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LIPID PROFILE IN WOMEN OF REPRODUCTIVE AGE WITH VARIOUS POLYCYSTIC OVARY SYNDROME PHENOTYPES

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▪ ***Hypothesis/Aims of study.*** Dyslipidemia is a common metabolic disorder and is an atherogenic factor in the development of cardiovascular disease in women with polycystic ovary syndrome. Currently, four phenotypes of polycystic ovary syndrome are distinguished, associated in varying degrees of severity with dyslipidemia, insulin resistance, impaired glucose tolerance, and diabetes mellitus on one hand and chronic inflammation and oxidative stress on the other. Hyperandrogenic phenotypes (A, B, C) in polycystic ovary syndrome are associated with the development of adverse metabolic disorders and associated complications. The aim of this study was to evaluate the lipid profile in the serum of women of reproductive age with various polycystic ovary syndrome phenotypes.

Study design, materials and methods. The study included 86 women of reproductive age from 22 to 37 years old (average age was 26.6 ± 4.3 years), who, in accordance with polycystic ovary syndrome phenotypes (A, B, C, D), were divided into four groups. We studied the levels of anti-Müllerian hormone, follicle-stimulating and luteinizing hormones, prolactin, estradiol, and androgens from days 2 to 5 of the menstrual cycle. The levels of progesterone in the blood serum were determined by the enzyme immunoassay on days 20 to 23 of the menstrual cycle for three consecutive cycles. We also used echographic methods for diagnosing polycystic ovaries. All women underwent a biochemical blood test with an assessment of the lipid profile parameters (total cholesterol, triglycerides, high-density lipoproteins (HDL), and low-density lipoproteins, LDL). Besides, an oral glucose tolerance test was assessed with the study of plasma glucose and insulin levels on an empty stomach and two hours after ingestion of 75 g of glucose, the HOMA-IR index being used to assess insulin resistance.

Results. Phenotype A was found in 40 (46.5%) women with polycystic ovary syndrome, phenotype B in 22 (25.6%), phenotype C in 10 (11.6%), and phenotype D (non-androgenic) in 14 (16.3%) patients with PCOS. Of those 42 (48.8%) individuals had changes in carbohydrate metabolism (impaired glucose tolerance), of whom 39 (92.8%) women had androgenic polycystic ovary syndrome phenotypes (A, B, C). Both non-androgenic phenotype D and impaired glucose tolerance were found in 7.2% of cases. In women with hyperandrogenic polycystic ovary syndrome phenotypes, both the fasting and stimulated insulin levels were increased significantly comparing to the non-androgenic anovulatory phenotype ($p < 0.05$). The HOMA-IR index in women with phenotypes A, B and C was significantly ($p < 0.05$) higher than in patients with non-androgenic phenotype D. When evaluating the lipid profile parameters, no significant differences in cholesterol level and atherogenic coefficient in women with various polycystic ovary syndrome phenotypes were found. The levels of triglycerides and LDL were significantly ($p < 0.05$) higher in women with androgenic phenotype B compared to those in patients with non-androgenic phenotype D and they correlated significantly ($p < 0.05$) with the serum levels of androgens and sex hormone-binding globulin (SHBG). Patients with androgenic polycystic ovary syndrome phenotypes (A and B) had significantly ($p < 0.05$) decreased HDL levels that correlated negatively ($r = –0.29$; $p < 0.05$) with the levels of free testosterone and SHBG, when compared to the same parameters in women with non-androgenic phenotype D. In women with androgenic polycystic ovary syndrome phenotypes (A, B, C), a significant correlation ($r = 0.27$; $p < 0.05$) between the levels of stimulated insulin and SHBG were found, and a direct relation ($r = 0.32$; $p < 0.05$) between those parameters and increased levels of triglycerides and LDL was also revealed.

Conclusion. In women with hyperandrogenic and anovulatory polycystic ovary syndrome phenotypes A and B, atherogenic dyslipidemia and impaired carbohydrate metabolism were significantly more pronounced, when compared with patients with non-androgenic phenotype D. A differential and personalized approach to the examination of patients with various polycystic ovary syndrome phenotypes is an important step in the prevention of the risks of developing cardiovascular diseases in women of reproductive age.

