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Insulin resistance in polycystic ovary syndrome phenotypes and the vicious cycle model in its etiology

Piotr Szkodziak[1]✉, Filip Szkodziak[1], Kamila Trzeciak[1], Sławomir Woźniak[1], Margaret Mlynarczyk[2] & Tomasz Paszkowski[1]

Polycystic ovary syndrome (PCOS) is a multifactorial disorder driven by at least three pathophysiological components: hypothalamic, ovarian, and obesity-related mechanisms. Insulin resistance (IR) is a unifying feature. Reciprocal interactions among androgen excess, hyperinsulinemia, and reduced hepatic sex hormone-binding globulin production create a self-sustaining "vicious cycle" that exacerbates PCOS manifestations, which vary in severity and define four clinical phenotypes. To evaluate insulin resistance across PCOS phenotypes A (HA + OD + PCOM), B (HA + OD), C (HA + PCOM), and D (OD + PCOM). A retrospective observational study (2018–2022) of 200 Caucasian women aged 18–36 diagnosed with PCOS according to the Rotterdam criteria. Insulin resistance was assessed using HOMA-IR. Clinical and anthropometric variables, Free Androgen Index (FAI), and Ferriman-Gallwey (mFG) scores were analyzed by phenotype. Insulin resistance was present in 57.5% of participants. HOMA-IR showed no correlation with PCOS duration but differed significantly between phenotypes. Mean HOMA-IR values exceeded reference thresholds in all phenotypes: A 3.59, B 2.59, C 2.05, D 2.73. Moderate to strong positive correlations were observed between HOMA-IR and mean arterial pressure, pulse rate, and waist-to-hip ratio, indicating an association with cardiometabolic risk across phenotypes. Positive associations among FAI, HOMA-IR, and mFG score support a contribution of ovarian androgens to insulin resistance and hirsutism. Insulin resistance predominated in this PCOS cohort and was phenotype-dependent rather than related to syndrome duration. All phenotypes exhibited elevated HOMA-IR, with phenotype A showing the highest and phenotype C the lowest mean values. The proposed "vicious cycle" model integrates hyperandrogenism and hyperinsulinemia in peripheral insulin resistance; further research into genetic and intracellular signaling mechanisms is warranted.

Keywords Hyperandrogenemia, Insulin resistance, Metabolic syndrome, Polycystic ovary syndrome, Vicious cycle model

Abbreviations

AE-PCOS	Androgen Excess & PCOS Society
AFC	antral follicle count
ANOVA	analysis of variance
BMI	Body Mass Index
DCI-IPG	D-chiro-inositol phosphoglycans
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
FAI	Free Androgen Index
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HA	hyperandrogenism
HbA1c	glycated hemoglobin
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance

[1]3rd Chair & Department of Gynecology, Medical University of Lublin, Lublin, Poland. [2]Department of Obstetrics & Gynecology, Eastern Virginia Medical School, Norfolk, USA. ✉email: piotr.szkodziak@gmail.com

IPG	inositol phosphoglycans
IR	insulin resistance
LH	Luteinizing hormone
MAP	Mean Arterial Pressure
MI-IPG	myo-inositol phosphoglycans
mFG	modified Ferriman-Gallwey Score
NIH	National Institutes of Health
OD	ovulatory dysfunction
P450	cytochrome P450 complex
PCOM	polycystic ovary morphology
PCOS	polycystic ovary syndrome
SD	standard deviations
SHBG	sex hormone binding globulin
WHR	Waist-to-Hip Ratio

Polycystic ovary syndrome (PCOS) is a multifactorial disease, which makes it possible to distinguish at least three pathophysiological components: "hypothalamic", "ovarian" and "obesity-related"[1,2].

In the "hypothalamic" component of PCOS, an imbalance in pituitary hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH) leads to underdeveloped ovarian follicles and excessive androgen production, primarily testosterone.

Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile manner, regulating pituitary secretion of LH and FSH in response to circulating estradiol, progesterone, and leptin. Kisspeptin neurons modulate GnRH pulse dynamics, with higher frequencies favoring LH release and lower frequencies promoting FSH secretion. In the "hypothalamic" subtype of PCOS, increased GnRH pulse frequency elevates LH levels relative to FSH, resulting in an increased LH/FSH ratio[3–6] (Fig. 1).

This hormonal imbalance contributes to insulin resistance (IR) in approximately 75% of affected women, affecting fat tissue, muscles, heart, and liver. Elevated insulin levels also suppress aromatase, an enzyme that normally converts testosterone into estradiol, while promoting further testosterone production from theca cells. Elevated circulating testosterone impairs ovarian follicle quality[1].

