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Polycystic ovaries as a cardiometabolic risk factor for arterial hypertension

Ovarios poliquísticos como factor de riesgo cardiometabólico para hipertensión arterial

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrinopathy that affects women of reproductive age and is diagnosed when at least two of the following criteria are present: oligo or anovulation, hyperandrogenism, and ultrasound imaging of polycystic ovaries.[1]

PCOS has a prevalence of 4-8% worldwide; however, this may vary depending on the diagnostic criteria used (National Institutes of Health, Rotterdam, among others). In Mexico, PCOS has an estimated prevalence of 6% (95% CI 1.9-10.1).[2]

PCOS is frequently associated with obesity due to increased visceral fat, insulin resistance, type 2 diabetes (T2DM), systemic arterial hypertension (SAH), and metabolic syndrome, which lead to an increased cardiometabolic risk.[3]

Women with PCOS have a higher prevalence of SAH, reaching 5.5% vs. 2.0% of their peers without the disease.[4] Some studies have reported a prevalence of SAH of up to 30% in specific groups of women aged 20-34.[5]

The pathophysiology of PCOS includes epigenetic, environmental, and inflammatory factors, insulin resistance, oxidative stress, and obesity, which together may be associated with increased risk of SAH in women.[6]

PATHOPHYSIOLOGY

Women with PCOS present endocrine disorders characterized by an increase in the frequency of pulsatile secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), hyperandrogenism, and increased secretion of gonadotropin-releasing hormone (GnRH), which consequently produces an absence of the late luteal and early follicular phase.[7]

On the other hand, androgens exert a negative feedback loop towards the pituitary, reducing the sensitivity to estrogens and progestogens and the frequency of pulsatile release of GnRH and inducing aromatization to estrogens.[7]

These endocrine disorders lead women to have impaired fertility, hyperandrogenism, obesity, insulin resistance, T2DM, dyslipidemia, endothelial dysfunction leading to peripheral vasoconstriction, increased peripheral resistance, and SAH.[8]

The etiology of SAH in women with PCOS is multifactorial, and various mechanisms have been proposed through which these hemodynamic changes are explained, such as obesity, alteration of the renin-angiotensin-aldosterone system (RAAS), proteinuria, and hyperandrogenism, among others *(Figure 1)*.[7-9]

Obesity is a common finding in women with PCOS and has a predominantly visceral distribution that exacerbates SAH and is associated with components of metabolic syndrome. Weight loss as the first line of treatment in these patients reduces hyperinsulinemia, insulin resistance, and hyperandrogenism.[8]

Regarding the renin-angiotensin-aldosterone system (RAAS) alteration, it

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has been shown that women with PCOS have elevated renin, angiotensin-converting enzyme (ACE), and angiotensin II levels. Visceral fat adipocytes produce high levels of angiotensinogen and contain high levels of androgens, causing RAAS overactivation. Evidence shows that angiotensin II type 1 receptor (AT1R) antagonists and type 2 receptor (AT2R) activation normalizes androgen levels by a not yet discovered mechanism.[8]

There is evidence in the literature suggesting elevated androgen levels also produce alterations in the cellular immune response and cytokine levels in association with a proinflammatory phenomenon such as occurs in cardiometabolic syndrome; these pathophysiological changes lead to endothelial dysfunction, oxidative stress, increased peripheral resistance, and kidney damage, all of which are factors that contribute to the pathophysiology of SAH.[9]

The role of the immune response and T lymphocytes in the pathogenesis of SAH and target organ damage has been established in clinical studies. In the case of women with PCOS, the combination of the inflammatory phenomenon induced by hyperandrogenism, immune activation, infiltration of T lymphocytes at the vascular level, and the imbalance of Th17/Treg cells can lead to vascular damage and nephropathy.[10]

Among the molecules involved in the pathophysiology of inflammation and immunity are reactive oxygen species, metalloproteinases, cytokines such as interleukin 6 (IL-6), interferon alpha (INF-α), and antibodies that lead to vascular damage (increased endothelial permeability, vasoconstriction, remodeling, and rarefaction) and renal (activation of sodium transporters, interstitial fibrosis, and glomerular damage).[10]