▪ **Keywords:** polycystic ovary syndrome; phenotype; impaired glucose tolerance; insulin resistance; HOMA-IR index; hyperandrogenism; lipid profile; cholesterol; triglycerides; high density lipoproteins; low density lipoproteins.

ОСОБЕННОСТИ ЛИПИДНОГО ПРОФИЛЯ ПРИ РАЗЛИЧНЫХ ФЕНОТИПАХ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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▪ ***Обоснование.*** Дислипидемия является частым нарушением обмена веществ и относится к атерогенным факторам развития сердечно-сосудистых заболеваний у женщин с синдромом поликистозных яичников. В настоящее время выделяют четыре фенотипа синдрома поликистозных яичников, ассоциированных в разной степени выраженности как с дислипидемией, резистентностью к инсулину, нарушением толерантности к глюкозе, сахарным диабетом, так и с хроническим воспалением и оксидативным стрессом. Гиперандрогенные фенотипы (A, B, C) при синдроме поликистозных яичников ассоциированы с развитием неблагоприятных метаболических нарушений и связанных с ними осложнений.

Цель исследования — изучить показатели липидного профиля у женщин с различными фенотипами синдрома поликистозных яичников в репродуктивном возрасте.

Материалы и методы. В исследование вошли 86 женщин репродуктивного возраста от 22 до 37 лет (средний возраст составил 26,6 ± 4,3 года), которые в соответствии с фенотипами синдрома поликистозных яичников (A, B, C, D) были распределены на четыре группы. Определяли уровень антимюллерова, фолликулостимулирующего, лютеинизирующего гормонов, пролактина, эстрадиола, андрогенов со 2-го по 5-й день менструального цикла. Уровень прогестерона в сыворотке крови исследовали иммуноферментным методом (с помощью тест-систем Алкор Био, Россия) на 20–23-й день менструального цикла в течение трех последовательных циклов. Использовали эхографические методы диагностики поликистозных яичников. Всем женщинам был выполнен биохимический анализ крови с определением липидного спектра (концентрация общего холестерина, триглицеридов, холестерина липопротеинов высокой и низкой плотности), также проводили пероральный глюкозотолерантный тест с оценкой уровня глюкозы в плазме крови натощак и через 2 ч после приема 75 г глюкозы, определяли уровень инсулина крови натощак и через 2 ч после перорального глюкозотолерантного теста, инсулинорезистентность оценивали с помощью индекса HOMA.

Результаты исследования. У 40 (46,5 %) женщин с синдромом поликистозных яичников выявлен фенотип A; у 22 (25,6 %) — фенотип B; у 10 (11,6 %) — фенотип C; у 14 (16,3 %) — фенотип D (неандрогенный). У 42 (48,8 %) больных с синдромом поликистозных яичников обнаружены изменения углеводного обмена (нарушение толерантности к глюкозе), из них 39 (92,8 %) женщин были с андрогенными фенотипами (A, B, C). Сочетание неандрогенного фенотипа D и нарушения толерантности к глюкозе зарегистрировано в 7,2 % случаев. У женщин с гиперандрогенными фенотипами синдрома поликистозных яичников по сравнению с неандрогенным ановуляторным фенотипом был достоверно увеличен как уровень инсулина натощак, так и уровень стимулированного инсулина ($p < 0,05$). Индекс HOMA-IR у женщин с фенотипами A, B и C был достоверно ($p < 0,05$) выше, чем у женщин с неандрогенным фенотипом D. При исследовании липидного профиля достоверных различий по уровню холестерина, коэффициенту атерогенности у женщин с различными фенотипами выявлено не было. Уровень триглицеридов и холестерина липопротеинов низкой плотности был достоверно ($p < 0,05$) выше у женщин с андрогенным фенотипом B по сравнению с аналогичными показателями у пациенток с неандрогенным фенотипом D и достоверно коррелировал ($p < 0,05$) с содержанием в сыворотке крови андрогенов, глобулина, связывающего половые гормоны. У больных с андрогенными фенотипами синдрома поликистозных яичников (A и B) обнаружено достоверное ($p < 0,05$) снижение уровня холестерина липопротеинов высокой плотности с отрицательной корреляцией ($r = –0,29$; $p < 0,05$) с уровнем свободного тестостерона, глобулина, связывающего половые гормоны, по сравнению с аналогичными показателями у женщин с неандрогенным фенотипом D. У женщин с андрогенными фенотипами синдрома поликистозных яичников (A, B, C) наблюдалась достоверная корреляция между уровнем стимулированного инсулина (после перорального глюкозотолерантного теста) и уровнем глобулина, связывающего половые гормоны ($r = 0,27$; $p < 0,05$), а также прямая зависимость ($r = 0,32$;