The "ovarian" component is associated with mutations in the aromatase genes of the cytochrome P450 complex (CYP19) within granulosa cells of the follicle. Reduced activity of P450 aromatase inhibits the conversion of testosterone to estradiol, resulting in an excess of the former hormone. The CYP19 gene, located on the long arm of chromosome 15 at position 15q21.1, has been implicated in various genetic studies. Reports indicate that several single nucleotide polymorphisms (SNPs) within the CYP19 gene are associated with variations in serum androgen concentrations among women, encompassing diverse racial and ethnic groups. Multiple studies have established a correlation between the SNP rs2414096 in the CYP19 gene and the occurrence of hyperandrogenism and PCOS[7–11] (Fig. 1.)

In the "obesity-related" variant of PCOS, ovulation disorders - sometimes resulting in complete absence of ovulation - are linked to elevated insulin levels (hyperinsulinemia). This occurs due to the negative impact of adipocytokines produced by excess adipose tissue on insulin receptors, leading to IR in the affected tissues. Enlarged adipocytes and decreased adiponectin levels are significant contributors to IR and hyperandrogenemia. These phenomena are associated with adipocyte hypertrophy, which impairs the differentiation of adipose stem cells into mature adipocytes. Differentiated adipocytes in women with PCOS exhibit increased lipid content, correlating with elevated androgen levels. PCOS-specific adipose tissue dysfunction encompasses impaired insulin-stimulated glucose uptake.

Adipocytes in PCOS exhibit dysregulated lipid storage, mobilization, and energy homeostasis. Upregulated intra-adipose synthesis of testosterone and dihydrotestosterone, mediated by increased aldo-ketoreductase expression promotes lipid accumulation and systemic lipotoxicity, with ectopic deposition in skeletal muscle and liver contributing to IR. Concurrent adipose inflammation, macrophage infiltration, fibrosis, and tissue expansion further exacerbate metabolic dysfunction[1,2,12–14].

Hyperinsulinemia secondary to insulin resistance suppresses hepatic sex hormone binding globulin (SHBG) synthesis, elevating serum free testosterone levels[13].

Approximately 3% of women with PCOS exhibit isolated functional adrenal hyperandrogenism, characterized by elevated dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). These androgens circulate to peripheral tissues, such as adipose and liver, where they are converted to estrogens and active androgens, exacerbating PCOS symptoms[13,14].

Insulin resistance and hyperinsulinemia are common features of PCOS. Their reciprocal interaction with androgen excess and reduced hepatic SHBG synthesis creates a self-perpetuating "vicious cycle" that exacerbates clinical manifestations (Fig. 1.)[1,2,13].

Three diagnostic criteria sets have been proposed for adult PCOS, all requiring exclusion of other endocrine disorders with overlapping symptoms, including thyroid dysfunction, non-classical congenital adrenal hyperplasia, adrenal hyperandrogenism, and hyperprolactinemia[15–17].

The first diagnostic criteria for PCOS were established by the National Institutes of Health (NIH) in 1990, emphasizing menstrual irregularities and hirsutism, but excluding polycystic ovary morphology (PCOM)[16]. In 2003, the Rotterdam criteria broadened the definition by requiring two of three features: hyperandrogenism (HA) (clinical or biochemical), ovulatory dysfunction (OD), and PCOM, aligning with international guidelines (International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome)[13,15,18].

