Clinical Phenotype-Based Analysis of Hormonal and Metabolic Abnormalities in Women with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and a frequent cause of menstrual irregularities, often presenting during adolescence. Diagnosis is based on the Rotterdam criteria, requiring at least two of oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology after excluding other causes. PCOS is a multifactorial condition involving genetic predisposition, dysregulation of the hypothalamic-pituitary-ovarian axis, insulin resistance, and ovarian steroidogenesis abnormalities. Increased GnRH pulsatility leads to elevated LH relative to FSH, promoting androgen excess, impaired follicular maturation, anovulation, and polycystic ovarian morphology. Hyperinsulinemia further aggravates hyperandrogenism by enhancing ovarian and adrenal androgen production. Early recognition is important, particularly in adolescents, in whom physiological cycle irregularity may overlap with early disease features.

Objectives: This study was conducted to evaluate the prevalence of different phenotypes of Polycystic Ovary Syndrome (PCOS) and to analyze the metabolic and hormonal abnormalities associated with each phenotype.

Materials and Methods: This study was conducted at a tertiary care hospital in South Telangana and included newly diagnosed patients with Polycystic Ovary Syndrome, as defined by the Rotterdam criteria. Fasting blood samples were collected between days 2 and 6 of the menstrual cycle to compare clinical, hormonal, and metabolic profiles.

Results: Phenotype A was most prevalent (33.8%), followed by D (24.19%), B (23.38%), and C (18.5%). BMI was higher in phenotypes A and C compared to controls and B. Fasting insulin was elevated in A, C, and D, with higher postprandial insulin in A and C. HOMA-IR was increased and QUICKI index reduced in A, C, and D, indicating greater insulin resistance, with lower QUICKI in C than D. TSH was higher in D compared to B, while total testosterone and LH/FSH ratio were elevated in B

Conclusion: This study highlights the heterogeneity of PCOS with distinct metabolic and reproductive phenotypes. Phenotypes A and C showed obesity-related insulin resistance, Phenotype B demonstrated mainly reproductive (gonadotropin-driven) hyperandrogenism with preserved insulin sensitivity, and Phenotype D exhibited obesity-independent insulin resistance. Overall, the findings emphasize that PCOS is a spectrum disorder with variable metabolic involvement, supporting the need for phenotype-based, individualized management strategies.

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, Hyperandrogenism, Body Mass Index, Ovulation Disorders, Gonadotropins

Introduction

Polycystic ovary syndrome (PCOS) represents a complex endocrine-metabolic condition and remains the most frequent cause of chronic anovulation among women of reproductive age. Clinically, it is commonly associated with disrupted menstrual cyclicity, androgen excess, and structural ovarian changes, and its manifestations often begin in adolescence, suggesting early disruption of reproductive endocrinology [1,2].

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The Rotterdam consensus defines polycystic ovary syndrome (PCOS) as the presence of at least two of the following features, following exclusion of alternative etiologies: ovulatory dysfunction, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography[1]. This broad definition reflects the biological variability of the syndrome and supports recognition of multiple phenotypic expressions with differing reproductive and metabolic profiles.

Although the exact origin of PCOS remains unresolved, current evidence supports a multifactorial pathogenesis involving genetic predisposition combined with endocrine and metabolic disturbances. Observations of familial aggregation and increased risk among first-degree relatives strongly indicate a heritable polygenic component[2-4]. Insulin resistance accompanied by compensatory hyperinsulinemia is a key acquired factor that enhances ovarian androgen synthesis and contributes to neuroendocrine dysregulation[8,9].

Normal reproductive cycling depends on coordinated hypothalamic-pituitary-ovarian (HPO) axis activity, where episodic gonadotropin-releasing hormone (GnRH) secretion from hypothalamic neurons regulates pituitary gonadotropin output. The downstream release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) orchestrates follicular recruitment, estradiol production, ovulation, and corpus luteum formation through tightly regulated endocrine feedback loops involving ovarian steroids and inhibins [5].

During pubertal maturation, instability of the HPO axis frequently results in irregular menstrual cycles due to inconsistent ovulatory activity. This transitional anovulatory pattern is considered physiological in early adolescence; however, persistence of such irregularity beyond expected maturation timelines raises suspicion for pathological conditions such as PCOS [6,7].

