



Diagnosis and Management of Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the common endocrine disorder seen in reproductive age group women. Latest consensus has been developed by 37 societies including ESHRE and ASRM with the objective to improve the management of women with PCOS worldwide.

They have endorsed the Rotterdam PCOS diagnostic criteria for adults. Whereas in adolescents both hyperandrogenism and ovulatory dysfunction are mandatory, but ultrasound not recommended. In adults ultrasound criteria are tightened with advancing technology. Education, self-empowerment, multidisciplinary care, and lifestyle intervention are important for prevention and management of overweight. Low dose combined oral contraceptive pills have been suggested as the first-line pharmacological management for menstrual irregularity and hyperandrogenism. For metabolic features metformin is recommended in addition or alone. Letrozole is the recommended first-line drug for infertility therapy; with clomiphene and metformin having a role alone or in combination. Gonadotrophins can be used as second line ovulation induction agents. *In vitro* fertilization can be offered as third-line treatment modality when other ovulation induction therapies have failed.

Key words: Gynaecology, Polycystic ovarian disease, Endocrinology, Lifestyle disease

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the significant health issues in women affecting their reproductive, metabolic, and psychological health. It is the most common endocrinopathy affecting 8–13% of women in reproductive age group^[1] and presentation varies by ethnicity.^[2] PCOS can have a wide variety of clinical features such as adult reproductive health issues (hirsutism, infertility, irregular menstrual cycles, and pregnancy complications),^[3] metabolic (insulin resistance, metabolic syndrome such as type 2 diabetes mellitus and cardiovascular diseases),^[4] and mental health issues (anxiety, depression, and body image).^[5]

Diagnosis of PCOS had remained controversial and assessment and management were inconsistent as the previous guidelines

lacked evidence-based protocols. In this context, international evidence based guideline was released on July 19, 2018, for the assessment and management of PCOS, addressing psychological, metabolic, and reproductive components of PCOS, promoting consistent evidence based care.

Governance

The governance was formed by six continent international advisory board, five guideline development groups, and consumer and translation committees. In total, 37 societies and organizations covering 71 countries engaged in developing the guideline. The Australian Centre for Research Excellence in PCOS, funded by NHMRC, led the guideline development. They partnered with ESHRE and ASRM in this endeavor. Thirty-five other societies partnered including the PCOS Society of India.

Guideline recommendations

Recommendations and practice points cover the following:

- Diagnosis, screening, and risk assessment depending on the life stage
- Lifestyle modification

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Received: 12-03-2021

Accepted: 27-03-2021

DOI: 10.15713/ins.jgog.7

- Pharmacological management for non-fertility issues
- Assessment and management of infertility
- Mental Health.

SUMMARY OF CLINICAL CHANGES IN THE RECOMMENDATIONS^[6]

Diagnosis, screening, and risk assessment depending on the life stage

Endorsement of the Rotterdam PCOS diagnostic criteria in adults

Rotterdam diagnostic criteria – requires two of the three:

1. Oligo/ anovulation
2. Biochemical and/or clinical signs of hyperandrogenism
3. Ultrasound suggestive of polycystic ovaries.

And exclusion of other etiologies of the above features (such as thyroid disorders, hyperprolactinemia, non-classical congenital adrenal hyperplasia, Cushing's syndrome, and adrenal tumors)

- In adolescents and those within 8 years of menarche, both ovulatory dysfunction and hyperandrogenism are mandatory, with ultrasound not recommended (as it overlaps with the normal physiology around puberty). If only ovulatory dysfunction or hyperandrogenism is present then consider them as "at risk" of PCOS and reassess later
- We have to make a note here that these changes have been made not to over diagnose PCOS in adolescents and to treat them unnecessarily
- In adults where irregular cycles and hyperandrogenism features are present – ultrasound not necessary for diagnosis.

Irregular cycles are more clearly defined based on gynecological age

Irregular menstrual cycles are defined as:

- 1st year post menarche, irregular cycles are normal as part of pubertal transition
- 1–3 years after menarche: menstrual cycle of <21 days or more than 45 days
- 3 years post menarche to perimenopause: <21 days or More than 35 days or <8 cycles per year
- 1 year post menarche: More than 90 days for any one cycle
- Primary amenorrhea by age 15 or more than 3 years post the larche (breast development).