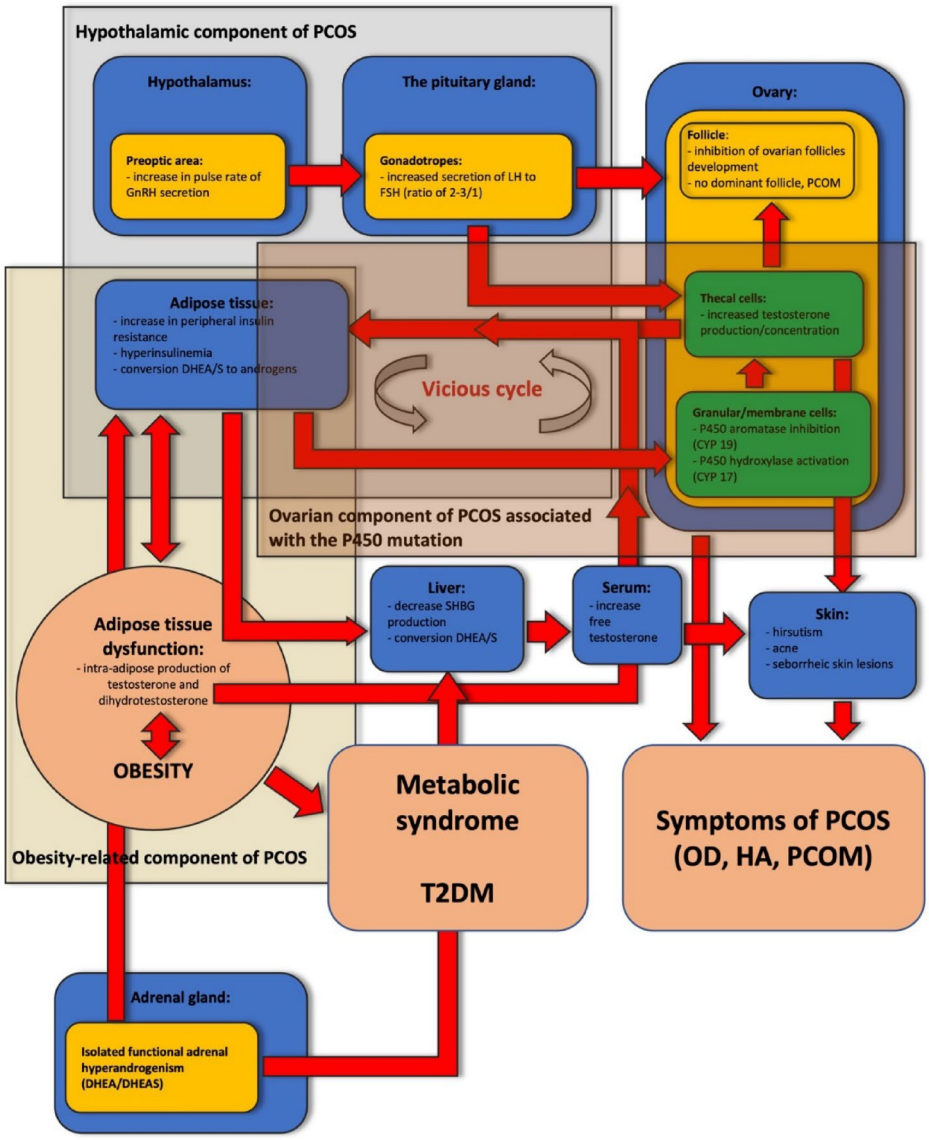

Fig. 1. Diagram showing pathophysiological components of PCOS divided into "hypothalamic", "ovarian" and "obesity-related". The diagram shows the "vicious cycle" model, associated with the progression of insulin resistance, intensifying the symptoms of the syndrome, and the possible development of the metabolic syndrome.

In 2006, the Androgen Excess and PCOS Society (AE-PCOS) proposed criteria requiring hyperandrogenism with either OD or PCOM, thereby excluding the non-hyperandrogenic phenotype permitted by Rotterdam and bridging the NIH and Rotterdam definitions[17].

In adolescents, a definitive diagnosis requires hyperandrogenism and irregular cycles, however ovarian morphology is not included, as it is a normal part of development during adolescence[13].

Differences and limitations between the three sets of diagnostic criteria are presented in the Table 1[15–17,19]..

There is a significant difference between the results of epidemiological studies regarding the prevalence of PCOS. The reported prevalence of PCOS across studies defined by the NIH criteria is mostly consistent and ranges from 5 to 10%, while for the Rotterdam and AE-PCOS criteria, PCOS rates range from 2 to 21% and 2–17%, respectively[20,21]. The variability may be due to the characteristics of the study population and selection, or bias in the selection of patients referred (clinical versus unselected population), limitations in the sampling methods used, protocols used, and the lack of a standardized definition for PCOS features[22].

The selected threshold for the antral follicle counts (AFC) may contribute to the differences in the incidence of the syndrome[23]. However, when an AFC of 20 was used instead of 12 as the definition of PCOM, the incidence of PCOS decreased from 19.9% to 10.2% and from 15.3% to 8.9% respectively by the Rotterdam and AE-PCOS criteria, in the same unselected population. It is worth noting that changing the definition of PCOM by setting the AFC threshold at 20 reduces the incidence of this syndrome by 40–50%[23].

