Ro J Prev Med. 2023, sept; 2 (3): 37–43

SCREENING AND DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME CORELATED WITH EVIDENCE-BASED INTERNATIONAL GUIDELINES 2023 RECOMMENDATIONS

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Abstract

The etiology of PCOS is complex, and clinical features are heterogeneous, involving metabolic, cardiovascular, dermatological, psychological, and reproductive changes. The diagnosis is applied using the evidence-based International Guidelines 2018, following the Rotterdam Criteria 2003. Evidence-based guidelines 2023 have additionally provided clear evidence of PCOS characteristics, which now include cardiovascular disease, with more solid information regarding the prevalence of sleep apnea and endometrial cancer. They have also included features such as the increased prevalence and severity of mood disorders as significant traits of this syndrome. Developing a lifestyle modification plan associated with individual needs is essential in managing Polycystic Ovary Syndrome.

Keywords: *Screening, heterogeneity, depression, hyperandrogenism, anovulation, guidelines, obesity, risk factors*

Introduction

Polycystic Ovary Syndrome is an endocrinopathy that affects women of reproductive age. It is one of the most common causes of anovulation and infertility, affecting between 10% and 13% of women of childbearing age, with over 70% of them going undiagnosed. Furthermore, this condition extends well beyond the potential childbearing years, affecting both postmenopausal women and adolescents. Often, the symptoms go unrecognized, and the management remains deficient. Studies in the literature regarding the experiences of PCOS diagnosis have reported delays in diagnosis due to insufficient information. The challenging process of achieving early diagnosis and education through communication represents clear opportunities for improving the patient experience (1,2).

The main issue faced by women with Polycystic Ovary Syndrome (PCOS) is hormonal imbalance, thus affecting multiple systems. The etiology is complex, and clinical features are heterogeneous, involving metabolic, cardiovascular, dermatological, psychological, and reproductive changes. The proper functioning of the mechanisms responsible for ovarian follicle maturation and ovulation depends on the physiological activity of the three organs: the hypothalamus, pituitary gland, and ovaries.

In patients with PCOS, there is reduced reactivity to negative feedback of gonadal steroid hormones, leading to an increased frequency of GnRH pulses, elevated LH release frequency, decreased FSH secretion frequency, and an abnormal increase in the LH/FSH ratio. The response of ovarian granulosa cells to reduced FSH levels leads to alterations in the selection of dominant follicles, resulting in multiple cysts described on ultrasound and infertility. Elevated LH levels cause ovarian thecal cells to produce excess androgens, leading in this way to hyperandrogenism. Additionally, peripheral estrogen synthesis occurs due to

elevated serum androgen levels in PCOS. Excess estrogen increases the synthesis of various inflammatory cytokines (3).

Diagnostic Criteria of PCOS

The diagnosis is made using the evidence-based International Guidelines from 2018, following the Rotterdam criteria from 2003. The presence of two of the following is required: 1) clinical/biochemical hyperandrogenism, 2) ovulatory dysfunction, and 3) polycystic ovaries visualized on ultrasound. Alternatively, anti-Müllerian hormone (AMH) can now be used instead of ultrasound criteria. This diagnostic algorithm needs to exclude other causes. Additionally, when irregular menstrual cycles and hyperandrogenism are present, the diagnostic algorithm can be simplified: Ultrasound or AMH evaluation is no longer necessary in this case. However, in adolescents, both hyperandrogenism and ovulatory dysfunction are required without the need for subsequent ultrasound evaluation or AMH measurement due to reduced specificity. An ultrasound finding of multiple ovarian cysts in adolescents suggests the need for further evaluation, as it indicates an increased risk of later being diagnosed with PCOS (4).

