Cardiometabolic risk in polycystic ovary syndrome

Ryzyko kardiometaboliczne w zespole policystycznych jajników

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the most frequently diagnosed endocrinopathies in women, and also one of the most heterogeneous endocrine disorders. In addition to being the most frequent cause of female infertility, PCOS is also said to increase the risk of cardiovascular disease, glucose intolerance and type 2 diabetes. Other risk factors such as obesity, a positive family history of type 2 diabetes and hyperandrogenism may also contribute to an increased risk of cardiovascular disease among women affected by PCOS. The risk assessment of metabolic disorders should be commonly recommended for PCOS patients in everyday medical practice. It makes possible to precisely determine the goals of nutritional interventions among PCOS women. The following work constitutes a review of articles from 1996–2019 available in the PubMed (National Center for Biotechnology Information) database and the Polish Medical Bibliography (Polska Bibliografia Lekarska). For this purpose, the following controlled vocabulary has been used: "PCOS", "overweight", "obesity", "insulin resistance", "hyperandrogenism", "hypertension", "lipid disorders", "diabetes", "cardiometabolic risk", "cardiovascular disease", and "lifestyle modifications".

Key words: obesity, polycystic ovary syndrome, cardiometabolic risk

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Streszczenie

PCOS jest jedną z najczęściej rozpoznawanych endokrynopatii u kobiet i jednocześnie jednym z najbardziej heterogennych zespołów endokrynologicznych. Schorzenie jest najczęstszą przyczyną niepłodności u kobiet i zwiększa ryzyko występowania chorób układu sercowo-naczyniowego, zaburzeń tolerancji glukozy oraz cukrzycy typu 2. Również inne czynniki ryzyka, takie jak otyłość, dodatni wywiad rodzinny w kierunku cukrzycy typu 2 i hiperandrogenizmu mogą przyczynić się do zwiększenia ryzyka chorób sercowo-naczyniowych w grupie kobiet, u których rozpoznano PCOS. W codziennej praktyce lekarskiej ocena ryzyka zaburzeń metabolicznych wśród kobiet chorujących na PCOS powinna być powszechnie zalecana. Dzięki niej można dokładnie określić cele interwencji żywieniowej u kobiet zmagających się z tym schorzeniem. Artykuł jest przeglądem piśmiennictwa bazy medycznej PubMed (National Center for Biotechnology Information) oraz Polskiej Bibliografii Lekarskiej z lat 1996–2019. Do analizy kwalifikowano artykuły zarówno w języku polskim, jak i angielskim, wyszukiwane za pomocą następujących słów oraz ich wzajemnych powiązań: „PCOS", „nadwaga", „otyłość", „insulinooporność", „hiperandrogenizm", „nadciśnienie tętnicze", „zaburzenia lipidowe", „cukrzyca", „ryzyko kardiometaboliczne", „choroby sercowo-naczyniowe", „modyfikacje stylu życia".

Słowa kluczowe: otyłość, zespół policystycznych jajników, ryzyko kardiometaboliczne

Introduction

Excessive body weight may result from genetic, biological, environmental, nutritional, pharmacological, and psychological factors. Secondary obesity, which accounts for only a few percent of the causes of excessive body weight, occurs in rare genetic syndromes, organic hypothalamic diseases and endocrinopathies. It may also result from the use of certain drugs. Obesity-related endocrinopathies include, i.a., polycystic ovarian syndrome (PCOS), which, apart from hyperandrogenemia and/or hyperandrogenism, menstrual disorders and polycystic ovarian image in ultrasound examination, is characterized by an increased cardiometabolic risk. It is estimated that PCOS increases the risk of ischemic heart disease and stroke by 55%. It should also be noted that higher value of the body mass index (BMI) is not the only cause of the increased cardiovascular risk in this syndrome.[1] New scientific reports suggest that PCOS should focus not only on gynecological-endocrine disorders, but also on the increased risk of metabolic complications, also in terms of cardiovascular diseases.

