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CARDIOMETABOLIC CONSEQUENCES OF PCOS

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ABSTRACT

Introduction and purpose

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder in terms of clinical symptoms and laboratory findings. It is one of the most common endocrinopathies in women of childbearing age. The development of symptoms and the degree of severity in the course of the disease are the results of changes in the ovaries which may be caused by many genetic, metabolic, neuroendocrine, and environmental factors. The main clinical manifestations are menstrual disorders, difficulties with becoming pregnant, and changes related to hyperandrogenism, e.g., acne, hirsutism. Recognition is above mainly based on Rotterdam criteria.

State of the knowledge

A comprehensive explanation of pathophysiology is still lacking. Nevertheless, it probably is a multifactorial condition with a genetic component. Women suffering from PCOS experience lipid and carbohydrate metabolism disorders, which lead to insulin resistance, obesity, hypertension, and cardiac complications. Insulin resistance affects 65-70% of women and not only plays a significant role in the development of the disease but also contributes to the development of hypertension and dyslipidemia. Potential mechanisms of hypertension in PCOS include endothelial dysfunction, increased aldosterone, and excess testosterone secretion, whereas lipid abnormalities consist of reduced high-density lipoprotein-cholesterol (HDL-C), increased triglycerides, and low-density lipoprotein-cholesterol (LDL-C). All of these factors cause high cardiovascular risk. Currently, therapy considers both lifestyle improvements and medications and must be tailored on a case-by-case basis.

Conclusion

It is very important not to consider PCOS only in the context of gynecological and endocrine diseases, but also metabolic changes and cardiovascular diseases. Treatment of PCOS should be individualized and dependent on the predominant disorders, as well as the short- and long-term goals chosen. It also should take the prevention of cardiovascular diseases into account.

Keywords: polycystic ovary syndrome; insulin resistance; cardiovascular risk; dyslipidemia; hypertension.

INTRODUCTION AND PURPOSE

Polycystic ovary syndrome (PCOS) is one of the most common hormone disorders affecting 6-10% of women of reproductive age [1]. This syndrome was first recognized in 1935 by Irving Stein and Michael Leventhal, from whose names the original name of the disease was derived [2]. The diagnostic criteria have been debatable for many years. Nowadays the Rotterdam criteria are the most widely-used tool for diagnosing PCOS. Two out of the three features of PCOS are required for a diagnosis: oligo-anovulation, hyperandrogenism, and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary) [2].

Additionally, there are the National Institutes of Health (NIH) criteria, where three of following must be met for diagnosis: hyperandrogenism and/or hyperandrogenemia, oligoovulation, exclusion of other known diseases associated with hyperandrogenism.

According to Androgen Excess and PCOS Society criteria (AE-PCOS), diagnosis is made on the basis of the presence of two criteria: hyperandrogenism: hirsutism and/or hyperandrogenemia, and ovarian dysfunction: oligoovulation or anovulation and/or the presence of polycystic ovaries on ultrasound [3]. Based on the Rotterdam criteria, 4 phenotypes of PCOS can be distinguished: (1) classic: hyperandrogenism (H), ovulation disorders (O), and a polycystic ovary (P) detected by USG (HOP); (2) with hyperandrogenism and ovulation disorders, but with a normal ovarian USG image (HO); (3) with hyperandrogenism and a polycystic ovary USG image, but without ovulation disorders (HP); (4) with ovulation disorders and a polycystic ovary USG image, but without evidence of hyperandrogenism (OP) [4, 5].

The development of symptoms and the degree of severity in the course of the disease are the result of changes in the ovaries, which may be caused by many genetic, metabolic, neuroendocrine, and environmental factors [6]. Clinical manifestations of PCOS include weight gain, hair loss, oily skin, acne, amenorrhea or oligomenorrhea, hirsutism, mood disorders, and infertility [7]. PCOS is the most common cause of anovulatory infertility, as it affects 40% of women with this disease [8].

In addition, in women diagnosed with PCOS, there is an increased incidence of classic risk factors for cardiovascular diseases, such as obesity, insulin resistance, hypertension, and dyslipidemia [6, 9]. These symptoms lead to cardiovascular disease or type 2 diabetes. Moreover, the most significant factor is insulin resistance and it plays a prominent role in the development of the diseases [6]. It is, therefore, very important to explore the link between PCOS and cardiometabolic changes. This review aims to provide you with knowledge about how to effectively prevent such complications.

