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REVIEW ARTICLE

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Prevalence of Metabolic Syndrome in PCOS Patients

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Abstract

The purpose of the review was to systematize the available data on the epidemiology and diagnosis of the metabolic syndrome (MetS) in polycystic ovary syndrome (PCOS). The information search was conducted using Internet resources (PubMed, EMBASE, Google Scholar, E-Library) and literature sources for the years 2000-2020. **T**he modern **s**tudies indicate that the prevalence of metabolic disorders varies in groups of women with different PCOS phenotypes. Numerous risk factors in PCOS lead to a significant increase in risk for cardiovascular diseases. Patients with PCOS diagnosed according to AE-PCOS Society criteria have the most severe metabolic features and risk of cardiovascular disease. Hyperandrogenism in PCOS is closely related to the aggravation of abdominal obesity, and together with insulin resistance forms the metabolic core for the development of cardiovascular diseases.(**International Journal of Biomedicine. 2022;12(1):95-99.**)

Key Words: metabolic syndrome • obesity • insulin resistance • hyperandrogenism • polycystic ovary syndrome

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Abbreviations

BMI, body mass index; **CVD**, cardiovascular diseases; **DM**, diabetes mellitus; **HDL-C**, high-density lipoprotein cholesterol; **HA**, hyperandrogenism; **IR**, insulin resistance; **IGT**, impaired glucose tolerance; **LDL-C**, low-density lipoprotein cholesterol; **MetS**, metabolic syndrome; **PCOS**, polycystic ovary syndrome; **PCOM**, polycystic ovarian morphology; **T2D**, type 2 diabetes; **WC**, waist circumference.

Metabolic syndrome (MetS) is one of the most important health problems in different countries. Experts of the World Health Organization (WHO) have described MetS as a pandemic of the twenty-first century.[1-5] MetS (also known as syndrome X, Reaven syndrome, insulin resistance syndrome) is a combination of hormonal and metabolic disorders that significantly accelerate the development of CVD. The high variability in the prevalence of MetS, according to various studies, is primarily associated with an insufficiently clear, consistent definition of diagnostic criteria. The main sources of information are epidemiological data and prognostic studies conducted in the *United States* and countries of Western Europe, and single epidemiological studies on the prevalence of MetS in Russia.

Several clinical definitions of MS have been proposed and widely used over the past decade, including those by the World Health Organisation (WHO),[6] National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII),[7] International Diabetes Federation (IDF),[8] American Heart Association/National Heart, Lung, and Blood Institute(AHA/NHLBI),[1] and The European Group for Study of Insulin Resistance (EGIR).[9]

The 2009 harmonized definition of MetS requires the presence of any 3 of the following: increased WC (men: ≥94 cm, women: ≥80 cm), low HDL-C (men: <40 mg/dL (1 mmol/L), women: <50 mg/dL (1.3 mmol/L)), hypertriglyceredimia ≥150 mg/dL (1.7 mmol/L), elevated BP (systolic BP ≥130 mmHg

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and/or diastolic ≥85 mmHg or drug treatment for hypertension) and elevated blood sugar (FPG ≥100 mg/dL (5.6 mmol/L) or diabetes mellitus.[10]

The prevalence of MetS varies within 20%-40%, averaging 26% among the adult population of the planet, according to an INTERHEART study.[11] In Russia, according to research results, 40% of the population has 2 components of MS, 11% – 3 or more of its components. It is more common in middle-aged and older people.[12] MetS prevalence is high among obese patients; among people with IGT, the frequency of MetS is 50%, and in DM - 80%. In addition, there is a steady trend of increasing prevalence of MetS. Currently, the number of patients with MetS is 2 times higher than the number of patients with T2D; in the next 20 years, an increase of 50% in the frequency of MetS is expected. The majority of patients with MetS are the working-age population, but over the past 2 decades, the MetS frequency has shown a steady increase among young people.[13]

The prevalence of MetS in PCOS

MetS is also associated with ovulation, conception, and pregnancy complications: increase of pregnancy losses and decrease of the number of live-born children. There is evidence of an increased prevalence of MetS among overweight or obese women with PCOS (OR=1.88; 95% CI: 1.16-3.04), but not among women with a normal BMI, even in the presence of PCOS(OR=1.45; 95% CI:0.35-6.12).[14] In addition, it is known that the presence of MetS in patients with PCOS reduces the chances of pregnancy and negatively affects the results of in vitro fertilization in infertile women with PCOS. MetS in patients with PCOS can reduce the antioxidant activity of the body and lead to the development of oxidative stress. A decrease in antioxidant activity in PCOS with MetS is associated with an increased level of triglycerides and LDL-C, which can worsen the course of these diseases.[14,15]

The main mechanisms of the pathogenesis of PCOS include disorders of the steroid-producing function of the ovaries[16] with an increase in the production of androgens and a violation of their conversion to estrogens, as well as an increase in the level of free testosterone against the background of low content of sex hormone-binding globulin.[17] In turn, hyperandrogenism (HA) is associated with an abdominal type of obesity and changes in the lipid profile.[18] In addition, PCOS is characterized by the presence of gonadotropic dysfunction, which naturally leads to anovulation or at least to progesterone deficiency. Along with this, anovulation and small-cystic ovarian transformation are the results of the so-called follicular arrest associated with excessive secretion of anti-müllerian hormone.

