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Metabolic Complications in Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is the most frequent endocrinopathy in women of childbearing age with a prevalence of approximately 9 to 18%, being more frequent in overweight women. It is a pathology that is manifested by irregular cycles and/or amenorrhea. At the same time, this pathology, also called Chronic Hyperandrogenic Anovulation, is usually accompanied by manifestations such as acne, hirsutism, and insulin resistance that can lead to diabetes, arterial hypertension, and alterations in the lipid profile in the long term.

Therefore, a Descriptive-Retrospective study of patients who presented metabolic complications due to Polycystic Ovarian Syndrome was carried out.

By knowing the clinical manifestations and pathophysiology of the disease, pharmacological treatment can be applied early, which will promote a healthy lifestyle in women with PCOS in order to limit and prevent the aforementioned subsequent metabolic complications.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine-metabolic disorder today. Affecting women of reproductive age, women with PCOS are at increased risk of metabolic dysfunction, from glucose intolerance and type 2 diabetes mellitus to nonalcoholic fatty liver disease and cardiovascular disease. The cause of this syndrome is still unknown, however, in the pathophysiology of PCOS there are three types of interrelated alterations: neuroendocrine dysfunction (LH hypersecretion), a metabolic disorder (insulin resistance and hyperinsulinemia) and steroidogenesis dysfunction. and ovarian folliculogenesis. Timely diagnosis is important since this syndrome is associated with reproductive, oncological and metabolic risks, patients must be diagnosed and treated promptly; they need to be informed and educated about their pathology and finally, to be controlled in a prolonged way. Treatment should always begin with the correction of metabolic abnormalities. The paper will discuss how the two key hormonal defects in PCOS, insulin resistance and hyperandrogenism, alter homeostasis and favor the development of metabolic diseases; as well as the relationship and participation that different hormones have in this pathology.

Polycystic ovary syndrome is the most frequent endocrinopathy in women of childbearing age, it is considered the main cause of anovulatory infertility; its prevalence varies between approximately 4% and 18%, being more frequent in overweight and obese women and certain ethnic groups, for example, indigenous women. (1,2)

There are 3 varieties regarding the diagnostic criteria, the Rotterdam criteria are the most accepted, it is necessary that the patient has 2 of them to be able to make a diagnosis of PCOS. These include: oligoovulation and/or anovulation, hyperandrogenism, and polycystic ovary disease (identified on ultrasound): It is important to rule out other pathologies before making the diagnosis.

The cause of this syndrome is still unknown, however, it is attributed to a multifactorial or polygenic genetic basis and it is also believed to have an autosomal dominant pattern. (1)

Insulin resistance (IR) and hyperandrogenism (HA) are the two key hormonal alterations in the development of PCOS. Compensatory hyperinsulinemia (HI) associated with insulin resistance is manifested in most cases with phenotypic characteristics such as acanthosis nigricans and plays a truly significant role in the development of metabolic complications such as pancreatic beta cell dysfunction, increasing the risk of type 2 diabetes mellitus, hypertension, dyslipidemia and heart disease. SOP has 2 varieties that are considered serious; Hairan's syndrome and hyperthecosis, both rare. The first is a syndrome of hyperandrogenic acanthosis nigricans with insulin resistance and the second is characterized by the presence of islets of theca lutein cells

distributed in the ovarian stroma and will be patients with pronounced hyperandrogenism, in addition to greater insulin resistance and acanthosis. nigricans. (3,4)

Pathophysiological aspects of this syndrome are still not fully understood, however, it is known that numerous biochemical abnormalities such as elevated circulating total testosterone, free testosterone, DHEAS and insulin, decreased SHBG, and elevated LH:FSH ratio are present in PCOS (3). In addition to menstrual and endocrinological disorders, most PCOS patients have metabolic disorders, mainly increased risk of developing insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases. The obesity and hyperinsulinemia that most PCOS patients have is considered the basis for all these alterations (5).