In PCOS, follicular development is arrested during early antral stages, preventing dominant follicle selection and ovulation. This leads to the persistence of multiple small follicles, producing the characteristic polycystic ovarian appearance. Excess androgen secretion from theca cells, driven predominantly by luteinizing hormone stimulation, disrupts intra-ovarian signalling and contributes to altered hypothalamic GnRH pulsatility. The resulting neuroendocrine shift favours increased LH output with relative suppression of FSH, reinforcing a cycle of androgen excess and impaired follicular maturation [4,8].

Metabolic dysfunction further intensifies this condition. Insulin resistance promotes ovarian steroidogenesis by sensitizing theca cells to gonadotropin stimulation and independently enhancing androgen synthesis. Additionally, hyperinsulinemia disrupts central feedback mechanisms and may contribute to increased adrenal androgen output, thereby compounding the hyperandrogenic state observed in PCOS [9].

Objectives

This study was conducted to evaluate the prevalence of different phenotypes of Polycystic Ovary Syndrome (PCOS) and to analyse the metabolic and hormonal abnormalities associated with each phenotype.

Materials and Methods.

Study Design and Setting

This was a hospital-based observational study conducted over two years at a tertiary care hospital in South Telangana. Ethical approval was obtained from the Institutional Ethics Committee before initiation, and written informed consent was obtained from all participants before enrolment.

Study Population and Recruitment

All eligible women with clinical suspicion of Polycystic Ovary Syndrome who met the Revised Rotterdam diagnostic criteria were recruited as cases. Additionally, 50 apparently healthy, age-matched females were included as controls.

Inclusion Criteria

Cases: Newly diagnosed PCOS patients fulfilling at least two of the Rotterdam criteria—oligo/anovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovarian morphology on ultrasound.

Controls: Apparently healthy women with regular menstrual cycles (26-35 days), normal ovarian morphology on ultrasound, and no evidence of endocrine or gynecological disorders.

Exclusion Criteria

Participants were excluded if they had conditions affecting endocrine or metabolic parameters, including non-classical congenital adrenal hyperplasia, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, pregnancy-related amenorrhea, or ovarian/adrenal tumors. Women receiving medications influencing metabolic or hormonal profiles were also excluded.

Clinical Assessment

Demographic details, medical history, and clinical findings such as acne, hirsutism, and acanthosis nigricans were recorded using a structured proforma. A detailed physical examination was performed for all participants.

Sample Collection and Laboratory Analysis

Venous blood samples were collected under aseptic precautions. Fasting blood samples were drawn during days 2-6 of the menstrual cycle using plain red-top vacutainers and fluoride grey-top vacutainers. Hormonal assays included total testosterone, DHEAS, TSH, LH, FSH, fasting insulin, and postprandial insulin.

Biochemical Measurements

Glucose levels were estimated using the hexokinase method, and Insulin, DHEAS (Dehydroepiandrosterone sulfate), TSH, and LH/FSH were measured using chemiluminescent microparticle immunoassay (CMIA) technology, Abbott Architect ci8200 analyser.

Insulin Resistance and Sensitivity Indices

Insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), while insulin sensitivity was evaluated using the Quantitative Insulin Sensitivity Check Index (QUICKI). Calculation of Insulin Resistance Indices: HOMA-IR (insulin (uIU/mL) x glucose (mg/dL)/405) and the Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated as 1/[log fasting insulin(μIU/ml) + log fasting glucose(mg/dL)]. QUICKI Score Interpretation: very high insulin sensitivity: >0.45; high insulin sensitivity: 0.40 - 0.45; moderate insulin sensitivity: 0.35-0.39; low insulin sensitivity (resistance):0.30-0.34; very low insulin sensitivity (severe insulin resistance): < 0.30. HOMA-IR values >2 may indicate insulin resistance.

Diagnostic Classification:

Participants were classified as either PCOS cases or healthy controls based on predefined inclusion and exclusion criteria, following comprehensive clinical evaluation and laboratory assessment.

PCOS Phenotype	Hyperandrogenism (HA)	Ovulatory Dysfunction (OD)	Polycystic Ovarian Morphology (PCOM)
Phenotype A	Present	Present	Present
Phenotype B	Present	Present	Absent
Phenotype C	Present	Absent	Present
Phenotype D	Absent	Present	Present

Statistical Analysis

Data were entered into a spreadsheet and analysed using Extended Excel Real Statistics software. Descriptive statistics, including mean and standard deviation (SD), were used to summarize quantitative variables, which were also expressed as mean ± SD with confidence intervals where applicable. Normality of the data distribution was tested using the Shapiro-Wilk test.

