International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	THE IMPACT OF NEUROENDOCRINE, GENETIC, AND ENVIRONMENTAL FACTORS ON THE PATHOPHYSIOLOGY OF POLYCYSTIC OVARY SYNDROME AND FEMALE FERTILITY: A COMPREHENSIVE REVIEW OF HORMONAL REGULATION AND CLINICAL IMPLICATIONS
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4354
RECEIVED	30 October 2025
ACCEPTED	17 December 2025
PUBLISHED	21 December 2025
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THE IMPACT OF NEUROENDOCRINE, GENETIC, AND ENVIRONMENTAL FACTORS ON THE PATHOPHYSIOLOGY OF POLYCYSTIC OVARY SYNDROME AND FEMALE FERTILITY: A COMPREHENSIVE REVIEW OF HORMONAL REGULATION AND CLINICAL IMPLICATIONS

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ABSTRACT

Polycystic ovary syndrome (PCOS) represents one of the most prevalent endocrine disorders among women of reproductive age, exerting significant effects on fertility, metabolic homeostasis, and overall health. The syndrome arises from complex interactions among hormonal, genetic, and environmental factors that disrupt the hypothalamic-pituitary-ovarian (HPO) axis. Neuroendocrine dysregulation, characterized by increased pulsatility of gonadotropin-releasing hormone (GnRH) and an elevated luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio, promotes excessive ovarian androgen production and follicular arrest. Hyperandrogenism, insulin resistance, and chronic anovulation form the core pathophysiological triad of PCOS. Genetic studies (GWAS) have identified loci associated with gonadotropin regulation, steroidogenesis, and insulin signaling, while environmental exposures, including endocrine-disrupting chemicals (EDCs), may act as epigenetic triggers in genetically susceptible individuals. Epidemiological analyses demonstrate a steady global increase in PCOS incidence, with the highest prevalence in high-income regions. Clinical heterogeneity is reflected by four Rotterdam phenotypes, differing in metabolic and reproductive consequences. PCOS not only impairs natural fertility but also affects assisted reproductive outcomes by altering oocyte quality and ovarian responsiveness. Comprehensive understanding of hormonal and metabolic disturbances is essential for individualized diagnosis and therapy. Future research should focus on elucidating epigenetic mechanisms and optimizing targeted treatments to improve fertility and reduce long-term metabolic risks in affected women.

KEYWORDS

Polycystic Ovary Syndrome, Hyperandrogenism, Insulin Resistance, Hypothalamic-Pituitary-Ovarian Axis, Female Fertility, Endocrine-Disrupting Chemicals

CITATION

Julia Kosęda, Ryszard Łagowski, Honorata Juniewicz, Zuzanna Kudlińska, Patryk Heryć, Karolina Kananowicz, Zofia Laska, Marianna Latour, Anna Jędrasiak, Jakub Piotrowski (2025) The Impact of Neuroendocrine, Genetic, and Environmental Factors on the Pathophysiology of Polycystic Ovary Syndrome and Female Fertility: A Comprehensive Review of Hormonal Regulation and Clinical Implications. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4354

1. Introduction

Female fertility is an important indicator of her reproductive health and overall biological well-being. It is the result of the coordinated action of the endocrine, metabolic, and immune systems, which together regulate the processes involved in oocyte maturation, ovulation, and pregnancy maintenance (1,2). The hypothalamic-pituitary-ovarian (HPO) axis is the central component in the regulation of menstrual cycles, and its proper functioning determines ovarian follicular maturation, ovulation, and hormonal balance (3).

The secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus initiates the release of gonadotropins-follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland, which determines the development of the ovarian follicle, ovulation, and luteinization (4). FSH stimulates the growth and maturation of antral follicles and the activation of granulosa cells, while LH is responsible for the rupture of the dominant follicle, the release of the oocyte, and the transformation of the corpus luteum (5). Estrogen promotes endometrial proliferation, increases uterine vascularization, supports follicular maturation, and modulates feedback mechanisms within the HPO axis (6). Progesterone plays a crucial role after ovulation. It stimulates secretory transformation of the endometrium, preparing the uterus for embryo implantation, limits excessive proliferation of the endometrium, and stabilizes the mucous lining. Progesterone also modulates immune mechanisms in the endometrium, promoting implantation tolerance. Disturbances in progesterone secretion or abnormal transformation of the corpus luteum can result in reduced implantation rates or early pregnancy loss (7). The interaction of these hormones - gonadotropins, estrogens, and progesterone - creates a precise hormonal cycle consisting of the follicular phase, ovulation, and the luteal phase. Disruptions in any of these mechanisms, such as insufficient levels of estrogen, LH, FSH, or progesterone, can lead to ovulation disorders and infertility (1,8).