Cardiometabolic risk in PCOS

The relationship between the androgen excess and fertility disorders with the associated metabolic complications is referred to as the Achard–Thiers syndrome, described as the "diabetes of bearded women" (in French *diabète des femmes à barbe*), published by Ahard and Thiers in 1921.[2] The report of Burghen et al., published in 1980,[3] confirmed the link between PCOS research and hyperinsulinemia, which additionally strengthened the belief that the syndrome, apart from fertility disorders, is also characterized by metabolic complications.

Overweight and obesity, visceral obesity in particular, are more common among women diagnosed with PCOS. In the European population, 35–38% of women with this condition are obese. This percentage is lower in women living in Mediterranean countries and higher in the American population.[4] According to the study by Glueck et al., obesity was diagnosed in 92.6% of Caucasian women from USA suffering from PCOS, while in one of the studies conducted in the Italian population, the percentage of obese women with PCOS was much lower and amounted to 38%.[5,6] On the other hand, Lim et al. established obesity in 12.5–100% of women (49% on average) diagnosed with the condition, based on a meta-analysis of studies from different countries of the world. This percentage was significantly higher among Caucasian women from USA and Europe than those of Asian descent. Different criteria used to diagnose PCOS did not affect the incidence of obesity in the studied populations, considering the studies included in the meta-analysis. The percentage of obese women and obese women with central fat distribution was similar both in the respondents diagnosed with PCOS using the National Institutes of Health (NIH) criteria and in women diagnosed with the criteria of the European Society for Human Reproduction and Embryology / American Society for Reproductive Medicine (ESHRE/ASRM).[7] It is worth noting, however, that the percentage of obesity diagnosed in women struggling with PCOS is significantly higher than in the population of healthy women, regardless of their place of residence and origin.[8] Additionally, women with PCOS are frequently predisposed to accumulate abdominal adipose tissue, which is additionally associated with higher fasting glucose values and insulin resistance.[9,10]

Nearly 50% of women with PCOS are diagnosed with visceral obesity.[7] However, regardless of obesity, this group of women has increased level of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). On the other hand, with the coexisting obesity, an increase in triglyceride concentration accompanied by a decrease in high-density lipoprotein (HDL) concentration is observed. Such lipid profile is present in carbohydrate metabolism disorders and insulin resistance.[11]

In a study conducted by Dewailly et al., abdominal obesity was diagnosed in 60.8% of women from among

841 people in the French population, aged 16–40, based on the waist circumference measurements according to the criteria of the International Diabetes Federation (IDF).[12] Similar results were also obtained in the study by Bernasconi et al., according to which women with central obesity and PCOS represented 61.5% of the studied Italian population.[13] A correct BMI value does not exclude the presence of visceral obesity in PCOS. In women with this condition, as in the general population, insulin resistance plays a key role in the development of carbohydrate metabolism disorders.[14] Insulin resistance and hyperinsulinemia are present in approx. 50% of women suffering from PCOS and they affect obese women more frequently.[15,16] Similarly as in the case of obesity, the percentage of obese women of Asian origin with abdominal fat distribution is lower than in the USA and European populations.[7] In women with PCOS, insulin resistance is more common in women without ovulation than in those with regular menstruation.[17] In terms of type 2 diabetes development, the risk of developing PCOS was found to be 7 times higher in individuals with PCOS when compared to the general population. It is also known that glucose intolerance will develop in more than 20% of obese women with this condition aged 30 and more.[18] The risk factors for type 2 diabetes in PCOS include: obesity, positive family history of diabetes, insulin disorder (insulin resistance or dysfunction of pancreatic islets β cells), and oligomenorrhea.[14] Although obesity significantly increases the risk of glucose intolerance and type 2 diabetes, it also occurs in lean women with PCOS. The syndrome is therefore an independent risk factor for type 2 diabetes in middle-aged individuals.[18] The study of Elting et al., conducted among 346 women in the Dutch population diagnosed with PCOS, found diabetes in 2.3% of respondents.[19] Another study conducted on 122 women in the American population with PCOS, established diabetes in 10% of respondents.[20] Higher incidence of diabetes in this population can be explained by a higher obesity rate in most countries of the American continent.