$p < 0,05$) между указанными показателями и повышенным уровнем триглицеридов и холестерина липопротеинов низкой плотности.

Выводы. У женщин с синдромом поликистозных яичников и гиперандрогенными, ановуляторными фенотипами A и B биохимические признаки атерогенной дислипидемии, нарушения углеводного обмена были более значимо выражены, чем у пациенток с неандрогенным фенотипом D. Дифференциальный и персонифицированный подход к обследованию больных с различными фенотипами синдрома поликистозных яичников является важным этапом в профилактике рисков развития сердечно-сосудистых заболеваний у женщин репродуктивного возраста с синдромом поликистозных яичников.

▪ **Ключевые слова:** синдром поликистозных яичников; фенотип; нарушение толерантности к глюкозе; инсулинорезистентность; индекс HOMA; гиперандрогения; липидограмма; холестерин; триглицериды; липопротеины высокой плотности; липопротеины низкой плотности.

Introduction

Polycystic ovary syndrome (PCOS) is a common disease that is diagnosed in 8%–13% of women of reproductive age [1]. Metabolic disorders in PCOS are associated with obesity, insulin resistance, hyperinsulinemia, dyslipidemia and chronic inflammation, and oxidative stress [2]. Dyslipidemia represents a common metabolic disorder and is an atherogenic factor in the development of cardiovascular diseases in women with PCOS. Dyslipidemia is known to be characterized by increased blood levels of low-density lipoproteins (LDL) and triglycerides (TG) and reduced levels of high-density lipoproteins (HDL). Small dense particles of LDL are the most atherogenic forms of lipoproteins related to metabolic predictors of coronary heart disease [3]. HDL prevents the oxidation of LDL particles and has anti-atherogenic and anti-inflammatory properties. Researchers suggested that in women with PCOS, not only the HDL level decreases, but the quality of HDL also changes [4]. This form of atherogenic dyslipidemia is often associated with insulin resistance. In addition, PCOS patients were found to have elevated levels of oxidized LDL, which are a proven predictor of coronary heart disease. Studies have shown that altered lipid metabolism in PCOS is associated with oxidative stress [5]. Oxidative stress is defined as an imbalance between excess production of reactive oxygen species and a reduced ability of cellular systems for antioxidant defense. Chronic inflammation and oxidative stress are believed to be involved in the implementation of endothelial dysfunction [6]. Hyperglycemia, dyslipidemia, chronic inflammation, and insulin resistance lead to excessive formation of reactive oxygen species, which exceeds the capabilities of cellular systems in the implementation of antioxidant protection [7]. Reactive oxygen species activate proinflammatory signaling pathways in endothelial cells and thereby initiate atherosclerosis development in women with PCOS [8]. Currently, PCOS is diagnosed using the criteria revised in 2012 by the US National Institutes of Health and the harmonized criteria of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ASRM/ESHRE), adopted in Rotterdam in 2003, with the definition of PCOS phenotypes [9]. Researchers recommend allocating patients with phenotypes A and B in PCOS to a special monitoring group for developing adverse metabolic disorders and associated complications [10, 11].