Features of PCOS	NIH (1990)[16]	Rotterdam* (2003)[15]	AE-PCOS (2006)[17]
HA	+	±	+
OD	+	±	±
PCOM	-	±	±
Diagnosis	HA and OD are essential characteristics	At least 2 out of 3 features (HA, OD, PCOM) for diagnosis	HA is an essential feature that should be accompanied by OD and/or PCOM

Table 1. Sets of diagnostic criteria for polycystic ovary syndrome. + Basic diagnosis criteria. ± May or may not be present (optional). - No identified or suggested features of the diagnosis. * Recommended sets of diagnostic criteria according to the latest "International evidence-based guidelines for the assessment and treatment of PCOS" from 2018.

As a heterogeneous disorder, PCOS reflects different potential etiologies with different clinical presentations. Therefore, the definition of PCOS is still under discussion[18].

Although not a diagnostic criterion, insulin resistance is strongly associated with PCOS. Its pathogenesis remains incompletely understood, but androgen-mediated adipose dysfunction plays a key role. Androgens act via adipocyte androgen receptors to alter preadipocyte differentiation, adipocyte size, fat distribution, and lipid metabolism, collectively impairing insulin sensitivity and glucose tolerance. The primary defect involves disrupted glucose transport due to impaired insulin-stimulated phosphorylation of Protein Kinase C ζ (zeta type), a downstream effector of Phosphoinositide 3-kinase essential for insulin signaling[24–26].

Recent studies identify inositol phosphoglycans (IPGs) as key intracellular mediators of insulin signaling[27,28]. Two isoforms - myo-inositol (MI-IPG) and D-chiro-inositol (DCI-IPG) - have distinct roles. Impaired insulin receptor signaling reduces IPG transport and intracellular levels[28]. Despite peripheral insulin resistance, ovarian insulin sensitivity remains intact, allowing hyperinsulinemia to stimulate androgen synthesis and preferential DCI-IPG release. This imbalance enhances theca cell androgen production and contributes to PCOS pathophysiology through disrupted inositol/IPG availability[29].

Insulin resistance-induced hyperinsulinemia stimulates androgen production through multiple mechanisms. The combined effect of elevated insulin and LH levels can prematurely express LH receptors. Additionally, insulin directly stimulates androgen synthesis in ovarian membrane cells by increasing the activity of cytochrome P450c17α, a crucial enzyme in androgen biosynthesis encoded by the CYP17 gene. The 17α-hydroxylase activity of P450c17 enhances androgen synthesis within membrane cells. Increased androgen production leads to hyperandrogenic symptoms such as hirsutism, seborrheic skin lesions, acne, and alopecia. It also contributes to premature ovarian follicle atresia, disrupting ovulation and this effect is enhanced by an additional pool of bioavailable testosterone caused by reduced secretion of SHBG by the liver[6,13,30–32]. Furthermore, insulin resistance correlates with metabolic alterations, hemodynamic shifts, and an elevated cardio-metabolic risk profile[33].

The euglycemic-hyperinsulinemic clamp is considered the "gold standard" for assessing insulin sensitivity. It directly measures insulin-dependent glucose utilization in tissues. However, due to its complexity and time requirements, it is primarily used for research purposes and is not practical for routine clinical diagnostics. Instead, simpler surrogate indices of tissue insulin sensitivity/resistance, such as the Matsuda or QUICKI index from oral glucose tolerance tests or the homeostatic IR scoring model based on fasting glucose, are commonly employed[34–37]. The latter probably reflects more hepatic than muscle insulin resistance[38]. Across numerous studies, all markers of insulin resistance have consistently demonstrated cross-correlation. Nevertheless, when evaluating indices for insulin sensitivity, the principal criterion remains their correlation with the euglycemic-hyperinsulinemic clamp, regarded as the definitive standard in this domain[37,39,40].

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is a widely accepted surrogate for evaluating insulin resistance. However, its diagnostic thresholds vary considerably. Although HOMA-IR demonstrates substantial reliability, population-based studies have revealed significant variability in cut-off values, typically ranging between the 80th and 90th percentiles of the general population[41].

A retrospective analysis of 859 Caucasian women aged 18–30 years with PCOS identified a HOMA-IR threshold of 2.1 for distinguishing IR, consistent with the European Group for the Study of Insulin Resistance, which recommends a cut-off above 2.0[38].

In the Spanish population, HOMA-IR values were stratified by age, Body Mass Index (BMI), and waist circumference, revealing gender-specific differences. Women over 50 exhibited elevated levels, likely due to postmenopausal fat redistribution, while younger women showed a mean value of 1.95 and a non-linear age association[42].

