

PHENOTYPIC STRATIFICATION, METABOLIC MARKERS, AND PROGNOSTIC SIGNIFICANCE OF EARLY DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME

Tojjeva Iroda Mirsoli qizi,

PhD, Tashkent State Medical University, Tashkent, Uzbekistan

Abstract: Relevance. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and is characterized by marked clinical and metabolic heterogeneity. Phenotypic stratification makes it possible to refine the clinical prognosis and individualize therapeutic approaches.

Objective. To evaluate the clinical, hormonal, and metabolic characteristics of different PCOS phenotypes and to identify informative markers for the early diagnosis of the disease.

Materials and methods. The study included 145 patients with PCOS, classified into four phenotypes according to the Rotterdam criteria (2003), and 22 women in the control group. Clinical, ultrasound, hormonal, and metabolic parameters were assessed. Statistical analysis included regression models, ROC analysis, and neural network algorithms.

Results. The most unfavorable profile was identified in patients with phenotype A, characterized by obesity, insulin resistance, dyslipidemia, and pronounced hyperandrogenism. Phenotype D was characterized by minimal abnormalities and was close to the control group. The key markers for early PCOS diagnosis were menstrual cycle duration, testosterone level, body mass index, ovarian volume, and antral follicle count.

Conclusion. Phenotypic stratification and the use of diagnostically significant markers improve the accuracy of early PCOS diagnosis and allow the development of personalized management strategies for patients.

Keywords: polycystic ovary syndrome; phenotypes; hyperandrogenism; metabolic disorders; insulin resistance.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, affecting 8–13% of the population [7]. The disease is characterized by pronounced clinical and metabolic heterogeneity, which complicates diagnosis and the selection of personalized therapy. According to the international ESHRE/ASRM consensus criteria (Rotterdam, 2003) [5], PCOS is diagnosed when two of the following three features are present: chronic anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology. However, accumulating evidence indicates that phenotypic classification has high prognostic value, as it enables differentiation of patients according to the severity of reproductive and metabolic disturbances [4].

In recent years, particular attention has been paid to the study of markers that allow early diagnosis of PCOS and prediction of the risk of associated metabolic complications. The most promising predictors include anthropometric parameters, such as body mass index and menstrual cycle duration; ultrasound characteristics, including ovarian volume and antral follicle count; and biochemical parameters, such as testosterone level, the

HOMA-IR insulin resistance index, and lipid profile [1,6]. The use of modern statistical methods, including ROC analysis and neural network algorithms, opens new opportunities for the development of prognostic models that may be integrated into clinical practice [3].

The aim of the study was to evaluate the clinical, hormonal, and metabolic characteristics of different PCOS phenotypes and to determine the most informative markers for constructing a prognostic model for early diagnosis of the disease.

MATERIALS AND METHODS

A cross-sectional study was conducted to characterize the phenotypic and metabolic features of women with polycystic ovary syndrome (PCOS), as well as to develop a prognostic model for early diagnosis of the disease. The study included 145 patients with a confirmed diagnosis of PCOS, who were divided into four phenotypes according to the criteria of the international Rotterdam ESHRE/ASRM consensus (2003): phenotype A (n=78; 53.8%) — hyperandrogenism (HA) + chronic anovulation (CA) + polycystic ovaries (PCO) on ultrasound; phenotype B (n=18; 12.4%) — HA + CA without signs of PCO; phenotype C (n=19; 13.1%) — regular menstrual cycle + HA + PCO; and phenotype D (n=30; 20.7%) — CA + PCO without signs of HA.

The control group consisted of 22 women of reproductive age with normal body mass (24.4 ± 2.9 kg/m²), a regular ovulatory menstrual cycle, and no clinical or biochemical signs of hyperandrogenism or polycystic ovarian morphology. Exclusion criteria included pregnancy, use of hormonal medications during the previous three months, endocrine disorders such as hyperprolactinemia, hypothyroidism, congenital adrenal hyperplasia, ovarian or adrenal tumors, and severe somatic disease.

All patients underwent a comprehensive examination, including collection of clinical data (age, age at menarche, duration and characteristics of the menstrual cycle, severity of hirsutism according to the modified Ferriman–Gallwey score, presence of acne, seborrhea, alopecia, acanthosis, body mass index, blood pressure, and heart rate), ultrasound assessment (ovarian volume, antral follicle count, and endometrial thickness), and metabolic evaluation (fasting glucose, insulin, and HOMA-IR). Statistical analysis included the Mann–Whitney test, ANOVA, and the Kruskal–Wallis test for intergroup comparisons; Pearson and Spearman correlation analysis; and multiple logistic regression with calculation of the coefficient of determination R^2 , Fisher’s test, and significance level. The diagnostic value of markers was assessed by ROC analysis with calculation of the area under the curve (AUC), sensitivity, specificity, and cut-off points. Neural network analysis using a multilayer perceptron (SPSS v.23) was used to verify the prognostic model. All study participants signed informed consent, and the protocol was approved by the local Ethics Committee.