The study aimed to analyze the lipid profile indicators in women with different PCOS phenotypes at reproductive age.

Materials and methods

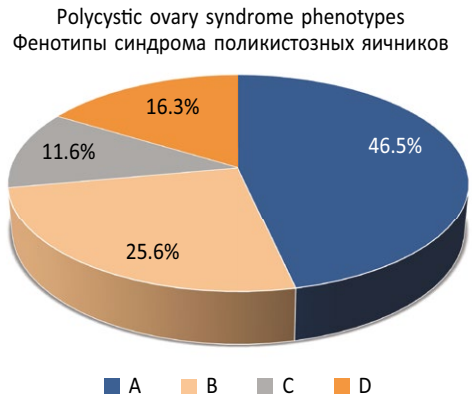
The study included 86 women with PCOS aged 22 to 37 years (mean age 26.6 ± 4.3 years). Menstrual cycle disorder by the type of opsomenorrhea was noted in 76 (88.4%) female patients. Infertility associated with the absence of ovulation (97.0 according to the International Statistical Classification of Diseases-10th Revision) was registered in 80 (93%) women. Of patients, 53 (66.3%) had primary infertility and 27 (33.7%) secondary infertility, and a history of miscarriage was found in 27 (31.4%) women. Overweight was found in 36 (41.9%) women, and 8 had degree I obesity. The body mass index (BMI) averaged 24.6 ± 2.9 kg/m^2, and in women with overweight and obesity, BMI was 27.6 ± 2.3 kg/m^2. The women did not have type 1 or 2 diabetes mellitus (DM).

The study included patients with various PCOS phenotypes, who were distributed into 4 groups (A, B, C, and D).

In all women, the levels of anti-Müllerian hormone, prolactin, estradiol, and androgens were examined on days 2 to 5 of the menstrual cycle. The progesterone blood serum level was determined by enzyme immunoassay (using the Alkor Bio test system, Russia) on days 20–23 of the menstrual cycle for 3 consecutive cycles. The menstrual cycle was considered anovulatory when the progesterone level was lower than 10 nmol/L.

The echographic methods for PCOS diagnostics were used. Based on the agreed ASRM/ESHRE criteria adopted in Rotterdam, the diagnostics of PCOS by ultrasonography requires the presence of 12 or more ovarian follicles with a diameter of 2–9 mm and/or an increase in ovarian volume of more than 10 mL. For PCOS diagnosis, it is sufficient if at least one ovary meets these criteria [2].

All women enrolled in the study underwent an oral glucose tolerance test (OGTT), and their fasting blood insulin and 2-h OGTT levels were determined; the fasting blood insulin and 2-h OGTT levels were determined. The homeostatic model assessment (HOMA) index, which was determined using the formula of fasting glucose (mmol/L) × insulin (μU/mL) / 22.5, was calculated to assess insulin resistance. An index value of more than 2.18 was regarded as insulin resistance [12]. All women underwent a biochemical blood test with determination of the lipid profile (concentration of total cholesterol, TG, HDL, and LDL).



Frequency of polycystic ovary syndrome phenotypes

Частота встречаемости фенотипов синдрома поликистозных яичников

Statistical analysis was performed using the SPSS program version 12.0 for Windows. Data were presented as mean (M) ± standard deviation. The significance of differences between the groups was assessed using the Student's *t* and Mann–Whitney *U* tests, and the incidence of the sign was assessed using the χ-square method and Fisher's exact test.

Results

The women were distributed into 4 groups according to their PCOS phenotypes. Phenotype A [a combination of clinical signs and/or biochemical hyperandrogenism (HA), chronic anovulation, and polycystic ovarian morphology according to ultrasound examination] was detected in 40 (46.5%) women, phenotype B (signs of HA and oligovulation/anovulation without PCOS by ultrasound) in 22 (25.6%), phenotype C [ovulatory; represented by HA and PCOS but with a regular ovulatory cycle (HA + PCOS)] in 10 (11.6%), and phenotype D (chronic anovulation and PCOS but without clinical/biochemical HA) in 14 (16.3%). The distribution of PCOS patients by phenotype is presented in Figure.