HORMONES AND PCOS

Gonadotropins: Anovulation in PCOS patients is characterized by inappropriate gonadotropin secretion, generating increased LH secretion and decreased FSH secretion. The increased LH will stimulate the ovarian production of androgens, mainly testosterone, this stimulation will inhibit the action of aromatase causing follicular atresia and in turn anovulation, oligoovulation. On the other hand, the shortage of FSH decreases the action of aromatase, which consists of transforming androgens into estradiol. (6)

Estrone: It is the estrogen in greater amount in postmenopausal women; they are formed from androgens by extraviral aromatases, mainly in adipose and breast tissue, which is why, in obese women with PCOS, estrogen production increases, since elevated serum androgens, mainly androstenedione, are converted to estrogens (estrone), mainly in stromal cells of adipose tissue. (7,8)

Insulin resistance: It is the reduced response to glucose uptake to a certain amount of insulin causing hyperinsulinemia. IR together with increased adipose tissue causes follicular atresia in the ovaries and AN in the skin. (9,10)

Sex hormone binding globulin (SHBG): Fixes most of the sex steroids and only 1% is free. Its biosynthesis is suppressed with insulin, androgens, corticosteroids, progestogens, and somatostatin, therefore, it will be reduced in women with PCOS. Due to its decrease, a greater amount of androgens are free to bind with end-organ receptors, generating more free testosterone, which we call hyperandrogenism. (eleven)

PCOS METABOLIC COMPLICATIONS

Systemic arterial hypertension.

The cohort study in the article Hypertension Risk in Young Women With Polycystic Ovary Syndrome: A Nationwide Population-Based Cohort Study provided evidence of increased risk of developing hypertension in women with PCOS. The factors that increased the risk were DM, hyperlipidemia, COPD, asthma, CKD, and age over 30 years. Hypertension rates in PCOS patients were 7.85, while those in the comparison cohort were 4.23 per 1,000 person-years. In patients with PCOS, a greater correlation was observed with the development of hypertension in those with DM, hyperlipidemia, COPD, and asthma. (6)

The mechanism by which the prevalence of hypertension in PCOS increases has been related to several factors such as IR, hyperinsulinemia, HA, obesity, and autonomic dysfunction of the heart. The hyperandrogenic state of PCOS develops an exacerbated cardiometabolic profile with consequent endothelial dysfunction and elevated blood pressure. In addition, compensatory hyperinsulinemia affects blood pressure through autonomic imbalance, decreased nitric oxide production, and increased renal sodium reabsorption. (12)

Nonalcoholic fatty liver disease.

Several studies have shown a higher prevalence of NAFLD in women with PCOS. PCOS is an independent risk factor for hepatic steatosis and possibly progression to fibrosis and cirrhosis, with hyperandrogenism and resistance to insulin as main determinants. In the study of the article: “Implicating androgen excess in propagating metabolic disease in polycystic ovary syndrome”, it was discovered that androgen excess is a risk factor that contributes to the development of NAFLD in PCOS. These associations have recently been supported by a meta-analysis showing a 2-3 times higher rate of NAFLD in women with PCOS, especially those with hyperandrogenism. (10)

A suppression of androgen-mediated lipolysis and an increase in de novo lipogenesis were found to occur in vivo and in vitro. This would lead to fat accumulation in adipocytes beyond their storage capacity, leading to fatty acid spillage, systemic lipotoxicity, insulin resistance, and fat accumulation in the liver, leading to the development of NAFLD. In the same study, serum metabolomics showed increased concentrations of glycerophospholipids and lysoglycerophospholipids in PCOS women with excess androgen, but not in controls with normal androgen concentrations, at baseline. Both glycerophospholipids and lysoglycerophospholipids have previously been observed to be increased in people with NAFLD and have been identified as potential markers of risk and progression of the condition. These data show that women with PCOS have a distinct metabolic response to androgens that contributes to the development of NAFLD. (13)

Hyperandrogenism and PCOS

According to the article Metabolic dysfunction in polycystic ovary syndrome, hyperandrogenism (HA) is the main trigger for metabolic complications in these patients; 80% of the patients with HA data have PCOS (4). In addition to HA and IR, an inadequate diet and a sedentary lifestyle also contribute to the development of cardiometabolic complications, since they favor insulin resistance and obesity. The excess of androgens causes central obesity, the accumulation of fat in the abdominal region leads to the development of metabolic syndrome, this occurs due to decreased sensitivity to leptin at

the central level (4). HA also increases adipocyte size, decreases lipolysis, and produces NAFLD due to increased insulin resistance, obesity, and alterations in lipid metabolism. Women with normal BMI also have a higher risk of developing it than women without PCOS (4). In women with HA, an increase in ALT may be observed, indicating damage to liver tissue. Androgen excess stimulates IR in skeletal muscle, this is believed to be due to decreased tyrosine phosphorylation and increased serious phosphorylation of the insulin receptor. In the pancreas, HA contributes to the deterioration of beta cells (4).