Global data on HOMA-IR thresholds remain inconsistent. Reported cut-offs range from 1.55 in the Thai population to ≥ 3.8 in the French population, reflecting methodological differences in defining IR-based on percentiles (66th, 75th, 80th, 90th) or ROC curve analysis[41].

HOMA-IR values correlate with metabolic syndrome and cardiovascular risk. In non-diabetic individuals, the risk of metabolic syndrome increases with HOMA-IR values between 3.04 and 3.46, while the median value in diabetic patients is approximately 4.8[41,43,44].

The existence of three distinct diagnostic criteria for PCOS, developed by separate scientific societies, contributes to heterogeneity in diagnosis and epidemiological estimates. Successive criteria have not replaced earlier ones, leading to variability in defining the clinical presentation. Symptom severity varies among affected individuals, enabling classification into distinct PCOS phenotypes[45].

The National Institutes of Health Evidence-Based Methodology Workshop on Polycystic Ovary Syndrome (2012) recommends the use of the broader Rotterdam diagnostic criteria, with explicit reporting of specific four phenotypes in all research and clinical care. This maximizes uniformity and comparability across research and clinical initiatives. This approach was also endorsed in the 2018 guidelines for the assessment and treatment of PCOS[13,18].

According to the Rotterdam criteria, PCOS comprises four phenotypes: A (HA + OD + PCOM), B (HA + OD), C (HA + PCOM), and D (OD + PCOM)[46,47].

Phenotypes A ("complete" PCOS) and B ("non-PCO PCOS") are collectively referred to as "classic" PCOS, identified through shared clinical features[48]. These women typically present with pronounced hirsutism, obesity, menstrual irregularities, and elevated risk of insulin resistance, dyslipidemia, hepatic steatosis, and metabolic syndrome compared to phenotypes C and D[46,47,49,50].

The AE-PCOS and Rotterdam criteria recognize phenotype C, or "ovulatory" PCOS, characterized by intermediate levels of hirsutism, androgens, lipids, and metabolic risk between "classic" PCOS and phenotype D[46,47]. An interesting observation was made in the Italian cohort: higher socioeconomic status was associated with a higher incidence of the "ovulatory" phenotype. Differences in ovulation patterns between social groups have been explained in part by differences in insulin levels and body fat distribution[51].

Phenotype D ("non-hyperandrogenic") is associated with the mildest endocrine and metabolic disturbances and the lowest prevalence of metabolic syndrome compared to healthy controls[52,53]. These women exhibit lower LH/FSH ratios, reduced total and free testosterone, and elevated SHBG levels relative to "classic" PCOS phenotypes[47]. Menstrual patterns are predominantly regular, with intermittent irregularity[50].

PCOS phenotype distribution varies markedly depending on population selection. A meta-analysis of 41 studies reported the following prevalence in clinical vs. unselected populations: phenotype A, 50% vs. 19%; B, 13% vs. 25%; C, 14% vs. 34%; and D, 17% vs. 19%[49]. Significant differences were noted for phenotypes A-C. Referred patients exhibited higher mean BMI than local controls, a trend not observed in unselected cohorts[49]. Hyperandrogenic phenotypes are generally linked to increased metabolic syndrome risk[47].

Objectives

Numerous publications explore the association between polycystic ovary syndrome and insulin resistance, often in the context of metabolic syndrome complications. However, few studies specifically investigate the relationship between insulin resistance and different PCOS phenotypes.

In this study, insulin resistance was evaluated across specific PCOS phenotypes, revealing significant correlations with syndrome-related parameters. Additionally, they proposed an explanation for the origin of IR in PCOS based on "vicious cycle" model.

Methods

This single-center retrospective observational study (2018–2022) was performed at the Medical University of Lublin with approval from the institutional Bioethics Committee (KE-0254/287/2019). Written informed consent was obtained from all participants, and procedures conformed to institutional regulations and the Declaration of Helsinki.

Participants

Two hundred Caucasian women aged 18–36 years, hospitalized for ovarian disorders (ICD-10: E28.9) at the 3rd Chair and Department of Gynecology, were enrolled. Inclusion required a PCOS diagnosis according to the Rotterdam criteria; exclusion criteria included any endocrinopathy other than PCOS that affects ovarian function[15,54].

Clinical and biochemical measurements

At recruitment, the following were recorded for each participant: Body Mass Index (BMI), Mean Arterial Pressure (MAP), pulse, Waist-to-Hip Ratio (WHR), LH/FSH ratio, HOMA-IR, and Free Androgen Index (FAI). Hirsutism was scored using the modified Ferriman-Gallwey (mFG) scale. Reference ranges and cut-offs from the literature were applied: BMI 18.5–24.9 kg/m^2 (obesity > 30.0 kg/m^2); MAP 75–110 mmHg; pulse 60–100 beats/min; WHR > 0.8; LH/FSH > 2:1; FAI > 10; mFG > 8[55–58].

