothalamic-Pituitary-Gonadal axis
HPA axis	Hypothalamic-Pituitary-Adrenal axis
IGF-1	Insulin-like Growth Factor 1
IKK	IκB Kinase
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-18	Interleukin-18
INSR	Insulin Receptor
IRS	Insulin Receptor Substrate
IκB	Inhibitor of κB
JAK	Janus Kinase
JNK	c-Jun N-terminal Kinase
KISS1R	Kisspeptin Receptor
LH	Luteinizing Hormone
LHCGR	Luteinizing Hormone/Choriogonadotropin Receptor
LKB1	Liver Kinase B1
LPS	Lipopolysaccharide
MAPK	Mitogen-Activated Protein Kinase
miRNAs	microRNAs
mTOR	Mechanistic Target of Rapamycin
mTORC1	mTOR Complex 1
NAD+	Nicotinamide Adenine Dinucleotide
NF-κB	Nuclear Factor Kappa-B
NICD	Notch Intracellular Domain

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 2352-2387 | ISSN:2251-6727

NLRP3	NLR Family Pyrin Domain Containing 3
Nrf2	Nuclear factor erythroid 2–related factor 2
PCOS	Polycystic Ovary Syndrome
PCOM	Polycystic Ovarian Morphology
PEPCK	Phosphoenolpyruvate Carboxykinase
PI3K	Phosphatidylinositol 3-Kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PKA	Protein Kinase A
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RXR	Retinoid X Receptor
SCFAs	Short-Chain Fatty Acids
SHBG	Sex Hormone-Binding Globulin
shRNA	short hairpin RNA
siRNA	small interfering RNA
SIRT1	Sirtuin 1
Smo	Smoothened
SNP	Single Nucleotide Polymorphism
STAT	Signal Transducer and Activator of Transcription
StAR	Steroidogenic Acute Regulatory Protein
T2D	Type 2 Diabetes
TGF-β	Transforming Growth Factor-beta
THADA	Thyroid Adenoma Associated
TLR4	Toll-like Receptor 4
TNF-α	Tumour Necrosis Factor-alpha
TGR5	Takeda G protein-coupled receptor 5
TZDs	Thiazolidinediones
UPR	Unfolded Protein Response
VDR	Vitamin D Receptor
Wnt	Wingless-related integration site

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Statements & Declarations

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(Initials: RK = Reshpal Kaur, AM = Avijit Mazumder, SD = Saumya Das, AA=Ankit Awasthi and RJ= Reenoo Juahari.)

Conflict of Interest

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