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.

Biochemical hyperandrogenism

Androgens to be measured in diagnosis of biochemical hyperandrogenism are specified along with optimal assays.

- Calculated free testosterone, free androgen index, or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS
- Accurate measurement of total or free testosterone should be done by High-quality assays such as liquid chromatography-mass spectrometry and extraction/ chromatography immunoassays

- If total or free testosterone levels are not elevated, measurement of Androstenedione and dehydroepiandrosterone can be done though their use is limited
- In women on hormonal contraceptive pills, these measurements must be done after 3 months of withdrawal of the drug.

Clinical hyperandrogenism

- A detailed history and physical examination should be done to identify clinical hyperandrogenism, including acne, alopecia and hirsutism
- Health professionals must be aware that clinical hyperandrogenism usually results in potential negative psychosocial impact on women
- Any unwanted excess hair growth and/or alopecia should be given importance, regardless of clinical severity
- Standardized visual scores for assessing hirsutism (Modified Ferriman Gallwey score) and alopecia (The Ludwig visual score) are preferred.

Ultrasound criteria are tightened with advancing technology, age specific cutoff, and follicle number per ovary (FNPO) number modified

- Diagnosis by ultrasound in patients within 8 years of menarche may yield false positive results as there is high incidence of multi-follicle ovaries in this age group
- For transvaginal ultrasound, transducers with a frequency bandwidth of 8 MHz should be used
- The threshold for polycystic ovarian morphology (PCOM) on either ovary, a FNPO of ≥ 20 (in the previous guidelines PCOM – FNPO ≥ 12) and/or an ovarian volume ≥ 10 ml on either ovary, confirming that no corpus luteum, cysts, or dominant follicles are present.

Anti-Müllerian hormone (AMH) – not yet recommended as sole diagnostic criteria

- At present AMH levels should not be used as a test to diagnose
- PCOS
- AMH in future may become more accurate in the detection of PCOM as there are emerging evidence with standardization of assays and specific cutoff levels for population of different ages and ethnicities on large scale.

Cardiovascular disease risk

- All women with PCOS should be assessed for cardiovascular risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, and lack of physical activity
- Weight, height, and ideally waist circumference should be measured and body mass index (BMI) must be calculated
- Regardless of age and overweight, and obese women should have fasting lipid profile monitoring
- Blood pressure must be measured annually.

Gestational diabetes, impaired glucose tolerance, and type 2 diabetes

- PCOS women are at five-fold increased risk for these complications

- Glycemic status should be assessed in all women with PCOS. An oral glucose tolerance test (OGTT), fasting plasma glucose, or HbA1c should be done once for all suspects
- In women with BMI >25kg/m² or >23 kg/m² (In Asians) or history of impaired fasting glucose or gestational diabetes or family history of Diabetes Mellitus (II) or hypertension, OGTT is recommended.

Endometrial cancer

Women with PCOS are at 2–6 times increased risk of developing endometrial carcinoma, which generally presents before menopause; though absolute risk of endometrial carcinoma is relatively low.

Emotional well-being

- Health practitioners should give importance for women's emotional wellbeing and address it with proper care and timely management helps women in improving their quality of life
- Women should be routinely screened for anxiety, depressive symptoms, psychosexual health, and impact on body image at diagnosis
- Health professionals and women should be aware of the increased prevalence of eating disorders associated with PCOS.

Healthy lifestyle

Lifestyle modification

- Multicomponent approach including diet, exercise, and behavioral strategies are recommended
- Achievable goals such as 5–10% weight loss in 6 months in those with excess weight yields significant clinical improvements
- Specific Measurable, Achievable, Realistic, and Timely (SMART) goal setting and self-monitoring enables in achieving realistic lifestyle goals.

Dietary interventions

- A variety of balanced diet is recommended
- To achieve weight loss in over-weight/obese women, an energy deficit of 30% or 500–750 kcal/day (1200 to 1500 kcal/day) to be prescribed.