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, and its occurrence is associated with significant reproductive, metabolic, and psychological consequences (9). PCOS is defined as a heterogeneous syndrome characterized by the coexistence of ovulatory dysfunction, hyperandrogenism (excessive androgen activity), and a the presence of polycystic ovarian morphology on ultrasound (10,11). The diversity of phenotypes of this syndrome means that its diagnosis and treatment require an individual approach, taking into account both hormonal and metabolic aspects.

The prevalence of PCOS in the population of women of reproductive age is estimated at approximately 6-10%, although depending on the diagnostic criteria and ethnic background, rates may reach up to 15% (12,13). Globally, PCOS is considered one of the main causes of anovulatory infertility, and its incidence continues to show an upward trend (14–16). Hormonal disorders observed in PCOS primarily include increased androgen secretion, an imbalance between LH and FSH gonadotropins, and often coexisting insulin resistance. Many patients also have elevated levels of anti-Müllerian hormone (AMH), which is associated with impaired follicular maturation in the ovary (17,18). PCOS is a condition with a complex etiology in which genetic, environmental, and epigenetic factors interact. It is believed that disturbances in gonadotropin secretion in the hypothalamic-pituitary-ovarian axis lead to excessive LH production relative to FSH, resulting in a predominance of androgens over estrogens and impaired follicular maturation (3,18). The consequence is anovulation or irregular ovulation and, as a result, reduced fertility.

The significance of PCOS in the context of reproduction is not limited to natural fertility mechanisms. Patients with this syndrome also often experience reduced effectiveness of assisted reproductive technologies such as in vitro fertilization (IVF) or ICSI micromanipulation. Women with PCOS may have a higher risk of ovarian hyperstimulation syndrome and lower oocyte quality, which affects the results of IVF procedures (18–20). On the other hand, thanks to advances in reproductive medicine, it is possible to treat infertility in women with PCOS more and more effectively, using modern stimulation protocols and an individualized therapeutic approach (19,21). PCOS is therefore not only a hormonal problem, but also a metabolic and reproductive one. Its significance goes beyond infertility itself, as hormonal disorders in this syndrome may increase the risk of other diseases, such as type 2 diabetes, hypertension, cardiovascular disease, obesity, and metabolic syndrome (22–24). A comprehensive understanding of these links is key to developing effective preventive and therapeutic strategies. In light of the above data, the problem of hormonal disorders in PCOS and their impact on fertility is of great importance for both diagnosis and clinical practice. A deeper understanding of hormonal pathomechanisms and their reproductive consequences may contribute to the development of new therapeutic methods and increase the effectiveness of infertility treatment in patients affected by this syndrome.

2. Research materials and methods

This review is based on an extensive analysis of recent peer-reviewed literature indexed in PubMed, covering studies published between 1935 and 2025. The inclusion criteria comprised original research, systematic reviews, and meta-analyses addressing the hormonal regulation of female fertility, the hypothalamic-pituitary-ovarian (HPO) axis, and the pathophysiology, epidemiology, and genetics of polycystic ovary syndrome (PCOS). Key search terms included "PCOS," "female fertility," "hyperandrogenism," "GnRH," "FSH," "LH," "insulin resistance," and "endocrine disruptors." Articles were selected based on methodological quality, relevance to reproductive endocrinology, and citation frequency. Data were extracted regarding diagnostic criteria (NIH 1990, Rotterdam 2003, AE-PCOS 2006), hormonal profiles, metabolic parameters, and genetic and environmental risk factors. Special attention was given to recent epidemiological datasets from the Global Burden of Disease (GBD) study, genome-wide association studies (GWAS), and molecular investigations of steroidogenesis and epigenetic regulation. The synthesis followed a narrative review format, integrating physiological, clinical, and mechanistic perspectives.