STATE OF KNOWLEDGE

Pathophysiology

Despite being one of the most common endocrinopathies, a comprehensive explanation of pathophysiology is still lacking. Nevertheless, it probably is multifactorial condition with a genetic component [6,10]. Apparently determined by the complex interaction between the functionality of the hypothalamic-pituitary-ovarian or hypothalamic-pituitary-adrenal axis and metabolic disorders, such as obesity, insulin resistance, and compensatory hyperinsulinemia [10]. These factors are associated with a genetic predisposition, confirmed by the identification of abnormal gene clusters involved in steroidogenesis and regulation of peripheral insulin sensitivity [10, 11].

Insulin resistance and obesity

Insulin resistance is a metabolic disorder in which there is a decrease in tissue sensitivity to insulin despite its normal or elevated levels in a blood test. This phenomenon causes elevated blood glucose levels which are compensated for by the increased production of insulin by the pancreas (hyperinsulinemia) [12].

Insulin resistance and compensatory hyperinsulinemia affect approximately 65–70% of women with PCOS, with these features being shared by 70–80% of obese women (BMI > 30) and 20–25% of lean (BMI < 25) ones [13].

When the response of pancreatic cells decreases, the patient develops glucose intolerance or type II diabetes [6]. Approximately 30%–40% of women with PCOS have impaired glucose tolerance and 7.5%–10% of them have type 2 diabetes [8].

Insulin resistance plays a significant role in the development of PCOS. Excess of insulin leads to excessive production of androgens, which reflects in symptoms.

Insulin resistance increases lipolysis and the accumulation of intrahepatic lipids, which activates the diacylglycerol/protein kinase C axis and inhibits the insulin receptor. In skeletal muscle, on the other hand, the inhibition of phosphoinositide-3 kinase and phosphorylation of insulin receptor substrate 1 leads to impaired insulin signaling by altering the GLUT-4 expression and glucose uptake.

Excess insulin activates 17- α -hydroxylases [14], increases ACTH-mediated adrenal androgen production, and decreases the synthesis of sex hormone binding globulin (SHBG) in the liver, with a consequent increase of both total and free androgen levels.

In addition, insulin acts both directly as a gonadotropin, enhancing LH activity by stimulating the expression of receptors for LH granulosa cells, and indirectly by impairing the regulation of the hypothalamic-pituitary-ovarian axis.

Altered secretion of adipokines and pro-inflammatory cytokines is also noticeable. Reduced adiponectin depletion and secretion by TNF- α secretion of tumor necrosis factor) may promote damage to pancreatic and endothelial cells. The consequence of this phenomenon is the increased incidence of diabetes [14,15,16].

Dyslipidemia

Polycystic ovary syndrome is the leading cause of dyslipidemia in women of reproductive age [9]. The probability of lipid metabolism disorders is almost twice as high in the group of women diagnosed with PCOS as compared to healthy individuals [17]. Women with PCOS would be predicted to be at high risk for dyslipidemia because they have elevated androgen levels and are frequently obese. Moreover, since they are also often hyperinsulinemic and insulin resistant, they would be expected to be at increased risk for dyslipidemia associated with insulin resistance [18]. Regardless of obesity, lipid abnormalities include reduced high-density lipoprotein-cholesterol (HDL-C), increased triglycerides, and low-density lipoprotein-cholesterol (LDL-C) [19]. Based on their meta-analysis, Wild et al. evaluated the difference in lipoproteins between women aged 18–45 years with PCOS and controls from the same catchment area. It showed that triglyceride levels were 26 mg/dL (95% confidence interval [CI] 17-35) higher and HDL-cholesterol concentrations 6 mg/dL (95% CI 4-9) lower in women with PCOS. Also, LDL-cholesterol and non-HDL-cholesterol concentrations were higher in PCOS: by 12 mg/dL (95% CI 10-16) and 19 mg/dL (95% CI 16-22), respectively. With BMI matching, LDL-cholesterol and non-HDL-cholesterol were still higher in PCOS: by 9 mg/dL (95% CI 6-12) and 16 mg/dL (95% CI 14-19), respectively [17].

Hypertension

Hypertension is a persistent increase in blood pressure, which value reaches 140/90 mm Hg or more [20].