Of women, 76 (88.4%) had normogonadotropic anovulation, which was diagnosed based on the follicle-stimulating and luteinizing hormone levels on days 2–5 of the menstrual cycle. The average progesterone blood level (on days 20–23 of the menstrual cycle) was 4.2 ± 1.7 nmol/L.

During hormonal examination, laboratory signs of HA were noted in patients with phenotypes A, B, and C. However, significant differences were detected when examining the levels of free testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and sex hormone-binding globulin (SHBG) in patients with androgenic phenotypes A, B, and C than in those with nonandrogenic phenotype D ($p < 0.05$). In addition, the luteinizing hormone level was significantly higher in women with phenotype A than in those with phenotypes D and C (13.8 ± 1.3 and 6.8 ± 1.1 IU/L, respectively; $p < 0.05$). There were no significant differences in the levels of follicle-stimulating hormones, anti-Müllerian hormones, prolactin, estradiol, dihydrotestosterone, and hydroxyprogesterone in PCOS patients with

Table 1 / Таблица 1

Serum levels of gonadotropins, prolactin, sex steroid hormones, and anti-Müllerian hormone in patients with various polycystic ovary syndrome phenotypes

Уровень гонадотропинов, пролактина, половых стероидных гормонов и антимюллерова гормона в периферической крови больных с различными фенотипами синдрома поликистозных яичников

Indicator	Phenotype A (*n* = 40) *M* ± *m*	Phenotype B (*n* = 22) *M* ± *m*	Phenotype C (*n* = 10) *M* ± *m*	Phenotype D (*n* = 14) *M* ± *m*	*p*
Follicle-stimulating hormone, IU/L	6.9 ± 1.2	6.1 ± 1.9	5.9 ± 0.6	6.3 ± 0.7	
Luteinizing hormone, IU/L	13.8 ± 1.3*	8.8 ± 2.3	6.4 ± 1.7	6.8 ± 1.1*	<0.05* (phenotypes A and D)
Anti-Müllerian hormone, ng/mL	9.8 ± 4.1	8.2 ± 3.9	8.5 ± 4.3	10.5 ± 4.3	
Estradiol, pmol/L	297.2 ± 79.4	238.8 ± 81.4	288.2 ± 81.4	171.3 ± 84.9	
Prolactin, mIU/L	270.8 ± 34.2	348.6 ± 25.0	388.6 ± 45.0	202.6 ± 38.1	
Dehydroepiandrosterone sulfate, µmol/L	13.1 ± 1.6*	14.7 ± 1.3**	14.5 ± 1.2***	7.3 ± 1.1*, **, ***	<0.05* (phenotypes A and D) <0.05** (phenotypes B and D) <0.05*** (phenotypes C and D)
Hydroxyprogesterone, nmol/L	3.6 ± 1.3	3.9 ± 1.5	3.9 ± 1.7	3.3 ± 0.7	
Androstenedione, nmol/L	12.9 ± 1.5*	14.5 ± 1.3**	14.2 ± 1.8***	7.8 ± 1.3*, **, ***	<0.05* (phenotypes A and D) <0.05** (phenotypes B and D) <0.05*** (phenotypes C and D)
Free testosterone, pmol/L	13.1 ± 2.1*	14.6 ± 2.5**	8.9 ± 2.3	6.7 ± 1.2*, **	<0.05 (phenotypes A and D)* <0.05 (phenotypes B and D**
Sex hormone-binding globulin, nmol/L	44.0 ± 7.5*	35.0 ± 5.9**	58.0 ± 9.5***	88.2 ± 5.5*, **, ***	<0.05* (phenotypes A and D) <0.05** (phenotypes B and D) <0.05*** (phenotypes C and D)
Progesterone, nmol/L	3.2 ± 1.7*	2.7 ± 1.3**	18.5 ± 1.3*, **, ***	3.2 ± 1.2***	<0.05* (phenotypes A and C) <0.05** (phenotypes B and C) <0.05*** (phenotypes D and C)

different phenotypes. Anovulatory PCOS phenotypes (A, B, and D) were comparable in terms of progesterone levels, which were significantly lower in these cases ($p < 0.05$) than phenotype C. The data of hormonal examination are presented in Table 1.