For comparisons among different Polycystic Ovary Syndrome phenotypes, Welch's ANOVA was applied. When significant differences were identified, post hoc analysis was carried out using the Games-Howell test to account for unequal variances between groups.

All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Results

Among the 223 women enrolled in the study, 124 were classified into different Polycystic Ovary Syndrome phenotypes, while 50 participants with normal ultrasonography findings were included as controls. The remaining 49 women, who exhibited isolated ovulatory dysfunction without additional PCOS features, were excluded as per the study criteria.

Table 1: Distribution of study participants across PCOS phenotypes and control group

Study Group	Subgroup	Number of Subjects (n)	Percentage (%)
PCOS (n = 124)	Phenotype A (Classical Full PCOS)	42	33.8
	Phenotype B	29	23.4
	Phenotype C (Ovulatory PCOS)	23	18.5
	Phenotype D (Non-hyperandrogenic PCOS)	30	24.2
Normal Controls	-	50	-
Total Included in Analysis	-	174	-

In this study, phenotype A was the most prevalent (33.8%), followed by phenotype D (24.19%), phenotype B (23.38%), and phenotype C (18.5%).

Table 2: Comparison of Age and BMI across Controls and PCOS Phenotypes

Paraeter	MEAN ± SD, 95% Confidence Interval for Mean (Lower CI, Upper CI)					Anova Welsh Test	
	CONTROLS	Phenotype A	Phenotype B	Phenotype C	Phenotype D	F (df_1, df_2)	P value
Age	20.5 ± 1.73 (19.9,21.0)	20.28 ± 1.71 (19.75,20.82)	20.96 ± 1.68 (20.32,21.60)	20.08 ± 2.21 (19.34,20.83)	20.43 ± 1.90 (19.72,21.01)	0.93 (4,73.36)	0.45
BMI	20.1 ± 1.36 (20.4,21.5)	22.83 ± 2.61 (22.21,23.46)	20.81 ± 1.40 (20.06,21.56)	23.39 ± 2.57 (22.54,24.22)	21.86 ± 2.15 (21.11,22.59)	9.14 (4,71.11)	0.001*

Values are expressed as mean ± standard deviation (SD) with 95% confidence interval (CI). Differences between groups were analyzed using Welch's ANOVA. A p-value < 0.05 was considered statistically significant.

Age was similar across all groups, with no statistically significant difference. In contrast, BMI differed significantly between groups, with Phenotypes A and C showing higher mean values compared with controls and the other phenotypes.

Compared to controls, PCOS women had significantly higher BMI.

