Review Article

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REVIEW ON ARTICLEON POLYCYSTIC OVARY SYNDROME

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Abstract

Polycysticovary syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation. Depending on diagnostic criteria, 6% to 20% of reproductive aged women are affected. Symptoms of PCOS arise during the early pubertal years. Both normal female pubertal development and PCOS are characterized by irregular menstrual cycles, anovulation, and acne. Owing to the complicated interwoven pathophysiology, discerning the inciting causes is challenging. PCOS typically involves hormonal imbalances, insulin resistance, and metabolic abnormalities, which significantly increase the risk of infertility, type 2 diabetes, and cardiovascular disease and affectquality of life.The diagnosis of polycystic ovary syndrome requires at least two of the following criteria: oligoovulation and/or anovulation, clinical and/or biochemical evidence of hyperandrogenism and morphology of polycystic ovaries The aim of this article was to present a review of the literature by searching the databases Pubmed and Scielo, focusing on publications related to polycystic ovaries, including its pathogenesis, clinical manifestations, diagnosis and therapeutic aspects.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age.Polycystic Ovary Syndrome (PCOS) is characterized by hyperandrogenism, amenorrhea, and polycystic ovaries. This endocrinopathy is associated with many metabolic disorders such as dyslipidemia and insulin resistance, with increased risk of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular complications [1].

Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts [2] Polycystic ovary syndrome (PCOS) is a condition with a range of reproductive and metabolic features that affects 4–18% of reproductive-age women, depending on the diagnostic criteria used [3,4].

Polycystic ovary syndrome (PCOS) is a complex condition characterized by increased androgen levels, irregularity in mensuration cycles ,and/or small cysts on one or both ovaries [5]. PCOS typically involves hormonal imbalances, insulin resistance, and metabolic abnormalities, which significantly increase the risk of infertility, type 2 diabetes, and cardiovascular disease (CVD) [6] and affect quality of life [7].The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development microcysts in the ovaries, anovulation, and menstrual changes [8]. Women with PCOS suffer from greater body dissatisfaction and are also at increased risk of mood, generalized anxiety, and eating disorders [3,9,10]. Despite its prevalence and

implications for reproductive, metabolic, and psychological health, PCOS is under-diagnosed, in part because of the diversity of phenotypes manifested by this condition. PCOS has also been noted to affect 28% of unselected obese and 5% of lean women [11,12].

EPIDEMIOLOGY, AETIOLOGY, PATHOPHYSIOLOGY

The World Health Organization estimates that it affects 116 million women worldwide as of 2010 (3.4% of women) [13]. Another estimate indicates that 7% of women of reproductive age are affected.

The exact pathophysiology of PCOS is complex and remains largely unclear. Although a detailed discussion is beyond the scope of this review, the underlying hormonal imbalance created by a combination of increased androgens and/or insulin underpin PCOSGenetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the aetiology of PCOS [14,15].Inflammation is likely to play an important role in the promoting the metabolic imbalances, while prothrombotic and pro-oxidative mechanisms futher contribute to the cardiovascular risk of these patients.However, greater understanding of pathophysiological contributors in PCOS have been hampered by a lack of ideal methods to assess either hyperandrogenism or insulin resistance [19].Insulin acts synergistically with LH to increase androgen production in the theca cell of the ovary [16] Another site for androgen production is the adrenal cortex, due to abnormalities in cortical stereoidogenesis promoted by stimulation of adrenocorticotropic hormone [17] And these excess androgen levels, mainly testosterone, androstenedione and dehydroepiandrosterone sulfate, cause premature atresia of ovarian follicles, forming multiple cysts and anovulation with persistent estrogen levels resulting from aromatization of androgens to estrogens without opposition of progesterone and associated with an increased risk of endometrial carcinoma [17,18].

Hyperandrogenism is a well established contributor to PCOS aetiology, detected in around 60% to 80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS(18)], especially in those with more severe .Some studies including a study by Soter et al [19].have demonstrated a definite influence of interleukin-6 and interleukin-10 gene polymorphisms, interferon-c and transforming growth factor-beta1 in the development of PCOS, although no clear pattern of inheritance has been identified(19). Other causal factors are epigenetic exposures, highlighting the association between intrauterine exposure and maternal androgens and phenotypes related to the syndrome [20].