3. Characteristics of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, involving hormonal, metabolic, and reproductive dysfunction (10,13). It was first characterized by Stein and Leventhal in 1935. They demonstrated a association between enlarged, polycystic ovaries and menstrual disorders and infertility. They described a group of seven women who shared common symptoms: menstrual disorders, excessive hair growth, and enlarged ovaries containing numerous small follicles. They were among the first to show that amenorrhea may be directly related to increased ovarian volume. They proposed surgical treatment in the form of ovarian wedge resection. After the procedure, all patients regained regular menstrual cycles, and two of them became pregnant spontaneously. Later clinical observations showed that after bilateral wedge resection of the ovaries, menstruation returned in about 90% of women, and about 65% of them became pregnant. However, with the development of pharmacotherapy, especially after the introduction of clomiphene citrate and urinary-derived follicle-stimulating hormone (FSH), surgical treatment has become a much less frequently used therapeutic method (25,26). Since then, the concept of PCOS has expanded significantly, and contemporary definitions encompass a wide spectrum of clinical and biochemical manifestations.

3.1. Diagnostic criteria for PCOS

The first formal diagnostic criteria were developed by the National Institutes of Health (NIH) in 1990 and assumed the coexistence of hyperandrogenism and chronic anovulation, excluding other causes (27). In 2003, a broader definition was proposed in Rotterdam, according to which PCOS can be diagnosed in the presence of two of three characteristics: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound (28). In 2006, the Androgen Excess and PCOS Society (AE-PCOS) proposed criteria that recognized hyperandrogenism as a fundamental element of diagnosis, with the aim of further standardizing the definition (27).

The criteria for diagnosing PCOS are not uniform, which leads to significant differences in the identification of patients and in the comparability of test results. Review studies show that the expanded Rotterdam criteria lead to greater sensitivity in detecting milder forms of the disease, but at the same time complicate the interpretation of comparative studies and the creation of uniform treatment recommendations (13,18). Based on a meta-analysis of 24 studies, it can be concluded that the prevalence of polycystic ovary syndrome (PCOS) in the population of women of reproductive age varies depending on the diagnostic criteria used. The estimated prevalence of PCOS is approximately 6% according to the NIH criteria, 10% according to Rotterdam, and 10% according to the AE-PCOS Society, confirming that broader criteria increase the recognition of the syndrome. In unselected populations, these prevalences remain similar, indicating high data stability despite differences in study methodology. The analysis also showed that the most commonly observed symptoms in the studies were polycystic ovarian morphology (28%), oligo- or anovulation (15%), hirsutism (13%), and hyperandrogenemia (11%). The authors emphasize that ethnic factors and the lack of a uniform definition of PCOS phenotypes play an important role in epidemiological differences, which makes it difficult to compare results (13). The pathophysiological analysis indicated by Diamanti-Kandarakis and Dunaif emphasizes that PCOS has significant metabolic components (especially insulin resistance) distinct from purely reproductive characteristics, therefore criteria that do not take into account the metabolic profile (e.g., ultrasound features alone without hyperandrogenism) may fail to identify the subgroup of patients at highest cardiometabolic risk. In clinical practice, this means that phenotype identification should include assessment of both endocrine and metabolic parameters in order to adequately assess risk and select a treatment strategy (17).

3.2. PCOS phenotypes

The diversity of diagnostic criteria has led to the identification of different PCOS phenotypes, which vary in terms of the severity of clinical symptoms and metabolic consequences. Under the Rotterdam criteria, four basic PCOS phenotypes are distinguished based on a combination of three diagnostic features: clinical or biochemical hyperandrogenism, oligo-/anovulation, and polycystic ovaries on ultrasound: A (classic, full-blown - hyperandrogenism, anovulation, and polycystic ovary morphology), B (hyperandrogenism and anovulation), C (hyperandrogenism and polycystic ovaries), and D (anovulation and polycystic ovaries without hyperandrogenism) (13,28,29). The "classic" phenotypes (A and B) are usually associated with more severe metabolic disorders, insulin resistance, and the risk of developing type 2 diabetes (23). The frequency of individual phenotypes varies; in some clinical cohorts, phenotype A was predominant, e.g., 56.7% in the study by Baldani et al. (30), while in other analyses, non-classical or D phenotypes often predominated, especially in less selected populations (31). From a metabolic perspective, many studies indicate that phenotypes with current hyperandrogenism (A, B, C) are more often associated with an unfavorable metabolic profile, increased incidence of insulin resistance, metabolic syndrome, and obesity, compared to phenotype D, although this effect is strongly modified by body weight and fat distribution. A prospective study observed a four- to five-fold higher incidence of metabolic syndrome in hyperandrogenic phenotypes compared to the non-hyperandrogenic phenotype (10%) (32,33). At the same time, some analyses suggest that after taking into account factors such as age and BMI, the differences in metabolic parameters between phenotypes are reduced or disappear, which emphasizes the dominant role of obesity and fat distribution in determining metabolic risk regardless of the PCOS phenotype. Studies have shown no significant differences in insulin sensitivity between phenotypes after adjusting for BMI, and in many cohorts, it was waist circumference and abdominal obesity that predicted the development of metabolic disorders (34,35). The above data indicate that phenotypic classification should be considered as an aid in characterizing the heterogeneity of PCOS, but it does not replace a comprehensive metabolic assessment of each patient. Therefore, it is recommended to combine the description of the phenotype with the assessment of metabolic parameters (e.g., HOMA-IR, OGTT, lipid profile) in order to more accurately estimate the risk and select a therapeutic strategy. In addition, geographical and ethnic differences in the distribution of phenotypes and severity of symptoms (especially hirsutism) need to be taken into account when formulating regional clinical recommendations (13,36).

