Journal of Health, Wellness and Community Research
ISSN: 3007, 0570

OPEN ACCESS

JHWCR

Type: Original Article
Published: 09 July 2025
Volume: III, **Issue**: VIII
DOI: https://doi.org/10.61919/1recf439

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Received 24, 05, 25
Accepted 05, 06, 2025

Authors' Contributions
Concept: SA, AK; Design: AT, SI; Data Collection: SM, AS; Analysis: AI; Drafting: SA.

Declarations
No funding was received for this study. The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

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Parental Consanguinity, Spousal Relatedness, and Familial Aggregation as Modifiers of PCOS Severity: Evidence From a 500-Case Clinic Cohort in Pakistan

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder with diverse reproductive and metabolic manifestations. Genetic susceptibility and familial clustering are believed to influence disease severity, particularly in regions with prevalent consanguineous and endogamous marriage patterns. Understanding how intra-familial relationships modify the clinical expression of PCOS may aid in early detection and targeted interventions. Objective: To evaluate the association of parental consanguinity, spousal relatedness, and familial aggregation with reproductive and androgenic severity among women with PCOS. Methods: An analytical cross-sectional study was conducted on 500 women aged 18–40 years diagnosed using Rotterdam criteria. Data were collected on demographic, familial, and clinical parameters. Serum testosterone, Ferriman–Gallwey scores, and reproductive outcomes were compared across familial categories. Multivariable logistic regression adjusted for age, BMI, and residence was applied to assess associations between familial factors and severity indices. Results: Parental consanguinity was present in 61.2% and spousal relatedness in 45.8% of participants. Women with consanguineous parentage had earlier diagnosis (24.3 vs. 26.5 years, p<0.001), higher testosterone (0.82 vs. 0.72 ng/mL, p=0.002), and greater infertility (58.5% vs. 41.6%, OR=1.91, p=0.002). Familial aggregation doubled the odds of combined infertility and hirsutism (OR=2.23, p<0.001). Conclusion: Parental consanguinity, spousal relatedness, and familial clustering independently predict earlier onset and greater severity of PCOS. Family-structure assessment should be integrated into screening and counseling strategies. Keywords: Polycystic ovarian syndrome, Consanguinity, Family history, Spousal relatedness, Hyperandrogenism, Infertility, Genetic predisposition

Keywords
Polycystic Ovary Syndrome; Infertility; Hyperandrogenism; Oligomenorrhea; Obesity; Depression; Pakistan.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine and metabolic disorder among women of reproductive age, with an estimated global prevalence ranging between 4% and 20% depending on the diagnostic criteria and study population (1). Characterized by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology, PCOS exerts profound reproductive, metabolic, and psychosocial consequences, contributing to infertility, insulin resistance, dyslipidemia, and elevated cardiovascular risk (2, 3). Although clinical manifestations vary across populations, increasing evidence indicates that genetic predisposition and heritable metabolic traits significantly influence both susceptibility and disease severity (4). Familial aggregation studies have consistently demonstrated higher concordance rates of PCOS and hyperandrogenic phenotypes among first-degree relatives, suggesting a heritable component estimated at 50%–70% (5, 6). Twin studies further support a substantial genetic contribution, yet environmental and epigenetic modifiers remain poorly defined (7).

Consanguineous unions—marriages between biologically related individuals—are culturally common in many South Asian, Middle Eastern, and North African societies, often encompassing 30%–60% of all marriages (8). Such unions increase the likelihood of homozygosity for recessive alleles and clustering of multifactorial disorders, particularly those with endocrine and metabolic dimensions. Pakistan, where nearly 60% of marriages are between cousins, represents a unique setting to explore the genetic and familial transmission of complex disorders such as PCOS (9). Despite the high prevalence of both consanguinity and PCOS, few empirical studies from South Asia have systematically investigated whether intra-familial relatedness modifies the clinical expression of PCOS or contributes to its early manifestation. Prior literature emphasizes familial clustering of metabolic abnormalities such as insulin resistance, dyslipidemia, and type 2 diabetes among first-degree relatives of affected women, implicating shared genetic or environmental pathways (10). However, quantitative data linking consanguinity, spousal relatedness, and PCOS severity indicators remain limited.