1. Hyperandrogenism is a key feature in the diagnosis of PCOS, affecting 60-100% of individuals with this condition. It is assessed as a form of clinical hyperandrogenism (hirsutism, hair loss, and acne) and biochemical hyperandrogenism (1). The evaluation of hyperandrogenism is characterized by variations depending on ethnicity, excessive weight, and age. Calculated bioactive testosterone, free testosterone (Vermeulen et al. formula), and the free androgen index (FAI) are usually used. Statistics results have shown that calculated free testosterone and calculated FAI have the highest sensitivity and specificity for diagnosing biochemical hyperandrogenism (greater than 80%) compared to all other tests (4).
2. A wide range of factors influence the characteristics of the menstrual cycle, such as body weight, smoking, alcohol consumption, physical activity, or pathological conditions, as well as PCOS. Oligoamenorrhea is generally defined as a cycle length of> 35 days. However, the diagnostic criteria for PCOS have changed over time. Nowadays, an irregular menstrual cycle is characterized by the following: (considering that the first year post-menarche is described as the pubertal transition stage): 1-3 years post-menarche: < 21 or > 45 days, more than three years post-menarche: < 21 or > 35 days or less eight cycles/ year or more than one year post-menarche > 90 days for a cycle, primary amenorrhea until the age of 15 or > three years post-menarche. It is worth emphasizing the need to diagnose PCOS when irregular menstrual cycles are present along with a complete evaluation of the individual features, following the new guidelines (4,5).
3. Identifying polycystic ovaries on ultrasound is not sufficient and not necessary for the diagnosis of PCOS; moreover, identifying only polycystic ovaries can lead to overdiagnosis (4). The ultrasound characteristics for polycystic ovarian morphology have undergone slight changes as the 2023 Guidelines recommend - the number of follicles per ovary has been modified to 20 or more. Recent literature has shown that ultrasound is valuable in uncertain cases, especially with hormonal tests. Although the number of follicles per ovary and the total number of antral follicles are necessary for diagnosis, several other characteristics are monitored: follicle distribution, the total number of antral follicles, resistance and pulsatility index of uterine and ovarian arteries, and ovarian stromal echogenicity (6). As for the adolescents with a gynecological age under eight years (under eight years post-menarche), it is known that maximum ovarian maturity has not yet been reached, anti-Müllerian hormone levels are still increasing, and defining polycystic ovaries at this stage of life is not

currently possible due to the high frequency. of multifollicular ovaries. The risk of over-diagnosis in adolescents has been recognized if ultrasound criteria were included in this age group (4,6)."

Serum levels of AMH are often elevated in women with PCOS due to the simultaneous activation of multiple antral follicles and increased production per follicle. Some studies recommend a group of AMH> 3.8-5 ng/mL to be used as a diagnostic factor for PCOS. Both serum AMH levels and ultrasound can sometimes be used to define PCOS, but performing both tests would result in overdiagnosis. Evidence-based guidelines from 2023 have described that although serum AMH levels have been used in all PCOS studies, there are overlaps with the population of women who do not have this diagnosis, especially in adolescents. AMH tests have improved with clear evidence of their efficiency, leading to a new recommendation: the evaluation of AMH should be used only in adults. Serum AMH levels should only be taken into consideration within the diagnostic algorithm, knowing that in patients with anovulation/irregular menstrual cycles and hyperandrogenism, the AMH level is not a necessary criterion for the diagnosis of PCOS (4,7).

Evidence-based international guideline recommendations for 2023

The main recommendations include:
• A more detailed assesment of individual diagnostic criteria, a simplified diagnostic algorithm - the alternative measurement of AMH levels in the absence of ultrasound evaluation (in adults).
• Establishing the diagnosis based on all aspects of Polycystic Ovary Syndrome (PCOS), with an emphasis on metabolic risk factors, cardiovascular disease, sleep apnea, the frequency of psychological features and the increased risk of pregnancy associated changes.
• An emphasis on the need for extensive education for healthcare professionals, patient awareness and involvement in decision-making
• Focusing on a healthy lifestyle, emotional well-being, and quality of life with awareness and consideration of weight-related stigma.
• The importance of evidence-based medical therapy and more accessible and safer fertility management (8).

Risk of type 2 diabetes in PCOS

Insulin resistance is part of the pathogenesis of PCOS and is associated with an increased risk of type 2 diabetes. Insulin resistance is also closely linked to obesity. Insulin resistance, a well-known mechanism in PCOS, is attributed to an inadequate response to insulin in metabolically active tissues such as adipose tissue and skeletal muscle. In addition, the increase in insulin levels reduces the circulating amount of sex hormone-binding globulin (SHBG) with a higher level of free androgens, thereby limiting the formation of follicles and leading to irregular menstruation. Certain adipokines released by adipose tissue have numerous effects on insulin resistance. Visfatin, which stimulates the insulin receptor and has insulin-like activity, and adiponectin, which has insulin-sensitizing effects, are described in this pathogenesis. Adiponectin is a rich protein structured in multimeric forms, including high, low, and intermediate molecular weights. Some studies demonstrate the association between adiponectin and PCOS independent of BMI, while others claim a direct influence on weight gain (9). A retrospective study that included women (over 19 years) with ICD-10 diagnosis of PCOS having hyperandrogenism and a history of anovulation concluded that PCOS is indeed an independent risk factor for type 2 diabetes, even after adjusting for body weight. It was found that type 2 diabetes was nearly four times more common in women with hyperandrogenism compared to women with PCOS and normal androgen levels (10).

