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Review Article
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Diabetes Mellitus and Polycystic Ovary Syndrome: Beyond A Dermatological Problem

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Abstract

Background and aim: Polycystic ovarian syndrome is a common endocrine disorder in reproductive age, with unknown etiology and a variable clinical presentation. Recognizing polycystic ovary syndrome in women presenting with oligo-ovulation and hyperandrogenism offers an important opportunity to begin a life-long conversation about prevention and treatment of a condition that has a multi-system impact on affected women. Recognition offers the chance for providers and patients to engage in discussions about prevention and early treatment of metabolic derangements. This review aims to review the polycystic ovarian syndrome and the approach to the metabolic complications such as insulin resistance and associated hyperinsulinemia.

Methods: It was performed a research on PubMed database of English and Portuguese publications (2004-2015), using the terms: "Polycystic Ovary Syndrome", "Dermatological manifestations" and "Diabetes Mellitus".

Review: Hyperandrogenism occurs in 60% to 80% with PCOS and presents with the following: hirsutism, acne and androgenetic alopecia. Metabolic complications are common, such as obesity, insulin resistance, dyslipidemia and high blood pressure. Thus, lifestyle modifications are essential and metformin or thiazolidinediones can be used. The combined hormonal contraception is the first-line treatment, being more effective with progestins with anti-androgenic activity. Antiandrogens may be used, too. Metformin and weight loss can improve ovulation rate.

Conclusion: It emphasizes the importance of early diagnosis and treatment, in order to prevent metabolic complications and the emotional impact associated with skin manifestations. The family doctor plays a key role in early diagnosis and managing the recommended multidisciplinary approach, including dermatology, endocrinology, obstetrics-gynecology, nutrition and psychology.

Keywords: Polycystic ovary syndrome; Dermatological manifestations; Diabetes mellitus

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in reproductive age, with unknown etiology and a variable clinical presentation [1-3].

The most recognized description for PCOS comes from Stein and Leventhal in 1935 [3], who described obese women with amenorrhea, hirsutism, and infertility with enlarged and cystic ovaries [3,4]. Following an international meeting in 1990, held at U.S. national institute of health (NIH) it was recommended that the diagnostic criteria for PCOS should comprise the concomitant presence of anovulation and evidence of hyperandrogenaemia-biochemical, clinical (hirsutism/acne) or both-but without reference to ovarian morphology [5]. The recommended criteria are those of the

European society for human reproduction and embryology/ American society for reproductive medicine (ESHRE/ASMR), developed in Rotterdam, in 2003, that allow to identify different phenotypes [5].

POCS is a hereditary, chronic and systemic disease with variable signs [3]. The prevalence of this disorder is from 6% to 15% depending on the diagnostic criteria and it begin at puberty or after the initial signs of puberty [2,5]. Metabolic complications are common, such as obesity, insulin resistance, dyslipidemia and high blood pressure [3]. The fact that PCOS is often characterized by the presence of insulin resistance and associated hyperinsulinemia and most of the patients in clinical series are overweight or obese is significant. These factors play an important role in the pathogenesis of androgen excess and the susceptibility to develop earlier than expected glucose intolerance states and type 2 diabetes. Proper diagnosis and management of PCOS is essential to address patient concerns but also to prevent future metabolic, endocrine, psychiatric, and cardiovascular complications.

This paper offers a review about PCOS and summarizes all major aspects related to aetiological factors, including early life events, potentially involved in the development of this disorder.

