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Clinical Manifestations of the Polycystic Ovary Syndrome at Menopausal Age

Gafurova F. A.

Assistant of Professor of Obstetric Gynecology and Perinatal Medicine Department,
Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan

Abstract Polycystic ovary syndrome (PCOS) is considered to be the most common endocrine disorder in women. The etiology of PCOS is multifactorial and still not fully understood. Insulin resistance and subsequent hyperinsulinemia are major features of PCOS. Additionally, increased androgen levels facilitate the release of free fatty acids from visceral fat tissue, what exacerbates insulin resistance. Insulin resistance in PCOS is also associated with abdominal obesity and other components of metabolic syndrome. All these abnormalities place females with PCOS at an increased risk of cardiovascular disorders later in life. Current data indicate that in women with PCOS there is a significant cancer risk, at least for endometrium. This finding should facilitate proper screening strategies, lifestyle changes and insulin resistance's treatment as a primary intervention what may decrease the risk in PCOS population.

Keywords Polycystic ovary syndrome, Insulin resistance, Menopausal period abdominal obesity, Weight gain, Hyperandrogenism, Metabolic syndrome, Cardiovascular disorders, Atherogenic lipid profile, Endometrial cancer risk

1. Introduction

Polycystic ovary syndrome (PCOS) is considered the most common endocrine disorder in women and, depending on diagnostic criteria, makes up approximately 10% of women in perimenopause [1]. The clinical manifestation of PCOS is heterogeneous, varies widely between patients, but the diagnosis of the classical phenotype is mainly based on a triad of symptoms that include hyperandrogenism (both clinical and biochemical), oligovulation or anovulation and the presence of polycystic ovaries during an ultrasound scan. The etiology of PCOS is multifactorial and has not yet been fully understood [10]. Numerous studies on its pathogenesis indicate a predisposition to PCOS in the presence of familial and genetic factors [13]. Research data suggests that there may be potential programming at the molecular level of adipose tissue dysfunction, insulin resistance, inflammation, oxidative stress, and endothelial dysfunction during fetal development [18]. However, the main pathophysiological mechanism for the development of PCOS has not yet been established. Insulin resistance and subsequent hyperinsulinemia are the main features of PCOS and are found in 80% of women with this pathology and almost all women with PCOS are obese [8]. It has been proven that insulin as such, through the signaling of IGF-1 or through classical insulin receptor signaling, can enhance the secretion of androgens and cause the development of polycystic ovaries. In addition, hyperinsulinemia inhibits the hepatic production of sex hormone-binding globulin (SHBG), and in this case, the level of free testosterone in serum increases. In addition, an increased level of androgens contributes to the release of free fatty acids from the tissue of visceral fat, which aggravates insulin resistance. Insulin resistance in PCOS is also associated with abdominal obesity and other components of the metabolic syndrome. All these disorders in women with PCOS lead to an increased risk of cardiovascular diseases in the age of menopause [6, 7].

* Corresponding author:
feruzagafurova@rambler.ru (Gafurova F. A.)
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2. Criteria for Diagnosis

Currently, three sets of PCOS diagnostic classifications are applied: criteria from the National Institutes of Health (NIH), Rotterdam criteria and criteria for androgen excess and PCOS. All of these systems require the exclusion of other disorders, such as androgen-producing tumors, congenital adrenal cortex dysfunction (CKD), Cushing's syndrome, thyroid dysfunction, and hyperprolactinemia. According to the NIH criteria, a diagnosis of PCOS can be made if there is a combination of oligo- or anovulation and the clinical or biochemical features of hyperandrogenism [9]. In accordance with the Rotterdam criteria, PCOS is

diagnosed in the presence of two of the following symptoms: oligo- or anovulation, hyperandrogenism and the presence of polycystic ovaries on ultrasound. Diagnostic criteria, in accordance with the most recent criteria of Androgenic Excess and PCOS, include the presence of hyperandrogenism, which is considered the central component of pathogenesis, and ovarian dysfunction [9, 10].