RESULTS

Analysis of clinical characteristics demonstrated pronounced phenotypic heterogeneity of PCOS. Patients with phenotype A had the earliest onset of menstrual cycle disorders (mean age 16.8 ± 2.5 years) and hirsutism (15.7 ± 1.4 years), as well as the longest menstrual cycle duration (42.6 ± 3.7 days), compared with other phenotypes and the control group (Table 1).

Table 1. Clinical characteristics of patients with different PCOS phenotypes

Parameters	A, n=78	B, n=18	C, n=19	D, n=30	Control, n=22
------------	---------	---------	---------	---------	---------------

Age, years	23.9±5.1	23.0±4.1	25.8±4.3	23.1±4.8	24.9±4.49
Age at menarche, years	13.2±1.2	13.0±1.1	12.7±0.9	12.8±1.4	12.9±1.4
Age at onset of menstrual cycle disorders, years	16.8±2.5 ● 0.02	18.9±4.8		17.9±2.8	
Age at onset of hirsutism, years	15.7±1.4 ● <0.0001	19.0±3.4	18.5±2.9		
Age at sexual debut, years	20.9±2.3	20.8±2.3	20.6±1.1	20.3±1.2	20.1±0.70
Menstrual cycle duration, days	42.6±3.7 *≈ <0.0001	41.3±3.5 *≈ 0.0001; 0.02	28.9±5.5 *0.001	39.1±3.1 *<0.0001	24.4±2.4

Note: data are presented as M±SD; * — significance compared with the control group; ● — significance compared with phenotype B; ▲ — significance compared with phenotype C; ≈ — significance compared with phenotype D.

According to the modified Ferriman–Gallwey scale, mean hirsutism scores were significantly higher in phenotype A (11.9±4.3 points), corresponding to a moderate degree of severity. In phenotypes C and D, mild hirsutism predominated, whereas severe hirsutism (≥15 points) was recorded only in phenotype A (21.8%) (Table 2).

Table 2. Comparative characteristics of hyperandrogenism indicators and ultrasound features in patients with different PCOS phenotypes

Parameters	A, n=78	B, n=18	C, n=19	D, n=30	Control, n=22
Hirsutism score, points	11.9±4.3 *●≈ <0.0001	8.28±2.02 *≈ <0.0001	8.11±4.16 *<0.0001; ≈ 0.002	4.67±1.09	4.68±1.25
Right ovarian volume, cm ³	12.1±3.24 *●≈ <0.0001	6.66±1.96 *0.01; ≈ <0.0001	11.7±2.8 *<0.0001	10.1±3.8 *<0.0001	4.95±2.11
Left ovarian volume, cm ³	11.5±2.81 *● <0.0001	6.90±2.30 *0.01; 0.02; ≈ <0.0001	10.8±5.8 *<0.0001	11.3±3.9 *<0.0001	5.08±2.14
Right antral follicle count	15.7±4.55 *● <0.0001	5.9±2.0 ≈ <0.0001	16.4±4.5 *<0.0001	14.9±1.9 *<0.0001	5.18±3.54
Left antral follicle count	16.3±3.90 *● <0.0001	6.2±2.6 ≈ <0.0001	15.1±5.1 *<0.0001	16.0±2.0 *<0.0001	4.68±3.59
Endometrial thickness, mm	4.47±1.16	4.42±1.3	4.29±0.79	4.38±1.07	4.43±1.1

Note: data are presented as Me; IQR; * — significance compared with the control group; ● — significance compared with phenotype B; ▲ — significance compared with phenotype C; ≈ — significance compared with phenotype D.

Ultrasound parameters also differed depending on phenotype. The highest values of ovarian volume and antral follicle count were observed in phenotypes A, C, and D, whereas the lowest values were characteristic of phenotype B. Endometrial thickness did not differ significantly between the groups (Table 2).

Anamnestic analysis showed that a family history of diabetes mellitus was significantly more common in patients with phenotype A (47.4% versus 8.96% in the other phenotypes, $p < 0.00001$). In addition, primary infertility (42.3% versus 16.4%, $p = 0.001$) and secondary infertility (28.2% versus 13.4%, $p = 0.03$) were diagnosed more frequently in this group (Table 3).

Table 3. Comparison of anamnestic data in women with different PCOS phenotypes

Parameters	A n	A %	B n	B %	C n	C %	D n	D %
Consanguineous marriage of parents	4	5.1	2	11.1			1	3.3
Consanguineous marriage in the patient	3	3.8			1	5.3	2	6.7
Menstrual cycle disorders in female-line relatives	9	11.5	2	11.1	1	5.3		
Family history of obesity	15	19.2	3	16.7	2	10.5		
Family history of diabetes mellitus	37	47.4	4	22.2	1	5.3	1	3.3
History of gestational diabetes	3	3.8						
Primary infertility	33	42.3	5	27.8	3	15.8	3	10.0
Secondary infertility	22	28.2	3	16.7	2	10.5	4	13.3

Disorders of carbohydrate metabolism predominated in patients with phenotypes A and B, manifested by increased fasting glucose, insulin levels, and HOMA-IR index values (A — 3.79 ± 3.10 ; B — 3.31 ± 1.60), whereas in phenotypes C and D these parameters were closer to control values (Figure 1).

