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CLINICAL, IMMUNOLOGICAL AND MOLECULAR GENETIC DETERMINANTS OF POLYCYSTIC OVARY SYNDROME AND STRATEGIES FOR PERSONALIZED TREATMENT

Nasiba Ismatullaevna Olimova
PhD, Associate Professor, Department of Obstetrics and Gynecology No. 1,
Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract

Background. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and is characterized by hyperandrogenism, ovulatory dysfunction, and metabolic abnormalities. Recent evidence highlights the significant role of immunological and molecular-genetic factors in the pathogenesis of PCOS, emphasizing the importance of personalized therapeutic strategies.

Objective. To investigate the clinical, hormonal, immunological, and molecular-genetic determinants of PCOS and to evaluate their significance in the development of personalized treatment approaches.

Methods. A total of 120 women of reproductive age were enrolled in the study, including 80 patients diagnosed with PCOS and 40 healthy controls. Clinical assessment included evaluation of menstrual and reproductive history, body mass index (BMI), and ultrasound examination. Hormonal profiling (LH, FSH, testosterone, AMH), immunological markers (IL-6, TNF-α, VEGF-A), and molecular-genetic polymorphisms (VEGF-A and AMH genes) were analyzed. Statistical processing was performed using SPSS software with significance set at $p < 0.05$.

Results. Patients with PCOS demonstrated significantly elevated levels of LH, LH/FSH ratio, testosterone, and AMH compared to controls ($p < 0.05$). Increased concentrations of pro-inflammatory cytokines IL-6 and TNF-α, as well as VEGF-A, indicated the presence of chronic low-grade inflammation and altered angiogenesis. Unfavorable genotypes of VEGF-A and AMH were significantly more frequent in the PCOS group. Correlation analysis revealed associations between hormonal imbalance, inflammatory activation, and genetic polymorphisms.

Conclusion. PCOS is characterized by a complex interplay of endocrine, immunological, and genetic alterations. The findings support the implementation of personalized diagnostic and therapeutic strategies based on the patient's clinical, immune, and molecular-genetic profile.

Keywords: polycystic ovary syndrome; hyperandrogenism; inflammation; cytokines; VEGF-A; AMH; genetic polymorphism; personalized medicine.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine and metabolic disorders affecting women of reproductive age, with a global prevalence ranging from 8% to 15% [1,2]. It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology

according to the Rotterdam diagnostic criteria [3]. In addition to reproductive impairment, PCOS is increasingly recognized as a systemic condition associated with metabolic abnormalities, including insulin resistance, obesity, dyslipidemia, and an elevated risk of type 2 diabetes and cardiovascular disease [4,5].

The pathogenesis of PCOS is complex and multifactorial, involving intricate interactions between endocrine, metabolic, genetic, and environmental factors [1,8]. Insulin resistance and compensatory hyperinsulinemia play a central role in enhancing ovarian androgen production and disrupting folliculogenesis [4,5]. Altered gonadotropin secretion, particularly elevated luteinizing hormone (LH) levels and an increased LH/FSH ratio, further contribute to hyperandrogenism and ovulatory dysfunction [2].

Growing evidence suggests that chronic low-grade inflammation is an important component in the development and progression of PCOS [6,7]. Increased circulating levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), reflect immune activation and may aggravate insulin resistance and ovarian steroidogenesis [6,7]. Additionally, dysregulation of angiogenic factors, including vascular endothelial growth factor (VEGF), has been implicated in abnormal ovarian vascularization and follicular development [9].

Genetic susceptibility also contributes significantly to PCOS heterogeneity. Genome-wide association studies and candidate gene analyses have identified multiple genetic variants associated with steroidogenesis, metabolic regulation, and ovarian function [8]. Variations in genes related to angiogenesis and anti-Müllerian hormone (AMH) signaling may influence ovarian reserve, follicular dynamics, and disease severity [9].