Table 3: Metabolic and Hormonal Differences Among PCOS Phenotypes and Controls

Parameter	MEAN ± SD, 95% Confidence Interval for Mean (Lower CI, Upper CI)					Anova Welsh Test	
	CONTROLS	Phenotype A	Phenotype B	Phenotype C	Phenotype D	F (df1, df2)	P value
Fasting Glucose mg/dL	88.3 ± 7.05 (85.54,91.11)	87.1 ± 10.41 (84.11,90.08)	93.83 ±12.08 (90.24,97.42)	87.84 ± 9.27 (83.81,91.85)	88.39 ±10.54 (84.86,91.92)	1.59 (4, 71.3)	0.10
PP Glucose mg/dL	98.56 ± 18.27 (93.4,103.7)	105 ± 17.5 (99.54,110.81)	98.43 ± 20.97 (91.65,105.21)	95.73 ± 22.9 (88.12,103.34)	100.7 ± 12.96 (94.05,107.38)	1.17 (4,73.74)	0.28
Fasting Insulin (uIU/ml)	2.44 ± 1.03 (1.55,3.33)	8.18 ± 4.64 (7.21,9.15)	2.73 ± 1.11 (1.56,3.90)	8.16 ± 3.00 (6.86,9.46)	6.32 ± 4.30 (5.17,7.46)	37.39 (4,67.28)	<0.001
PP Insulin (uIU/ml)	9.15 ± 7.77 (1.91,16.39)	36.72 ± 41.66 (29.07,44.38)	16.64 ± 20.08 (7.26,26.02)	22.19 ± 19.09 (11.61,32.77)	19.01 ± 19.56 (9.95,28.07)	7.92 (4,62.20)	<0.001
HOMA IR	0.51 ± 0.21 (0.32,0.69)	1.73 ± 0.95 (1.54,1.93)	0.63 ± 0.24 (0.39,0.87)	1.78 ± 0.70 (1.51, 2.08)	1.33 ± 0.79 (1.09, 1.56)	38.06 (4, 66.55)	<0.001
QUICKI INDEX	0.43 ± 0.03 (0.41,0.43)	0.36 ± 0.03 (0.34,0.37)	0.42 ± 0.04 (0.4,0.44)	0.36 ± 0.02 (0.34,0.37)	0.37 ± 0.03 (0.37,0.39)	38.40 (4,74.93)	<0.001
TSH (mIU/L)	1.30 ± 0.58 (0.99,1.611)	1.8 ± 1.44 (1.47,2.13)	1.28 ± 0.80 (0.87,1.67)	1.45 ± 0.61 (1.01, 1.89)	2.27 ± 1.54 (1.46,2.13)	3.6 (4,72.26)	<0.01
FREE T4 (ng/dl)	0.91 ± 0.11 (0.88, 0.94)	0.91 ± 0.12 (0.87, 0.95)	0.91± 0.09 (0.87, 0.94)	0.92 ± 0.14 (0.86,0.96)	0.90 ± 0.1 (0.86,0.95)	0.02 (4, 73.93)	0.9
Prolactin (ng/ml)	11.14 ± 6.82 (9.02,13.25)	12.05 ± 6.43 (9.75, 14.35)	12.9 ± 7.96 (10.15,15.7)	11.60 ± 8.90 (8.49,14.71)	13.29 ± 8.61 (10.57,16.01)	0.46 (4, 72.02)	0.76
Total Testosterone (ng/ml)	0.27 ±0.16 (0.15,0.39)	0.45 ± 0.73 (0.31,0.57)	0.40 ± 0.20 (0.24,0.55)	0.28 ± 0.18 (0.10,0.46)	0.34 ± 0.43 (0.17,0.50)	2.46 (4,71.73)	0.052
DHEAS (µg/Dl)	97.47 ± 55.86 (76.39,118.54)	126.95±86.29 (103.91,149.94)	117.82 ±65.30 (90.14,145.49)	108.08 ±73.27 (77.09,139.16)	120.68±96.03 (93.47,147.89)	1.19 (4,72.11)	0.31
LH/FSH ratio	1.48 ±1.22 (0.98,1.95)	1.74 ± 1.83 (1.22,2.26)	2.81 ±1.80 (2.18,3.45)	1.53 ± 1.60 (0.82,2.23)	1.61 ± 2.16 (0.99,2.23)	3.15 (4,71.32)	0.02

Data are presented as mean ± standard deviation (SD) with 95% confidence intervals (CI). Group comparisons were performed using Welch's ANOVA due to unequal variances. A p-value < 0.05 was considered statistically significant. Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate.

Fasting glucose and postprandial glucose levels were comparable across all groups, with no statistically significant differences observed. In contrast, markers of insulin resistance showed marked variation between groups. Fasting and postprandial insulin levels were significantly elevated in Phenotypes A and C compared with controls and other phenotypes. Similarly, HOMA-IR was significantly higher, and QUICKI was significantly lower in Phenotypes A, C, and D, indicating reduced insulin sensitivity, with the most pronounced impairment observed in Phenotypes A and C.

TSH levels showed a statistically significant difference among groups, with higher values observed in Phenotype D, although free T4 levels remained comparable across all groups. Prolactin levels did not differ significantly between groups. Total testosterone levels showed an increasing trend across PCOS phenotypes but did not reach statistical significance.

DHEAS levels and LH/FSH ratio demonstrated variability among groups, with a significantly higher LH/FSH ratio observed in Phenotype B compared with other phenotypes and controls

Table 4: Phenotype-Specific Differences in Metabolic and Hormonal Profiles: Post Hoc Games-Howell Analysis