Recommendations from the new International Guidelines 2023 outline the idea that healthcare professionals should be aware that PCOS has an increased risk of glucose intolerance and developing type II diabetes over time, regardless of age and body mass index (BMI). Therefore, glycemic status should be included in the evaluation of any woman with PCOS, regardless of her age, and reevaluated every 1-3 years depending on the individual risk factors (4).

The metabolic syndrome and cardiovascular risk in PCOS

Patients with PCOS may experience metabolic disorders associated with lipid metabolism disturbances, obesity, hypertension, diabetes, and other metabolic diseases. Studies have shown that up to 95% of obese women with PCOS and 75% of women with low body weight and PCOS have insulin resistance. These mechanisms of PCOS imply an increased risk of developing atherosclerosis with a significant risk of cardiovascular disease.

Abnormal lipid metabolism may be present in PCOS patients, with a prevalence of approximately 70%, according to the literature, manifested by low high-density lipoprotein (HDL) and high low-density lipoprotein (LDL). Currently, there are various studies on the risk of PCOS and CVD, but the results are different (1).

Insulin resistance and frequent hyperinsulinemia in PCOS can induce and intensify oxidative stress, with adverse effects on endothelial function and decreased vascular flexibility, thus contributing to the progression of cardiovascular diseases. Additionally, in PCOS, there is an accelerated transition of cholesterol from HDL to LDL. Furthermore, levels of inflammatory cytokines and leptin increase due to excessive fat accumulation, further contributing to insulin resistance and sympathetic nerve excitation, ultimately resulting in hypertension (12).

The 2023 Guidelines have established that metabolic syndrome and risk factors for cardiovascular diseases are certainly increased in the case of PCOS, and overall cardiovascular health is an important feature. Overall, women with PCOS have had a higher odds ratio and/or incidence rate ratio for cardiovascular conditions, including myocardial infarction and stroke. However, the risk of cardiovascular events remains uncertain, and the level of certainty in these results is deficient, as they are derived from observational studies (4).

Endometrial cancer in PCOS

An increasing number of clinical studies and research focus on the association between PCOS and endometrial cancer. PCOS is characterized by chronic anovulation, nulliparity, and exposure to high estrogen levels, which have been shown to be associated with the development of endometrial hyperplasia, leading to endometrial cancer. Most studies are based on the assumption that chronic anovulation is a major factor in both conditions, and high estrogen levels affect the endometrium. Additionally, it has been shown that polycystic ovarian morphology is significantly more common in younger patients aged 20 to 40 years with a diagnosis of endometrial cancer (13).

In the evidence-based guideline from 2023, the increased risk of endometrial cancer in premenopausal women with PCOS is described, along with anovulation and the increased prevalence of higher weight. However, the recommendations do not support routine screening for endometrial cancer because the absolute risk remains low. Nevertheless, the relative risks are much higher in PCOS, emphasizing the importance of clinicians being aware of this risk (4).

Obstructive Sleep Apnea Syndrome in PCOS (OSA)

The prevalence of OSA is significantly higher in men than in women, especially in women of reproductive age, suggesting that higher testosterone levels may predispose to OSA. Hyperandrogenemia is a distinctive feature of PCOS and

has been correlated with the risk of obstructive sleep apnea (OSA) in women with PCOS in some studies. Changes in pharyngeal anatomy that can predispose to obstructive sleep apnea (OSA) have been reported in association with higher testosterone levels. Testosterone is not the only hormone that has been implicated in the pathophysiology of OSA. Progesterone is a dilator of the upper airway muscle activity, and lower progesterone levels in PCOS due to anovulation can increase the risk of OSA (14).
Recommendations from the 2023 International Guidelines state that widespread screening in the general population with PCOS is not justified at present. Women with PCOS should be properly evaluated to recognize symptoms such as snoring, restless sleep, and daytime sleepiness. When these symptoms are present, screening with simple validated questionnaires (such as the Berlin Questionnaire) that can identify obstructive sleep apnea in women with PCOS is necessary (4).

