REVIEW ARTICLE

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Cardiovascular system diseases in patients with polycystic ovary syndrome – the role of inflammation process in this pathology and possibility of early diagnosis and prevention

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Abstract

Polycystic ovary syndrome is a disorder which affects 5–10% of women in reproductive age. PCOS is a cause of hyperandrogenism, menstrual disorders and infertility. The most common clinical symptoms are hirsutism, acne and obesity. Patients often suffer from metabolic disorders: insulin resistance, hyperinsulinemia, dislipidemia, leading to atherosclerosis and others irregularities of the metabolic syndrome. Patients are in the high risk group for cardiovascular diseases (CVD) development because of the metabolic abnormalities. Obesity is observed in 35–60% of women with PCOS. Lean women with PCOS are also exposed to a greater risk of glucose intolerance development and abnormalities in lipid profile than women without PCOS with comparable BMI. Adipocytes are the source of many compounds of the paracrine and endocrine activity. Some of them are also markers and mediators of inflammation. Increased levels of proinflammatory cytokines in blood can promote atherosclerosis and cardiovascular disease. Markers: IL-18, TNF, IL-6 and hs-CRP are often elevated in patients with polycystic ovary syndrome. An increase in inflammatory markers may be an early indicator of the risk of developing insulin resistance and atherosclerosis, and may become a useful prognostic and therapeutic tool for monitoring patients with PCOS: lean and those with overweight and obesity. Assessment of the concentrations of inflammatory markers may become a very useful test in evaluating the risk of developing atherosclerosis and cardiovascular disease, long before their clinical manifestation. It will also allow for the appropriate prophylaxis.

Key words

PCOS, CVD, insulin resistance, obesity, inflammation

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder which affects 5–10% of women in reproductive age. PCOS is the cause of hyperandrogenism and menstrual disorders with chronic anovulation and infertility. The most common clinical symptoms are hirsutism, acne and obesity. Patients often suffer from metabolic disorders: insulin resistance, hyperinsulinemia, dislipidemia, leading to atherosclerosis and other irregularities of the metabolic syndrome.

During ultrasound examination, polycystic ovaries are found – with 12 or more follicles measuring 2–9 mm in diameter or with increased volume (>10 cm^3) [1, 2]. Diagnosis of PCOS sometimes causes many difficulties due to the complexity of symptoms and disorders that make up this condition. For years, there was no clear diagnostic criteria for PCOS. The first attempt to systematize the diagnosis of PCOS was taken in 1990 at the National Institute of Health (NIH) conference in Bethesda, Maryland, USA. It was assumed that the diagnosis of PCOS can be made when two criteria are met: clinical and biochemical markers of hyperandrogenism and menstrual disorders after exclusion of other causes of this condition [2].

In 2003, at The European Society for Human Reproduction & Embryology and the American Society of Reproductive Medicine (ESHRE / ASRM) conference in Rotterdam, The Netherlands, criteria for the diagnosis of polycystic ovaries syndrome were established which are valid to this day. For a diagnosis of PCOS, 2 of 3 criteria must be met: A – Rare ovulation or anovulation; B – Clinical and / or biochemical hyperandrogenism; C – The image of polycystic ovaries on ultrasound must also exclude other diseases with a similar clinical picture, such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome [3].

Due to the fact that polycystic ovary syndrome concerns even 10% of women in reproductive age, this makes it a major problem, not only for the health of the women but also for their self-perception and self-evaluation. In women with PCOS, lack of self-acceptance exists because of the presence of obesity and hirsutism or acne [2].

Although polycystic ovary syndrome is a very common endocrine disorder, considered for more than 70 years, the etiology and pathogenesis of this disease is not completely understood. Recent studies suggest that inflammation may play a role in the pathogenesis of polycystic ovary syndrome. This theory may confirm the fact that chronic inflammation is also associated with the development of pathologies that often concern patients with PCOS; they are: obesity, insulin

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resistance, diabetes, atherosclerosis and hypertension [4, 5, 6]. Because of the metabolic abnormalities observed in patients with PCOS, they are in the high risk group for development of cardiovascular diseases (CVD). They can occur in women with PCOS of a different phenotype, regardless of the presence of overweight, obesity and insulin resistance. Due to the fact that PCOS affects mostly young women and is recognized in reproductive age, is important for patients to have particular medical care from the time of diagnosis. It should consist not only in the treatment of hormonal disorders and infertility, but also in early diagnosis, prevention and treatment of metabolic disorders. This will reduce the risk of cardiovascular disease and its complications in the future and improve the patient's quality of life [4, 5]. All these aspects make the polycystic ovary syndrome a multi-disciplinary problem. In the diagnostics and treatment of women with PCOS there should be involved not only gynecologists, but also dermatologists, internists, gastroenterologists, surgeons and psychologists, dieticians and physiotherapists. This will ensure optimal patient care in such a complex condition which is PCOS.