3.3. Epidemiology: prevalence, genetic and environmental factors

Data from the Global Burden of Disease 2019 study shows that the number of new cases of PCOS worldwide has increased from 1.4 million in 1990 to 2.1 million in 2019, representing a 54.3% increase over three decades (15). Analysis of data from the Global Burden of Disease 2021 (GBD 2021) clearly indicates that polycystic ovary syndrome (PCOS) is a growing global public health problem and one of the main causes of anovulatory infertility in women of reproductive age. Between 1990 and 2021, there was a significant increase in both the incidence and prevalence of PCOS, the global age-standardized incidence rate increased by 26.77% (to 30.7 cases per 100,000 women), while the prevalence increased by 28.21%, reaching 867.7 cases per 100,000 women. At the same time, the DALY (disability-adjusted life years) index was 7.6 per 100,000 women in 2021, an increase of 27.58% compared to 1990, confirming the growing health and social burden of this disease entity. The highest PCOS prevalence rates were reported in highly developed countries such as Italy (3,978.9/100,000), Japan (3,104.7/100,000), and New Zealand (2,789.7/100,000), indicating a strong association between socio-demographic development (SDI) and disease burden-particularly as regions with high SDI also had the highest incidence rates (70.2/100,000) and DALYs (15.2/100,000). The analyses also revealed that the global peak incidence of PCOS occurs in women aged 15-19, highlighting the need for early diagnosis and intervention to prevent hormonal, metabolic, and reproductive complications (16). An analysis covering European countries showed that in European regions, the highest PCOS prevalence rates were in the 35-39 and 40-44 age groups (37). The relationship between PCOS burden and SDI is nonlinear, with the highest prevalence observed at SDI values around 0.9, which may reflect the influence of environmental, dietary, and epigenetic factors characteristic of highly developed societies (16).

The etiopathogenesis of PCOS is multifactorial, involving genetic, environmental, and metabolic factors. Genome-wide association studies (GWAS) have identified numerous gene loci associated with PCOS, including genes responsible for regulating the hypothalamic-pituitary-ovarian axis, indicate pathologies related to gonadotropin regulation, steroidogenesis, insulin metabolism and adipogenesis (38). Analyses by Hiam et al. indicate a common genetic architecture between different PCOS phenotypes, confirming that this disorder is a heterogeneous entity with a multigenic basis (39). Family and twin studies have repeatedly demonstrated a strong genetic predisposition. Twin analyses suggest that a large proportion of the variance in PCOS risk is genetically determined. Based on studies conducted in the Dutch twin, involving over 1,300 pairs of identical twins and nearly 1,900 fraternal twins and sisters, a significant contribution of genetic factors to the development of polycystic ovary syndrome has been confirmed. It was shown that the concordance rate for PCOS in monozygotic twins was more than twice as high as in dizygotic twins, indicating a significant hereditary basis for the disease. Analysis of variance and genetic modeling have revealed that the co-occurrence of symptoms such as oligomenorrhea, acne, and hirsutism is mainly due to genetic factors rather than the influence of the family environment (40).