Hemostatic imbalance. Hemostasis is also worth highlighting in the study of PCOS, since women affected by this syndrome have an imbalance between pro-coagulant and anticoagulant mediators, with a moderate prothrombotic tendency and a consequently increased thromboembolic risk [21].

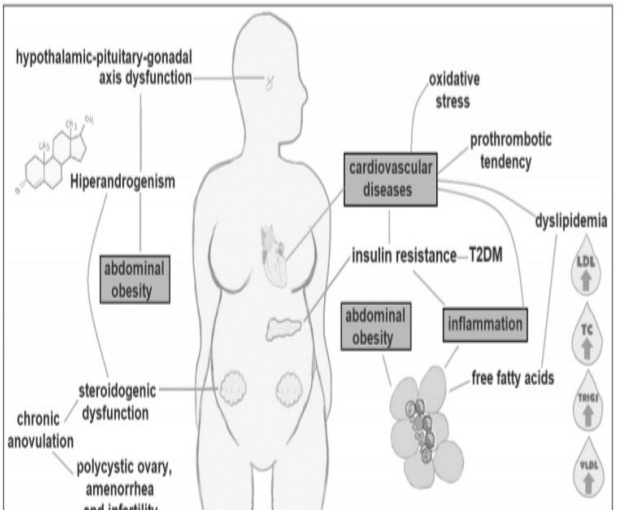

Figure 01. Important biochemical pathways involved in the pathophysiology of PCOS.

Hyperandrogenism is a central feature in PCOS. Patients have a dysfunction in the hypothalamic-pituitary-gonadal axis, which influences steroidogenesis. In the ovaries, theca cells exhibit steroidogenic dysregulation that elevates circulating androgens. In addition, women with PCOS have lower levels of SHBG, which raise the level of free testosterone. Hormonal imbalance causes the follicular development to be prematurely disrupted, causing chronic anovulation, amenorrhea, polycystic ovaries and infertility. Hyperandrogenism is also associated with accumulation of fat in the abdominal region and hyperinsulinemia secondary to insulin resistance (IR). Inflammation is considered an important link between the metabolic effects of PCOS, such as IR, dyslipidemia and T2DM. Visceral obesity causes an increase in plasma levels of inflammatory mediators and the adipocytes release fatty acids by lipolysis, causing dyslipidemia. PCOS

women have higher oxidative stress markers and also an imbalance between pro- and anti-coagulant mediators. Hemostatic and oxidative imbalances, combined with inflammation, IR and dyslipidemia are factors that increase cardiovascular risk in these patients. TC = total cholesterol, Trigs = triglycerides, T2DM = type 2 diabetes mellitus.

Follicular development. In addition to androgens and insulin, other hormones also have abnormal secretion in PCOS. These changes include follicle-stimulating hormone (FSH) deficiency and LH hyper-secretion, increasing the LH/FSH ratio in about 55 to 75% of the women with PCOS. Healthy women show a decrease in the secretion of gonadotrophin-releasing hormone (GnRH) in the luteal phase due to a negative feedback caused by progesterone. However, inPCOS women, hyperandrogenism reduces progesterone negative feedback on GnRH , therefore a fast GnRH pulse frequency is observed in this group, favouring the production of LH over FSH(21)

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Oxidative stress:Oxidative stress may also be related to a higher incidence of cancer in PCOS women by inducing DNA damage, such as DNA chain rupture, base modification, DNA-DNA cross-linking, DNA-protein cross-linking, and also epigenetic changes, including elevated DNA methylation level [23].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the Rotterdam Consensus, it was defined that at least two of the following three findings are required for diagnosis of PCOS: oligoovulation or chronic anovulation, clinical and/or laboratory evidence of hyperandrogenism, and pelvic ultrasonography indicative of polycystic ovaries [24]. These criteria recognize that PCOS is a diagnosis of exclusion [25]. Therefore, to confirm this syndrome, disorders that mimic the clinical characteristics of PCOS must be excluded, such as thyroid disorders, hyperprolactinemia and non-classical congenital adrenal hyperplasia [26].

Although PCOS has been traditionally considered a disorder that affects women in their reproductive years, clinical manifestations may be observed at menarche [27]. In addition, clinical complications vary according to different phenotypes, age, ethnicity and body weight [28].