Risk factors for cardiovascular diseases in women with PCOS. Women with PCOS who are in the risk group of developing cardiovascular disease are mainly patients with confirmed overweight and obesity, dyslipidemia, hypertension, impaired glucose tolerance. PCOS women with metabolic syndrome and/or type 2 diabetes are in the high risk group for CVD [4, 6]. To assess the degree of cardiovascular risk in patients with polycystic ovary syndrome, diagnostic criteria for this disease should be considered.

Criteria developed at the ESHRE/ASRM conference in Rotterdam in 2003 are currently applicable. According to these criteria, patients diagnosed with PCOS may have different phenotypes, and the same diagnosis can be made in more cases than those based on NIH criteria alone [4]. Patients with 'classic PCOS' are those with menstrual and ovulation disorders and hyperandrogenism. They are characterized by a higher incidence of obesity and insulin resistance, and thus exposed to the risk of the development of metabolic complications. Patients diagnosed with PCOS, but with regular ovulation and no hyperandrogenism, are less obese and insulin resistance, and hyperinsulinemia and dyslipidemia less frequently observed. More rarely, patients with PCOS and without hyperandrogenism have an abnormal lipid profile [4, 5, 6].

The presence of insulin resistance is emphasized among the risk factors of cardiovascular disease. This abnormality may affects 60–80% of women with PCOS and 95% of obese women with this syndrome [4, 7]. Dyslipidemia is a very common metabolic disorder that occurs in women with PCOS. It can manifest itself in LDL-C, VLDL, triglycerides increase and lower HDL-C concentrations. The differences in lipid disorders in patients with PCOS may depend on the coexistence of insulin resistance, hyperandrogenism and the impact of environmental and genetic factors [4, 8].

Metabolic syndrome is associated with insulin resistance. It is recognized when three of the following abnormalities appear: high blood pressure (BP) (≥ 130/85 mm Hg), increased waist circumference (≥88 cm), elevated fasting glucose concentrations (≥100 mg/dl), reduced HDL cholesterol concentrations (≤50 mg/dl in women), and elevated triglycerides concentrations (≥150 mg/dl). It is estimated that the prevalence of metabolic syndrome in women with classic PCOS is two or three times higher than in women without the PCOS. Insulin resistance, which is associated with metabolic syndrome in women with PCOS, causes an increase level of inflammation markers (CRP protein, endothelin-1, PAI-1, fibrinogen). They cause endothelial damage, increased vessel wall reactivity to pressure substances and the development of atherosclerosis [4, 9, 10]. It is emphasized that elevated markers of chronic inflammation in young women with PCOS may suggest an increased risk of cardiovascular disease in the future [11].

Inflammatory markers. One of the most important markers of inflammation is C-reactive protein (CRP), an acute phase protein produced by hepatocytes, the production of which is stimulated by cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) [5, 12]. CRP is not only an inflammation marker, but also a mediator involved in its formation in the case of endothelial dysfunction and atherosclerotic process [13]. Elevated levels of high-sensitivity CRP (hs-CRP) is considered as one of the most important predictors of cardiovascular disease risk [14].

Chronic inflammatory processes are associated with elevated levels of several cytokines, including interleukin -6 (IL-6) and interleukin-18 (IL-18). IL-18 appears to be closely involved with insulin resistance and metabolic syndrome, and has also become an important indicator of cardiovascular disease mortality [5]. IL-6 is associated with increased risk of cardiovascular disease, atherosclerosis, dyslipidemia, and hypertension. Moreover, it is a potent inducer of hepatic production of CRP. CRP is a marker the concentration of which increases in patients with severe atherosclerosis and acute vascular incidents (myocardial infarction and cerebral stroke) [15]. Cytokines such as macrophage migration inhibitory factor (MIF), tumour necrosis factor (TNF-α) and interleukin-18 (IL-18) are also markers of inflammatory processes within the adipose tissue, and their increased blood concentrations are observed in obese women with PCOS [16].

Obesity and inflammation in PCOS. Obesity is observed in 35–60% of women with PCOS. Abdominal obesity adds to the risk of development of carbohydrate metabolism disorders, dislipidemia and insulin resistance. It leads to hypertension, diabetes type 2 and cardiovascular disease. Although obesity is not a criteria for the diagnosis of PCOS, it significantly affects the severity of hirsutism and testosterone concentrations. Lean women with PCOS are also exposed to a greater risk of glucose intolerance development and abnormalities in lipid profile than women without PCOS with comparable BMI. Regardless of body weight, insulin resistance with compensatory hyperinsulinemia is found in PCOS patients, and plays a basic role in the pathogenesis of PCOS. Insulin resistance and hyperinsulinemia are now considered to be risk factors for atherosclerosis, and contribute to the development of hypertension. Thus, metabolic disorders, and their long-term consequences should be evaluated in patients, both lean and obese with PCOS, but has been established, obesity is a major risk factor for cardiovascular disease [17, 18].