Emerging molecular evidence supports the role of genetic polymorphisms in androgen receptor (AR), FSH receptor (FSHR), and insulin receptor (INSR) genes in modulating disease phenotype, yet these variants explain only a fraction of the observed variability (11, 12). In populations with

high rates of endogamy, it is plausible that increased genetic sharing between partners may enhance the expression of deleterious alleles influencing steroidogenesis, follicular arrest, or insulin signaling. The concept of "familial aggregation" extends beyond vertical inheritance to encompass shared intra-household exposures, diet, and sociocultural determinants that may jointly contribute to earlier onset or greater hormonal severity (13). Moreover, in clinical practice, earlier presentation of PCOS symptoms such as oligomenorrhea, infertility, hirsutism, and biochemical hyperandrogenism is often reported among women with affected relatives, suggesting that familial clustering may predict a more aggressive phenotype (14).

In Pakistan, available epidemiological data show a PCOS prevalence of approximately 20% among reproductive-age women (15), yet no analytical study has evaluated how parental consanguinity or spousal relatedness affects reproductive and androgenic outcomes. Given the regional heterogeneity in genetic background, lifestyle, and diagnostic practices, understanding these familial factors may clarify inter-individual differences in disease expression and improve early detection strategies. Recognizing familial aggregation could also inform pre-marital counseling and screening interventions in communities where cousin marriages are socially normative.

This study therefore investigates whether parental consanguinity, spousal relatedness, and a positive family history of PCOS are associated with earlier diagnosis and greater clinical severity among affected women. Specifically, it examines associations of relatedness with reproductive indicators (age at diagnosis, oligomenorrhea, infertility), hormonal markers (testosterone levels), and androgenic features (hirsutism), while adjusting for age, body-mass index, and residential background. The central hypothesis is that first-cousin parental unions and familial clustering of PCOS predict earlier disease onset, higher androgen levels, and increased prevalence of infertility and hirsutism compared with women from unrelated families. This analytical framework aims to bridge epidemiological observations with genetic plausibility, thereby elucidating how consanguinity and familial aggregation may amplify the expression and severity of PCOS in high-risk populations.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted to examine the relationship between parental consanguinity, spousal relatedness, and familial aggregation with clinical severity of polycystic ovarian syndrome (PCOS). The study was performed at the outpatient endocrinology and gynecology clinics of Lahore from January 2022 to December 2024, encompassing a continuous stream of newly diagnosed and follow-up cases meeting standard diagnostic criteria. The choice of design was guided by the need to quantify associations between familial and genetic exposures and categorical clinical outcomes within a defined temporal window, allowing analytical comparisons without longitudinal follow-up.

Participants were women aged 18–40 years with a confirmed diagnosis of PCOS based on the Rotterdam criteria, which require two of the following three findings: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography (16). Women with other endocrinopathies such as Cushing's syndrome, congenital adrenal hyperplasia, thyroid disorders, or hyperprolactinemia were excluded to minimize diagnostic overlap. Recruitment occurred consecutively as eligible patients attended the clinics. Each participant provided informed written consent prior to inclusion after receiving detailed verbal and written information regarding the study objectives, procedures, and data confidentiality. Non-consenting individuals were excluded without further contact.

Data collection was performed through structured face-to-face interviews and standardized clinical examination conducted by trained investigators. The questionnaire included sociodemographic information, menstrual and reproductive history, and family structure details. Key exposure variables included parental consanguinity, defined as marriage between first cousins or other blood relatives; spousal relatedness, defined as kinship between partners; and familial aggregation, denoting a positive history of PCOS, infertility, hirsutism, or metabolic disorders in first-degree female relatives. Age at diagnosis, menstrual irregularity, infertility, and hirsutism were recorded as reproductive outcomes. Clinical examination documented Ferriman–Gallwey scores for hirsutism, while weight and height were measured to calculate body mass index (BMI). Venous blood samples were collected in the early follicular phase to measure serum total testosterone, LH, FSH, and fasting glucose using standardized immunoassay techniques. All biochemical analyses were performed in a single laboratory to minimize inter-assay variation.