Exercise interventions: Encourage women with PCOS to avoid weight gain and maintain healthy lifestyle

- In adults from 18 years to 64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days every week
- In adolescents, at least 60 min/day of moderate to vigorous intensity physical activity including muscle and bone strengthening for thrice a week
- Activity be performed in at least 10-min bouts/around 1000 steps, thus to achieve physical activity for at least 30 min daily.

Pharmacological treatment for non-fertility indications

- Combined oral contraceptive pills (COCP) should be recommended to manage hyperandrogenism and/or irregular menstrual cycles
- When prescribing COCP's in adults and adolescents with PCOS:
 - For treatment of hirsutism, various COCP preparations have similar efficacy
 - The choice of COCP should be done balancing efficacy, side effects, metabolic risks, cost, and availability. Consideration of lowest effective estrogen doses (20–30 mgs of ethinyl estradiol or equivalent)
 - Due to adverse effects including venous thromboembolism, combination of 35 mg ethinyl estradiol and cyproterone acetate should not be considered first-line treatment.
- Metformin should be considered if COCP and lifestyle changes alone are not successful
- Antiandrogens should only be used if treatment with oral contraceptive and cosmetic therapy is not effective after being used for 6 months
- Inositol needs further research and more evidence and treatment with it should be considered experimental.

Assessment and treatment of infertility

Ovulation induction principles

- Treatment of choice or drug for first line for induction of ovulation should be letrozole
- If the woman is having only PCOS and no other infertility factor, Clomiphene can be considered
- Metformin alone or in combination can be used for ovulation induction after proper patient counseling regarding its dose and side effects
- If first line therapy for ovulation induction in women with PCOS is failed, gonadotropin can be used as a second line therapy
- The following should be considered before prescribing gonadotropin:
 - Cost and availability
 - Expertise required for use in ovulation induction
 - Low dose gonadotrophin protocols optimize mono-follicular development
 - There may be lack of efficacy of different gonadotropin preparations
 - Risk and implications of potential multiple pregnancy
 - Degree of intensive ultrasound monitoring required
- Prolonged use of ovulation induction agents should be avoided because of poor success rates.

Laparoscopic ovarian surgery

In patients are clomiphene citrate with anovulatory cycles and no other cause of infertility, laparoscopic ovarian surgery can be considered a second-line therapy.

- Following considerations should be kept in mind before surgery:
 - Cost of procedure
 - Associated risk of decrease in ovarian reserve or loss of ovarian function
 - Expertise required for use in ovulation induction
 - In overweight and obese women, intraoperative and post-operative risks are higher
 - Risk of adhesion formation and further decrease in fertility.

In vitro fertilization (IVF)

If first- and second-line therapies for ovulation induction have failed, IVF should be offered as third line therapy even in absence of an absolute indication for IVF ± ICSI.

SUMMARY

1. Endorsement of the Rotterdam PCOS diagnostic criteria for diagnosis of PCOS
2. Where irregular cycles and hyperandrogenism are present, ultrasound not necessary in diagnosis
3. In adolescents and those within 8 years of menarche, both ovulatory dysfunction and hyperandrogenism are required, but ultrasound not recommended, as it overlaps with the normal physiology around puberty
4. The definition of irregular cycles more clearly defines based on gynecological age
5. Ultrasound criteria are tightened with advancing technology – TVS recommended with FNPO ≥ 20 and/or ovarian volume ≥ 10 ml in either ovary
6. CVS disease risk and glycemic status must be assessed
7. Lifestyle modification, exercise, and weight reduction must be encouraged
8. COCP is considered for adults and adolescents for treating irregular cycles and hyperandrogenism
9. Metformin should be considered if COCP and lifestyle changes alone are not successful

10. Antiandrogens should only be used in treatment of hirsutism if 6 months or more of COCP and cosmetic therapy have not been successful
11. Letrozole considered as the first-line pharmacologic agent for ovulation induction in women with PCOS
12. Gonadotropins and LOD are second line of treatment. IVF – third line of treatment.

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How to cite this article: Louis TF, Chavan N, Aparna N, Shikhanshi. Diagnosis and Management of Polycystic Ovary Syndrome. *J Glob Obstet Gynecol* 2021;1(1):33-36.

Source of support: Nil, **Conflict of Interest:** Nil.

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