The prevalence of PCOS is usually influenced by the characteristics of the population sample. Thus, in a non-selective sample of women of reproductive age, the PCOS prevalence ranges from 6% to 19.9%, in menstrual disorders - from 17.4% to 46.4%, in women with clinical manifestations of HA -72.1%-82%, and in anovulatory infertility - in 55-91% of cases.[19,20] Chronic anovulation in women with PCOS is a risk factor for endometrial hyperplasia and cancer, which is largely facilitated by the presence of overweight or obesity in 40%-85% of women with PCOS. Along with reproductive disorders, PCOS, especially its classical phenotype, is associated with IR, IGT, DM, CVD, all of which determine the long-term consequences of this disease.[21]

PCOS is the most common cause of HA, a common endocrine disorder, the main clinical markers of which are skin problems and menstrual cycle disorders such as hypomenstrual syndrome.[22] The diagnosis of PCOS is based on the criteria presented and approved in various consensuses. The NIH criteria (1990) established the presence of oligo-/anovulation and HA as a necessary condition for the diagnosis of PCOS (after excluding conditions with similar symptoms).[23] At the same time, the appearance of a polycystic ovarian structure by ultrasound is not considered a mandatory sign of PCOS.

Possible combinations of components of the Rotterdam criteria have allowed identifying 4 PCOS phenotypes:[24-27] phenotype A (oligo-/anovulation (OA), clinical and/or biochemical HA, and PCOM), phenotype B (HA+OA), phenotype C (HA+PCOM), and phenotype D (OA+PCOM). The more severe PCOS phenotypes are associated with a greater magnitude of CVD risk and this has been found in obese and non-obese women.[28]

The Harmonized Criteria of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ASRM/ESHRE), adopted in Rotterdam,[24] are currently used to diagnose PCOS. According to this consensus, the diagnosis of PCOS can be confirmed by the presence of at least two of the following three criteria: oligo- or anovulation, clinical or biochemical signs of HA, polycystic ovarian morphology on ultrasound.

Based on the available data, in 2006, the Androgen Excess and PCOS Society (AE-PCOS) experts proposed their version of the PCOS diagnostic criteria. According to the AE-PCOS consensus, PCOS should have been diagnosed with the obligatory presence of HA(clinical and/or biochemical) in combination with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders.[25,29]

The prevalence of MetS among 248 women with different PCOS phenotypes was analyzed in a study by Bahadur et al.[4] The prevalence of phenotypes A, B, C, and D were 36.7%, 10.1%, 4.4%, and 48.8%, respectively. Phenotype D had the highest prevalence of MetS. Phenotype A was at higher risk of adverse MetS risk profile.

A study performed by Karee et al.[30] included 382 Indian women with PCOS. MetS was present in 147(38.5%) PCOS women. The most frequently observed individual components of MetS were increased WC and decreased HDL-C.

A retrospective cohort study conducted in Germany found that the prevalence of underweight in patients with PCOS is very low. Underweight in PCOS was associated with higher postprandial insulin levels.[31]

A study conducted by Kim et al.[32] investigated the various HOMA-IR cutoff values in a population of healthy controls (n=579) and evaluated the prevalence of IR in women with PCOS(n=699). Overweight/obese PCOS patients were the most high-risk group, but lean patients also showed an elevated prevalence of IR similar to that of overweight/obese controls. The authors concluded that although IR is common

in women with PCOS, it does not seem to be universal, and patients without IR had reassuring metabolic features**.**

A study performed by Carmina et al.[33] investigated the prevalence of MetS according to ATP-III and WHO criteria in 282 women with PCOS, aged 18-40 years, living in western Sicily. Patients were divided into 2 groups: Group 1 included 225 patients with chronic anovulation and hyperandrogenism (classic PCOS); Group 2 included 57 patients with hyperandrogenism and polycystic ovaries who were ovulatory (ovulatory PCOS). In classic PCOS patients, MetS was higher (8.9% by ATP-III, 17.3% by WHO) than in ovulatory PCOS (5% and 10.6%, respectively).

In a study performed by Dargham et al.,[34] the prevalence and metabolic features of PCOS among 750 Qatari women aged between 18-40 years were estimated. By NIH guidelines, the prevalence of PCOS in this Qatari cohort was 12.1%, which would likely reflect 20% by Rotterdam criteria. Over 61% of investigated women identified were either overweight (BMI 26–29.9; 31.4%) or obese (BMI greater than 30; 29.7%). Clinical HA defined by the Ferriman and Gallwey score was not validated in that ethnic population.