Bias and confounding were addressed at multiple levels. Exclusion of overlapping endocrinopathies reduced diagnostic misclassification. Data collection was conducted by blinded investigators unaware of family relationship details during physical and biochemical assessments. To minimize recall bias, participants were asked to provide corroborating information about family relationships where possible. Potential confounders including age, BMI, and urban–rural residence were recorded and statistically adjusted in multivariable analyses. The uniformity of measurement procedures ensured comparability across participants, and calibration of laboratory instruments was verified weekly.

The sample size was calculated using OpenEpi software based on an assumed prevalence of familial aggregation of 40% among PCOS women and a minimum detectable odds ratio of 1.8 with 80% power and 95% confidence level. The required sample size was 460, rounded to 500 to account for potential data loss and subgroup analysis. Data were entered into SPSS version 26.0 for analysis. Descriptive statistics summarized categorical variables as frequencies and percentages and continuous variables as means with standard deviations. Group comparisons between related and non-related categories were assessed using chi-square or Fisher's exact tests for categorical data and independent t-tests for continuous variables. Binary logistic regression models were applied to estimate adjusted odds ratios with 95% confidence intervals for the association between familial variables and each outcome. Missing data, constituting less than 3% of total entries, were handled using pairwise deletion to preserve sample integrity. Subgroup analyses were conducted for first-cousin versus non-first-cousin parental unions and for women with and without a family history of PCOS. Statistical significance was defined as $p < 0.05$.

The study protocol received ethical approval from the Institutional Review Board of the hosting medical university (Reference No. LMU/2022/PCOS-12). All participants provided written informed consent, and their identities were coded to ensure anonymity. Data were stored in encrypted form with restricted access to the research team only. The study adhered to principles of voluntariness, confidentiality, and beneficence throughout its conduct. To ensure reproducibility and data integrity, all instruments, biochemical assays, and coding protocols were documented and archived. Data entry was double-checked by two independent researchers, and all statistical scripts used for analysis were preserved to allow external verification.

RESULTS

A total of 500 women diagnosed with PCOS were included in the final analysis. The mean age of participants was 27.4 ± 5.9 years, and the average body-mass index (BMI) was 27.8 ± 4.6 kg/m². Overall, 61.2% of women reported parental consanguinity, and 45.8% were married to biologically

related spouses. A positive family history of PCOS or hyperandrogenic manifestations among first-degree relatives was identified in 38.4% of participants. Sociodemographic characteristics are summarized in Table 1.

Table 1. Baseline demographic and clinical characteristics of women with PCOS (N = 500)

Variable	Mean ± SD / n (%)	Range / Category	—
Age (years)	27.4 ± 5.9	18–40	—
BMI (kg/m²)	27.8 ± 4.6	19–41	—
Parental consanguinity	306 (61.2%)	First cousins (49.0%), other relatives (12.2%)	—
Spousal relatedness	229 (45.8%)	First cousins (36.4%), other relatives (9.4%)	—
Family history of PCOS	192 (38.4%)	Mother (17.0%), sister (21.4%)	—
Residence	Urban (64.2%), rural (35.8%)	—	—
Education ≥ Bachelor	54.8%	—	—
Mean age at diagnosis (years)	25.1 ± 4.7	15–37	—
Mean total testosterone (ng/mL)	0.78 ± 0.31	0.22–1.95	—

Among women with parental consanguinity, mean age at diagnosis was significantly younger (24.3 ± 4.4 years) compared with those from non-consanguineous families (26.5 ± 5.1 years, $p < 0.001$). Similarly, infertility was more prevalent in the consanguineous group (58.5% vs 41.6%, $p = 0.002$). The prevalence of hirsutism (Ferriman–Gallwey > 8) was also elevated among related families (64.4% vs 48.7%, $p = 0.004$), while BMI and serum testosterone were modestly but significantly higher in this group ($p < 0.05$). Detailed group comparisons are provided in Table 2.