Mean difference (P -Value)	AGE	BMI	Fasting Glucose	PP Glucose	Fasting Insulin	PP Insulin	HOMA IR	QUICKI INDEX	TSH	Free T4	Pro Lactin	Total Testo Strone	DHEAS	LH/ FSH
A X D	0.08	0.981	1.296	4.458	1.8642	17.717	0.4081	0.0193	0.473	0.005	1.235	0.105	6.273	0.129
A X C	0.19	0.549	0.747	9.446	0.0191	14.532	0.0455	0.0043	0.347	0.002	0.452	0.164	18.87	0.213
A X B	0.67	2.027 (0.001)	6.737	6.749	5.4504 (0.0001)	20.081	1.1046 (0.0001)	0.0627 (0.0001)	0.522	0.003	0.873	0.049	9.133	1.075
A X Control	0.21	1.866 (0.001)	1.231	6.621	5.7404 (0.0001)	27.573 (0.001)	1.2286 (0.0001)	0.0669 (0.0001)	0.494	0.001	0.915	0.175	29.48	0.263
D X C	0.27	1.530	0.549	4.987	1.8450	3.1852	0.4536	0.0236 (0.02)	0.820	0.008	1.688	0.058	12.60	0.084
D X B	0.59	1.046	5.441	2.291	3.5861 (0.0009)	2.3637	0.6965 (0.0004)	0.0434 (0.0001)	0.996 (0.02)	0.002	0.362	0.055	2.859	1.204
D X Control	0.13	0.884	0.065	2.162	3.8762 (0.0003)	9.8560	0.8204 (0.0001)	0.0476 (0.0001)	0.967 (0.02)	0.006	2.151	0.069	23.21	0.134
C X B	0.87	2.577 (0.001)	5.990	2.696	5.4312 (0.0001)	5.5490	1.1502 (0.0001)	0.0671 (0.0001)	0.175	0.005	1.325	0.114	9.742	1.289
C X Control	0.41	2.415 (0.001)	0.483	2.825	5.7212 (0.0001)	13.041 (0.03)	1.2741 (0.0001)	0.0713 (0.0001)	0.147	0.002	0.463	0.011	10.61	0.050
B X Control	0.46	0.161	5.506	0.128	0.2900	7.4922	0.1239	0.0041	0.028	0.003	1.789	0.125	20.35	1.339 (0.01)

Data represent mean differences between groups. Post hoc pairwise comparisons were performed using the Games-Howell test following Welch's ANOVA to adjust for unequal variances and unequal group sizes. A p-value < 0.05 was considered statistically significant.

Post hoc pairwise comparisons using the Games-Howell test revealed significant differences in metabolic and hormonal parameters across PCOS phenotypes and controls. Phenotypes A and C showed significantly higher fasting insulin, postprandial insulin, and HOMA-IR compared with controls and Phenotype B, indicating greater insulin resistance. QUICKI was significantly lower in Phenotypes A, C, and D compared with controls, reflecting reduced insulin sensitivity.

Phenotype D demonstrated significantly higher insulin resistance indices compared with controls and Phenotype B despite a relatively normal BMI. Phenotype B showed comparatively preserved metabolic parameters but significantly differed from other phenotypes in gonadotropin and androgen-related measures, particularly the LH/FSH ratio.