Echographic examination revealed an increase in ovarian volume, as a diagnostic criterion for PCOS, in women with phenotypes A, C, and D. However, a significantly greater average ovarian volume was noted in patients with phenotype A (11.5 ± 0.6 cm^3) than in women with phenotype B (7.9 ± 1.3 cm^3).

When studying the lipid profile, there were no significant differences in the cholesterol levels and atherogenicity coefficient in women with different

phenotypes. However, the TG and LDL cholesterol levels were significantly higher in women with androgenic phenotype B than in patients with nonandrogenic phenotype D ($p < 0.05$). There was a significant positive relationship between the levels of TG and LDL and the serum levels of free testosterone, DHEAS, androstenedione, and SHBG in patients with androgenic PCOS phenotypes (A, B, and C; $r = 0.35$; $p < 0.05$). In addition, women with PCOS with phenotypes A and B had a significant decrease in HDL levels compared with women with nonandrogenic phenotype D ($p < 0.05$). A significant negative correlation was revealed for low HDL levels with serum levels of free testosterone and SHBG in patients with androgenic-anovulatory PCOS phenotypes (A and B; $r = -0.29$; $p < 0.05$).

Table 2 presents the results of the study of the lipid profile in women with different PCOS phenotypes.

Excess weight was detected significantly less frequently (14.3% of women) in patients with nonandrogenic phenotype D than in those with androgenic phenotypes ($p < 0.05$). Thus, overweight was noted in half of patients with phenotypes A and C, and BMI exceeded normal values in 31.8% of cases in women with PCOS (phenotype B).

According to OGTT, impaired glucose tolerance (IGT) was detected in 42 (48.8%) patients with PCOS, and 39 (92.8%) of them were women with androgenic phenotypes (A, B, and C). In the structure of IGT detection in PCOS, the number of cases of nonandrogenic phenotype D amounted to 7.2%. IGT was recorded in most patients with androgenic phenotypes (A, B, and C), namely, in 55%, 59.1%, and 40% of women with phenotypes A, B, and C, respectively. Meanwhile, IGT was revealed significantly less often in women with phenotype D (only 21.4%; $p < 0.05$). In women with hyperandrogenic PCOS phenotypes (A, B, and C), both fasting and stimulated insulin levels were significantly increased compared with those with nonandrogenic anovulatory phenotype (D; $p < 0.05$). The HOMA for insulin resistance index in women with phenotypes A, B, and C was significantly higher than in women with nonandrogenic phenotype D ($p < 0.05$). The carbohydrate metabolism study results are presented in Table 3.

In women with androgenic PCOS phenotypes (A, B, and C), there was a significant correlation between the stimulated insulin (after OGTT) and SHBG levels ($r = 0.27$; $p < 0.05$) and a direct relationship between these indicators and the TG and LDL levels ($r = 0, 32$; $p < 0.05$).

Discussion

PCOS is known to be associated with metabolic disorders, insulin resistance, IGT, and DM as well as an increase in the number of risk factors for cardiovascular diseases [10, 11]. Based on a meta-analysis of 35 studies, conducted by Kakoly et al. (2018), IGT, type 2 DM, and metabolic syndrome were detected more often in women with PCOS [13]. In a 2017 Danish population

Table 2 / Таблица 2

Lipid profile in women with various polycystic ovary syndrome phenotypes
Показатели липидограммы у женщин с различными фенотипами синдрома поликистозных яичников