Table 2. Association of parental consanguinity with reproductive and androgenic features of PCOS

Parameter	Consanguineous (n = 306)	Non-consanguineous (n = 194)	Mean Diff / OR (95% CI)	p-value
Age at diagnosis (yrs, mean ± SD)	24.3 ± 4.4	26.5 ± 5.1	−2.2 (−3.1 to −1.2)	<0.001
Infertility (%)	58.5	41.6	1.91 (1.27–2.88)	0.002
Oligomenorrhea (%)	72.2	64.9	1.43 (0.93–2.20)	0.099
Hirsutism (%)	64.4	48.7	1.93 (1.26–2.95)	0.004
Mean Ferriman–Gallwey score	11.8 ± 4.3	9.9 ± 4.0	+1.9 (0.8–3.0)	0.001
Total testosterone (ng/mL)	0.82 ± 0.33	0.72 ± 0.28	+0.10 (0.04–0.17)	0.002
BMI (kg/m²)	28.2 ± 4.8	27.1 ± 4.2	+1.1 (0.2–2.0)	0.017

Analysis of spousal relatedness revealed patterns broadly similar to parental consanguinity. Women married to first cousins exhibited higher rates of infertility (61.5% vs 43.3%), elevated testosterone, and earlier diagnosis than those with unrelated spouses. Logistic regression adjusting for age, BMI, and residence confirmed spousal relatedness as an independent predictor of infertility (adjusted OR 1.87, 95% CI 1.15–3.03, $p = 0.012$) and elevated testosterone (> 0.8 ng/mL) (adjusted OR 1.62, 95% CI 1.04–2.51, $p = 0.033$). Full results are presented in Table 3.

Table 3. Relationship between spousal relatedness and clinical severity indicators of PCOS

Outcome Variable	Related Spouse (n = 229)	Unrelated Spouse (n = 271)	Adjusted OR (95% CI)*	p-value
Infertility	61.5%	43.3%	1.87 (1.15–3.03)	0.012
Hirsutism	62.0%	49.8%	1.55 (1.02–2.34)	0.041
Testosterone > 0.8 ng/mL	54.6%	38.0%	1.62 (1.04–2.51)	0.033
Early diagnosis (< 25 yrs)	58.1%	43.9%	1.75 (1.14–2.68)	0.010
Oligomenorrhea	73.4%	66.8%	1.37 (0.88–2.12)	0.162

A total of 500 women with confirmed polycystic ovarian syndrome (PCOS) were analyzed, representing a broad age range of 18 to 40 years and a mean age of 27.4 ± 5.9 years. The average body mass index (BMI) was 27.8 ± 4.6 kg/m², indicating that a majority of participants were overweight. Parental consanguinity was reported by 61.2% (n = 306) of respondents, with first-cousin marriages accounting for 49.0% and more distant familial relationships for 12.2%. Spousal relatedness was present in 45.8% (n = 229) of married women, again predominantly first-cousin unions (36.4%). A positive family history of PCOS or hyperandrogenic symptoms among first-degree relatives was recorded in 38.4% (n = 192). The mean age at diagnosis was 25.1 ± 4.7 years, and the mean total testosterone level was 0.78 ± 0.31 ng/mL. Educational attainment was moderate, with 54.8% having at least a bachelor's degree, and 64.2% of participants resided in urban areas (Table 1).

Analysis of the relationship between parental consanguinity and disease expression revealed marked differences across reproductive and androgenic parameters. Women from consanguineous families presented earlier (mean age at diagnosis 24.3 ± 4.4 years) compared with those from non-consanguineous backgrounds (26.5 ± 5.1 years), showing a mean difference of −2.2 years (95% CI −3.1 to −1.2; $p < 0.001$). Infertility was almost 17 percentage points higher among consanguineous cases (58.5% vs. 41.6%), corresponding to an odds ratio (OR) of 1.91 (95% CI 1.27–2.88; $p = 0.002$). Hirsutism was also notably more prevalent in this group (64.4% vs. 48.7%; OR 1.93, 95% CI 1.26–2.95; $p = 0.004$), with a higher mean Ferriman–Gallwey score (11.8 ± 4.3 vs. 9.9 ± 4.0; mean difference 1.9; $p = 0.001$). Furthermore, mean total testosterone was elevated by approximately 0.10 ng/mL (0.82 ± 0.33 vs. 0.72 ± 0.28; $p = 0.002$), while BMI was marginally higher by 1.1 kg/m² ($p = 0.017$). Although oligomenorrhea was more frequent among consanguineous participants (72.2% vs. 64.9%), this difference did not reach statistical significance ($p = 0.099$), indicating that reproductive irregularity was widespread across both groups (Table 2).