Disease duration and phenotyping

PCOS duration was calculated as current age minus age at symptom onset, with onset defined by menstrual history (secondary amenorrhea or irregular menses). Each subject was assigned one of four PCOS phenotypes[53,59].

Insulin-resistance groups

Participants were stratified by HOMA-IR into two groups: non-insulin-resistant (HOMA-IR ≤ 2.00) and insulin-resistant (HOMA-IR ≥ 2.01)[38].

Characteristics Mean (± SD) (ANOVA)	Phenotype A (HA + OD + PCOM)	Phenotype B (HA + OD)	Phenotype C (HA + PCOM)	Phenotype D (OD + PCOM)
N	92	52	23	33
Age (years)*	22.7 (± 3.3)	25.21 (± 3.97)	28.83 (± 5.18)	24.94 (± 4.15)
	Post-hoc* A-B, A-C, A-D, C-B, C-D			
PCOS duration (years)*	5.72 (± 2.93)	7.71 (± 3.18)	10.52 (± 4.01)	7.7 (± 3.39)
	Post-hoc* A-B, A-C, C-B, C-D			
HOMA IR*	3.59 (± 2.37)	2.59 (± 1.94)	2.05 (± 0.82)	2.73 (± 1.23)
	Post-hoc* A-B, A-C			
IR (%)* (HOMA IR ≥ 2.01) **(Chi^{2}Test)**	69.57	53.85	26.09	51.52
BMI (kg/m^2)*	25.99 (± 7.88)	22.5 (± 4.37)	22.13 (± 2.03)	23.46 (± 4.79)
	Post-hoc* A-B, A-C			
MAP (mmHg)*	97.66 (± 9.36)	96.77 (± 11.21)	96.29 (± 6.56)	108.15 (± 11.97)
	Post-hoc* A-D, B-D, C-D			
Pulse (bits/min)*	81.93 (± 8.19)	77.19 (± 11.16)	77.57 (± 2.63)	89.97 (± 9.03)
	Post-hoc* A-B, A-D, B-D, C-D			
WHR	0.8 (± 0.08)	0.79 (± 0.07)	0.83 (± 0.05)	0.84 (± 0.1)
LH/FSH*	2.09 (± 1.37)	1.41 (± 1.12)	2.35 (± 0.89)	3.25 (± 3.82)
	Post-hoc* A-D, B-D			
FAI*	13.35 (± 1.85)	15.0 (± 3.93)	12.18 (± 1.24)	6.3 (± 1.65)
	Post-hoc* A-B, A-D, B-D, C-B, C-D			
mFG*	10.59 (± 5.2)	11.37 (± 3.99)	6.57 (± 4.62)	4.73 (± 1.68)
	Post-hoc* A-C, A-D, B-D, C-B			

Table 2. Concise characteristics of the study group. The statistical significance of the hypotheses ($p < 0.05$) was determined through the ANOVA or Chi^2 tests, assessing between-group differences, and further validated using the bonferroni post-hoc test for multiple comparisons among individual phenotypes. * $p < 0.05$.

Statistical analysis

Statistical analysis was conducted using the DATAtab: DATAtab Team (2023). DATAtab: Online Statistics Calculator. DATAtab e.U. Graz, Austria, (https://datatab.net). The examined features followed normal distributions, allowing us to use arithmetic means with standard deviations (SD) for further analysis. Parametric tests were employed to analyze correlations and hypotheses at a 5% significance level. Between-group comparisons utilized the ANOVA test (analysis of variance), with post-hoc Bonferroni tests when the null hypothesis was rejected. Additionally, relationships between categorical features were assessed using the Chi^2 Test. Pearson's two-tailed linear correlation test analyzed normally distributed features[60,61].

Results

In the study group, the mean age was 24.43 years (±4.31). Participants were categorized into four PCOS phenotypes (A, B, C, D) based on characteristic features. Phenotype A (HA + OD + PCOM) was the most common (46%), followed by phenotype B (HA + OD) (26%), phenotype D (OD + PCOM) (16.5%), and phenotype C (HA + PCOM) (11.5%).

The mean age was lowest in phenotype A (22.7 years), similar in phenotypes B and D (25.2 and 24.9 years, respectively), and highest in phenotype C (28.3 years). Syndrome duration was shortest in phenotype A (5.72 years) and longest in phenotype C (10.52 years).