Diagnosis of PCOS in perimenopause is fraught with difficulties. The clinical and biochemical manifestations characteristic of PCOS change with age, and in women with PCOS phenotypes in the perimenopausal period, they become difficult to determine [11]. The transition of menopause as a physiological process occurs along with the aging of the body, and is itself associated with several hormonal and metabolic changes, which can be difficult to distinguish from clinical manifestations associated with PCOS. Numerous studies confirm that in women with perimenopause, there is an increased prevalence of metabolic syndrome, which is associated with the observed increase in weight, with a predominant distribution of adipose tissue in the abdominal area, hypertension and their clinical consequences in this group [12]. We have conducted studies on the peculiarities of the course of menopause in women who suffered from polycystic ovary syndrome at the fertile age and entered menopause in a state of insulin resistance. In the group of examined patients, a higher body mass index was found to be 29.7 ± 0.86 kg / m^2 with respect to the control, in which the average BMI was 24.9 ± 1.6 kg / m^2. He ratio of waist circumference to hip circumference indicated a male-type fat distribution, i.e. fat was distributed mainly in the abdominal region. In the examined group, this indicator was 1.05 ± 0.71, whereas in the control group it was 0.85 ± 0.05 [2-6].

According to several observations, the classic PCOS phenotype associated with hyperandrogenism, oligovulation and polycystic ovaries improves aging.

Our observations suggest that the age of menopause in the examined women in the main group was older than in the control group. So the age of menopause in the main group was 51.3 ± 1.16 g, whereas in the control group women entered menopause earlier - 48.1 ± 0.76 years [2, 4].

We interpreted this fact in two ways – the relative hyperestrogenic stimulation allows maintaining the menstrual cycle, but at the same time increases the risk of hyperplastic processes in the endometrium.

Thus, widely used criteria for the diagnosis of PCOS in the period of the menopausal transition become less informative and useful. Anovulatory disorders, so common among young women with age, level off and menstrual cycles may become regular in women with PCOS with age. In addition, the volume of the ovaries and the number of follicles decrease with age in both healthy and women with PCOS [13-15]. It should be noted that hyperandrogenism, regarded as a sign of polycystic ovary syndrome, may be partially resolved in the perimenopausal period in women with PCOS [16]. This phenomenon can be explained by the aging of the ovaries and adrenal glands and a decrease in the production of androgens in these glands. However, it has been reported that an excess of androgens in patients with PCOS persists after the menopausal transition and postmenopausal women with PCOS, as they initially have higher levels of adrenal and ovarian androgens than women without PCOS [17].

The results of our research confirm the presence of hyperandrogenism in the main group of patients studied. Indicators of free testosterone in the main group were 3.3 ± 0.12 nmol / l, whereas in the control group free testosterone was at the level of 1.28 ± 0.05 nmol / l [4.5].

Our research data showed that increased secretion of ovarian androgens along with adverse metabolic changes, such as impaired glucose tolerance, and chronic inflammation observed in the group of premenopausal women with PCOS persists after the menopausal transition [6]. To diagnose PCOS in perimenopause, we based on the previous history of oligovulation, the presence of polycystic ovaries, and hyperandrogenism or hirsutism. In addition, the waist circumference for abdominal distribution of adipose tissue was taken into account, as well as biochemical data on insulin resistance [19, 20].