Aetiology

There are no certains about the origins of PCOS and a variety of hypotheses about either the genetic or the environmental origins of PCOS have been postulated [6-9]. There is some evidence that PCOS may partly depend on genetic factors. However, it is unlikely that PCOS represents a single gene defect and it is more likely to be polygenic or olygogenic [5]. On the other hand, low birth weight and fetal exposure to androgens may contribute to development of the PCOS phenotype. In addition, low birth weight is particularly associated with insulin

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resistance and obesity in adulthood [5,10]. Previous publications have shown that one of the key features of the PCOS theca cells is their significant higher expression of some metabolism-associated genes, including CYP11A, 3BHSD2, and CYP17 [11]. Interestingly, since one of the up-regulated gene, CYP11A, is controlled by the Sp family of transcription factors [12] and the molecular mechanisms that associated with Sp1 include transcriptional repressors p53, DNA methyltransferase 1, histone methyltransferase G9a, and histone de-acetylase HDAC1 [13], it is very likely that both DNA and histone methylation are involved in the regulation of PCOS sensitive genes. In addition, as recent observation has revealed that G9a is able to interact with DNMTs and maintains DNA methylation [14], the PCOS sensitive genes are probably controlled by Sp1-G9a-DNMTs complex in humans. Therefore, it is important to understand the level of G9a and its related H3K9me2 and DNA methylation levels in patients with PCOS.

Pathophysiology

Multiple causal factors have emerged in the pathophysiology of PCOS. It is unclear which of these abnormalities triggers the vicious cycle of anovulation, androgen excess, and hyperinsulinemia seen in PCOS. One of the primary neuroendocrine defects described is alterations in the gonadotropin secretion. There is intrinsic abnormality in gonadotropin-releasing hormone (GnRH) pulse generator to increased luteinizing (LH) pulse amplitude and frequency with relative impairment in follicle-stimulating hormone (FSH) secretion. Augmented LH activity amplified by increased insulin drives the increased androgen production in the variant theca cells with reduced aromatase levels. Hyperinsulineamia further inhibits the production of sex hormone-binding protein (SHBG) in the liver, thereby increasing the proportion of free testosterone compared with total testosterone [5,15-17].

Clinical Presentation

Key clinical features are anovulation with menstrual irregularities, hyperandrogenism, infertility and metabolic abnormalities [3,8,9].

Hiperandrogenismo

Sixty to eighty percent of women with PCOS have hyperandrogenism that have some dermatological manifestations such as hirsutism, acne and androgenetic alopecia, along with acanthosis nigricans, a common sign of hyperinsulinaemia [1,4,18].

Hirsutism: The hirsutism is the most frequent clinical manifestation (60% of the women with PCOS) [18]. It is also the most frequent feature that leads the women to seek medical help. Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas in women. The modified F-G scale is the most commonly used method of assessing clinical hirsutism (Figure 1). This visual scoring system grades nine androgen-dependent areas of the body on a scale of 0 (absence of terminal hairs) to 4 (frank virilization), producing a score ranging from 0 to 36. The sum of the 9 areas results in a total that if it is equal or superior to 8 indicates hirsutism. This can be classified into light [8-12], moderate [13-18] and severe (≥19) [19-21].

Acne vulgaris: Acne is also a marker of hyperandrogenism, although less prevalent in PCOS than hirsutism. It happens in 15% to 25% of the cases. Acne has an overall prevalence in women of about 12%, tends to persist until menopause, and then declines with age [22]. Acne is an androgen-dependent disorder of pilosebaceous follicles (or pilosebaceous unit). There are four primary pathogenic factors, which

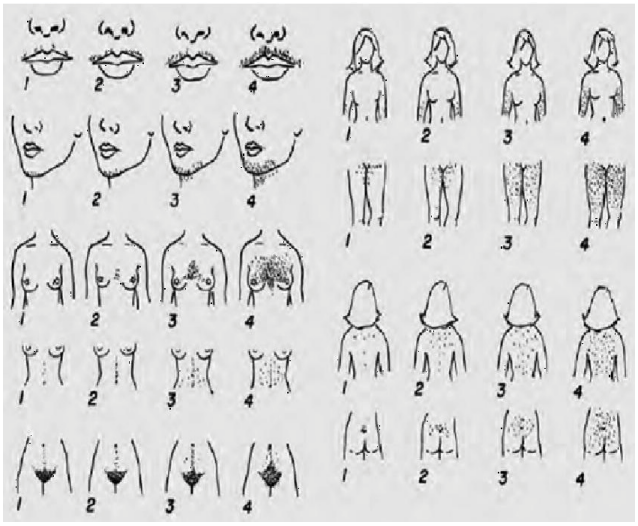

Figure 1: Modify Ferriman-Gallwey Scale to evaluate the hirsutism [1]. This scale is used to the initial evaluation and to monitor the treatment response.

