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Diagnosis, Management of Polycystic ovarian syndrome

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Abstract

Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder with a high prevalence affecting reproductive-aged women and adolescent girls. The most common presentations are infertility, hyperandrogenism and menstrual cycle abnormalities. The disease significantly impacts patients, impairing their quality of life. Although the exact cause of PCOS is still unclear, many factors interact to formulate the clinical features of that syndrome. This review aims to provide a straightforward approach for diagnosing and managing PCOS and its comorbidities.

Keywords: Polycystic ovarian syndrome; Diagnosis;mManagement

Introduction

Epidemiology

In women, polycystic ovary syndrome (PCOS) is a common endocrine/metabolic disorder. Its prevalence depends on the diagnostic criteria used since each criterion includes various PCOS phenotypes.

In a 2016 meta-analysis of 24 population studies performed in Europe, Australia, Asia, and the United States, the rates of PCOS (and 95% confidence interval) according to diagnostic criteria in unselected populations were [1].

- The National Institutes of Health (NIH) – 6 per cent (5 to 8 per cent, n = 18 trials)
- Rotterdam criteria – 10 per cent (8 to 13 per cent, n = 15 trials)
- Androgen Excess and PCOS (AE-PCOS) Society criteria – 10 per cent (7 to 13 per cent, n = 10 trials)

Therefore, the estimate prevalence of PCOS is approximately 6 per cent, but the actual prevalence probably closer to 10 per cent of reproductive-age women. Although the disorder is primarily heritable, this prevalence likely translates to the entire female population, regardless of age [2].

Phenotypes of PCOS

1-Phenotype A "full PCOS" includes biochemical or clinical hyperandrogenism, oligo ovulation, and polycystic ovarian morphology

2-Phenotype B "classic PCOS" includes hyperandrogenism and oligo anovulation

3-Phenotype C "ovulatory PCOS" includes hyperandrogenism and polycystic ovarian morphology

4-Phenotype D "non-hyperandrogenic PCOS" includes oligo anovulation and polycystic ovarian morphology

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The NIH criteria include only phenotypes A and B, the AE-PCOS Society criteria for phenotypes A, B, and C, and the Rotterdam criteria for all four phenotypes. These criteria, with minor adjustments, have been reaffirmed by a recent international evidence-based guideline for the assessment and management of PCOS[3].

Pathogenesis

In their original report[4], Stein and Leventhal emphasized the dyad of what they called "polycystic" ovaries in association with amenorrhea. Although they also noted that some of their subjects had hirsutism or acne, these features were not as central to the syndrome. They observed that "bilateral polycystic ovaries are most probably a result of some hormonal stimulation and very likely relate to the anterior lobe of the pituitary gland" [5].

Genetics: PCOS is a complex genetic trait similar to cardiovascular disease, type 2 diabetes mellitus, and metabolic syndrome, where multiple genetic variants and environmental factors interact to foster the development and features of the disorder[6-8].

Altered LH: PCOS patients often have higher serum LH concentrations[9,10] and increased LH pulse frequency and amplitude [11] than matched controls. However, serum LH tends to be lower in obese women with PCOS compared with their lean counterparts [12,13].

Insulin secretion and action: Insulin resistance, and the development of compensatory hyperinsulinemia, is a frequent finding in PCOS [14-20].

Obesity and energy regulation: The presence of obesity worsens insulin resistance, the degree of hyperinsulinemia, the severity of ovulatory and menstrual dysfunction, and pregnancy outcome in PCOS and is associated with an increasing prevalence of metabolic syndrome, glucose intolerance, cardiovascular risk factors, and sleep apnea [21-25].

Androgen biosynthesis and action:Hyperandrogenism is a central feature for most forms (phenotypes A through C) of PCOS. The androgens are secreted primarily by the ovaries and secondarily by the adrenals [26].

Environmental factors: The most clearly defined environmental factor likely affecting the development of PCOS is diet and its association with Obesity, despite wide variations in the prevalence of Obesity and type of diet [27]. The prevalence of PCOS appears to be relatively uniform across the globe [1,28-31].

Risk factors for PCOS

Many risk factors were proven to increase the risk of PCOs, such as:

- Oligoovulatory infertility [32-34], Obesity [35-39] and insulin resistance [40,41].
- Type 1, type 2, or gestational diabetes mellitus [42-47].
- A history of premature adrenarche [48]
- First-degree relatives with PCOS [49]
- Antiseizure medications –mainly valproate [50-51].

Diagnosis

Clinical features Of PCOS

Menstrual dysfunction: Menstrual irregularity typically begins in the peripubertal period and may be delayed menarche. The menstrual pattern is typically either oligomenorrhea or amenorrhea.

Hyperandrogenism: (hirsutism, acne, male-pattern hair loss) associated with or without elevated serum androgen concentrations.

Polycystic ovaries: The typical polycystic appearance of the ovaries on transvaginal ultrasound (TVUS) in most women with irregular menses and hyperandrogenism. However, this ultrasound appearance is nonspecific as it may also present in normal-cycling women.