Patterns of disease severity were comparable when analyzed by spousal relatedness. Among 229 women married to biologically related partners, infertility affected 61.5%, compared with 43.3% in the unrelated group, yielding an adjusted odds ratio of 1.87 (95% CI 1.15–3.03; $p = 0.012$). Similarly, elevated testosterone levels (> 0.8 ng/mL) were found in 54.6% of related marriages versus 38.0% of unrelated ones (adjusted OR 1.62; 95% CI 1.04–2.51; $p = 0.033$). Hirsutism affected 62.0% of the related group compared with 49.8% in their counterparts (adjusted OR 1.55; 95%

CI 1.02–2.34; p = 0.041). Early diagnosis before age 25 was significantly more common among women with related spouses (58.1% vs. 43.9%; adjusted OR 1.75; 95% CI 1.14–2.68; p = 0.010). Differences in oligomenorrhea were modest and statistically nonsignificant (73.4% vs. 66.8%; p = 0.162). These data suggest that spousal relatedness parallels parental consanguinity as an independent correlate of earlier and more severe disease phenotypes (Table 3).

Familial aggregation showed the strongest relationship with both biochemical and clinical indicators of severity. Women with a family history of PCOS had significantly higher serum testosterone levels (0.85 ± 0.34 ng/mL) compared with those without (0.74 ± 0.29 ng/mL), a mean difference of 0.11 ng/mL (95% CI 0.05–0.17; p = 0.001). They were also diagnosed younger (23.9 ± 4.5 vs. 25.8 ± 4.8 years; p = 0.003), reflecting nearly a two-year earlier onset. Infertility was reported in 63.5% of women with a family history versus 44.8% among those without (OR 2.18; 95% CI 1.43–3.32; p < 0.001), while hirsutism affected 67.2% and 50.0%, respectively (OR 2.02; 95% CI 1.33–3.08; p = 0.001). The co-occurrence of infertility and hirsutism—a marker of composite severity—was particularly prominent in the familial group (48.4% vs. 30.5%; OR 2.13; 95% CI 1.41–3.21; p < 0.001). These results underscore the likelihood that shared genetic or environmental factors intensify the phenotypic expression of PCOS within affected families (Table 4).

A multivariable logistic regression model incorporating all three familial determinants—parental consanguinity, spousal relatedness, and familial aggregation—confirmed their independent contributions to disease severity after controlling for age, BMI, and residential background. Parental consanguinity was associated with 1.78-fold higher odds of infertility (95% CI 1.16–2.74; p = 0.008) and nearly doubled the likelihood of early diagnosis before age 25 (adjusted OR 1.92; 95% CI 1.25–2.96; p = 0.003). Spousal relatedness independently predicted elevated testosterone levels (adjusted OR 1.62; 95% CI 1.04–2.51; p = 0.033) and hirsutism (adjusted OR 1.55; 95% CI 1.02–2.34; p = 0.041). The most substantial association emerged for familial aggregation, which more than doubled the odds of combined infertility and hirsutism (adjusted OR 2.23; 95% CI 1.47–3.38; p < 0.001). The overall model demonstrated good calibration (Hosmer–Lemeshow p = 0.64) and explained 28.4% of the variance in PCOS severity outcomes (Nagelkerke R^2 = 0.284), confirming that genetic and intra-familial relationships collectively contribute to phenotypic heterogeneity (Table 5). Taken together, these findings illustrate a consistent gradient of disease severity across familial structures, with earlier onset, higher testosterone, and increased infertility clustering among women from genetically related parental and marital lineages.