interact to produce acne lesions: 1) sebum production by the sebaceous gland, 2) alteration in the keratinization process, 3) Propionibacterium acnes follicular colonization, and 4) release of inflammatory mediators. Patients with seborrhoea and acne have a significantly greater number of lobules per gland compared with unaffected individuals [1]. The lesions often appear ate the face, neck, pectoral region, shoulders and back [1,18].

Androgenetic alopecia: Androgenetic alopecia (AGA) is a less well-studied and poorer marker of androgen excess, with a generally lower prevalence reported in PCOS. It is the most common cause of alopecia in women [22]. Typically, AGA diffusely involves the crown, sparing the occiput and the frontal hairline [22].

Menstrual disfunction/Chronic oligoanovulation

Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding. However, 30% of women with PCOS will have normal menses. Approximately 85% to 90% of women with oligomenorrhea have PCOS while 30% to 40% of women with amenorrhea will have PCOS [4]. Dysfunction uterine bleeding is occasionally encountered from unopposed estrogen stimulation with lack of progesterone from anovulation [3]. These alterations can be mascaraed by the effect of the hormone contraceptive [4]. Oligoanovulation typically presents as oligomerrohea (<9 cycles per year) or amenorrhea [4].

Insulinorresistence

Women with PCOS are frequently overweight or obese particularly with visceral adiposity [23,24]. They have a significantly increased risk for impaired glucose tolerance and type 2 diabetes. Large cross-sectional studies have found 23% to 35% prevalence of impaired glucose tolerance and 4% to 10% for diabetes. Prevalence of obesity varies considerably in women with polycystic ovary syndrome. Previously, prevalence rates of obesity were estimated based on populations of women with polycystic ovary syndrome seeking care. A recent study comparing patients presenting for care in a polycystic ovary syndrome clinic with an unselected population evaluated during a pre-employment physical suggests that obesity and overweight may not be more common in polycystic ovary syndrome. In that study, 63.7% of polycystic ovary

syndrome clinic patients were obese, compared with 28% of unselected women with polycystic ovary syndrome identified during screening, and 28% of non-polycystic ovary syndrome controls. Polycystic ovary syndrome symptoms, including hyperandrogenism and oligovulation are exacerbated by obesity [22].

Women should be examined for clinical signs of insulin resistance such as acantosis nigricans, multiple skin tags and keratosis pilaris. Acanthosis nigricans is characterized by velvety, brown, thickened plaques with accentuated skin markings in intertriginous areas such as the axillae, groin, anogenital region, and inframammary region and can occur in 5% of women [1]. While acanthosis nigricans is most commonly observed in settings such as obesity, PCOS, and diabetes, it can also be associated with multiple genetic variants (including mutations of the insulin receptor or hypersecretion of transforming growth factor-α), reactions to medications such as nicotinic acid, and malignancy. Obese patients with acanthosis nigricans had markedly higher fasting plasma insulin levels than obese patients without acanthosis nigricans. Among obese patients with PCOS, there was no difference in fasting insulin levels between those with acanthosis nigricans and those without, suggesting that insulin resistance alone does not predict the presence of acanthosis nigricans in patients with PCOS. However, epidemiologic studies need to be conducted to establish the prevalence of acanthosis nigricans in patients with PCOS. Hyperandrogenic insulin-resistant acanthosis nigricans syndrome, a disorder of severe insulin resistance, is comprised of hyperandrogenism, insulin resistance, and acanthosis nigricans and should be excluded when considering a diagnosis of PCOS [1,22].