Insulin resistance was present in 57.5% of the cohort. Phenotype A showed the highest prevalence (69.57%), phenotypes B and D had comparable rates (53.85% and 51.52%), and phenotype C the lowest (26.09%). Phenotype A also had the highest mean HOMA-IR value (3.59), phenotypes B and D showed intermediate values (2.59 and 2.73), and phenotype C the lowest (2.05). The combined A and B phenotypes (classic phenotype) had a mean HOMA-IR of 3.23.

A detailed summary of these parameters is provided in Table 2.

Strong correlations were observed between BMI and HOMA-IR ($r = 0.72$; $p < 0.001$) and between age and PCOS duration ($r = 0.90$; $p < 0.001$). Moderate correlations were found for BMI - pulse ($r = 0.50$; $p < 0.001$), BMI - WHR ($r = 0.52$; $p < 0.001$), and pulse - WHR ($r = 0.62$; $p < 0.001$). Additional moderate associations were observed between MAP - pulse ($r = 0.32$; $p < 0.001$), MAP - WHR ($r = 0.47$; $p < 0.001$), pulse - HOMA-IR ($r = 0.32$; $p < 0.001$), WHR - HOMA-IR ($r = 0.49$; $p < 0.001$), FAI - HOMA-IR ($r = 0.35$; $p < 0.001$), and FAI - mFG ($r = 0.44$; $p < 0.001$).

Discussion

In this study, nearly half of the patients (46%) presented with the "complete" PCOS phenotype (A), while the "classic" phenotype (A + B) accounted for almost three-quarters (72%). The "ovulatory" phenotype (C) was the least common, representing just over 10%, and 16.5% of patients exhibited the "non-androgenic" phenotype (D). The distribution of the "classic" phenotype aligns with previous reports, although phenotype A was more dominant, and the proportions of phenotypes C and D were reversed compared with literature data.

Insulin resistance was observed in almost two-thirds of the cohort. Among phenotypes, IR was most prevalent in phenotype A (69.57%). Phenotypes B and D showed similar distributions of women with and without IR, with a slight predominance of IR, whereas most women with phenotype C were insulin-sensitive (73.91%). The mean HOMA-IR exceeded the diagnostic threshold for IR across all phenotypes, with the highest value in phenotype A (3.59) and the lowest in phenotype C (2.05). Phenotypes B (2.59) and D (2.73) demonstrated intermediate values. Statistically significant differences in HOMA-IR among phenotypes were consistent with published findings[62–66].

Phenotype A was also associated with the lowest mean age (22.7 years), while phenotype C had the highest (28.8 years). Phenotypes B and D showed similar mean ages. A strong correlation was observed between age and PCOS duration, although disease onset was comparable across phenotypes. Despite statistically significant differences in age and duration, other studies have reported similar mean ages ranging from 24 to 30 years)[62–66].

BMI also differed significantly among phenotypes. Phenotype A had the highest mean BMI (25.99 kg/m^2), while the other phenotypes remained within the normal range. A strong positive correlation was found between BMI and HOMA-IR. However, previous studies reported higher BMI values in phenotype B than observed here[62–66].

The maximum BMI in phenotype A reached 42 kg/m^2, the highest across all phenotypes. In phenotypes B and D, maximum BMI values corresponded to class I obesity, whereas in phenotype C, BMI remained within the normal range.

Markers of metabolic syndrome (MAP, pulse, WHR) were also evaluated. Mean MAP and pulse values were within normal limits across all phenotypes, though the highest averages were observed in phenotype D. ANOVA revealed statistically significant differences between phenotypes, and mean MAP and pulse values were approximately 10% higher than those reported in comparable studies[62,63].

WHR was elevated in phenotypes A, C, and D, indicating android obesity, while phenotype B had a near-normal WHR (0.79). No significant differences in WHR were found among phenotypes. Literature findings remain inconsistent: Głuszak reported android obesity only in phenotype D, whereas Sachdeva observed it across all phenotypes, with WHR values 10–15% higher than those reported by Głuszak[62,63]. These discrepancies may reflect population-specific or dietary differences[67]. Correlations between metabolic syndrome markers and HOMA-IR confirmed proportional relationships, consistent with prior studies[41].

Although PCOS duration might be expected to influence IR severity, our data showed that duration correlated strongly only with patient age, consistent with previous reports[62–64].