The systematic review and meta-analysis conducted by Behboudi-Gandevani et al.[35] showed that in PCOS patients, regardless of age, BMI and recruitment sources of samples had higher odds of MetS than healthy controls (OR=2.5, 95% CI: 2.0-3.2). Adolescents with PCOS had an increased OR of MetS compared to healthy adolescents in population- and nonpopulation-based studies (OR=4.7, 95% CI: 1.8-11.9; OR=6.1, 95% CI: 6.0-6.1, respectively). Subgroup analysis based on PCOS diagnostic criteria showed that HA is an important component of this disorder.

The prevalence of MetS in PCOS has been studied in different populations. Reported prevalence is 43% in U.S., 28.4% in Brazil, 24.9% in Hong Kong Chinese women, and only 1.6% in Czech women.[36-39] The prevalence of MetS in PCOS is strongly influenced by the criteria used to diagnose MetS as well as the criteria used to diagnose PCOS. The prevalence of MetS (the ATP-III criteria) among women from southern Italy was only 8.2% in comparison with a prevalence of 43%–46% reported in the USA.[40,41]

A prospective cross-sectional study performed by Mandrelle et al.[42] in infertile Indian women with PCOS, according to Rotterdam criteria (2003), showed that the overall prevalence of MetS, according to the modified AHA/NHLBI ATP III (2005) criteria, was 37.5%. A total of 5.8 % cases were found to have DM, 8.3% had impaired fasting glucose, and 11.7 % had an IGT.

A case-control, cross-sectional, observational study of consecutive women with anovular PCOS (47 South Asians, 40 Caucasians) and their age-matched controls (11 South Asians and 22 Caucasians) [43] showed that South Asians with anovular PCOS seek treatment at a younger age and have more serious symptoms, higher fasting insulin concentrations and lower insulin sensitivity than Caucasians.

In 2019, a retrospective study of 1,215 Mediterranean women from Sicily was conducted to better characterize the metabolic alterations in various phenotypes of PCOS. [44] Among 1,215 women with PCOS, phenotype A was diagnosed in 701(57.7%), phenotype B - in 112(9.2%), phenotype C - in 364(30%), and phenotype D - in 38(3.1%). According to the results of the study, the prevalence of obesity was 31%, MetS - 6.6%, DM - 2.1%, altered glucose metabolism - 13.1%, and abnormal lipid profile - 60%. Phenotype B was characterized by the highest prevalence of obesity, MetS, IGT, and lipid abnormalities, compared to other PCOS phenotypes and controls. Women with phenotype A were more obese and more women had MS, than women with phenotypes C and D; however, women with phenotype C had a prevalence of altered glucose metabolism and lipid abnormalities similar to phenotype A. These metabolic abnormalities in phenotypes A and C were higher than in phenotype D and controls. Multivariate analysis showed that BMI allows predicting only deviations in fasting glucose and triglycerides, regardless of the level of androgens. Only women with norm-androgenic phenotype D had no metabolic abnormalities. Thus, the risk of MetS and CVD may vary depending on the PCOS phenotype, based on the Rotterdam criteria.

To compare the prevalence of various metabolic and cardiovascular risk factors and IR between PCOS patients with or without HA, a retrospective cross-sectional study involving women with PCOS, as diagnosed according to AE-PCOS Society criteria (n=504), and women with normoandrogenemic PCOS (n=183) was performed.[45] Women with PCOS diagnosed according to the AE-PCOS Society criteria had a significantly higher prevalence of MetS than in the normoandrogenemic PCOS phenotype (25.4% vs. 10.3%; P=0.01). There was no significant difference in the prevalence of the IGT test between the groups. The prevalence of HDL-C<50 mg/dL in the group under the AE-PCOS criteria was higher than in the normoandrogenemic PCOS group (59.4 vs 41.2%, respectively; P=0.002).

The evidence currently suggests that patients with PCOS diagnosed according to AE-PCOS Society criteria have the most severe metabolic features.[29,46] Rizzo et al.[47] found that women with hyperanderogenemic PCOS showed the most atherogenic lipid profiles, with higher apolipoprotein B than the other PCOS phenotypes.

Conclusion

The modern **s**tudies indicate that the prevalence of metabolic disorders varies in groups of women with different PCOS phenotypes. Numerous risk factors in PCOS lead to a significant increase in risk for cardiovascular diseases. Patients with PCOS diagnosed according to AE-PCOS Society criteria have the most severe metabolic features and risk of cardiovascular disease. HA in PCOS is closely related to the aggravation of abdominal obesity, and together with insulin resistance forms the metabolic core for the development of cardiovascular diseases.

Competing Interests

The authors declare that they have no competing interests.

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