Indicator	Phenotype A ($n = 40$) $M \pm m$	Phenotype B ($n = 22$) $M \pm m$	Phenotype C ($n = 10$) $M \pm m$	Phenotype D ($n = 14$) $M \pm m$	p
Triglycerides, mmol/L	1.3 ± 0.2	1.4 ± 0.1*	1.1 ± 0.1	0.8 ± 0.2*	<0.05** (phenotypes B and D)
Cholesterol, mmol/L	4.1 ± 1.3	4.0 ± 1.5	4.8 ± 1.0	5.1 ± 1.1	
High-density lipoprotein cholesterol, mmol/L	0.8 ± 0.2*	0.9 ± 0.1**	1.1 ± 0.6	1.6 ± 0.2*, **	<0.05* (phenotypes A and D) <0.05** (phenotypes B and D)
Low-density lipoprotein cholesterol, mmol/L	3.2 ± 0.2	3.3 ± 0.1*	3.1 ± 0.2	2.8 ± 0.2*	<0.05** (phenotypes B and D)
Atherogenic index	4.1 ± 1.2	4.5 ± 1.2	3.5 ± 1.5	2.1 ± 1.2	

Table 3 / Таблица 3

Oral glucose tolerance test scores, fasting and stimulated insulin levels, and the HOMA-IR index in women with various polycystic ovary syndrome phenotypes

Показатели перорального глюкозотолерантного теста, уровни инсулина (натощак и стимулированного), индекс HOMA-IR у женщин с различными фенотипами синдрома поликистозных яичников

Indicator	Phenotype A (*n* = 40) *M* ± *m*	Phenotype B (*n* = 22) *M* ± *m*	Phenotype C (*n* = 10) *M* ± *m*	Phenotype D (*n* = 14) *M* ± *m*	*p*
Glucose (1), mmol/L	5.7 ± 0.8	5.9 ± 0.4	5.7 ± 0.6	5.8 ± 0.8	
Glucose (2), 2 h after OGTT, mmol/L	7.6 ± 1.0*	7.8 ± 1.6	7.3 ± 0.9	7.2 ± 0.9	<0.05* phenotypes A and D <0.05** phenotypes B and D
Insulin (1), mIU/L	10.8 ± 2.4*	11.1 ± 2.1**	10.7 ± 1.8***, ***	7.3 ± 0.7***	<0.05* phenotypes A and D <0.05** phenotypes B and D <0.05*** phenotypes C and D
Insulin (2), 2 h after OGTT, mIU/L	68.9 ± 27.4*	117.8 ± 22.8**	58.7 ± 14.6	45.9 ± 18.3*, **	<0.05* phenotypes A and D <0.05** phenotypes B and D
HOMA-IR	2.7 ± 0.9*	2.9 ± 0.8**	2.7 ± 0.6***	1.9 ± 0.4*	<0.05* phenotypes A and D <0.05** phenotypes B and D <0.05*** phenotypes C and D

N o t e. OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment for insulin resistance.

study, the incidence of type 2 DM was four times higher in women with PCOS than in the control group. In addition, type 2 DM was diagnosed at a younger age in patients with an established diagnosis of PCOS [14].

According to a previously conducted prospective study of 1212 patients with PCOS and 254 healthy women, comparable in BMI, phenotype A was associated with a greater severity of insulin resistance and HA, whereas phenotype B was more metabolically unfavorable than phenotype C. The authors suggested including patients with phenotypes A and B into a special study group for developing adverse metabolic disorders and associated complications [10]. The combination of carbohydrate metabolism disorders and diseases associated with normogonadotropic anovulation contributes to changes in the system of steroidogenesis and folliculogenesis in the ovaries [15, 16]. In our study, IGT was detected in 42 (48.8%) patients with PCOS, and 39 (92.8%) of these female patients with impaired carbohydrate metabolism were found to have androgenic-anovulatory PCOS phenotypes, namely, 22 (52.4%) with phenotype A, 13 (31%) phenotype B, and 4 (9.5%) phenotype C. Phenotype D (nonandrogenic) was registered only in 3 (7.1%) women with PCOS and IGT. In women with PCOS without disorders of carbohydrate metabolism, the PCOS androgenic-anovulatory phenotypes (A, B, and C) were significantly less frequent ($p < 0.05$). Phenotype D (nonandrogenic) was registered in 20.5% of women without disorders of carbohydrate metabolism. Clinical manifestations of androgen-dependent dermopathy (acne, seborrhea adiposa, and hirsuteness) were noted in 34 (85%), 21 (95.5%), and 5 (50%) PCOS patients with phenotypes A, B, and C, respectively. Meanwhile, these clinical manifestations were found significantly less often in women with phenotype D (30%; $p < 0.05$).