No significant correlations were observed between PCOS duration and other parameters in the overall cohort. However, phenotype-specific patterns emerged: phenotype A, with the highest mean HOMA-IR, had the shortest duration, while phenotype C, with the lowest HOMA-IR, had the longest duration (nearly twice as long). Phenotypes B and D showed intermediate, comparable values. These findings suggest that factors beyond disease duration contribute to IR development in different phenotypes.

The LH/FSH ratio, a marker of hypothalamic–pituitary–ovarian axis function, is normally close to 1.0 but may deviate in conditions such as hypothalamic–pituitary insufficiency, menopause, or PCOS[68].

In this study, phenotype D exhibited a markedly elevated mean LH/FSH ratio (3.25). Phenotypes A and C had lower mean ratios (approximately 40% lower), while phenotype B showed a normal ratio. These results contrast with previous reports[62–65,69].

Hyperandrogenism was assessed using the Free Androgen Index (FAI) and the modified Ferriman-Gallwey (mFG) score. Both measures were consistent and revealed statistically significant differences among phenotypes. The highest values were observed in phenotype B, while the lowest occurred in phenotype D. These findings are in line with published data[62–64].

Significant positive correlations were also found between FAI and HOMA-IR, and between FAI and mFG, supporting the role of ovarian androgens in the pathogenesis of IR and hirsutism[70].

It is widely known that PCOS is closely related to carbohydrate metabolism disorders in the form of peripheral IR. As shown in this publication, IR appears with varying intensity and at different times in all PCOS phenotypes. Moreover, IR was correlated with markers of the metabolic syndrome, which indirectly proves that this syndrome may develop sooner or later in women with PCOS. Therefore, the typical symptoms of PCOS are only the "tip of the iceberg", and the health problem will concern the metabolic syndrome and its complications[71].

How is this happening? This is explained by the "vicious cycle" model.

Three pathophysiological components of this syndrome can be identified in the etiology of PCOS. Although each of them has a different starting point, ultimately the metabolic disorders that occur come down to a common set, which includes adipose tissue/hepatocytes and granulosa and thecal cells of the ovary (Fig. 1). Excess testosterone secreted by thecal cells leads to increased insulin resistance and secondary hyperinsulinemia. Elevated insulin levels enhance the activity of P450c17α, a critical enzyme regulating androgen biosynthesis encoded by the CYP17 gene, within the endoplasmic reticulum of ovarian membrane cells. This results in a further increase in blood testosterone concentration, adversely affecting adipose tissue, skeletal muscles, the heart, and the liver. This effect is additionally enhanced by other components, described in the introduction[32].

The mechanism described above closes like a carousel, creating a pathological "vicious cycle" model that ultimately leads to insulin resistance in all components of PCOS.

The strengths of this study include its relatively large, homogeneous cohort of young Caucasian women with PCOS and a broad BMI range, as well as the comprehensive evaluation of both IR and metabolic syndrome markers. The extensive literature review and detailed pathophysiological discussion enhance the educational value of the work, while robust statistical analyses strengthen the reliability of the findings.

Limitations include the retrospective design and the absence of hyperinsulinemic-euglycemic clamp testing, alternative IR indices, HbA1c, and lipid profile assessments. However, it should be noted that the clamp technique lacks established reference values and is not recommended for identifying hepatic IR.

Conclusions

The results obtained and the ensuing discussion support and justify the following conclusions drawn from this study:

- Insulin resistance (IR) predominated in this PCOS cohort (in nearly two-thirds of study group) and was phenotype-dependent rather than related to syndrome duration.
- All four PCOS phenotypes exhibited elevated mean HOMA-IR values above reference thresholds.
- Phenotype A (complete) had the highest HOMA-IR; phenotype C (ovulatory) had the lowest.
- The phenotype with the highest IR had the shortest PCOS duration, suggesting that core clinical features, not disease duration, drive IR development.
- Moderate-to-strong correlations between HOMA-IR and MAP, pulse, and WHR indicate a link to metabolic syndrome across phenotypes.
- Associations among FAI, HOMA-IR, and mFG score highlight the role of ovarian androgens in IR and hirsutism.
- A "vicious cycle" model is proposed to explain peripheral IR in PCOS; further research into genetic and intracellular mechanisms is recommended.

Data availability

Data is provided within the supplementary information files.

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Author contributions

PS, FS made substantial contributions to the concept and design of the manuscript.PS, FS, KT contributed to the acquisition, analysis, and interpretation of data.PS, KT, SW, MM, TP participated in drafting the manuscript and its critical revision.All authors read and approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to P.S.

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