

Polycystic Ovary Syndrome (PCOS)

Prohibited Substances: clomiphene, spironolactone, letrozole

1. Introduction

PCOS is the most common endocrinopathy affecting women of reproductive age, with a prevalence of between 8% and 13% depending on the population studied and definitions used. It is characterized by reproductive, psychological, and metabolic features ¹ and impacts across the adult lifespan.

2. Diagnosis

a. Medical History

Family and personal history of PCOS diagnosis including features of cardio-metabolic disease, reproductive health and infertility, and psychological health. Assessment of lifestyle and dietary history are important as the condition is affected by insulin resistance and exacerbated by weight gain.

PCOS Symptoms

PCOS symptoms will vary both between individuals and at different life stages. These include:

- i. Irregular menstrual periods (Note that periods may be normal in the first-year post menarche as part of the normal pubertal transition):
 - > 1 to < 3 years post menarche: < 21 or > 45 days
 - > 3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year
 - > 1 year post menarche > 90 days for any one cycle
 - Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)
- ii. When irregular menstrual cycles are present, a diagnosis of PCOS should be considered and other clinical symptoms should be assessed:
 - hirsutism - face, stomach, back (terminal hairs)
 - androgenic alopecia
 - acne may be severe (comedonal acne)
 - overweight/obese
 - infertility
 - pregnancy complications

- early onset type II diabetes mellitus (DM2)
 - gestational diabetes
 - sexual dysfunction (poor body image)
 - sleep apnea
 - poor quality of life
 - depression and/or anxiety (to assess, questionnaires or Generalized Anxiety Disorder Scale ex: GAD-7 should be used)
- iii. Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including:
- a relatively mild phenotype in Caucasians
 - higher body mass index (BMI) in Caucasian women, especially in North America and Australia
 - more severe hirsutism in Middle Eastern, Hispanic, and Mediterranean, South Asian women
 - increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in Southeast Asians and Indigenous Australians
 - lower BMI and milder hirsutism in East Asians
 - higher BMI and metabolic features in Africans

b. Diagnostic Criteria

The diagnosis is based on the Rotterdam criteria for PCOS² in adult women. At least 2 of the following should be present:

1. Irregular cycles with oligo/anovulation
2. Biochemical hyperandrogenism or clinical hyperandrogenism (hirsutism and moderate to severe acne)
3. Polycystic ovarian morphology on pelvic ultrasound

It must be noted that up to 8 years post menarche, ultrasound is not valuable in diagnosis as it is non-specific for PCOS in this age group. Cycle abnormalities and hyperandrogenism are both required for diagnosis in adolescents.

Athletes

Other causes should be excluded: hyperprolactinemia, thyroid disease, congenital adrenal hyperplasia, Cushing's syndrome and, particularly in athletes, hypothalamic amenorrhea.

Athletes are prone to exercise- or weight-induced hypothalamic amenorrhea secondary to pituitary dysfunction as indicated by lower levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol (E2). Furthermore, late onset of congenital adrenal

hyperplasia could be excluded by measurement of 17-hydroxyprogesterone in follicular phase of the menstrual cycle.

These need to be excluded before making the diagnosis of PCOS, however diagnosis can be challenging and is based on history, examination, sex hormone-binding globulin (SHBG) (usually low in PCOS) and androgen status.

c. Physical examination

A general examination should be performed including:

- Assessment of hair growth distribution and quantity using a scoring system such as the Modified Ferriman–Gallwey Score and include physical examination of the jaw line for the presence of terminal hairs (cosmetic reduction of excess hair may be used).
- Blood pressure, height, waist circumference and weight.
- A pelvic examination may be useful if gynecological symptoms are significant.
- Assessment and history of psychological features is very important.

d. Laboratory Testing

Laboratory testing for PCOS should be performed and may include:

- Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.
- Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS.
- Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy, and precision.
- Note: Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on SHBG and altered gonadotrophin-dependent androgen production.
- Thyroid-stimulating hormone (TSH), prolactin, FSH, LH
- Glycemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors
- An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycemic status. In high-risk women with PCOS (including a BMI > 25kg/m² or in Asians > 23kg/m², history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended.
- An OGTT is also recommended pre-pregnancy and pre-fertility treatment, and at 25-28 weeks gestation given high risks of hyperglycemia and high risks in pregnancy and treatment.

- Lipid profile: baseline, if BMI > 25
- The current knowledge does not support use of anti-müllerian hormone (AMH) as a single test for diagnosis of PCOS

e. Imaging

The transvaginal ultrasound approach is preferred to an abdominal ultrasound in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed. It measures endometrial thickness, ovarian volume, antral follicle count and distribution of follicles within the ovary.