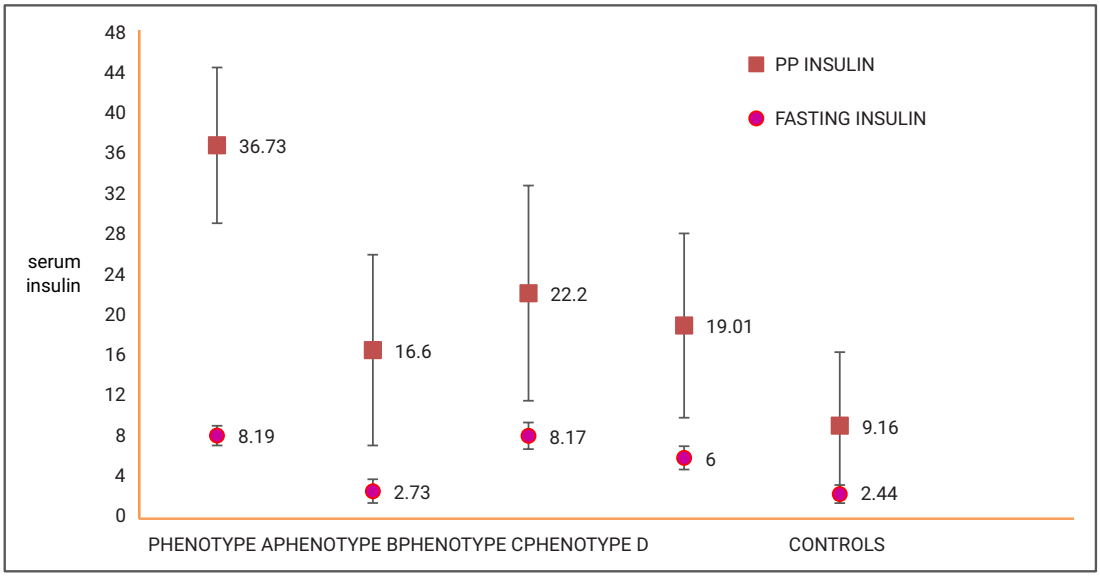
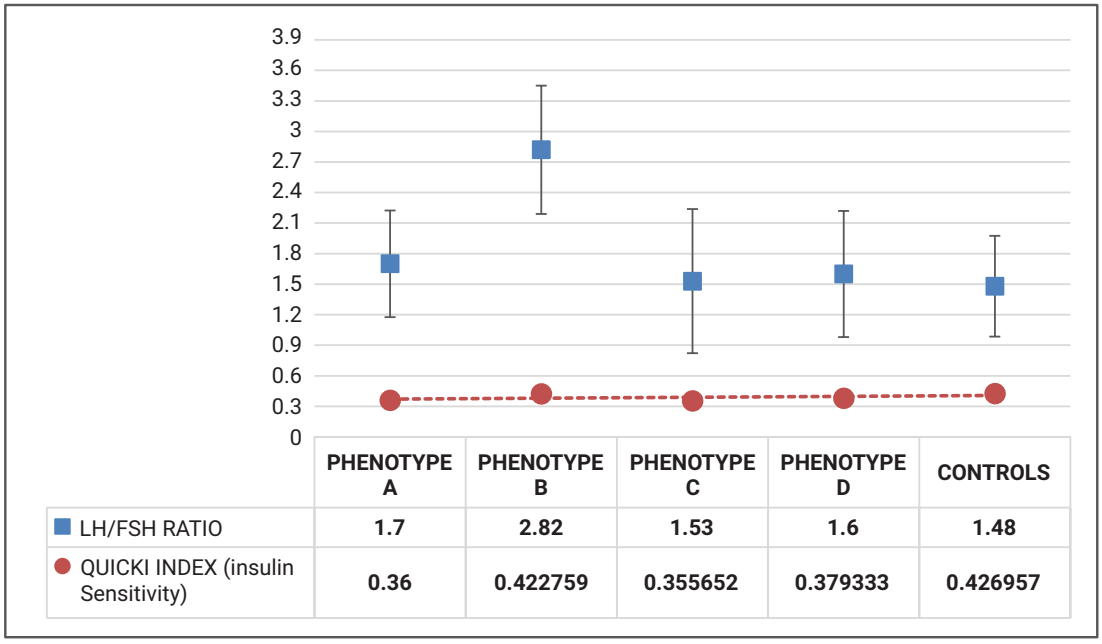
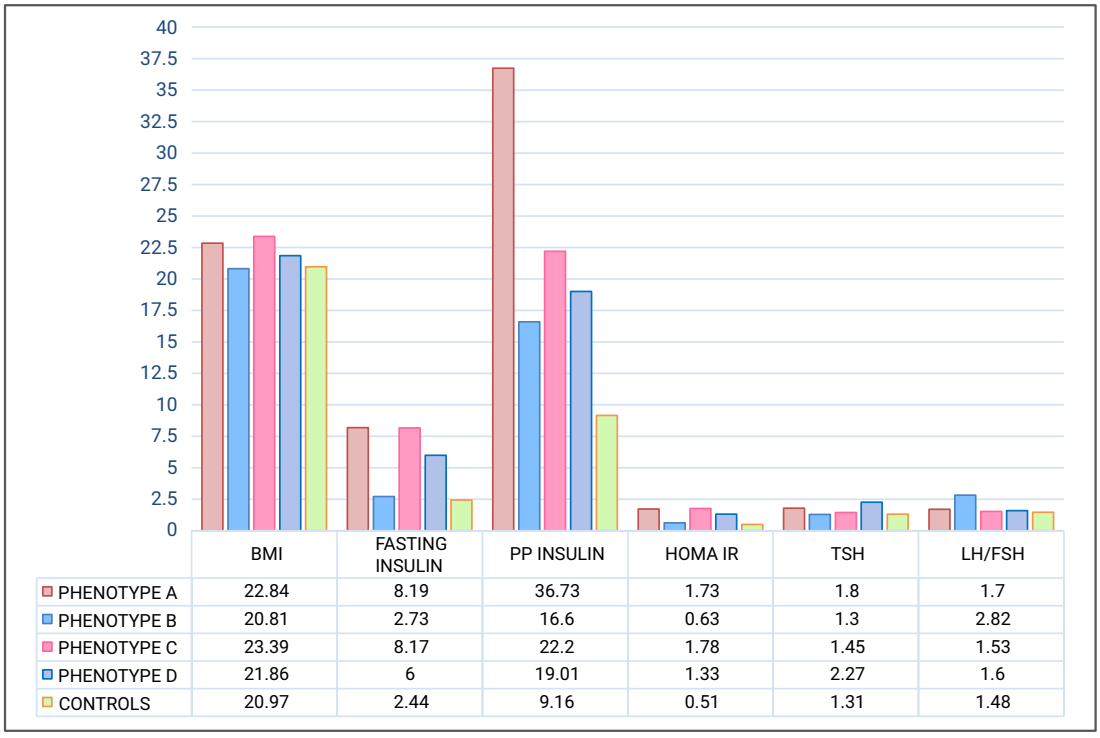