Environmental factors and lifestyle also play a significant role. Obesity, insulin resistance, a high-calorie diet, and low physical activity exacerbate the symptoms of hyperandrogenism and metabolic disorders, worsening the clinical course of PCOS. In populations with an increasing prevalence of overweight and obesity, there is a parallel increase in the diagnosis of PCOS. Meta-analyses indicate that each 1% increase in the prevalence of obesity in the population is associated with an approximate increase in the prevalence of PCOS of ~0.4% (Rotterdam criteria) (41). Clinically, it is important to note that obesity exacerbates insulin resistance and hyperinsulinemia, mechanisms which in turn stimulate androgen production in the ovaries and exacerbate hyperandrogenism and menstrual cycle disorders. It is estimated that the percentage of PCOS patients showing signs of insulin resistance varies widely (approx. 35–80%), and in obese women with PCOS, IR is particularly common and severe (42). Furthermore, classic comparative analyses show that women with PCOS have a significantly higher risk of being overweight and obese (e.g., RR for obesity ~2.7 in some reviews). However, this risk varies depending on ethnicity, in Caucasian women with PCOS, the RR for obesity was significantly higher than in Asian women (~10.8 vs. ~2.31) compared to the respective control groups without PCOS (43).

In addition to metabolic factors, a growing number of studies indicate that, apart from genetics and lifestyle, an epigenetic mechanism may also be involved in the development of PCOS, consisting of permanent changes in gene expression that do not result from DNA mutations but from modifications such as DNA methylation, histone modifications, or the action of microRNAs. A study by Z. Y. Zhong and colleagues showed that women with PCOS are characterized by global DNA hypomethylation and altered methylation of genes associated with ovarian steroidogenesis, which may contribute to excessive androgen production and ovarian dysfunction (44). A review by Sadeghi et al. emphasized that epigenetics may be useful both diagnostically and therapeutically in determining the PCOS phenotype (45). At the same time, many studies are analyzing the impact of environmental factors on the risk of PCOS, in particular endocrine-disrupting chemicals (EDCs), such as bisphenols, phthalates, and parabens (46). A review by E. Peebles and colleagues indicated that exposure to, for example, air pollution, micro- and nanoplastics, heavy metals, and EDCs can specifically disrupt the functioning of the hypothalamic-pituitary-ovarian axis and fertility by affecting estrogen and androgen receptors and thus modulating the expression of genes related to reproduction, which promotes the manifestation of PCOS traits (47). In another study, significant correlations were found in adolescent girls with PCOS between phthalate (DEHP/MEHP) concentrations and insulin resistance indices and triglyceride levels, regardless of body mass index (48). EDCs are believed to act on several levels: modifying the actions of sex hormone receptors, altering the regulation of genes critical for ovarian function (47), affecting DNA methylation or other epigenetic changes (44), and disrupt insulin metabolism, which is crucial in PCOS. Consequently, in women with a genetic predisposition, additional environmental exposure may act as a “trigger” for the phenotype- the “second hit”. The authors of “Polycystic Ovary Syndrome: A Comprehensive Review of Etiology, Diagnosis and Management” discuss the “two-hit hypothesis,” according to which genetic susceptibility is the first “hit” and environmental exposures (including EDCs) are the second factor triggering the development of PCOS. As a result, prenatal conditions, childhood, and early adulthood are windows of particular vulnerability (45,46).

4. Pathophysiology and hormonal disorders in PCOS

4.1. Hypothalamic-pituitary-ovarian axis

There is considerable evidence that one of the early and central disturbances in PCOS is neuroendocrine dysregulation, a change in the dynamics of gonadotropin-releasing hormone (GnRH) pulses in the hypothalamus leads to a relative increase in the frequency (and, in some conditions, amplitude) of GnRH pulses. The higher pulse frequency promotes preferential secretion of LH over FSH by the pituitary gland, resulting in relatively elevated LH and reduced or normal FSH levels, which are typical for many PCOS patients. This gonadotropin configuration has direct consequences for follicular maturation: relatively higher LH promotes excessive steroidogenesis in theca cells, while lower FSH impairs aromatase activity and estradiol synthesis in granulosa cells, which disrupts the normal growth of the dominant follicle and inhibits ovulation. Small antral follicles accumulate, leading to the development of polycystic ovary morphology. Mechanisms that maintain an enhanced pulsatile rhythm include reduced sensitivity of the pulse generator to negative feedback from progesterone or estrogen and the direct influence of androgens and AMH on hypothalamic-pituitary regulation. These neuroendocrine relationships create a “vicious circle” in which increased androgens sustain abnormal GnRH pulses, which in turn sustain increased LH and further androgen production (49).