Body image, self-esteem, obesity in PCOS

A negative body image affects both physical and mental health and can negatively influence self-esteem, essential emotional spectrum, and social and professional functioning. Low body image plays a significant role in the development and maintenance of various eating disorders. The literature demonstrates that PCOS is strongly associated with an increased prevalence of eating disorders.
Lower self-esteem due to weight gain seems to be more pronounced among women with PCOS who experience hirsutism and fertility problems compared to women with PCOS without these characteristics. Additionally, this subpopulation of women shows a higher prevalence of depressive and anxiety symptoms.
Recognizing these issues provides an opportunity to address those psychological aspects and work on harmful physical elements such as hirsutism, overweight, and acne. Screening women with PCOS to identify negative body image is uncommon, so an individualized approach focusing on individual priorities is necessary. Available scales for characterizing body image should be considered in all clinical research and healthcare services aimed at the PCOS population (15).
Changes in lifestyle over the years and associated sedentary behavior have increased the prevalence of obesity in the population. Although obesity is not the cause of PCOS, when associated with insulin resistance, it can initiate a cascade of hyperinsulinemia, excessive androgen production, and anovulation. The presence of polycystic ovaries alone should alert clinicians to advise women to avoid weight gain, as it can worsen and lead to more significant long-term morbidity.

Affective Disorders in PCOS

Women with PCOS are susceptible to various conditions, including mental disorders. Depression is the most common in PCOS, with a significant impact on the quality of life. Neurotransmitters such as serotonin (5-HT), dopamine (DA), gamma-aminobutyric acid (GABA), and acetylcholine (Ach) are decreased in PCOS, in contrast to increased levels of glutamate, which are the central stimulators of GnRH and LH. These neurotransmitter changes are described in the literature as playing a role in the pathophysiology of depression in PCOS (3).
The increased prevalence of depression in PCOS may be associated with the pathological features of PCOS, including obesity, insulin resistance, hyperandrogenism, inflammation, and infertility. Recent studies have mainly focused on the similarities and correlations between the pathological features of PCOS and depression, with an emphasis on lifestyle changes and improving the quality of life for women with this syndrome. The evidence-based international guidelines of 2023 firmly state and describe the existence of more pronounced symptoms of depression and anxiety, as well as a higher prevalence of depression and anxiety among women with PCOS.

These symptoms may be related to the stress associated with PCOS. Recommendations suggest that the severity of symptoms and the clinical aspect of depression or anxiety should guide management.
The optimal algorithm suggests screening being done at the time of diagnosis, with repeated screening based on individual criteria. Screening for mental health disorders includes assessing risk factors, symptoms, and the risk of self-harm and suicidal intent (4).

Conclusions

Women with PCOS have an increased risk for several cardio-metabolic comorbidities, including early cardiovascular disease, non-alcoholic fatty liver disease, lipid disorders, and diabetes. Women with PCOS may face challenges regarding diet and weight management. Lifestyle modifications are considered the first-line treatment in improving the chances of achieving a pregnancy in overweight or obese women due to its benefits for metabolism, reproduction, and mental health. However, despite the association between PCOS and obesity, as well as the role of diet and weight loss in treatment, there is limited data on the best intervention for achieving sustainable lifestyle changes (16,17).
Achievement of 5% reduction in total body weight is demonstrated to have health, metabolic, reproductive, and psychological benefits in women with PCOS and excess weight. Creating a regular exercise and low-fat, low-sugar diet plan is the first step in this algorithm. In some cases, it is recommended to consider using complementary and alternative medicine strategies (2).
Lifestyle intervention (physical exercises or a multi-component diet combined with physical activities and behavioral strategies) should be recommended to all women with PCOS to improve metabolic health, including central adiposity and lipid profile.
The incidence of long-term risks can best be evaluated through prospective cohort studies. In women having PCOS, it is not easy to achieve given that the diagnosis is often established relatively early, in the 20-30-year age range. At the same time, cardiovascular diseases frequently occur in women over 60 years of age. For evident reasons, long-term follow-up studies lasting more than 30 years are difficult to conduct, and existing studies of this kind have often included a small number of participants and limited observation periods (18).

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