Polycystic ovary syndrome, adipose tissue, and metabolic syndrome

Polycystic ovary syndrome is a reproductive disorder and a systemic metabolic condition, for which they have risk factors for cardiovascular disease and diabetes, among which are altered fasting plasma glucose, SAH, elevated triglyceride levels, low levels of HDL-C cholesterol and abdominal obesity. (8)

The risk of metabolic syndrome is twice that of women of similar age and BMI without PCOS. Women with PCOS, regardless of their BMI, usually present an atherogenic lipid profile, along with other biochemical cardiovascular risk factors. This is attributed to the fact that the PCOS-related increase in estrogen aggravates visceral adiposity and perpetuates IR. which in turn is associated with visceral obesity. The available data suggest that PCOS patients also have a 5- to 8-fold increased risk of developing type 2 DM (8).

IR affects metabolic actions, while mitogenic and steroidogenic actions are usually conserved. When insulin reaches high concentrations, it induces an increase in androgen production by theca cells and synergistically with LH. (8)

PCOS is associated with an increased risk of cardiovascular disease. Therefore, patients with PCOS should be fully evaluated for baseline metabolic parameters and all available weight loss procedures should be used in conjunction with pharmacologic interventions to improve metabolism. (8)

Cardiovascular disease.

An association between PCOS and cardiometabolic dysfunction is common. Cardiovascular risk profiles vary with genotype, age, ethnicity, and BMI. (8)

Features such as hyperandrogenism and obesity in women with PCOS are associated with metabolic syndrome and insulin resistance. Women with PCOS have an unfavorable metabolic profile compared to healthy women, resulting in long-term cardiovascular complications. (8)

Polycystic ovary syndrome is diagnosed between the ages of twenty and thirty, when there is a desire to conceive. However, cardiovascular disease manifests itself three to four decades later. (8)

Several studies have shown an increase in non-insulin-dependent diabetes mellitus in patients with PCOS, this supports that women with PCOS have a higher risk of coronary artery disease (CAD). Postmenopausal women with a history of irregular menses and hyperandrogenism, regardless of ovarian morphology, are at increased risk of myocardial infarction and stroke at later stages. (8)

Metabolic complications in non-obese women with PCOS

Various studies have shown that non-obese women with PCOS are at greater risk of developing metabolic complications than non-obese women without PCOS. The article Metabolic disturbances in non obese women with PCOS showed that women with PCOS despite having a normal BMI have a higher risk of developing type 2 DM and glucose intolerance. Although insulin resistance is considered to be strongly related to obesity in women with PCOS, it is frequently encountered, even if they are not obese (5). The risk of developing cardiovascular diseases also increases, the main alteration being high levels of triglycerides and low HDL (5). Hypertension is no more prevalent in nonobese women with PCOS than in healthy nonobese women. The risk of developing metabolic syndrome is increased 2.6 times in women with PCOS despite having a normal BMI (5).

Women with PCOS are at risk of endometrial hyperplasia related to unopposed estrogen exposure; oral contraceptives or progestins are administered to achieve endometrial protection. Oral contraceptives are also used to treat hyperandrogenism. Spironolactone and cyproterone acetate act as weak androgen receptor blockers. For women who want to be fertile, the first crucial step is weight control. Clomiphene citrate is effective as a first-line treatment to induce ovulation.

Treatment of metabolic complications in PCOS

Therapeutic options are limited. Currently the main therapeutic indication is a balanced diet and physical activity since weight loss reduces metabolic complications and hyperandrogenism in these patients (4). Studies have shown that insulin sensitizers such as metformin or thiazolidinediones reduce plasma insulin and androgen levels, increase SHBG levels, and improve ovarian function. Flutamide has been shown to reduce visceral fat stores in women with PCOS. Another option is GLP1 analogues that, in addition to improving hyperinsulinemia and hyperandrogenism in obese women with PCOS, help reduce body weight and improve menstrual cycles. Some studies have shown that GLP-1 analogues are superior to metformin in treating these complications. therapy with both drugs is suggested (4). Another therapeutic option for patients with severe obesity who have not reached therapeutic goals with pharmacological therapy and lifestyle changes is bariatric surgery, which reduces BMI, improves blood glucose levels, insulin resistance and hypertension. it also reduces hyperandrogenism, menstrual disorders and improves ovulation rates (4).