Figure 1. Visualization of the distribution of carbohydrate metabolism parameters in patients with PCOS according to phenotype.

Note: data are presented as Me; IQR; * — significance compared with the control group; ● — significance compared with phenotype B; ▲ — significance compared with phenotype C; ≈ — significance compared with phenotype D.

DISCUSSION

The results of the present study confirm the clinical and metabolic heterogeneity of polycystic ovary syndrome (PCOS), emphasizing the importance of phenotypic stratification for diagnosis and prognosis. The findings are consistent with numerous studies indicating that the classic phenotype A, which combines hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, is the most severe phenotype in both reproductive and metabolic terms [4,6]. In our cohort, patients with phenotype A had an earlier onset of symptoms, a higher degree of hyperandrogenism, a higher frequency of obesity, dyslipidemia, arterial hypertension, and insulin resistance, as well as the highest prevalence of infertility. These results confirm data from international meta-analyses in which phenotype A is considered the most vulnerable to the development of metabolic complications and cardiovascular risk [1].

Phenotype B, although demonstrating similar hormonal changes, including increased testosterone levels and free androgen index, was characterized by less pronounced ultrasound changes and a lower metabolic burden. Nevertheless, dermatological manifestations of hyperandrogenism, such as acne, seborrhea, and alopecia, were more common in this group, which is consistent with published data on differences in the clinical phenotype of hyperandrogenism [2].

Phenotype C represented an intermediate variant, combining biochemical hyperandrogenism with moderate lipid metabolism disturbances. According to current observations, this phenotype is less frequently associated with insulin resistance but retains an unfavorable reproductive prognosis [6]. Phenotype D, in contrast, was close to the control group for most parameters, allowing it to be considered a clinically “milder” variant of PCOS. However, it remains diagnostically important in the context of reproductive disorders.

An important finding of the study was confirmation of the diagnostic value of several markers. Menstrual cycle duration, testosterone level, body mass index, ovarian volume, and antral follicle count demonstrated high sensitivity and specificity in ROC analysis and were also confirmed by neural network algorithms as key predictors. These findings are consistent with the latest FIGO recommendations (2023), which emphasize the need to integrate phenotypic and metabolic assessment for early diagnosis of PCOS.

The practical significance of the results lies in the fact that phenotypic classification makes it possible not only to refine diagnostic criteria but also to identify risk groups for personalized follow-up and therapy. Patients with phenotype A require more careful monitoring of the metabolic profile and early intervention, including weight correction, administration of insulin sensitizers, and control of cardiovascular risk factors. At the same time, for phenotype D, the emphasis shifts toward the reproductive sphere, with minimal need for aggressive metabolic intervention.

Thus, phenotypic stratification of PCOS should be regarded as an essential stage of clinical practice, ensuring optimization of diagnosis and increasing the effectiveness of personalized therapy.

CONCLUSION

The study confirmed the importance of phenotypic stratification in polycystic ovary syndrome as a tool that allows consideration of the clinical and metabolic diversity of the disease. The findings showed that phenotype A is associated with the greatest severity of hyperandrogenism, obesity, insulin resistance, and a high risk of infertility, whereas phenotype D is characterized by minimal clinical and metabolic abnormalities and is close to the control group. The identified markers — menstrual cycle duration, testosterone level, body mass index, ovarian volume, and antral follicle count — have high diagnostic value and are consistent with current international criteria. Their use in clinical practice may improve the effectiveness of early diagnosis and support the development of personalized approaches to treatment and prevention of complications in women with PCOS.

REFERENCES

1. Dewailly D, Lujan ME, Carmina E, et al. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update*. 2017;23(5):575–592.
2. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol*. 2018;14(5):270–284.
3. Kahal H, Kyrou I, Uthman OA, Randeva HS. Machine learning in the prediction of polycystic ovary syndrome: current state and future directions. *Reprod Biomed Online*. 2020;41(3):405–415.
4. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Phenotypes and prevalence of polycystic ovary syndrome. *Fertil Steril*. 2016;106(1):6–15.
5. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Hum Reprod*. 2004;19(1):41–47.
6. Teede HJ, Joham AE, Boyle J, et al. FIGO recommendations on polycystic ovary syndrome: An international expert consensus. *Int J Gynaecol Obstet*. 2023;163(2):323–341.
7. Teede HJ, Misso ML, Costello MF, et al. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod*. 2018;33(9):1602–1618.