Polycystic ovarian syndrome is also a major cause of lipid disturbances in women of childbearing age.[21] The risk of dyslipidemia in people with this condition is nearly twice as high as in the general population.[22]

Increased levels of total cholesterol, LDL cholesterol and triglycerides, and lower levels of HDL cholesterol are observed among women struggling with PCOS.[4,22,23] Regardless of body weight, PCOS patients show an increased proportion of LDL cholesterol and non-HDL cholesterol.[22] A study conducted by Cascella et al. found statistically significant higher values of total cholesterol and LDL cholesterol, as well as significantly lower values of HDL cholesterol in the group of women diagnosed with PCOS in comparison, with the control group.[24] Other studies, carried out, i.a., on the Asian and American population, also revealed significant differences in the total cholesterol, triglyceride and individual lipoprotein concentrations between women suffering from PCOS and healthy persons.[25,26] Higher concentrations of androgens are associated with higher triglyceride values in women struggling with PCOS.[4] It is worth noting that those women with hirsutism but regular menstruation are less likely to be affected by lipid disturbances. In contrast, women with hirsutism but with irregular menstruation manifest lower HDL cholesterol values and higher triglyceride values.[27]

It was observed that arterial hypertension is more common in the group of respondents with PCOS than in the general population.[21] The study, conducted among 69 women with PCOS in Brazil, indicated that arterial hypertension was diagnosed in 20.3% of the respondents.[28] Lo et al. noted that race and ethnicity have an impact on blood pressure values in women struggling with PCOS. The incidence of hypertension was the lowest among Asian and Latino women and the highest among Afro-American women.[29] It seems that the value of blood pressure in women struggling with the condition is not directly related to the value of body weight. It has been demonstrated that ambulatory all-day measurement of PCOS is higher than in the general population, regardless of BMI and the adipose tissue distribution.[30] Etiopathogenesis of hypertension in PCOS is associated with hyperinsulinism, insulin resistance, hyperandrogenism, or increased activity of the sympathetic system in addition to the more common PCOS-related obesity. Insulin resistance increases the contractility and reactivity of smooth muscles to pressure factors, e.g., angiotensin and catecholamines.[11] Diastolic blood pressure is lower in the group of women with PCOS without insulin resistance than in the group of women diagnosed with that condition and with insulin resistance.[31] In addition, hyperinsulinemia is responsible for increasing sodium resorption and natriuresis disorder by activating the renin-angiotensin-aldosterone system.[11,32] The concentration of total and free testosterone, which is excessively secreted in PCOS, correlates with the values of systolic and diastolic blood pressure, regardless of age, insulin resistance, obesity, and dyslipidemia.[33]

Women with PCOS also manifest an increased cardiovascular risk through the intensified subclinical atherosclerosis and the occurrence of elevated inflammatory markers, such as: interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), homocysteine, and C-reactive protein (CRP).[11,34] An indicator that illustrates the severity of atherosclerosis is the evaluation of vascular stiffness. Soares et al. observed that PCOS patients manifested a statistically significantly higher common carotid stiffness index than healthy women (3.72 ±0.96 vs 3.36 ±0.96; $p = 0.04$), but these changes were independent of body weight and arterial hypertension.[34] In their meta-analysis, Meyer et al. found a higher thickness of the endothelial complex – carotid artery intima-media thickness (CIMT) in women with PCOS in comparison with the control group. Evalu-

ation of the CIMT complex enables diagnosis and monitoring of atherosclerotic diseases, because each 0.1 mm increase in CIMT increases the risk of stroke by 18% and of myocardial infarction by 15%.[11,35]

Adipose tissue activity in PCOS

It is important to note that the overall clinical picture of female patients with PCOS may indicate an increased risk of metabolic syndrome, in which adipose tissue itself can play a major role.[36] Adipocytes of adipose tissue can synthesize and release many biologically active substances with autocrine, paracrine and endocrine effects.[37] Excess adipose tissue is not regarded solely as a cosmetic defect. In the light of the latest scientific research, it synthesizes many biologically active compounds which may increase metabolic risk. These include leptin, visfatin, vaspine, and pro-inflammatory cytokines, such as IL-6, which play an important role in the pathomechanisms of insulin resistance. Their high concentrations may increase the incidence of cardiovascular risk.[36] Adipose tissue may affect brain, ovary and uterus function through the synthesis of adipocytes, thus affecting fertility and metabolic traits of women with PCOS.[38]