Diagnostic criteria

Rotterdam criteria: Most expert groups use Rotterdam criteria to make the diagnosis of PCOS [52-55], two out of three of the following criteria are required to make the diagnosis [56]

- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound).

- In 1990, the National Institutes of Health (the NIH criteria) allowed for a clinical diagnosis without using an imaging study. In addition, the NIH criteria require the presence of irregular menses, while the other criteria do not [57].
- In 2006, the Androgen Excess (AE) and PCOS Society proposed the AE-PCOS Criteria [58]In contrast to the Rotterdam criteria, the majority of the AE-PCOS task force agreed that there were insufficient data to define women with ovulatory dysfunction and polycystic ovaries, but no evidence of hyperandrogenism, as having PCOS [58].

Differential Diagnosis

The diagnosis of PCOS is confirmed once other conditions with features similar to PCOS have been excluded, such as non-classic congenital adrenal hyperplasia (NCCAH), thyroid disease, and hyperprolactinemia. Women with severe hyperandrogenism and virilization require a more extensive

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evaluation for the most serious causes of androgen excess (androgen-secreting ovarian and adrenal tumors and ovarian hyperthecosis) [55].

Nonclassic congenital adrenal hyperplasia (NCCAH) is less common than PCOS but should be ruled out because there are risks that offspring could be affected with the more severe classic 21-hydroxylase deficiency.Testing for NCCAH deficiency by measuring 17-hydroxyprogesterone at 8 AM. This test is most important in high-risk women, including Mediterranean, Hispanic, and Ashkenazi Jewish women.

A. **Androgen-secreting tumors/ovarian hyperthecosis**

Present with recent onset of severe hirsutism, sudden progressive worsening of hirsutism, and symptoms or signs of virilization, including frontal balding, severe acne, clitoromegaly, increased muscle mass or deepening of the voice.

Their serum testosterone concentrations are almost always greater than 150 ng/dL (5.2 nmol/L) [59], and those with adrenal tumors typically have serum dehydroepiandrosterone sulfate (DHEAS) concentrations higher than 800 mcg/dL (21.6 micromol/L).

B. **Oligomenorrhea can be seen with** hypothyroidism, hyperthyroidism, and hyperprolactinemia. These disorders are distinguished by their clinical features and biochemical testing (high TSH, low TSH, high prolactin).

Common Comorbidities

Cardiovascular

There is a high prevalence of obesity and insulin resistance among women with PCOS; they are at increased risk for type 2 diabetes, dyslipidemia, and Coronary Heart Disease (CHD).

Several professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), the American Association of Clinical Endocrinologists (AACE) [60].the Androgen Excess Society [61], and a consensus panel representing the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) [56]. suggest the following assessments:

- Blood pressure and body mass index (BMI) at initial diagnosis and after that. Waist circumference should also be measured.
- Fasting lipid profile at initial diagnosis.
- A two-hour oral glucose tolerance test (OGTT) (with measurement of fasting and two-hour glucose) in all women with PCOS at initial diagnosis. If this is not feasible, fasting glucose should be obtained by measuring the glycatedhaemoglobin (A1C) concentration.

Furthermore, the Androgen Excess Society also suggest the following [61]:

- Patients with standard glucose tolerance should be rescreened at least once every two years or more frequently if additional risk factors are identified.
- Patients with impaired glucose tolerance should be screened annually for the development of type 2 diabetes.

Sleep apnea

women with PCOS should be questioned about the signs and symptoms of sleep apnea (snoring, excessive daytime sleepiness, and morning headaches). If signs and symptoms suggest the diagnosis, the patient should be referred to a sleep medicine clinician

Anovulatory infertility

Transvaginal ultrasound (TVUS): monitors follicular growth and number in those with anovulatory infertility undergoing ovulation induction.

Nonalcoholic fatty liver disease

Although women with PCOS appear to be at increased risk for nonalcoholic fatty liver disease (NAFLD),. Current guidelines do not recommend screening for any groups at high risk for this disorder[62].

Depression and anxiety disorders

Women with PCOS may be more likely to have mood disorders (depression and anxiety) than women with similar BMI without PCOS. They are also at risk for eating disorders (binge eating). Several expert societies suggest screening all women with PCOS for depression and anxiety [52-55]. The best approach is to use brief, validated screening tools such as the Patient Health Questionnaire (PHQ-9) for depression and the Generalized Anxiety Disorder 7 (GAD-7) anxiety scale for anxiety disorders.

Management

Menstrual irregularities

The chronic anovulation seen in PCOS is associated with an increased risk of endometrial hyperplasia and possibly endometrial cancer.

First-line therapy for menstrual dysfunction and endometrial protection is combined estrogen-progestin oral contraceptives (COCs) [52,55]. The absence of pregnancy should be confirmed before initiating COCs.

COCs benefit women with PCOS, including:

1) Daily exposure to progestin, which antagonizes the endometrial proliferative effect of estrogen.
2) Contraception, as women with oligomenorrhea ovulate intermittently and unwanted pregnancy may occur.

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3) Cutaneous benefits for hyperandrogenic manifestations.