Given the heterogeneity of clinical manifestations and underlying mechanisms, the integration of clinical, immunological, and molecular-genetic data is essential for improving diagnostic precision and therapeutic effectiveness. In this context, personalized medicine approaches tailored to the individual hormonal, immune, and genetic profile of patients with PCOS represent a promising direction for optimizing treatment outcomes [2].

Materials and Methods

The study was conducted at the Department of Obstetrics and Gynecology of Bukhara State Medical Institute in collaboration with the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Women of reproductive age with a clinically and instrumentally confirmed diagnosis of polycystic ovary syndrome (PCOS) were enrolled in the study. The diagnosis was established based on clinical presentation, hormonal evaluation, and ultrasound findings. The control group consisted of age-matched healthy women without clinical or laboratory signs of endocrine or metabolic disorders.

Comprehensive evaluation included clinical and instrumental assessments such as detailed medical history, evaluation of menstrual and reproductive function, measurement of body mass index (BMI), and pelvic ultrasound

examination. In selected cases, additional imaging studies were performed when clinically indicated.

Laboratory investigations comprised complete blood count, coagulation profile, and biochemical parameters. Hormonal analysis included serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, total testosterone, estradiol, progesterone, anti-Müllerian hormone (AMH), and insulin.

Immunological assessment was performed by measuring pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as selected growth and paracrine factors using enzyme-linked immunosorbent assay (ELISA).

Molecular-genetic analysis involved detection of polymorphisms in the VEGF-A and AMH genes using polymerase chain reaction (PCR) followed by genotyping.

Statistical analysis was carried out using SPSS and Statistica software. Data were expressed as mean (M), standard deviation (SD), and standard error of the mean (SEM). Differences between groups were considered statistically significant at $p < 0.05$.

Results

A total of 120 women of reproductive age were included in the study. The main group consisted of 80 patients diagnosed with polycystic ovary syndrome (PCOS), while 40 healthy women formed the control group. The mean age of participants did not differ significantly between groups (26.8 ± 0.9 years in the PCOS group vs. 25.9 ± 1.1 years in controls, $p > 0.05$).

Clinical evaluation revealed that 72.5% of women with PCOS had menstrual irregularities (oligomenorrhea or amenorrhea), and clinical signs of hyperandrogenism were observed in 65.0% of patients. The mean body mass index (BMI) was significantly higher in the PCOS group compared to controls (27.4 ± 0.8 kg/m² vs. 22.6 ± 0.7 kg/m², $p < 0.01$).

Hormonal analysis demonstrated significant alterations in gonadotropin secretion. Luteinizing hormone (LH) levels were nearly twofold higher in the PCOS group compared to controls (12.8 ± 0.6 IU/L vs. 6.4 ± 0.4 IU/L, $p < 0.001$). The LH/FSH ratio was significantly elevated (2.3 ± 0.2 vs. 1.1 ± 0.1, $p < 0.001$). Serum testosterone and anti-Müllerian hormone (AMH) levels were also significantly increased in patients with PCOS ($p < 0.01$ and $p < 0.001$, respectively). Detailed clinical and hormonal parameters are presented in Table 1 (see Table 1).

Table 1.

Clinical and Hormonal Parameters (Mean ± SEM)

Parameter	PCOS (n=80)	Control (n=40)	p-value
BMI (kg/m²)	27.4 ± 0.8	22.6 ± 0.7	<0.01
LH (IU/L)	12.8 ± 0.6	6.4 ± 0.4	<0.001
LH/FSH ratio	2.3 ± 0.2	1.1 ± 0.1	<0.001
Testosterone	2.9 ± 0.3	1.4 ± 0.2	<0.01

(ng/mL)			
AMH (ng/mL)	7.6 ± 0.5	3.1 ± 0.4	<0.001

Immunological assessment revealed evidence of chronic low-grade inflammation. Concentrations of IL-6 and TNF-α were significantly higher in the PCOS group compared to controls ($p < 0.001$). Additionally, VEGF-A levels were elevated, suggesting altered angiogenic activity in ovarian tissue. Immunological findings are summarized in Table 2 (see Table 2).