4.2. Hyperandrogenism

Hyperandrogenism in PCOS has multiple causes. The main source of androgens are the ovaries (mainly theca cells) and, in some patients, the adrenal glands. In the ovary, LH stimulates steroidogenesis in theca cells by activating enzymes such as CYP17A1, which increases the synthesis of androstenedione and testosterone, while reduced FSH concentrations and aromatization disorders limit the conversion of androgens to estrogens in granulosa cells. As a result, androgen levels increase locally and systemically. Cell-level observations also show increased expression of steroidogenic enzymes and altered regulation of intracellular signals (including cAMP/PKA pathways and transcription factors regulating steroidogenesis) (50). Studies on isolated theca cells from the ovaries of women with PCOS have consistently shown increased activity and expression of key steroidogenic enzymes (including CYP17A1, HSD3B2), which translates into greater synthesis of androstenedione and testosterone under the influence of LH. Additionally, molecular models and transcriptome analyses have described the overexpression of regulatory genes (e.g., DENND1A.v2) associated with the phenotype of increased androgenogenesis. In practice, this means that even with “normal” gonadotropin concentrations, conditions conducive to excessive production and accumulation of androgens arise in the ovarian follicle itself (51).

Clinically, excess androgens manifest as hirsutism, acne, androgenic alopecia, and in terms of reproduction, lead to anovulation, a shortened luteal phase, and deterioration in oocyte quality. Follicular maturation disorders are possible, which affects the parameters of oocytes assessed in reproductive cycles (50).

In some women with PCOS, the adrenal glands also play a significant role in androgen excess. Meta-analyses and cohort studies indicate that increased concentrations of dehydroepiandrosterone sulfate (DHEAS) and other adrenal precursors occur in a significant proportion of patients, especially in atypical PCOS phenotypes, and correlate with both a more severe metabolic profile and poorer outcomes of assisted reproductive treatment. Studies show that adrenal androgen sources may reduce the chances of pregnancy in assisted reproduction (lower rates of clinical pregnancy and cumulative live birth) (52). A study by Carmina et al. assessed the frequency of elevated DHEAS levels, a marker of adrenal androgen secretion, in young women with PCOS in different disease phenotypes. In a group of 648 patients aged 20-29, elevated DHEAS levels were found in approximately 33% of women, significantly more often in phenotypes B and C than in the classic phenotype A. The average DHEAS concentration was higher in patients with PCOS than in healthy women, indicating a significant contribution of the adrenal glands to the pathogenesis of hyperandrogenism. Women with higher DHEAS also had increased testosterone and androstenedione concentrations, but no significant differences in BMI, insulin resistance, or LH/FSH ratio were found, suggesting that adrenal hyperandrogenism is not directly related to metabolic disorders. The authors emphasize that DHEAS assessment is important in the diagnosis of PCOS, as the adrenal source of androgens may coexist with the ovarian source, differentiating the clinical course and response to treatment. (52). The diagnosis of elevated androgen levels is important in the context of pregnancy in patients with PCOS, as evidenced, among others, by the study “Association between preconception anti-androgen therapy and pregnancy outcomes of patients with PCOS: A prospective cohort study”. This prospective study observed 296 patients with PCOS who, prior to assisted reproduction treatment or pregnancy, received androgen-reducing therapy (including drospirenone + ethinyl estradiol) or did not. In the group that received androgen pretreatment, a lower percentage of adverse pregnancy outcomes (12.16% vs. 27.03% in the group without pretreatment) and a lower percentage of neonatal complications (17.16% vs. 36.67%) were observed. Subanalyses showed that pretreatment therapy was significant in reducing the risk of preterm birth and pregnancy loss. This indicates that targeting hyperandrogenism before pregnancy may improve pregnancy outcomes in women with PCOS (53).