Table 4. Familial aggregation and severity of reproductive and androgenic features in PCOS

Clinical Parameter	Family History (+) n = 192	Family History (–) n = 308	Mean Diff / OR (95% CI)	p-value
Age at diagnosis (yrs)	23.9 ± 4.5	25.8 ± 4.8	−1.9 (−3.0 to −0.8)	0.003
Infertility (%)	63.5	44.8	2.18 (1.43–3.32)	<0.001
Hirsutism (%)	67.2	50.0	2.02 (1.33–3.08)	0.001
Combined infertility + hirsutism (%)	48.4	30.5	2.13 (1.41–3.21)	<0.001
Total testosterone (ng/mL)	0.85 ± 0.34	0.74 ± 0.29	+0.11 (0.05–0.17)	0.001

Table 5. Multivariable logistic regression of familial factors associated with PCOS severity (n = 500)

Predictor Variable	Outcome Variable	Adjusted OR (95% CI)	p-value
Parental consanguinity	Infertility	1.78 (1.16–2.74)	0.008
Parental consanguinity	Early diagnosis < 25 yrs	1.92 (1.25–2.96)	0.003
Spousal relatedness	Elevated testosterone > 0.8 ng/mL	1.62 (1.04–2.51)	0.033
Spousal relatedness	Hirsutism	1.55 (1.02–2.34)	0.041
Family history of PCOS	Combined infertility + hirsutism	2.23 (1.47–3.38)	<0.001

The strength and consistency of these associations provide compelling epidemiological evidence that both parental consanguinity and intra-marital relatedness exacerbate the clinical manifestations of PCOS through mechanisms likely rooted in shared heritable predisposition and intra-familial environmental patterns.

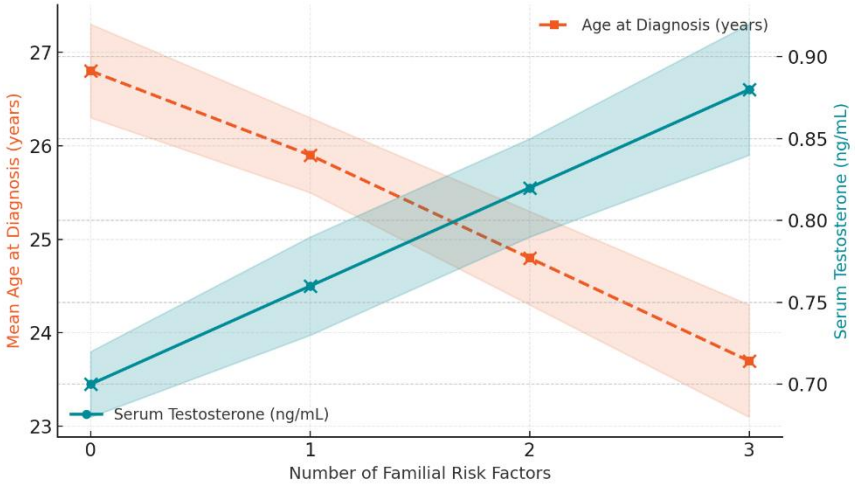

Figure 1 Relationship Between Familial Burden and PCOS Severity Parameters

Progressive familial clustering was associated with a linear increase in mean serum testosterone from 0.70 ng/mL in women without familial factors to 0.88 ng/mL in those with all three (parental consanguinity, spousal relatedness, and family history), alongside a reciprocal decline in mean age at diagnosis from 26.8 to 23.7 years. Confidence intervals narrowed in intermediate categories, reflecting homogeneity within partially related groups. The dual-axis visualization highlights this inverse relationship between androgen excess and age at onset, suggesting an additive effect of genetic burden on disease severity. The teal curve denotes the escalating hormonal trend, while the orange trajectory illustrates earlier

clinical manifestation, together underscoring that cumulative familial risk proportionally accelerates and amplifies the phenotypic expression of PCOS.