Table 2.

Immunological Markers (Mean ± SEM)

Parameter	**PCOS (n=80)**	**Control (n=40)**	**p-value**
IL-6 (pg/mL)	8.4 ± 0.7	3.2 ± 0.4	<0.001
TNF-α (pg/mL)	14.6 ± 1.1	6.8 ± 0.6	<0.001
VEGF-A (pg/mL)	286.3 ± 15.4	172.5 ± 12.7	<0.01

Molecular-genetic analysis demonstrated a significantly higher frequency of the unfavorable GG genotype of the VEGF-A gene in the PCOS group (42.5%) compared to controls (17.5%, $p = 0.009$). The AA genotype of the AMH gene was also more common among patients with PCOS (38.7% vs. 15.0%, $p < 0.05$). Genotype distribution is shown in Table 3 (see Table 3).

Table 3.

Frequency of Genotypes (%)

Gene / Genotype	PCOS (n=80)	Control (n=40)	p-value
VEGF-A (GG)	42.5%	17.5%	0.009
AMH (AA)	38.7%	15.0%	<0.05

The results of the present study demonstrate that PCOS is associated with significant endocrine, immunological, and genetic alterations. Women with PCOS had a significantly higher body mass index compared to controls (27.4 ± 0.8 kg/m² vs. 22.6 ± 0.7 kg/m², $p < 0.01$). Hormonal analysis revealed nearly a twofold increase in LH levels (12.8 ± 0.6 IU/L vs. 6.4 ± 0.4 IU/L, $p < 0.001$) and a markedly elevated LH/FSH ratio (2.3 ± 0.2 vs. 1.1 ± 0.1, $p < 0.001$). Testosterone levels were significantly higher in the PCOS group (2.9 ± 0.3 ng/mL vs. 1.4 ± 0.2 ng/mL, $p < 0.01$), and AMH concentrations were more than twice as high compared to controls (7.6 ± 0.5 ng/mL vs. 3.1 ± 0.4 ng/mL, $p < 0.001$), indicating pronounced ovarian dysfunction.

Immunological findings showed evidence of chronic inflammatory activation. IL-6 levels were elevated by more than 2.5 times in the PCOS group (8.4 ± 0.7 pg/mL vs. 3.2 ± 0.4 pg/mL, $p < 0.001$), while TNF-α concentrations were more than doubled (14.6 ± 1.1 pg/mL vs. 6.8 ± 0.6 pg/mL, $p < 0.001$). VEGF-A levels were also significantly increased (286.3 ± 15.4 pg/mL vs. 172.5 ± 12.7 pg/mL, $p < 0.01$), suggesting enhanced angiogenic activity in ovarian tissue.

Molecular-genetic analysis revealed that the unfavorable GG genotype of the VEGF-A gene was present in 42.5% of PCOS patients compared to 17.5% in controls ($p = 0.009$). Similarly, the AA genotype of the AMH gene was identified in 38.7% of patients versus 15.0% in the control group ($p < 0.05$), indicating a significant association between these polymorphisms and PCOS susceptibility.

Overall, the quantitative differences observed in hormonal parameters, inflammatory markers, and genotype distribution confirm that PCOS is a multifactorial disorder involving endocrine dysregulation, chronic immune activation, and genetic predisposition. These findings provide a strong rationale for implementing personalized diagnostic and therapeutic strategies based on individual clinical, immunological, and molecular profiles.

Discussion

The present study confirms that polycystic ovary syndrome (PCOS) represents a multifactorial disorder characterized by endocrine imbalance, immune activation, and genetic predisposition. The observed twofold increase in LH levels and the significantly elevated LH/FSH ratio (2.3 ± 0.2 vs. 1.1 ± 0.1, $p < 0.001$) support the concept of hypothalamic–pituitary–ovarian axis dysregulation as a key mechanism underlying ovarian dysfunction. Elevated testosterone (2.9 ± 0.3 ng/mL) and AMH levels (7.6 ± 0.5 ng/mL) further indicate disrupted folliculogenesis and persistent hyperandrogenism.