In our study, significant differences in the androgen blood serum levels (free testosterone and DHEAS) were revealed in women with androgenic-anovulatory phenotypes (A and B), which is consistent with the recommendations of the

ESHRE 2018 to determine the diagnostic criteria for PCOS [2].

In an epidemiological study, to analyze the development of risk factors for metabolic and cardiovascular disorders in women with PCOS of reproductive age, it was revealed that patients with this disease had lower HDL levels with increased cholesterol and TG and LDL levels compared with healthy women [17]. The authors found that the metabolic disorders identified are typical for young women. In our work, in women of reproductive age (the average age of the participants was 26.6 ± 4.3 years), lipid profile changes associated with androgenic phenotypes of PCOS were revealed, namely, the TG and LDL levels were significantly higher in female patients with androgenic phenotype B than in those with nonandrogenic phenotype D ($p < 0.05$). There was a significant positive relationship of TG and LDL levels with the blood serum levels of free testosterone, DHEAS, androstenedione, and SHBG in patients with androgenic PCOS phenotypes (A, B, and C; $r = 0.35$; $p < 0.05$), which is consistent with previous studies on the relationship of HA with changes in lipid metabolism and oxidation. One study revealed that women with PCOS with HA and insulin resistance had increased LDL levels [3, 17], but another study found that women with PCOS had significantly lower HDL levels than healthy women, whereas other lipid parameters did not differ between the study groups [18]. In our study, in women with PCOS with phenotypes A and B, a significant decrease in HDL level as an antiatherogenic type of lipoproteins was revealed compared with representatives of nonandrogenic phenotype D ($p < 0.05$). Thus, a decreased HDL blood level may be associated with cell system failures in the implementation of anti-inflammatory and antioxidant protection, which contributes to the development of atherogenic dyslipidemia in PCOS.

Researchers recommend including patients with phenotypes A and B into a special study group for developing adverse metabolic disorders and associated complications [19]. Insulin resistance is generally accepted to be a link between obesity and cardiovascular disease, which causes a high risk of vascular catastrophes in metabolic syndrome [20, 21]. In our work, a significant relationship was noted between the increased stimulated insulin (after OGTT), SHBG ($r = 0.27$; $p < 0.05$), and TG and LDL levels ($r = 0.32$; $p < 0.05$). This confirms that PCOS androgenic phenotypes (A, B, and C) are associated with the risk of developing disorders of carbohydrate metabolism, metabolic syndrome, and cardiovascular diseases [22].

Conclusion

Thus, in women with androgenic PCOS phenotypes (A, B, and C), changes in carbohydrate metabolism by the IGT type and insulin resistance were revealed, and lipid disorders associated with the development of metabolic syndrome, compared with nonandrogenic, anovulatory phenotype D, were verified.

A significant positive dependence of the levels of TG and LDL with the levels of free testosterone, DHEAS, androstenedione, and SHBG in the blood serum and a significant decrease in the blood level of HDL in patients with androgenic PCOS phenotypes (A, B, and C) are associated with cellular system failures in the implementation of anti-inflammatory and antioxidant protection, contributing to the development of atherogenic dyslipidemia and cardiometabolic risks in PCOS.

Changes in the lipid profile and associated disorders of carbohydrate metabolism were significantly more pronounced in women with PCOS, and phenotypes A and B were associated with anovulation and HA.

A differential approach to the examination of patients with different phenotypes of PCOS contributes to the determination of a set of preventive measures to improve the quality of life of reproductive age women and to personalize the therapy for this disease.

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