Reproductive complications

There is an increased risk of infertility (40%) by oligoanovulation, endometrial alterations and obesity [4]. The women present double risk of abortion, hyperplasia or endometrial, ovary and breast cancer [1,3].

Psychological complications

These women present higher prevalence of depression, anxiety, food disorders and sexual desire dysfunction [18]. The obesity, hirsutism, acne and alopecia seems do have an important role in the development of this conditions [25].

Treatment

Rational treatment of the cutaneous manifestations of hyperandrogenism includes hormonal therapy directed at reducing androgen levels as well as inhibiting the actions of androgens in target tissues. In addition, there are a number of non-hormonal therapies for each of the primary dermatologic conditions that may be employed on an adjunctive or alternative basis [22].

Although patients with PCOS often present to dermatologists with cutaneous concerns, it is essential to provide education regarding the metabolic and fertility implications of PCOS and to form a multidisciplinary team that includes a primary care physician and an endocrinologist. Pharmacological treatment is not necessary for all patients with PCOS, and mild form of hirsutism, acne, and androgenetic alopecia may be managed with standard non-hormonal agents, such as laser air removal.

Findings of many researches indicate that women with PCOS benefit from caloric restriction (even if it is not accompanied by weight loss), and naturally even more from body mass reduction. Lifestyle modification leads to the improvement in insulin sensitivity, normalization of plasma insulin level and regaining of normal gonadotropin and androgen metabolism (including normalization of P450 and 17α-hydroxylase activities). Moreover, weight loss can result in regression of acanthosis nigricans and restoration of ovulations. Among potential factors responsible for these benefits are: a decrease in insulin-induced gonadotropin release, reduction of the direct impact on the ovary, normalization of SHBG and insulin like growth factor-binding protein 1 (IGF-BP1) levels, and probably also reduction of leptin concentration. The latter effect leads to lower activity of hypothalamus-pituitary-ovary axis. In women with PCOS, but not in obese patients without this syndrome, the diet can diminish 17-hydroxyprogesterone level. Elevated concentration of this hormone is characteristic of PCOS, indicating that ovarian hyperactivity can be decreased by the reduction in insulin secretion. In many clinical trials, lifestyle modification, through insulin and free androgen level reduction, caused the regaining of normal ovulation [25, 26].

Metformin and thiazolidinediones have insulin-lowering effects by improving insulin sensitivity, and in consequence itturn can decrease circulating androgen levels. Additionally, these agents have a role in the treatment of PCOS due to the fact that women with PCOS are at an increased risk of insulin resistance, and in turn the development of metabolic disorders and cardiovascular disease. Although no antidiabetic agents have US Food and Drug Administration approval for the treatment of PCOS, metformin is preferred at this time due to the fact that it appears to have the safest risk-benefit ratio, and it can cause weight loss, while thiazolidinediones can increase weight as a result of fluid retention [24,27-33].

Conclusion

PCOS is heterogeneous in its manifestations and far reaching in its health implications. No single diagnostic criterion or blood test is sufficient for clinical diagnosis. Peripheral insulin resistance, as seen in PCOS, has been implicated as the root cause for the diseases of syndrome X (hypertension, type 2 diabetes, dyslipidemia, coronary artery disease, obesity, abnormal glucose tolerance). With an international consensus recently established for this diagnosis, hopefully we will gain a greater understanding of how to manage this multifaceted and complex syndrome. The relationship of PCOS with the metabolic syndrome/syndrome X and its paraneoplastic implications remain to be defined. The PCOS treatment must be individualized and the choice of a drug in each case should be based on the age of the patient, severity of symptoms, priorities of therapy and comorbidities. In the light of the recent studies, not only traditional drugs (oral contraceptives, clomiphene and antiandrogens) but also newer treatment options (dietary treatment, metformin, thiazolidinediones and probably also other insulin-sensitizing drugs) are effective, and in some groups of patients, the latter ones seem to be even the drugs of choice.

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