Leptin is a significant hormone of adipose tissue which plays an important role in the mechanism of food intake. It has been shown to have an enormous influence on the regulation of immune processes, modulation of carbohydrate and lipid metabolism, as well as reproductive processes.[36,37] Leptin receptors are found in many tissues and organs of the body, including the central nervous system, skeletal tissue, muscle tissue, β cells of the pancreas, and even in ovaries, and therefore it is becoming an interesting subject of research in patients with PCOS. Increased body fat content correlates with increased leptin levels.[36] Some studies have shown that patients with PCOS manifest hyperleptinemia that negatively correlates with fertility rates.[37] However, it is important to stress that the relationship between the levels of leptin and its role in PCOS still remains unclear and needs further studies.[37]

In meta-analysis evaluating the concentration of inflammatory markers, such as CRP, IL-6 and TNF-α, in patients with PCOS compared to the properly selected control group, it has been shown that women with PCOS manifest elevated CRP compared to the control group, regardless of obesity, which stresses the presence of chronic inflammation in this group of patients.[39] Similar statistically significant correlations were not observed for other inflammatory markers.[39] Many studies have shown that the mechanism of fat hormones secretion in patients with PCOS is altered, with increased levels of leptin and pro-inflammatory cytokines, and reduced levels of adiponectin observed in patients with PCOS.[36] Abnormal adipocyte function and altered synthesis of adipose tissue hormones in women with PCOS play an important role in the pathomechanism of insulin resistance and metabolic syndrome in this group of patients.[36] A better understanding of adipokine interactions in PCOS could be helpful in reducing the cardiovascular risk in this group of patients.[36]

A Polish study by Bika et al. assessed the concentration of leptin, resistin and adiponectin in 148 women (81 of whom were affected by PCOS).[37] The group of women with PCOS was divided into: patients with BMI < 25 kg/m^2 (mean BMI 22.35 ±2.35 kg/m^2) and BMI ≥ 25 kg/m^2 (mean BMI 30.1 ±4.8 kg/m^2). Body mass index in the control group was 21.96 ±1.80 kg/m^2. There were no statistically significant differences between the groups in terms of resistin concentration, but adiponectin concentration was higher in the control group (11.92 ±6.72 ng/mL) than in the PCOS group (BMI < 25 kg/m^2 – adiponectin 9.50 ±4.8 ng/mL; BMI ≥ 25 kg/m^2 – adiponectin 8.11 ±4.68 ng/mL). The highest concentration of leptin was found in the group of women with PCOS, whose BMI was ≥25 kg/m^2 (leptin concentration: 22.98 ±8.83 ng/mL). In the PCOS-affected women with BMI < 25 kg/m^2, it amounted to 11.21 ±4.99 ng/mL, whilst it the control group to 12.24 ±6.17 ng/mL.[37]

Zheng et al. analyzed 238 studies evaluating leptin levels in PCOS patients and found that the elevated leptin levels were more common in PCOS patients than in control groups. The authors also pointed out that increased leptin concentrations may play an important role in insulin resistance, metabolic syndrome and infertility, and may increase cardiovascular risk.[40] A detailed understanding of the relationship between adipose tissue hormones and the occurrence of PCOS is an important subject for further research.[38]