Figure 1: Comparison of Fasting and Postprandial Insulin Levels Across PCOS Phenotypes and Controls (mean ± 95 % CI)



	PHENOTYPE A	PHENOTYPE B	PHENOTYPE C	PHENOTYPE D	CONTROLS
LH/FSH RATIO	1.7	2.82	1.53	1.6	1.48
QUICKI INDEX (insulin Sensitivity)	0.36	0.422759	0.355652	0.379333	0.426957

Figure 2: Comparison of Gonadotropin Ratio and Insulin Sensitivity Across Polycystic Ovary Syndrome Phenotypes and Controls (mean ± 95% CI)



	BMI	FASTING INSULIN	PP INSULIN	HOMA IR	TSH	LH/FSH
PHENOTYPE A	22.84	8.19	36.73	1.73	1.8	1.7
PHENOTYPE B	20.81	2.73	16.6	0.63	1.3	2.82
PHENOTYPE C	23.39	8.17	22.2	1.78	1.45	1.53
PHENOTYPE D	21.86	6	19.01	1.33	2.27	1.6
CONTROLS	20.97	2.44	9.16	0.51	1.31	1.48

Figure 3: Metabolic and Hormonal Profile Variations Across Polycystic Ovary Syndrome Phenotypes Compared with Controls

Discussion

The present study identified Phenotype A as the most prevalent PCOS phenotype (33.8%), followed by Phenotype D (24.19%), Phenotype B (23.38%), and Phenotype C (18.5%). This distribution is consistent with previous Indian studies reporting Phenotype A as the predominant phenotype among women with PCOS, followed by the remaining phenotypes in varying frequencies [10,11]. Similar findings have been reported across Asian populations, reflecting the heterogeneous yet reproducible clinical spectrum of PCOS [13-15]. Variations in phenotype distribution are likely attributable to differences in ethnicity, geographic region, referral patterns, sample size, and

diagnostic criteria [12-14].

Age distribution was comparable between the PCOS and control groups, with no statistically significant difference. The demographic characteristics, particularly age and BMI, were similar to those reported previously [15,16]. According to the revised Indian BMI classification, participants were categorized as either normal weight or overweight [17]. Phenotypes A and C demonstrated significantly higher BMI than the control group and the remaining phenotypes, with mean values falling within the overweight category. These findings are consistent with systematic reviews demonstrating that obesity is more prevalent in the classic hyperandrogenic phenotypes of PCOS and contributes substantially to metabolic dysfunction [8,9,18,19].

Phenotypes A and C were further characterized by significantly elevated fasting and postprandial insulin concentrations, indicating marked insulin resistance associated with increased adiposity. The accompanying hyperinsulinemia likely represents a compensatory response to reduced insulin sensitivity. Excess adiposity, particularly visceral fat accumulation, promotes insulin resistance through chronic low-grade inflammation, altered adipokine secretion, lipotoxicity, and impaired insulin signaling pathways [19]. Hyperinsulinemia further enhances LH-mediated ovarian theca-cell steroidogenesis while suppressing hepatic sex hormone-binding globulin synthesis, thereby increasing circulating free androgen concentrations [9,20,21,22]. These findings support the central role of insulin resistance in the reproductive and metabolic manifestations of the classic PCOS phenotypes.