4.3. Insulin resistance and hyperinsulinemia

Insulin resistance (IR) with accompanying hyperinsulinemia is a common component of PCOS and plays a central role in linking metabolic and reproductive disorders. Review articles and clinical studies have reported that the percentage of patients with symptomatic or detected IR ranges from 35-80% depending on the source, with average estimates often ranging from 60-70%, especially in overweight or obese patients. Hyperinsulinemia directly affects the ovaries, together with LH, it enhances theca cell steroidogenesis, increases androgen conversion, and decreases the concentration of androgen-binding proteins, including SHBG, which increases the fraction of free androgens. Insulin additionally affects granulosa cell function and follicular metabolism (glucose, substrate transport), which can disrupt oocyte maturation and ultimately impair fertility. IR in PCOS has genetically determined components resulting from abnormal adipokine secretion and the impact of abdominal obesity. At the same time, some skinny women with PCOS also show insulin sensitivity deficiency, suggesting heterogeneous causes. Lowering insulin levels through lifestyle changes or metformin use often improves cycle irregularity and metabolic parameters, confirming the clinical significance of this axis (54). A large retrospective cohort study from 2023 analyzed the association between the level of insulin resistance and ovarian sensitivity to gonadotropin stimulation and reproductive outcomes in women with polycystic ovary syndrome (PCOS) undergoing their first in vitro fertilization (IVF) procedure. The analysis included over two thousand patients, who were divided into three groups based on their HOMA-IR score, which reflects the severity of insulin resistance. Higher HOMA-IR scores were found to be significantly associated with reduced ovarian sensitivity to gonadotropin stimulation, as measured by the ovarian sensitivity index (OSI). In a multivariate analysis, after adjusting for age, BMI, AMH, FSH, LH, testosterone, antral follicle count, and PCOS phenotype, a significant negative effect of HOMA-IR on OSI was demonstrated (β

= -0.24; 95% CI -0.35 to -0.13), which was particularly pronounced in lean women (BMI < 25 kg/m²; β = -0.33; 95% CI -0.51 to -0.16). Additionally, higher insulin resistance was associated with an increased risk of early miscarriage (OR = 2.21; 95% CI 1.13–4.33), although it did not significantly affect the overall rate of clinical pregnancy or live births. These results suggest that insulin resistance may limit ovarian response to stimulation and indirectly impair oocyte quality, especially in women of normal weight, which is important when planning IVF protocols (54). Similar observations were reported by Chen et al., who studied the impact of insulin resistance on reproductive and obstetric outcomes in women with PCOS undergoing their first embryo transfer in an IVF cycle. In this analysis, higher HOMA-IR values were associated not only with a higher rate of early miscarriages (from approximately 7% in the group with the lowest insulin resistance to over 16% in the group with the highest), but also with a higher incidence of gestational diabetes and macrosomia in newborns. At the same time, a decrease in the percentage of live births was observed in groups with higher HOMA-IR, despite no significant differences in the frequency of clinical pregnancy or late miscarriages (55). The conclusions of both studies clearly indicate that insulin resistance is a key risk factor for adverse reproductive outcomes in women with PCOS, both through impaired ovarian response to hormonal stimulation and increased risk of early pregnancy loss and metabolic disorders in the perinatal period. Therefore, assessment and possible correction of carbohydrate metabolism parameters before starting infertility treatment may improve both the effectiveness of assisted reproduction procedures and the safety of pregnancy.

4.4. Other hormone disorders

Significantly higher concentrations of anti-Müllerian hormone (AMH) are observed in PCOS. Typically, it is 2-3 times higher than in women without PCOS, which is associated with the presence of many small antral follicles and impaired folliculogenesis (56,57). AMH produced by granulosa cells has a paracrine function, inhibits the recruitment of primordial follicles, and reduces the sensitivity of antral follicles to FSH. In PCOS, both the excess of AMH-producing follicles and the increased AMH production per cell contribute to the maintenance of anovulation. In addition, AMH may interact with the hypothalamic-pituitary-ovarian axis by modulating the gonadotropin response. (57). In the meta-analysis "Association between serum AMH levels and IVF/ICSI outcomes in patients with PCOS," the authors showed that higher AMH concentrations (upper quartile) were associated with a lower likelihood of clinical pregnancy (OR ≈ 0.77; 95% CI 0.63-0.93) and live births (OR ≈ 0.71; 95% CI 0.58-0.87) compared to the lower quartile, even though the number of oocytes retrieved was statistically higher (SMD ~0.90; 95% CI 0.30-1.51) (58). The conclusion is that although elevated AMH in PCOS often means a large number of follicles and oocytes, this does not necessarily translate into better reproductive outcomes (59). Prolactin concentration disorders (hyperprolactinemia) or thyroid diseases (hypothyroidism or hyperthyroidism) may mask or exacerbate the symptoms of menstrual disorders and affect fertility, which is why they are routinely assessed in differential diagnosis. In a Dutch analysis by van der Ham et al. assessed the prevalence of thyroid dysfunction and hyperprolactinemia in 528 women with PCOS. The results showed that approximately 11.4% of women in this group had elevated prolactin levels, of which 43.2% also had thyroid dysfunction. Furthermore, the study suggests that thyroid hormone (TSH) and prolactin disorders may coexist with PCOS and potentially impair reproductive function by affecting the hypothalamic-pituitary-ovarian axis and the menstrual cycle (60).

