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Key Inforbits

- What is PCOS?
- Clinical Presentation
- Diagnosing PCOS
- PCOS Treatment and Management
- Current Investigations and Future Research

What is PCOS?

Polycystic ovary syndrome (PCOS) is a multi-system disorder that causes metabolic, endocrine, and reproductive dysfunction. The global incidence rate of PCOS is approximately 5% to 10% of women,[1] but the etiology of PCOS is still unclear.[2] PCOS is known as the leading cause of infertility, but PCOS can also affect patients' long-term health and quality of life, such as increasing the risk of obesity, cardiovascular disease, diabetes, endometrial cancer, depression, and anxiety.[3] Even though PCOS affects millions of women around the world and there are serious and life-threatening health risks associated with PCOS, this disorder is unrecognized by many physicians and patients, and it is estimated that about 50% of women living with PCOS are undiagnosed.[4]

Clinical Presentation of PCOS	• **Menstrual dysfunction**: Patients may present with amenorrhea or oligomenorrhea (fewer than 6-8 menstrual periods a year). Laboratory findings may include increased levels of luteinizing hormone (LH) or low to normal levels of follicle stimulating hormone (FSH).[5] • **Hyperandrogenism**: Women with clinical hyperandrogenism may present with hirsutism, acne, or hair loss. Biochemical evidence of hyperandrogenism may include increased levels of total testosterone and dehydroepiandrosterone (DHEA).[6] • **Polycystic ovaries**: A "string of pearls" (the cysts) may be

seen on a transvaginal ultrasound in the majority of women with irregular menstrual cycles and hyperandrogenism.[7]

- **Metabolism/Cardiovascular Effects**: Unfortunately, it is estimated that 40-85% of women with PCOS are overweight or obese compared to women without PCOS.[8] Additionally, women with PCOS are at an increased risk for type 2 diabetes, coronary heart disease, dyslipidemia, and nonalcoholic fatty liver disease.[9] Insulin resistance is also present in women with PCOS, affecting approximately 30% of lean women with PCOS and 70% of obese women with PCOS.[8]
- **Mood Disorders**: There is evidence that women with PCOS may be more likely to suffer from mood disorders, such as depression and anxiety.[10]

Diagnosing PCOS

There are 3 different organizations that provide diagnostic criteria for PCOS.

(1) National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD) diagnostic criteria of 1992[11]
(2) European Society for Reproductive Medicine (ESHE/ASRM) Rotterdam criteria of 2004[12]
(3) Androgen Excess and PCOS Society in 2006[13]

The Rotterdam criteria is most used for diagnosing PCOS, and it requires at least two out of three clinical signs to be present:[12]

- Polycystic ovaries present on ultrasound
- High androgen levels and/or clinical hyperandrogenism
- Menstrual irregularity

Unfortunately, approximately 50% of women with PCOS remain undiagnosed.[14] A cross-sectional study found that about half of women with PCOS saw three or more healthcare professionals prior to being diagnosed, and it took, on average, over 2 years before a diagnosis was made.[15]

PCOS Treatment and Management:

Due to the lifelong and life-threatening risks and comorbidities associated with PCOS, it is important to provide early diagnosis and treatment interventions for improved quality of life. However, multiple studies have shown that women with PCOS have been unhappy and unsatisfied with their healthcare experiences regarding PCOS.[15] Therefore, it is important to use shared-decision making when creating a treatment plan for patients with PCOS. The following interventions are some recommendations for treatment in women with PCOS (Teede 2018):[7]