In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype. In addition, ultrasound should not be used for the diagnosis of PCOS in those with a gynecological age of < 8 years (< 8 years after menarche), due to the high background incidence of multi-follicular ovaries in this life stage.

f. Summary

In accordance with the International Standard for Therapeutic Use Exemptions and consistent with current good medical practice, the medical file required to support an application for a TUE in the case of an athlete with PCOS should include the following details:

- *a complete medical history as described and clinical examination*
- *list of necessary laboratory findings*
- *Imaging e.g., ultrasound if indicated*

3. Treatment

The treatment for PCOS in athletes should follow the same medical practice as for the individual who is not an athlete

Once diagnosed, reproductive, metabolic, and psychological features should be assessed and managed. The treatment should address the individual range of symptoms and risk factors ranging from obesity and infertility to excessive hair growth or anxiety.

Education, self-empowerment, multidisciplinary care and lifestyle intervention for prevention or management of excess weight are important.

- Depressive and anxiety symptoms should be screened, assessed, and managed with the need for awareness of other impacts on emotional wellbeing. Referral to appropriate health professionals is recommended.
- Combined oral contraceptive pills (COCP) are first-line pharmacological management for

menstrual irregularity and hyperandrogenism, with no specific recommended preparations and general preference for lower dose preparations.

- In the case of excess hair growth, the COCP and cosmetic options are first line and can take up to 12 months to work. Then anti-androgens such as cyproterone acetate, spironolactone or rarely, 5-alpha reductase inhibitors such as flutamide, may be used in combination with contraception. Cosmetic options include laser hair removal, depilatory creams, threading, plucking, waxing and electrolysis.
- In the case of amenorrhea or irregular cycles, the oral contraceptive pill or intermittent progestins may be used.
- Metformin is recommended in alone or in addition to other therapies, primarily for metabolic features.
- Letrozole is first-line pharmacological infertility therapy in the case of anovulation for induction to improve fertility outcomes. Clomiphene citrate and metformin could also be used as pharmacological therapy, although both are less effective than letrozole.
- Gonadotrophins or laparoscopic surgery are second line and in- vitro fertilization is third line in isolated PCOS.
- In the case of impaired glucose tolerance or in [diabetes mellitus](#), metformin, other oral hypoglycemic agents or insulin may be used.
- Lifestyle changes including a balanced diet, regular physical activity for prevention of excess weight gain, and a weight loss (if needed) of 5-10% of total body weight is recommended.

a. Name of Prohibited Substances

Letrozole

2.5 to 5 mg orally once daily for 5 days per cycle for infertility, sometimes in doses up to 10mg

Clomiphene citrate

50 to 150 mg orally daily for 5 days per cycle for infertility

Spironolactone

50 to 200 mg orally daily continuously for hyperandrogenism

Note that there may be geographical specific medical practices based on cost and availability of medications.

4. Non-prohibited alternative treatments

Metformin has not been proven to be as effective as clomiphene or letrozole as a first line treatment for infertility. However, in some cases, metformin can be used as a simple low cost treatment and it may be added to clomiphene or letrozole.

Cyproterone acetate (indicated as third line treatment and not recommended in all countries): 25 to 50 mg orally daily or for 10 days per month for hyperandrogenism

5. Consequences to health if treatment is withheld

- PCOS is one of the most common cause of [infertility](#) and if untreated this can be compounded by age related infertility
- Untreated hyperandrogenism can impact self-esteem, body image and mood
- Untreated oligomenorrhea, amenorrhea increases endometrial cancer risk
- It is vital that women with PCOS are monitored for the onset of a metabolic sequelae including diabetes mellitus, obesity, and cardiovascular risk factors.
- Monitoring of mental health in women with PCOS is important with higher prevalence of depression, anxiety, suicidal ideation, eating disorders and disordered eating
- Additional risks; sexual dysfunction, sleep apnea and reduced quality of life.

If treatment is withheld reproductive, metabolic, and psychological features may be left untreated with physical and psychological consequences.

6. Treatment monitoring

Standard medical and PCOS features, ongoing metabolic screening for BMI, diabetes, blood pressure and lipid profiles (the latter if overweight), treatment monitoring.

7. TUE duration

A TUE can be granted for letrozole or clomiphene if the PCOS and infertility diagnosis is adequately established. The recommended duration of a TUE should be 12 months with an annual review by a physician experienced in PCOS and infertility if the TUE needs to be extended

A TUE can also be granted for spironolactone if PCOS diagnosis with moderate to severe hyperandrogenism is adequately established. The recommended duration of a TUE should be 2 years with an annual review by a physician experienced in PCOS.

8. Appropriate cautionary matters

Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production.

References

1. Teede H, Misso M, Costello M, Dokras A, Laven J, Moran L, et al. International evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome (PCOS). Melbourne: Monash University; 2018.
2. Group REA-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(01):19-25.