Adipocytes are the source of many compounds of paracrine and endocrine activity, some of which are also markers and mediators of inflammation [5]. Fat cells have

impaired function in obese patients. The presence of large adipocytes and their abnormal differentiation can lead to insulin resistance and diabetes. Hypertrophied adipocytes exhibit a higher expression of genes involved in inflammation and produce increased amounts of cytokines. This is probably due to tissue hypoxia and leads to the accumulation of macrophages and other immune cells within adipose tissue.

Inflammation in the adipose tissue causes disorders of liver regulated carbohydrate metabolism, and a reduction in insulin sensitivity in skeletal muscles. Indicators of the inflammation process are increased blood levels of cytokines, such as TNF, interleukin-6 (IL -6) and interleukin-1β (IL-1β). It is believed that these cytokines have mainly a paracrine effect, but when its high levels are observed in blood, can cause effects of insulin resistance in peripheral tissues and other organs [19, 20, 21, 22]. In addition, increased levels of proinflammatory cytokines in blood can promote atherosclerosis and cardiovascular disease [23].

Interleukin-18 (IL-18), TNF, IL-6 and hs-CRP are the main markers the levels of which are elevated in patients with polycystic ovary syndrome. Interestingly, both lean and obese patients with PCOS have increased circulating levels of inflammatory markers, suggesting that inflammation may contribute to insulin resistance, atherosclerosis, and other pathologies associated with PCOS. [24]

The first reports of the presence of elevated levels of CRP in patients with PCOS date back more than a decade [25]. These value were higher in women with PCOS compared with healthy women, regardless of age and body weight [26]. Due to the fact that abnormal endothelial function states in polycystic ovary syndrome, it is recognized that elevated CRP levels are markers, and are associated with an increased risk of cardiovascular disease in PCOS [5, 27, 28].

IL-6 is also marker of inflammation. Elevated concentrations of this interleukin are considered to be the determinant of the risk of atherosclerosis, heart disease and hypertension. Moreover, it is a potent inducer of CRP production by hepatocytes, and CRP is a marker of severe atherosclerosis and suggests the possibility of vascular complications, such as myocardial infarction and cerebral stroke. Its elevated levels were observed in women with PCOS and insulin resistance. Due to the fact that leukocytes located within the visceral adipose tissue is a source of large amounts of cytokines, these results may suggest that insulin resistance is a factor that enhances the activity of leukocytes [29]. The correlation between hsCRP and IL-6 concentrations with BMI, and the presence of insulin resistance in women with PCOS, is emphasized [30].

However, not all studies confirm a significant increase in the concentration of proinflammatory cytokines in patients with PCOS. A meta-analysis by Escobar-Morreale et al. indicates no difference in the concentration of IL-6 and TNF-α between women with PCOS and those without it [26]. Both these cytokines stimulate the production of CRP, which is a recognized risk marker of cardiovascular diseases. This fact indicates the need to establish whether the marker should be used for population screening, or should be reserved for determining the cardiovascular disease risk only in some women with PCOS.

It seems that the determination of CRP concentrations in conjunction with the analysis of other risk factors, such as dislipidemia, impaired glucose metabolism and hypertension, may be more useful [5, 31]. These studies indicate a need for further research, necessary to determine PCOS participation in the development of the inflammatory response. Evaluation of inflammatory markers may be an early indicator of the risk of developing insulin resistance and atherosclerosis, and may become a useful prognostic and therapeutic tool for monitoring patients with PCOS, both lean and those with overweight and obesity.

Prevention of cardiovascular diseases and treatment of metabolic disorders in women with PCOS. Risk factors for atherosclerosis and diseases of the cardiovascular system, such as disorders of carbohydrate metabolism, obesity, hypertension, dyslipidemia and metabolic syndrome, are frequently reported in young women with PCOS.

The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society, on the basis of meta-analysis, has developed recommendations for the prevention of cardiovascular disease in women with PCOS [4].

Patients with PCOS belonging to the group of cardiovascular risk are women with obesity, hypertension, dyslipidemia, impaired glucose metabolism and a family history of CVD. Women with PCOS and the metabolic syndrome, diabetes and overt vascular disease or kidney disease are in the very high risk group. Therefore, it should be remembered that in addition to routine gynecological examinations, patients with PCOS must be included in more detailed diagnostics. It should be recommended by a gynecologist or specialist in internal medicine who also diagnose patients with PCOS due to the metabolic abnormalities observed in these patients. Based on such studies, there is a possibility to identify individual lifestyle recommendations for each patient, and the possible use of drugs or surgical treatment, as is the case in morbid obesity [4].