Lifestyle Interventions for PCOS		
Smoking cessation is an important intervention to help reduce the risk of cardiovascular disease.[16]	Several studies have shown that overweight and obese women should reduce their weight by 5-10% to help re-establish regular menstruation and ovulation.[17] Weight loss interventions may include a minimum of 250 minutes/week of moderate intensity exercises or 150 minutes/week of vigorous intensity exercises and muscle strengthening activities.[7]	Behavioral strategies, such as goal-setting, and cognitive behavioral therapy (CBT) should be included to reinforce changes for a healthy lifestyle and emotional well-being.[7]
Pharmacological Interventions for PCOS		
Combined oral contraceptives (COCs) should be recommended in women with PCOS to help manage hyperandrogenism symptoms and/or irregular menstruation.[7]	Metformin should be used for the treatment of insulin resistance and/or type 2 diabetes in women with PCOS.[18]	Antiandrogens (i.e., finasteride, spironolactone) may be used in combination with COCs to treat hirsutism and/or androgen-related alopecia in women with PCOS.[7]
Several studies have shown that metformin ± clomiphene may increase ovulatory cycles in women with PCOS,[19] but this has not been shown to increase live birth rate.[20] However, clomiphene is considered first-line therapy for ovulation induction in women with PCOS experiencing infertility.[19]	Letrozole, an aromatase inhibitor, may be used as a second-line therapy in women with PCOS suffering from infertility. Unlike clomiphene, letrozole reduces the risk of multiple follicle development and does not affect estrogen receptors located in the endometrium.[21]	Many studies have found that inositol (specifically myo-inositol) may increase the rate of ovulation, regulate menstrual cycles,[22] and improve in-vitro fertilization (IVF) outcomes for patients with PCOS.[23]

Current Investigations and Future Research:

Current studies have observed the effects of glucose-lowering agents, such as glucagon-like peptide-1 receptor analogs/agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) and their effects on insulin resistance, obesity, and cardiovascular disease in women with PCOS.[24-26]

GLP-1 RAs	SGLT-2 Inhibitors
• Studies have shown that treatment with GLP-1 RAs in obese women with PCOS reduce body weight, regulate menstruation, and improve symptoms and clinical lab values of hyperandrogenism more effectively than metformin. [26-28] Additionally, a recent study showed that GLP-1 RAs result in significant reductions in liver fat and non-alcoholic fatty liver disease (NALFD), visceral adipose tissue, triglycerides, and total cholesterol. [28] • Liraglutide and exenatide have shown to be more effective in reducing body weight and BMI in women with PCOS compared to metformin. [29,30] • Liraglutide and exenatide in combination with metformin has shown to improve pregnancy outcomes in women with PCOS.[31,32] • A recent study compared the effects of once-weekly exenatide, dapagliflozin, exenatide + dapagliflozin, dapagliflozin + metformin, and phentermine + topiramate in non-diabetic, obese women with PCOS. Exenatide + dapagliflozin resulted in the highest amount of weight loss. It was found that dual therapy with exenatide + dapagliflozin was superior to dapagliflozin + metformin, exenatide monotherapy, dapagliflozin monotherapy, and phentermine + topiramate in regards to metabolic and clinical benefits. [33]	• SGLT-2 inhibitors could be beneficial for patients with PCOS due to their impact on glycemic control and cardioprotective properties. [34] • A randomized controlled trial (RCT) studies the effects of empagliflozin 25 mg versus metformin 1500 mg in women with PCOS, and it was found that women with PCOS treated with empagliflozin had a more beneficial impact in regard to weight, BMI, waist circumference, and total body fat compared to metformin. Empagliflozin, therefore, has shown to improve body composition in patients with PCOS, but it has shown no effect on insulin resistance or androgen levels compared to metformin. [35] • A new study found that dapagliflozin 10 mg in women with metabolic syndrome showed decreases in body weight, BMI, fasting glucose, and uric acid. [36]

ONGOING RESEARCH: Licogliflozin (LIK066) is a dual SGLT-1 and SGLT-2 inhibitor that is currently being studied in clinical trials. It has shown promising results in reducing postprandial glucose and weight in patients with and without diabetes who are obese.[37] In women with PCOS, licogliflozin showed a statistically significant reduction in A4 (androstenedione) and DHEAS (dehydroepiandrosterone sulfate) levels after 2 weeks of treatment compared to placebo in addition to reductions in insulin levels and fasting and postprandial glucose levels.[38]

A4 is an androgen steroid hormone that is responsible for the synthesis of testosterone. Additionally, DHEAS is a steroid hormone that is produced by the adrenal cortex that is responsible for production of estrogen and testosterone as well as affecting insulin sensitivity.

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The last "dose" …

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-William Osler [Canadian Physician, 1849-1918]

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