Selected lifestyle modifications in PCOS

The risk of cardiovascular disease can be reduced through a proper diet and physical activity. Weight reduction leads to improved insulin sensitivity, reduced insulin resistance and improved lipid profile, and it affects the regularity of ovulation and thus fertility in women diagnosed with PCOS.[41] Reducing body weight (by only 5–10% of baseline weight) reduces insulin levels and hyperandrogenism in this group of patients.[42] The systematic review and meta-analysis by Haqq et al. found that the use of an energy-poor diet and physical activity improves the concentration of follicle-stimulating hormone (FSH), sex hormone-binding globulins (SHBG), total cholesterol, and androstendion.[43] In addition, there is scientific evidence for a total, or at least partial, reduction of PCOS symptoms in obese women with the condition following weight loss resulting from reduced-calorie diet.[44] On the other hand, Hollmann et al. proved improvement

in ovulation in 80% of obese patients with menstrual disorders, and in 29% of them an increase in pregnancy rate in case of 10% loss of body weight was demonstrated.[45]

It seems significant to take into account the proportions of the macroelements themselves in addition to calorie balance of the diet. Many studies focus on carbohydrate content and its effects on insulin levels and insulin resistance in women with PCOS. The study by Moran et al., comparing the high-protein and low-carbohydrate diets (40% carbohydrates, 30% protein and 30% fat) with the low-protein and high-carbohydrate diets (55% carbohydrates, 15% protein and 30% fat), proved the results of both diets to be equally effective in improving the carbohydrate and endocrine metabolism indicators.[46]

The study carried out by Fisher et al. did not show any differences either in the efficiency of weight reduction and improvement of selected results of studies on metabolic and hormonal disorders, as well as in leptin levels among women with PCOS who have a low-energy diet with different macroelements (40% carbohydrates, 30% protein and 30% fat vs 55% carbohydrates, 15% protein and 30% fat).[47]

Additionally, the study by Toscani et al. found that the reduction of fat content alone, waist circumference and the selected measurements of skin and fat folds did not differ between groups of women on diets with different protein contents.[48] The study by Marsh et al., carried out among women with PCOS, found, however, significant increase in insulin sensitivity and regularity of menstrual cycles in women on the low-glycemic index (GI) diets – higher than among women on a healthy diet with limited fat supply and higher fiber content from cereal products. Interestingly, both diets contained the same percentage of macroelements, with the only difference in GI and glycemic load values.[49]

Another study, evaluating the effect of polyunsaturated fatty acids from the n-3 family, showed a significant decrease in total testosterone concentration in the group of women with PCOS who had daily intake of n-3 acids obtained from soybean oil amounting to 3.5 g daily for 6 weeks. The same study found a significant effect on the reduction of triglyceride levels in the blood of women taking the same dose of n-3 acids, but obtained from fish and linseed oil.[50]

Proper supply of phytoestrogens is also important in a diet of women affected by PCOS. The study carried out by Fisher et al. showed a significant decrease in testosterone, dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone, triglycerides, and LDL cholesterol in women with PCOS who consumed 18 mg of soya genistein twice a day when compared to the control group with the same daily intake of cellulose.[51]

In addition to the dietary recommendations in PCOS, attention should also be paid to physical activity. The qualitative systematic review of scientific research by Harrison et al. found that physical activity reduces body weight and improves insulin resistance and ovulation, regardless of type, frequency and duration of ovulation. The same authors recommend that women with PCOS should perform regular oxygen exercises (90 min/week) of medium intensity (60–70% VO_{2max}) to reduce cardiometabolic risk and improve fertility.[52]

Conclusion

Increased risk of glucose intolerance, development of type 2 diabetes, dyslipidemia, atherosclerosis, and hypertension are observed in women with PCOS. Many researchers consider PCOS as an early variant of metabolic syndrome, referring to it as the "XX syndrome", thus emphasizing the risk of its impact on the development of cardiovascular diseases.[53] Many recommendations and algorithms concerning treatment of women with PCOS stress that lifestyle modifications, including diet and physical activity, should be the first step in the treatment of infertility in these patients, as well as of metabolic disorders in women with PCOS and coexisting excess body weight.[54,55] Therefore, PCOS treatment must be based on both short-term activities, e.g., reproductive medicine, and long-term actions, consisting of health promotion and prevention activities, including the introduction of an individual diet and physical activity and other elements of a healthy lifestyle in order to reduce the cardiovascular risk for this group of patients in subsequent years of their life.

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