4.5. The role of inflammation and metabolic factors

PCOS is associated with chronic, low-grade inflammation. Patients show elevated markers of inflammation: IL-6, TNF-α, CRP-independently or partially dependent on BMI. Cytokines directly affect ovarian cell function and insulin signaling, which exacerbates both IR and local androgen production. Adipokines (leptin, adiponectin) play a key role here: abdominal obesity is associated with an increase in leptin and a decrease in adiponectin, which promotes inflammation, insulin resistance, and ovarian metabolic dysfunction. These changes lead to an unfavorable follicular microenvironment (oxidation, endoplasmic stress, abnormal use of energy substrates), which in turn impairs oocyte maturation, endometrium, and the quality of response to assisted reproduction treatment. Meta-analyses and systematic reviews confirm the association of pro-inflammatory cytokines with the clinical and metabolic features of PCOS, although the magnitude of the effects and their independence from obesity vary between studies (45). The study "Intra-ovarian inflammatory states and their associations with embryo quality in normal-BMI PCOS patients undergoing IVF treatment" analyzed women with PCOS who had a normal body weight (normal BMI) and underwent in vitro fertilization. The authors examined cytokines present in follicular fluid (FF) and ovarian granulosa cells to determine whether inflammation in the ovary, and not just systemic inflammation, affects embryo quality. It was shown that the levels of certain cytokines, including MIP-1β in follicular fluid, were significantly elevated in patients with PCOS compared to the control group ($p = 0.005$). In addition, higher MIP-1β concentrations correlated negatively with the number of good-quality embryos on day three and with the percentage of top-quality blastocysts ($p = 0.003$). The authors suggest that even in women with PCOS and normal body weight, there is local inflammation in the ovary, which may negatively affect the follicular microenvironment and embryo quality (61).

5. Discussion

The findings indicate that PCOS is a multifactorial disorder arising from both intrinsic and extrinsic disruptions of the HPO axis. Dysregulated GnRH pulsatility leads to disproportionate LH secretion and enhanced ovarian androgen production, while relatively low FSH levels impair follicular maturation. The resulting hyperandrogenism perpetuates anovulation and contributes to metabolic alterations through insulin resistance and adipokine imbalance. Although obesity exacerbates PCOS manifestations, insulin resistance is also observed in lean phenotypes, suggesting inherent metabolic defects. Genetic studies have identified multiple loci implicating neuroendocrine and insulin signaling pathways, supporting the concept of a polygenic, heterogeneous disorder. Environmental exposures, especially endocrine-disrupting chemicals and high-calorie diets-further modulate gene expression through epigenetic mechanisms, exemplifying the "two-hit" hypothesis. Phenotypic variability (A–D types) demonstrates differential metabolic risk, with hyperandrogenic phenotypes showing the strongest association with metabolic syndrome and cardiovascular risk. Clinically, PCOS reduces spontaneous fertility and complicates assisted reproduction, though preconception androgen suppression and insulin-sensitizing therapy have shown promising outcomes. Therefore, PCOS should be regarded not only as a reproductive but also as a systemic metabolic disorder requiring multidisciplinary management.

6. Conclusions

PCOS remains a major cause of anovulatory infertility and a significant global health burden. Its pathogenesis involves the interplay of neuroendocrine dysregulation, androgen excess, insulin resistance, and environmental influences. Understanding the mechanisms that link hormonal imbalance to metabolic dysfunction is essential for developing personalized therapeutic strategies. The identification of specific genetic and epigenetic determinants provides new opportunities for precision medicine in reproductive endocrinology. Future studies should emphasize early diagnosis, metabolic monitoring, and targeted interventions to improve reproductive outcomes and long-term health in women with PCOS.

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All authors have read and agreed with the published version of the manuscript.
Conflict of Interest Statement: Authors have declared no conflict of interests.
Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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