Alternative treatments for endometrial protection are intermittent or continuous progestin therapy or a progestin-releasing intrauterine device (IUD) [63].

Medroxyprogesterone acetate (5 to 10 mg) for 10 to 14 days every one to two months. Progestin therapy alone will not reduce the symptoms of acne or hirsutism, nor will it provide contraception. However, continuous progestin therapy with norethisterone 0.35 mg daily provides contraception and endometrial protection.

Metformin is a potential alternative to restore menstrual cycles as it restores ovulatory menses in approximately 30 to 50 percent of women with PCOS [64,65]. However, Its ability to provide endometrial protection is less well established, so consider it second-line therapy [66,67].

Hirsutism

The Endocrine Society Clinical Practice Guidelines 2018 on Hirsutism suggest a COC as first-line pharmacologic therapy for most women [68]. In addition, both the Endocrine Society Clinical Practice Guidelines on the Diagnosis and Treatment of Polycystic Ovary Syndrome and international guidelines for assessing and managing PCOS [55] suggest COCs as first-line therapy for hirsutism [52]. After six months, if the patient is not satisfied with the clinical response to COC monotherapy (for hyperandrogenic symptoms), we typically add spironolactone 50 to 100 mg twice daily.

Hirsutism can also be treated by removal of hair by mechanical means such as shaving, waxing, depilatories, electrolysis, or laser treatment. In addition, eflornithine hydrochloride cream (13.9%) is a topical drug that inhibits hair growth. It is not a depilatory and must be used indefinitely to prevent regrowth [68].

Metabolic abnormalities

Obesity

Weight loss, which can restore ovulatory cycles and improve metabolic risk, is the first-line intervention for most women. The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle changes (diet and exercise) [69], followed by pharmacotherapy and, when necessary, bariatric surgery

Weight reduction

They suggest weight-loss strategies using calorie-restricted diets combined with exercise for women with PCOS and obesity. Although there are no large randomized trials of exercise-specific interventions, a systematic review of exercise therapy in PCOS concluded that there may be modest weight loss and improvements in ovulation and insulin sensitivity [70]. Even modest weight loss (5 to 10 per cent reduction in body weight) in women with PCOS may result in the restoration of regular ovulatory cycles [71-73] and improved pregnancy rates [74]in short-term studies.

Insulin resistance/type 2 diabetes

Several drugs, including biguanides(metformin) and thiazolidinediones (pioglitazone, rosiglitazone), can reduce insulin levels in women with PCOS. These drugs may also reduce ovarian androgen production (and serum-free testosterone concentrations) and restore normal menstrual cyclicity [75-78].

Dyslipidemia

The approach to the treatment of dyslipidemia in women with PCOS is the same as for other patients with dyslipidemia. Exercise and weight loss are the first-line approaches, followed by pharmacotherapy. Statin therapy decreased serum low-density lipoprotein (LDL) and triglycerides but did not affect high-density lipoprotein (HDL), fasting insulin, or C-reactive protein. A slight decrease in serum testosterone was observed, but there were no improvements in menstrual cycle regularity, ovulation, acne, hirsutism, or BMI [79].

Obstructive sleep apnea

Sleep apnea, a common disorder in women with PCOS, is an essential determinant of insulin resistance, glucose intolerance, and type 2 diabetes. Obstructive sleep apnea, treatment with continuous positive airway pressure (CPAP) improved insulin sensitivity and reduced diastolic blood pressure [80]. A similar benefit was reported in a meta-analysis of eight studies [81].

Nonalcoholic steatohepatitis

The prevalence of nonalcoholic steatohepatitis (NASH) appears to be increased in women with PCOS. Both weight loss and metformin use appear to improve metabolic and hepatic function in these women [82,83].

Depression/anxiety

There is evidence that women with PCOS have impaired quality of life and higher rates of depression and anxiety when compared with women of similar BMI without PCOS [84]. However, the efficacy and safety of antidepressant therapy has not yet been established in women with PCOS and anxiety or depression [85].

Anovulation and Infertility

Weight loss

The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle changes (diet and exercise) [69] and bariatric surgery if necessary[86].

Ovulation induction medications:

For oligo-ovulatory women with PCOS undergoing ovulation induction, letrozole is first-line therapy over

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clomiphene citrate, regardless of the patient's BMI. the drug is not approved by the US Food and Drug Administration (FDA) for this purpose, Therefore, Clomiphene citrate had been the first-line drug for this population for many years, with metformin as an alternative. However, clomiphene and metformin appear less effective for live birth rates than letrozole [87].

- **Gonadotropin therapy** is the administration of exogenous gonadotropins [88]. Women with PCOS and anovulatory infertility treated with gonadotropins are at high risk for ovarian hyper stimulation syndrome (OHSS).
- **In vitro fertilization (IVF)** If the over mentioned strategies fail, the next step is IVF, however, the risk of OHSS is high in women with PCOS undergoing controlled ovarian hyperstimulation for IVF, and metformin administration before or during IVF cycles may reduce this risk [89-91].

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