It is recommended that during each examination during each examination, waist circumference and BMI should be evaluated in all women with PCOS [4, 32]. Lipid profile (LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol and triglycerides) should be determined every two years if the lipid values are normal, or more often if the values are invalid or the patient's body weight increases [4, 33]. Oral glucose tolerance test with 75 g glucose is the best method for detecting carbohydrate metabolism disorders in women with PCOS, even in those with normal fasting glucose. This test should be carried out especially in women with a BMI greater than 30 kg/m^2, and those with gestational diabetes in the past, a family history of type 2 diabetes, and over 40 years of age [4, 34]. Also very important in assessing the risk of developing cardiovascular disease is the measurement of blood pressure, which should be made at each visit. Valid values should not exceed 120/80 [4, 35]. It is also recommended that a collection be made of the history of mood disorders and evaluation of the life quality of patients [4].

In addition to assessment of the risk factors for cardiovascular disease, it is very important to start early prevention of this disease. The first step is lifestyle modification, consisting of diet, exercise, giving up smoking, and the introduction of behavioural techniques [4, 3, 6]. It has been proved that weight loss and reduction of visceral adipose tissue in PCOS patients results in lipid profile improvement, reduction in glucose metabolism disorders, hyperandrogenism reduction and ovulatory cycles resumption [4, 37, 38]. 5–10% and 20% target body weight reduction is suggested in overweight and obese women to reduce the risk of vascular disease [32].

Pharmacological therapy includes the use of drugs that increase insulin sensitivity, lower cholesterol levels, lower blood pressure and reduce weight. The longest-used drug that increases insulin sensitivity is metformin. It should be used in women with impaired glucose metabolism in the first stage of treatment, or in the case where lifestyle modification has not helped [4, 3, 9]. As shown, metformin has little effect on body weight, but its use improves the lipid profile. However, lipid disorders should not be a major prerequisite for metformin use because, as demonstrated in several studies, it does not reduce the levels of LDL and VLDL [4]. It has been observed that metformin administration results in the reduction of CRP levels, which may indicate that metformin affects endothelial function and reduces the development of atherosclerotic plaques [4, 40]. Due to the mechanism of metformin action increasing tissue insulin sensitivity, the main indication for its use remains insulin resistance and hyperinsulinemia [41].

Cholesterol-lowering drugs should be reserved for PCOS patients who have elevated levels of LDL and VLDL. This treatment should be implemented when LDL concentrations are greater than 160 mg / dl, and / or VLDL concentrations are greater than 190 mg / dl. Treatment may also be implemented when LDL concentrations are above 130 mg / dl and there are at least two other risk factors for cardiovascular disease in a patient, and a three-month period involving lifestyle modification did not produce results [4, 32]. The most commonly used drugs in this group are statins. A number of studies on their effectiveness in PCOS have shown that statins reduce LDL and testosterone concentrations, reduce insulin resistance and improve endothelial function [4, 42].

The implementation of antihypertensive treatment is recommended when systolic blood pressure exceeds the value of 140 mm Hg and diastolic blood pressure of 90 mmHg. Optimal values significantly reducing the risk of cardiovascular disease is 120/80 [4, 32]. It has been observed that sibutamine, an oral anorexiant used with lifestyle modification, reduces body weight and concentrations of insulin, testosterone, and triglycerides. However, due to the small number of studies on the effects of the use of this drug and the possible side- effects of this therapy, it is not recommended in patients with PCOS [4, 43].

Bariatric surgery allows for a significant reduction in body weight and reduction in the risk of diabetes, hypertension and dyslipidemia, as well as the risk of death due to cardiovascular disease and cancer. It is a solution for PCOS patients with significant obesity, when other treatments are not effective [4, 44].

CONCLUSIONS

Polycystic ovary syndrome is a common disorder occurring in young women. In addition to typical hormonal disorders belonging to the image of PCOS, patients also have a number of metabolic abnormalities. These are mainly obesity, insulin resistance, hyperinsulinemia, dyslipidemia and atherosclerosis. If left untreated, they may lead to the development of complications, such as type 2 diabetes, hypertension, ischemic heart disease or cerebral stroke. Because of cardiovascular risk factors stated in a many cases of women with PCOS, it is important – independent of weight – to cover medical care and take preventive action for each woman after the diagnosis of PCOS. It is important to qualify each of them to the appropriate risk groups of complications and preventing such complications. Thus, in each patient diagnosed with PCOS, regardless of body weight, there should be carried out clinical evaluation of changes in BMI, measurements of blood pressure, and laboratory tests assessing lipid profile and presence of glucose intolerance. It seems that the assessment of concentrations of inflammatory markers may become a very useful test in assessing the risk of developing atherosclerosis and cardiovascular disease, long before their clinical manifestation, which will allow for the appropriate prophylaxis.

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