Impact of dietary macronutrient balance on PCOS traits

PCOS encompasses reproductive, metabolic, and endocrine abnormalities, which increase the risk of type 2 DM and cardiovascular disease, therefore, all women with PCOS are recommended to modify their lifestyle, including diet, exercise, and behavioral strategies. There are few studies on the impacts of diet on PCOS, however, high-fat diets have been shown to aggravate obesity and PCOS traits, low-carbohydrate diets improve IR and total cholesterol by 1 to An additional 5% weight loss, a hyperprotein hypocaloric diet and a low glycemic load, increases insulin sensitivity, these studies also show that weight loss of at least 5 to 15% has a beneficial effect. (13)

DISCUSSION

This paper mentions the relationship and participation of different hormones in the development of PCOS, among these GnRH is mentioned, which has a continuous pulsation, which conditions a greater secretion of LH and FSH, with a ratio of 2:1, which translates into an increase in ovarian androgen production, with the consequent follicular atresia, anovulation, oligoovulation or subsequent amenorrhea, in addition to the decrease in FSH resulting in lipid profile abnormalities, hirsutism and acne. Other hormonal abnormalities involved in the pathophysiology of PCOS are elevated serum androgens, increased estrogen production, and decreased synthesis of sex hormone-binding globulin, which, when suppressed, causes an increase in free androgens. , with consequent hyperandrogenism.

The hormonal defects that cause the appearance of this endocrinopathy condition the development of metabolic pathologies, which is verified with the development of this research, thanks to the cohort study of the article Hypertension Risk in Young Women With Polycystic Ovary Syndrome: A Nationwide Population- Based Cohort Study, it is shown that there is a higher risk of developing hypertension in women of reproductive age with PCOS, because of the 20,652 patients analyzed, a higher rate of hypertension was found, in addition to a higher frequency of different comorbidities, within the which highlighted DM, hyperlipidemia, COPD, asthma and CKD.

The increase in DM2 and IR in women with PCOS from the aforementioned study is corroborated by the article (Metabolic complications in non-obese women with PCOS), in which it was shown that women with PCOS have a higher risk of developing metabolic complications compared to with women without PCOS, despite not presenting any degree of obesity, among which type 2 DM and IR stand out, also mentioning that there is an increased risk of developing cardiovascular diseases, due to increased levels of triglycerides and decrease in HDL, therefore the risk of developing metabolic syndrome increases 2.6 times. This agrees with what was mentioned in the article Polycystic ovary syndrome, adipose tissue, and metabolic syndrome, since it mentions that patients with PCOS have a higher risk of developing cardiovascular disease and diabetes, due to their fasting plasma glucose. elevated blood pressure, elevated triglyceride levels, low HDL-C cholesterol levels, and abdominal obesity, making the risk of metabolic syndrome twice that of women of similar age and BMI without PCOS, abdominal obesity in turn it is associated with an increase in visceral adiposity and perpetuates IR, for which, according to this article, patients with PCOS have a 5 to 8 times greater risk of developing type 2 DM, data that agrees with the authors of the previously mentioned articles.

Another complication found with the research carried out is non-alcoholic fatty liver disease, since according to the article (Implicating androgen excess in propagating metabolic disease in polycystic ovary syndrome) a higher prevalence of non-alcoholic fatty liver disease has been demonstrated. mentions that PCOS is a risk factor for hepatic steatosis and possibly progression to fibrosis and cirrhosis, because in this it was discovered that excess androgens, which as mentioned at the beginning, contributes to the development of non-fatty liver disease. alcohol, in addition to the fact that there is suppression of androgen-mediated lipolysis and increased de novo lipogenesis in vivo and in vitro, which leads to a positive accumulation of fat beyond the storage capacity of adipocytes, which would lead to the development of NAFLD in women with PCOS.

CONCLUSION

Polycystic ovarian syndrome is a fairly common pathology in women of childbearing age, it causes gynecological, endocrinological and metabolic problems in women who suffer from it. As it is one of the main causes of infertility and alterations in menstrual cycles, it is important to know the clinical manifestations and pathophysiology of the disease in order to give pharmacological treatment (the ideal will be regulators of the menstrual cycle: monophasic, biphasic or triphasic hormonal schemes known as contraceptives and/or progestogens in case of amenorrhea, metformin if there is insulin resistance, cyproterone to treat hyperandrogenism, etc) and thus promote a healthy lifestyle in women with this syndrome (suggesting a balanced diet and the practice of minimal exercise 3 times a week), this in order to limit and prevent metabolic complications caused by insulin resistance, obesity and hyperandrogenism characteristic of the disease and thus improve their quality of life, achieving a decrease in morbidity and mortality derived from diseases such as diabetes, systemic arterial hypertension, steate non-alcoholic liver disease, acute myocardial infarction, cerebrovascular accident, among the other complications that were reviewed.

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