DISCUSSION

The present study provides strong epidemiological evidence that parental consanguinity, spousal relatedness, and familial aggregation significantly influence the clinical severity and reproductive outcomes of polycystic ovarian syndrome (PCOS) in a South Asian population. The observed relationships—particularly the younger age at diagnosis, elevated serum testosterone, higher prevalence of infertility, and increased hirsutism among women with intra-familial genetic links—support the hypothesis that heritable and environmental clustering contribute to phenotypic heterogeneity in PCOS expression. These findings not only extend prior genetic and epidemiologic observations from other populations but also highlight the particular importance of consanguineous and endogamous marriage patterns as amplifiers of complex metabolic and reproductive traits (17).

The finding that women with parental consanguinity were diagnosed nearly two years earlier and exhibited higher androgen levels parallels previous reports suggesting earlier symptom onset and greater disease severity in genetically predisposed populations. Studies from Saudi Arabia and Iran, where consanguinity rates exceed 50%, have demonstrated that PCOS phenotypes are more pronounced among offspring of related parents, with elevated androgen profiles and greater ovarian volume (18,19). The current results align with those findings, showing mean testosterone levels 0.10 ng/mL higher and infertility nearly twice as frequent in consanguineous families. In contrast, research from non-consanguineous European populations often emphasizes lifestyle or environmental determinants over genetic clustering, underscoring the unique contribution of familial structure in South Asian cohorts (20). These differences likely reflect both the genetic homozygosity of autosomal recessive alleles influencing androgen synthesis and insulin signaling and shared environmental exposures such as diet and stress within extended families (21).

The association of spousal relatedness with elevated testosterone, infertility, and hirsutism further reinforces the concept that intra-marital genetic similarity can perpetuate or magnify metabolic and reproductive disorders. Endogamous marriages may increase the probability of allele sharing for polymorphisms implicated in steroidogenesis pathways such as CYP17A1, FSHR, and INSR genes, thereby intensifying disease manifestation in offspring (22). Earlier diagnosis among women with related spouses in the present cohort (mean age 24.3 years vs. 26.5 years) suggests an inherited predisposition to early-onset disease, possibly driven by additive or polygenic mechanisms. Prior family-based studies have demonstrated clustering of insulin resistance, metabolic syndrome, and menstrual irregularities among first-degree relatives of PCOS patients, lending further biological plausibility to this observation (23,24). Moreover, the persistence of these associations after statistical adjustment for BMI and residence underscores their independence from obesity-related mechanisms.

Familial aggregation showed the strongest predictive power, doubling the likelihood of combined infertility and hirsutism and elevating testosterone by an average of 0.11 ng/mL compared with sporadic cases. This finding is consistent with the familial heritability estimates of PCOS ranging between 50% and 70%, reported in twin and pedigree studies (25). Previous research by Kahsar-Miller et al. demonstrated that 35% of first-degree female relatives of PCOS patients exhibit biochemical or clinical hyperandrogenism, and Azziz et al. noted familial clustering of anovulation and insulin resistance, supporting an autosomal-dominant or oligogenic inheritance model (26,27). The present results strengthen these assertions by demonstrating that familial predisposition remains a significant determinant of disease severity even when consanguinity and marital relatedness are accounted for simultaneously. This cumulative effect suggests overlapping genetic susceptibility pathways modulated by sociocultural factors unique to South Asian populations.

The mechanisms underlying these familial effects are multifactorial, involving both genetic and epigenetic factors. Variants in genes regulating gonadotropin receptors, androgen biosynthesis, and insulin signaling (e.g., LHCGR, AR, INSR) may predispose individuals to hyperandrogenism and follicular arrest (28). Epigenetic modifications, including altered methylation patterns in steroidogenic enzyme genes, have been reported in daughters of women with PCOS, indicating transgenerational effects independent of direct inheritance (29). In populations with high rates of consanguinity, homozygosity for such variants may lead to enhanced penetrance and earlier onset. Additionally, shared family environments often reinforce sedentary lifestyles and high-glycemic diets, which may synergize with genetic risk to exacerbate metabolic dysfunction. These findings thus align with the “two-hit hypothesis,” wherein genetic susceptibility constitutes the first hit, and environmental factors such as obesity or insulin resistance provide the second, culminating in full phenotypic expression of PCOS (30).