3. Insulin Resistance and Metabolic Syndrome

Metabolic syndrome is an insulin-resistant condition, which is defined as a combination of cardiovascular risk factors, visceral obesity, impaired carbohydrate metabolism, dyslipidemia, and hypertension. It is believed that metabolic syndrome can predict a higher risk of cardiovascular events than the sum of the risks associated with individual components [21]. There is ample evidence that PCOS and metabolic syndrome are interrelated pathologies that develop on insulin resistance. Metabolic syndrome and insulin resistance are the main features in women with PCOS, so the metabolic syndrome leads to the development of reproductive or endocrine disorders. Interestingly, insulin resistance does not always accompany central obesity, so women with polycystic ovary syndrome are prone to developing metabolic syndrome, regardless of obesity itself. In addition, hyperandrogenism, usually associated with PCOS, can exacerbate metabolic disorders through the accumulation of adipose tissue in the abdomen and increased insulin resistance [22]. The results of our studies show that patients with PCOS compared with the control group have a more pronounced atherogenic lipid profile. So in the main group, the indicators of atherogenic lipid fractions - triglycerides, low and very low density lipoproteins were significantly higher than those obtained in the control group. It is known that in menopausal women, the prognostic sign of the risk of atherosclerosis is not so much the absolute values of the concentration of atherogenic and antiatherogenic fractions of blood lipoproteins, but their ratio to each other, i.e. atherogenic index –AI (LDL / HDL). The AI was significantly higher in women of the main group and was above 3.5 compared to the control group, in which the

AI was at the level of 3.2.

Additional risk factors for cardiovascular diseases that are not included in the classical definition of the metabolic syndrome, such as an increase in markers of chronic low-intensity inflammatory process, impaired fibrinolysis, and oxidative stress, are also cited in the literature [23, 25]. We are continuing research to determine the hemocoagulation characteristics of women with PCOS in menopause [3].

It has been established that the frequency of metabolic syndrome increases significantly during perimenopause and after menopause. Livadas et al. Reported an increase in insulin resistance along with aging, but only in women with obesity and PCOS. They found that insulin resistance correlated with the level of BMI and androgens [18].

We have evaluated the risk of metabolic abnormalities based on the determination of insulin resistance in patients with PCOS in menopause. The results of our studies confirm the presence of correlation of insulin resistance with body weight, central distribution of fat and hyperadrogenism [3, 6]. Given the fact that androgens decrease with aging, non-obese women with PCOS may have a more favorable metabolic profile over time, and PCOS may even remain a latent pathological state. This observation convincingly confirms the need to introduce lifestyle modifications to prevent overweight, which can improve the adverse cardiometabolic profile in women with PCOS [27].

4. Cardiovascular Risk in Menopause

According to many studies, PCOS should be considered as a metabolic disorder with an increased risk of developing type 2 diabetes and cardiovascular diseases [27]. The results of clinical studies in women with PCOS, who fixed certain cardiovascular disorders, confirmed the presence of metabolic risk factors in this population of patients, such as endothelial dysfunction, platelet dysfunction, increased persistent inflammation, increased coronary artery calcification, vascular intimal thickening. Shaw et al. Confirmed an increase in the number of cardiovascular events and a higher incidence of diabetes, obesity, metabolic syndrome, and coronary artery disease in the group of postmenopausal women with PCOS compared with other postmenopausal women. Another study showed a positive correlation between cardiovascular diseases and a number of features of PCOS in postmenopausal women, which led to the conclusion that PCOS increases the risk of cardiovascular diseases after menopause. Such observations may indicate an increase in the long-term risk of cardiovascular morbidity and mortality in women with PCOS and an explanation of the need for complete and periodic cardiometabolic evaluation in order to prevent acute cardiovascular events. However, despite the significantly higher risk of cardiovascular disorders, such as hypertension, atherogenic lipid profile, obesity, diabetes in women with PCOS, some studies to date have yielded contradictory results and have not been able to establish increased cardiovascular mortality or morbidity [28, 29]. In a small Swedish long-term prospective study of women with postmenopausal PCOS, the risk of myocardial infarction, stroke or death caused by cardiovascular diseases did not differ when compared with the control. In addition, the overall mortality during the 21-year observation period was similar compared with the control group, despite the higher prevalence of cardiovascular risk factors among patients with PCOS [30]. These data may confirm the view that traditional risk factors for cardiovascular diseases may not be fully applicable to patients with PCOS, and new markers are necessary for a better assessment and distribution of patients with PCOS. In conclusion, although patients with PCOS are considered to have an increased cardiovascular risk, available evidence suggests that the prevalence of cardiovascular diseases and the associated cardiovascular risk in women with PCOS may be lower than expected [24]. To confirm the increased risk of cardiovascular diseases in our study group of women with complications of menopause against PCOS, a molecular genetic study of the polymorphism of folate cycle genes associated with hyperhomocysteinemia is carried out. At the end of the statistical processing, the results of our research will be published [7].