The significant increase in BMI (27.4 ± 0.8 kg/m² vs. 22.6 ± 0.7 kg/m², $p < 0.01$) highlights the metabolic component of PCOS and its association with insulin resistance and adipose tissue–mediated endocrine alterations. These findings are consistent with current evidence suggesting that metabolic disturbances exacerbate ovarian steroidogenesis and reproductive dysfunction.

Importantly, our results demonstrate marked activation of inflammatory pathways. IL-6 and TNF-α levels were more than doubled in the PCOS group ($p < 0.001$), confirming the presence of chronic low-grade inflammation. This inflammatory state may contribute to insulin resistance, endothelial dysfunction, and altered ovarian microenvironment. The significantly elevated VEGF-A concentration (286.3 ± 15.4 pg/mL vs. 172.5 ± 12.7 pg/mL, $p < 0.01$) suggests enhanced angiogenic activity, which may influence abnormal follicular development and cyst formation.

Molecular-genetic findings further support the heterogeneity of PCOS. The higher frequency of the unfavorable VEGF-A GG genotype (42.5% vs. 17.5%, $p = 0.009$) and AMH AA genotype (38.7% vs. 15.0%, $p < 0.05$) indicates that genetic polymorphisms may predispose individuals to more pronounced endocrine and inflammatory disturbances. The interaction between genetic susceptibility and immune-endocrine mechanisms may explain the variability in clinical presentation and treatment response among patients with PCOS.

Taken together, the results emphasize that PCOS should be regarded as a systemic disorder rather than solely a reproductive pathology. The integration of hormonal, immunological, and genetic markers may improve risk stratification and facilitate individualized therapeutic interventions.

Conclusion

The study demonstrates that women with polycystic ovary syndrome exhibit significant endocrine, immunological, and molecular-genetic alterations. Elevated LH, testosterone, and AMH levels reflect ovarian dysfunction, while increased IL-6, TNF-α, and VEGF-A concentrations indicate chronic inflammatory activation and altered angiogenesis. The higher prevalence of unfavorable VEGF-A and AMH gene polymorphisms confirms the contribution of genetic susceptibility to disease development.

These findings highlight the multifactorial nature of PCOS and support the implementation of personalized diagnostic and therapeutic strategies based on individual hormonal, immune, and genetic profiles. A comprehensive, multidisciplinary approach may enhance treatment effectiveness and improve long-term reproductive and metabolic outcomes.

REFERENCES

1. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011;7(4):219–231.

2. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347–363.

3. Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in polycystic ovary syndrome. Mol Cell Endocrinol. 2011;335(1):30–41.

4. Welt CK, Carmina E. Lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. Endocrinol Metab Clin North Am. 2013;42(4):781–795.

5. Day FR, Hinds DA, Tung JY, Stolk L, Styrkarsdottir U, Saxena R, et al. Causal mechanisms and genetic architecture of polycystic ovary syndrome. PLoS Genet. 2015;11(10):e1005459.

6. Qin L, Chen Y, Li M, Wu X. Association between VEGF gene polymorphisms and risk of polycystic ovary syndrome: a meta-analysis. Reprod Biol Endocrinol. 2017;15:20.

7. Barber TM, Franks S. The link between polycystic ovary syndrome and both type 1 and type 2 diabetes mellitus. Womens Health (Lond). 2012;8(4):371–382.

8. Kelly CC, Lyall H, Petrie JR, Gould GW, Connell JM, Sattar N. Low-grade chronic inflammation in women with polycystic ovarian syndrome. J Clin Endocrinol Metab. 2001;86(6):2453–2455.

9. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106(1):6–15.