According to research studies, the classical PCOS phenotype is linked to hyperandrogenism, anovulation and polycystic ovaries. Symptoms usually worsen with time [29]. Among these characteristics, hyperandrogenism is considered a cardinal element for diagnosing this condition and to define a patient as hyperandrogenic may be of major clinical significance [30]. The clinical manifestation of hyperandrogenism in these women varies in different ethnic groups, with external manifestations like oily skin, acne, hirsutism, central obesity, and even androgenetic alopecia [26,31].

The cardiovascular system of women with PCOS is affected, regardless of obesity, due to metabolic disturbance associated with the respective syndrome [32] Factors such as dyslipidemia, diabetes and obesity are all potent risk factors for cardiovascular disease, explaining why women with PCOS are more predisposed to hypertension [33].

TREATMENT

The primary treatments for PCOS include: lifestyle changes and medications.Goals of treatment may be considered under four categories:Lowering of insulin resistance levels,Restoration of fertility,Treatment of hirsutism or acne,Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer [34].Diet:The American Association of Clinical Endocrinologists guidelines recommend a goal of achieving 5 to 15% weight loss or more, which improves insulin resistance and all hormonal disorders[34]. Vit D deficiency:may play some role in the development of the metabolic syndrome, so treatment of any such deficiency is indicated. However, a systematic review of 2015 found no evidence that vitamin D supplementation reduced or mitigated metabolic and hormonal dysregulations in PCOS 35].Medications:include oral contraceptives and metformin. The oral contraceptives increase sex hormone binding globulin production, which increases binding of free testosterone. This reduces the symptoms of hirsutism caused by high testosterone and regulates return to normal menstrual periods. Metformin is a medication commonly used in type 2 diabetes mellitus to reduce insulin resistance, and is used off label (in the UK,

US, AU and EU) to treat insulin resistance seen in PCOS. In many cases, metformin also supports ovarian function and return to normal ovulation [80-84]. Spironolactone can be used for its antiandrogenic effects.A 2012 and 2017 review have found myo-inositol supplementation appears to be effective in improving several of the hormonal disturbances of PCOS [36].

DISCUSSION AND CONCLUSION

The concept that androgen excess may be responsible for the development of insulin resistance also needs to be re-examined, since studies performed in the last decade in experimental animals have supported the hypothesis that early exposure to modest androgen excess may favour the development of insulin resistance and enlarged visceral adiposity, although available data in humans are still sparse and controversial and preliminary prospective data in humans seem to not support this hypothesis. There have been a number of recent well designed adequately powered trials examining infertility treatment in women with PCOS. While this is a positive development, it is only a start. PCOS status is expected to lead to many long-term consequences in women, specifically the development of type 2 diabetes, cardiovascular diseases and hormone dependent cancers. Identifying susceptible individuals would help to individualize therapeutic and, possibly, preventive strategies. The role of diet in the pathogenesis of PCOS: Focus on dietary Advanced Glycated End products (AGEs) Lifestyle contributors to disease include not only calorie excess but also the dietary intake of specific nutrients. Advanced Glycated End products (AGEs) is a class of nutrients incriminated in the pathogenesis of diet-related diseases. AGEs are reactive derivatives of non-enzymatic glucose–protein reactions either produced endogenously or ingested from dietary sources. Cooking or processing at high temperatures such as broiling, grilling, frying, and roasting are the major sources of AGEs. By modulating the activity of protein kinases, AGEs promote oxidative stress and insulin resistance in peripheral tissues. PCOS women have increased serum AGEs levels and these have been positively correlated with serum androgen levels . In women with PCOS dietary modification or use of a gastric lipase inhibitor may reduce serum AGEs and oxidative stress markers as well as serum testosterone levels . PI3K mediates insulin signalling at the post receptor level and also, mediates the clearance of AGEs via the Macrophage Scavenger Receptor (MSR) pathway. The inhibition of Phosphatidylinositol 3 kinase (PI3K) may play a dual role in the coexistence of AGE excess and insulin resistance in PCOS. By activating protein kinase C, AGEs may impair insulin action, thereby perpetuating insulin resistance, an intrinsic feature of PCOS. Furthermore, a potential direct action of AGEs on ovarian function is suggested by their increased immunohistochemical localization in polycystic ovaries. Overall, AGEs, both endogenously and exogenously derived, may play a part in the pathogenesis of PCOS. However, there are no data in comparing different ethnic populations with different diets regarding the impact of AGEs. The environmental source of AGEs can be reduced by dietary modifications.

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