In contrast, Phenotype B exhibited lower fasting insulin concentrations, lower HOMA-IR values, and preserved QUICKI scores, indicating relatively maintained insulin sensitivity and metabolic homeostasis. Despite this favorable metabolic profile, Phenotype B demonstrated a significantly elevated LH/FSH ratio together with increased total testosterone concentrations, suggesting that androgen excess in this phenotype is predominantly gonadotropin-driven rather than insulin-mediated. Increased pulsatile GnRH secretion preferentially stimulates LH release, thereby enhancing ovarian theca-cell androgen production. This neuroendocrine mechanism has been well described in lean or metabolically healthy women with PCOS, in whom reproductive endocrine abnormalities predominate despite preserved insulin sensitivity[13,22,23]. The 2023 International Evidence-Based Guideline similarly recognizes that significant metabolic dysfunction is not uniformly present across all PCOS phenotypes, reflecting the biological heterogeneity of the disorder [14].

Phenotype D demonstrated a distinct metabolic profile. Although BMI was comparable to that of Phenotype B and the control group, fasting insulin concentrations and HOMA-IR were significantly elevated, whereas QUICKI values were significantly reduced, indicating insulin resistance despite the absence of excess adiposity. This finding suggests that factors other than obesity contribute to impaired insulin sensitivity in this subgroup. Proposed mechanisms include intrinsic defects in insulin receptor signaling, post-receptor abnormalities, mitochondrial dysfunction, oxidative stress, chronic low-grade inflammation, and genetic susceptibility, all of which have been implicated in PCOS independent of BMI [9,21,24]. Recent evidence further suggests that tissue-specific insulin resistance involving skeletal muscle, adipose tissue, liver, and ovarian tissue contributes to the metabolic heterogeneity observed across PCOS phenotypes [14].

Another notable finding was the relatively higher TSH concentration observed in Phenotype D, although values remained within the euthyroid range. Emerging evidence suggests that even subtle elevations in TSH may adversely affect insulin sensitivity by reducing peripheral glucose uptake, impairing insulin signaling, increasing oxidative stress, and promoting dyslipidemia [24-26]. Such alterations may contribute to metabolic dysfunction in susceptible women with PCOS. Accordingly, the 2023 International Evidence-Based Guideline recommends excluding thyroid disorders during the evaluation of women with suspected PCOS because of their overlapping reproductive and metabolic manifestations [14].

QUICKI-derived insulin sensitivity was significantly reduced in Phenotypes A, C, and D, with the greatest impairment observed in Phenotypes A and C. These findings reinforce the close association between excess adiposity and insulin resistance in the classic hyperandrogenic phenotypes. However, the persistence of moderate insulin resistance in Phenotype D despite a normal BMI further supports the concept that insulin resistance in PCOS is not exclusively obesity-dependent but also reflects intrinsic metabolic abnormalities [8,23]. Recent systematic reviews similarly demonstrate that insulin resistance may be present across the full spectrum of PCOS phenotypes, including lean women, although its severity varies considerably [14,23].

Overall, the findings of the present study reinforce the concept that PCOS is a heterogeneous disorder comprising metabolically distinct phenotypes. Phenotypes A and C appear to represent predominantly metabolic phenotypes characterized by obesity-

associated insulin resistance and compensatory hyperinsulinemia. In contrast, Phenotype B appears to represent a predominantly reproductive phenotype in which hypothalamic-pituitary-ovarian axis dysregulation predominates despite relatively preserved metabolic homeostasis. Phenotype D occupies an intermediate position, demonstrating obesity-independent insulin resistance that may reflect intrinsic metabolic abnormalities together with subtle endocrine alterations. These findings are consistent with current international recommendations advocating individualized phenotypic assessment and tailored management strategies based on the metabolic and reproductive characteristics of each patient [14].

Conclusion

This study highlights the marked metabolic and reproductive heterogeneity of PCOS, demonstrating that its phenotypes are characterized by distinct endocrine and metabolic profiles. These differences reinforce the concept of PCOS as a spectrum of disorders with diverse underlying pathophysiological mechanisms rather than a single clinical entity. Recognition of phenotype-specific characteristics may improve understanding of disease pathogenesis, facilitate early identification of women at increased metabolic risk, and support individualized clinical management.

Limitations of the Study

The present study has certain limitations. Its relatively small, single-center sample may limit the generalizability of the findings. The cross-sectional design precludes causal inferences regarding the relationship between metabolic and hormonal parameters across PCOS phenotypes. Insulin resistance was assessed using surrogate indices (HOMA-IR and QUICKI), which may not fully capture subtle variations in insulin sensitivity. In addition, lifestyle factors such as diet and physical activity were not comprehensively evaluated, which could have influenced metabolic outcomes.

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