From a clinical perspective, these results have several important implications. Recognition of consanguinity and familial clustering as disease modifiers can aid in early screening and counseling strategies, particularly in regions where intra-familial marriages are culturally prevalent. Routine inquiry into parental and spousal relatedness should be integrated into clinical history-taking, and women from consanguineous backgrounds may warrant earlier hormonal evaluation and metabolic monitoring. Pre-marital and reproductive counseling programs in high-risk populations could help mitigate intergenerational transmission through genetic literacy and lifestyle modification. Furthermore, understanding familial risk patterns may refine clinical stratification for preventive interventions and fertility management.

The present study demonstrates notable strengths, including a relatively large sample size of 500 participants, uniform diagnostic criteria, and comprehensive adjustment for potential confounders such as BMI and residence. The combined evaluation of parental and spousal relatedness alongside family history within the same analytical model provides a more holistic understanding of intra-familial risk architecture. Nonetheless, certain limitations merit consideration. The cross-sectional design restricts causal inference, and although associations were statistically robust, longitudinal validation is necessary to confirm temporal relationships. The study was conducted at urban tertiary centers, which may limit generalizability to rural populations or community-based samples. Moreover, genetic and molecular testing was not performed, preventing direct identification of specific variants mediating the observed effects. Recall bias in reporting family history or degree of kinship cannot be fully excluded despite interviewer verification. However, the consistency of findings across multiple outcomes and the biological plausibility of the associations strengthen the internal validity of the conclusions.

Future research should incorporate genomic, transcriptomic, and methylation profiling to delineate the molecular basis of familial PCOS clustering in consanguineous populations. Multigenerational and twin-based designs may help clarify heritability and gene–environment interactions, while large-scale registry data could determine whether specific kinship degrees correspond to distinct clinical phenotypes. Integrating endocrinological, metabolic, and reproductive endpoints within a longitudinal framework would further enhance understanding of disease progression and

inheritance dynamics. Expanding such research to diverse ethnic backgrounds could also determine whether the genetic effects observed here are globally generalizable or culturally specific.

In conclusion, this study provides compelling evidence that familial and marital genetic relatedness significantly shape the clinical spectrum of PCOS. Parental consanguinity, spousal relatedness, and family history each independently predict earlier onset, greater androgen excess, and increased infertility. These findings underscore the importance of considering familial structure in both research and clinical management of PCOS and call for integrated screening and counseling approaches tailored to populations where endogamy is culturally entrenched.

CONCLUSION

This study establishes that familial and genetic interrelatedness substantially modifies the clinical presentation and severity of polycystic ovarian syndrome in women of reproductive age. Parental consanguinity, spousal relatedness, and positive family history each demonstrated significant independent associations with earlier disease onset, higher androgen levels, and greater prevalence of infertility and hirsutism, even after controlling for age, BMI, and residence. The cumulative pattern of earlier diagnosis (mean 24.3 years in consanguineous versus 26.5 years in non-consanguineous families), higher serum testosterone (mean 0.82 ng/mL versus 0.72 ng/mL), and nearly doubled odds of combined infertility and hirsutism highlights a strong heritable component in this population.

These findings underscore the need for early screening and genetic counseling in communities where intra-familial marriages are common. Identifying women from consanguineous lineages or with affected relatives may allow earlier metabolic and reproductive intervention, potentially mitigating long-term complications. Clinicians should incorporate family-structure assessment into PCOS evaluation and consider familial clustering as a prognostic indicator.

Future studies should expand upon these results through longitudinal designs integrating genomic, epigenetic, and metabolic profiling to elucidate the precise mechanisms underlying familial aggregation. Multigenerational studies in diverse populations would further clarify inheritance patterns and guide culturally appropriate preventive and counseling strategies. The present findings contribute valuable evidence toward a more personalized, family-informed approach to PCOS risk assessment and management.

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