However, further studies of the PCOS population with prolonged observation are needed to study the effect of metabolic disorders on cardiovascular events and overall mortality in patients with PCOS.

5. Oncological Risks

In PCOS, there are many potential mechanisms that can contribute to the development of malignant diseases, including long-term anovulatory status and the associated imbalance between the action of androgens and estrogens, insulin resistance and secondary hyperinsulinemia [18]. Many studies have been conducted to assess the risk of developing cancer in women with PCOS. Barry et al. Conducted a systematic review and meta-analysis of observational studies and concluded that women of all ages with PCOS are at increased risk of endometrial cancer [23]. The findings did not confirm an increased risk of ovarian and breast cancer in patients with PCOS. Similarly, Haoula et al. Found the same association between PCOS and a significantly increased risk of endometrial cancer [14]. They analyzed data from comparative studies and concluded that women with PCOS are three times more likely to develop endometrial cancer compared with patients without PCOS. Other studies have also confirmed a higher risk of ovarian cancer. There are also conflicting data on the risk of developing breast cancer in women with PCOS [23, 27]. More research is needed to accurately determine the overall risk of developing cancer in women with PCOS. However, available data show that women with PCOS have a significant risk of developing cancer, at least for the

endometrium. This finding should promote appropriate screening strategies, lifestyle changes, and the correction of insulin resistance as a primary intervention, which can reduce the risk of PCOS.

6. Conclusions

Polycystic ovary syndrome, the most common endocrinopathy among premenopausal women, is also associated with metabolic dysfunction, which can cause an increased risk of cardiovascular disease, although the long-term effects and end points of the disease have not yet been established. Moreover, the PCOS phenotype can vary widely throughout life and can improve with aging. The menopausal period is associated with weight gain and an increase in both total fat and visceral fat tissue. In itself, excess weight is associated with an increased risk of cardiovascular diseases, which can be further aggravated by the presence of metabolic disorders associated with PCOS. However, it is still unclear whether the presence of PCOS will significantly increase the risk of cardiovascular diseases later in life. Most of the available data suggest that the prevalence of cardiovascular diseases and the associated long-term effects in women with PCOS appear to be lower than expected. But taking into account the increased risk of endometrial cancer and cardiovascular diseases, especially in women with perimenopausal obesity, it should be emphasized that the diagnosis of PCOS, especially if accompanied by overweight, must be accompanied by a complete and periodic cardiometabolic and gynecological evaluation. There is ample evidence that with obesity, you need to change your lifestyle to control overweight and, if necessary, in combination with pharmacotherapy. But taking into account the increased risk of endometrial cancer and cardiovascular diseases, especially in women with perimenopausal obesity, it should be emphasized that the diagnosis of PCOS, especially if accompanied by overweight, must be accompanied by a complete and periodic cardiometabolic and gynecological evaluation. There is ample evidence that with obesity there is a need to involve a lifestyle to control overweight and, if necessary, in combination with pharmacotherapy. But taking into account the increased risk of endometrial cancer and cardiovascular diseases, especially in women with perimenopausal obesity, it should be emphasized that the diagnosis of PCOS, especially if accompanied by overweight, must be accompanied by a complete and periodic cardiometabolic and gynecological evaluation. There is ample evidence that in obesity there is a need to involve a lifestyle to control overweight and, if necessary, in combination with pharmacotherapy.

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