Arterial hypertension is more common in PCOS than in the general population of women [8]. The probable causes of hypertension in this group are insulin resistance-related hyperinsulinism and excess testosterone secretion. Insulin resistance is one of the basic risk factors for the development of arterial hypertension. In the course of impaired insulin sensitivity, an increase in contractility and an increase in the reactivity of smooth muscles to pressure factors (including endothelin, angiotensin, catecholamines) are observed, the increased synthesis of which is a consequence of excessive insulin action [21, 22]. Potential mechanisms of hypertension in PCOS include endothelial dysfunction, as evidenced by increased endothelin-1 levels and increased aldosterone concentrations related to insulin resistance [22]. Chen et al. Demonstrated a positive correlation of testosterone concentration with the values of systolic and diastolic blood pressure, regardless of obesity or insulin resistance in women with PCOS [24]. The postulated mechanism influencing the occurrence of arterial hypertension in women with PCOS manifests as an increase in renal sodium reabsorption and impairment of natriuresis through activation of the renin-angiotensin-aldosterone system in overweight or obese women [21]. The disproportion between estrogens and androgens often observed in women with PCOS, may also affect higher blood pressure values in these patients as evidenced by Lecke SB, Morsch DM, and Spritzer PM in Hospital de clinicas de Porto Alegre (HCPA) research [24].

They demonstrated a link between CYP19 gene expression, levels of aromatase, and blood pressure: androgen excess may be involved in the high levels of CYP19, which is a gene encoding for the enzyme aromatase, and

expressed in abdominal tissue fat. A high expression of this gene induces low estrogen and high androgen concentrations. Furthermore, subcutaneous CYP19 mRNA was higher in hypertensive PCOS than in control and normotensive PCOS women ($P < 0.014$). The CYP19 gene expression correlated positively with SBP ($P = 0.006$) and DBP ($P = 0.009$) [25].

Cardiovascular risk

PCOS patients, compared to healthy people, present an increased cardiovascular risk as the intensification of subclinical atherosclerosis was observed, as well as increased inflammatory markers [26, 27]. A meta-analysis by Meyer et al. showed greater thickness of the intima-media complex (CIMT) in women with PCOS than in the control group. Each increase in CIMT by 0.1 mm heightens the risk of myocardial infarction by 15% and of a stroke by 18%, and De Groot et al. showed a 55% increase in the risk of cardiovascular disease and stroke in these women. They also noted that BMI is not the sole cause of the increased cardiovascular risk [28, 29].

One of the new, non-invasive methods of assessing subclinical atherosclerosis is the assessment of vascular stiffness. In the studies inducted by Soares et al., it was observed that patients with PCOS have a statistically significantly higher index of vascular stiffness compared to the healthy population, and these changes were independent of the patient's body weight and the presence of arterial hypertension [30].

Treatment

Due to the lack of causal treatment for PCOS, the management should consider take into account the current needs of the patient and reduce the risk of complications. The aims of treatment consist of reduction of the production and concentration of androgens in the serum, protection of the endometrium against the constant action of estrogens, regulation of menstrual cycles, and induction of ovulation in order to become pregnant. It is also important to reduce the risk of metabolic diseases.

Non-pharmacological treatment is recommended, such as weight loss, regular physical activity, a diet with reduced animal fats and simple sugars. Reducing body weight by 5-10% decreases the concentration of insulin, androgens, LH and increases the concentration of SHBG. The reduction of adipose tissue is an essential factor in the improvement of ovarian function [31].

In order to achieve gynecological effects, the most common are contraceptives and medications that inhibit the secretion of androgens (GnRH analogs, ketoconazole, glucocorticosteroids) or block the androgen receptor (cyproterone, spironolactone, flutamide) and induce ovulation (clomiphene, letrozole).

Clomiphene is the best therapy for patients planning pregnancy. It is an estrogen receptor modulator that directly affects the hypothalamic-pituitary axis, 75% of patients using clomiphene become pregnant within 3 months.

Metformin is a drug often used in the case of PCOS, which contributes to lowering the level of insulin and androgens, thus restoring the regularity of ovulatory periods. Additionally, it not only improves the lipid profile and antioxidant characteristics and increases the levels of sex hormone binding globulin (SHBG), but also (through its pleiotropic effect on the vascular endothelium) acts to protect the cardiovascular system. [32]

CONCLUSIONS

Women suffering from PCOS are more prone to insulin resistance, dyslipidemia, hypertension and consequently, cardiovascular complications.

Therefore, it is very important not to consider PCOS only in the context of gynecological and endocrine diseases, but also metabolic changes and cardiovascular diseases. [33]

According to the AES recommendations, each woman with PCOS should be assessed for cardiovascular disease risk, such as waist circumference, blood pressure measurement, lipid profile assessment. In women with: BMI > 30 kg / m², a history of gestational diabetes, and a family history of diabetes, an oral glucose load test should be performed every 2 years [34]. Treatment of PCOS should be individualized and dependent on the predominant disorders, as well as the short- and long-term goals chosen. It also should take the prevention of cardiovascular diseases into account.

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