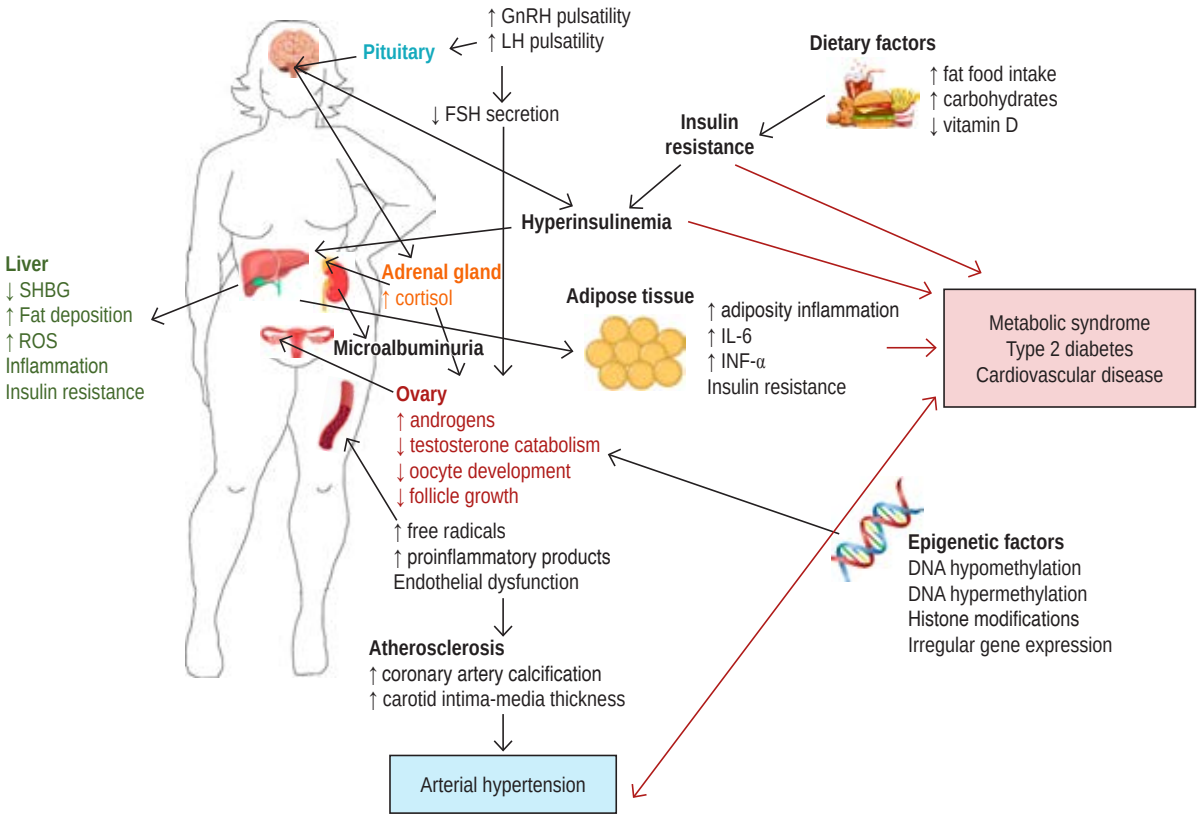

Figure 1: Pathophysiology of arterial hypertension in women with polycystic ovarian syndrome.
GnRH = gonadotropin-releasing hormone. LH = luteinizing hormone. FSH = follicle-stimulating hormone. SHBG = sex hormone binding globulin. ROS = reactive oxygen species. IL-6 = interleukin 6. INF-α = alpha Interferon.

CARDIOVASCULAR RISK

According to a meta-analysis, Anderson et al. demonstrate that young women with PCOS tend to have an increased risk of non-fatal stroke (OR 1.61; 95% CI 0.82-3.15) and coronary heart disease (OR 1.63; 95% CI 0.96-2.78). The higher prevalence of SAH, obesity, dyslipidemia, and cardiometabolic syndrome in women with PCOS explains this tendency.[11]

In postmenopause, the cardiovascular risk in women with PCOS and hypertension is practically the same compared to healthy women matched by age. In contrast, in premenopausal, the risk is higher (RR 1.7).[12]

Meta-analysis studies also confirm an increased risk of SAH in women with PCOS, but only in women of reproductive age; after menopause, having a history of PCOS may not be a significant predisposing factor for developing SAH.[12]

CONCLUSIONS

Early detection of cardiovascular risk factors in women with PCOS is essential for the prevention of cardiovascular outcomes (myocardial infarction, stroke, heart failure, cardiovascular death) because these women present chronic inflammation, endothelial dysfunction, oxidative stress, immune system disorders, kidney damage, hypertension, insulin resistance, and cardiometabolic syndrome.

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