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**Objectives**

1. Identify symptoms and clinical signs concerning for PCOS.
2. Develop a differential and initial evaluation for patients presenting with symptoms concerning for PCOS.
3. Identify gynecologic and non-gynecologic co-morbidities commonly associated with PCOS.

**Teaching Instructions**

Plan to spend at least 30-60 minutes preparing for this talk. Read through the Facilitator Guide/Teaching instructions and familiarize yourself with the Interactive Board. All clickable elements are denoted with a shaded, rounded rectangle and/or mouse cursor icon.

This talk can be presented in two ways:

1. Project the “Interactive Board for Presentation” OR
2. Reproduce a drawing of the presentation on a whiteboard (use learner guide for whiteboard organization)

With either method, print out copies of the Learner’s Handout so they may follow along during the presentation and take notes as you expand on the decision tree and apply it through the practice cases. Begin with reviewing the objectives for the session.

The anticipated time to give this talk is 20 min without cases and 30 min with cases.

**Objective 1: Identify symptoms and clinical signs concerning for PCOS. *(Diagnosis)***

Polycystic ovary syndrome (PCOS) is an endocrine disorder affecting 8-13% of women (people with ovaries) of reproductive age.1 Its primary clinical features are hyperandrogenism and menstrual dysfunction, though it can be associated with several metabolic, cardiovascular, and psychiatric conditions. However, many other conditions present with similar clinical signs and symptoms, making PCOS a diagnosis of exclusion.

Although there are multiple scoring systems, the most used diagnostic criterion currently is the Rotterdam criteria. A patient must meet 2 of the 3 criteria to be diagnosed with PCOS. Exclusion of other clinical diagnoses that can present with similar features/phenotype is required to confirm the diagnosis.

*Ask your learners to list 3 Rotterdam criteria. Click on "Rotterdam criteria" to reveal the different criteria. Then click on each of the criteria to reveal more information.*

1. Hyperandrogenism – via lab testing or clinical signs.
	* Clinical signs of hyperandrogenism include acne, male-patterned hair loss (androgenic alopecia), and hirsutism. Hirsutism is defined as excessive growth of pigmented, coarse hair in a pattern consistent with androgen sensitivity - around the upper lip, chest, chin, buttocks, linea alba, inner aspect of thighs, or lower back. Semi-quantitative measures of hirsutism such as the Ferriman-Gallwey score can be used to clinically follow patients with hirsutism. Acne and alopecia in isolation are unreliable signs of hyperandrogenism.1,2
	* While most patients with clinical features of hyperandrogenism will also have elevated levels of androgens on lab testing, serum analysis fails to detect biochemical hyperandrogenism in 20-40% of patients.3
	* Signs of severe androgen excess, like voice deepening or clitoromegaly, are far less common in PCOS and should increase suspicion for alternate etiology of symptoms, like an androgen secreting tumor.2-4
2. Menstrual irregularities – chronic anovulation
	* A normal menstrual cycle is 21 to 35 days long. Often, women with PCOS have cycles which are unpredictable and longer than a standard menstrual cycle. Oligomenorrhea is defined by the presence of <8 menstrual cycles per year or cycle length > 35 days. Amenorrhea is defined by lack of menstruation for 3 months.1,3,4
	* Menstrual irregularities usually begin prepubertally. For 2-3 years following menarche, irregular cycles can be normal. After this time, irregular periods warrant further evaluation.1,2,4
	* Dysfunctional uterine bleeding can occur because of unopposed estrogen effect, so the presence of regular cycles does not necessarily exclude chronic anovulation.3
3. Polycystic ovaries – seen on pelvic ultrasound.
	* There are two different ways to define polycystic ovaries – volume and number of cysts. Polycystic ovaries are ovaries that have more than 12 follicles and/or have a volume > 10 ccs.1-4
	* It is important to remember that multiple follicles can be seen in the ovaries of normally cycling patients (especially in adolescence and early adulthood), so this finding in isolation is non-specific.1

**Objective 2:** **Develop a differential and initial evaluation for** **patients presenting with symptoms concerning for PCOS.** ***(Differential and Evaluation)***

PCOS is a diagnosis of exclusion. It is essential to exclude secondary causes of hyperandrogenism and menstrual irregularities in your workup for PCOS.

Ask your learners – what are other causes of hyperandrogenism, menstrual irregularities and polycystic ovaries? Click on each of these buttons to reveal the answer. Emphasize the most common causes, which are highlighted in larger and bolded text. Then click on the “Evaluation” buttons to reveal initial diagnostic work-up. Emphasize the diagnostic evaluation that should be completed in all patients, which are highlighted in larger and bolded text. Other diagnostic evaluation should be considered based on the clinical picture.

1. Hyperandrogenism –
	* *Differential:* Other causes of hyperandrogenism include congenital adrenal hyperplasia (CAH), acromegaly, androgen secreting tumors, and Cushing’s syndrome.
	* *Evaluation:* If physical signs of hyperandrogenism are subtle or difficult to determine, additional lab evaluation can be ordered.
		+ - The single best test is to get a **total testosterone**. Free testosterone measurements can be inaccurate or unreliable. Free serum testosterone can be calculated by free androgen index (FAI). FAI is the ratio between the total testosterone and the sex hormone binding globulin (SHBG), which is another measure of hyperandrogenemia.1,3
			- Consider a **17-hydroxyprogesterone level** to rule out 21-hydroxylase deficiency, a type of non-classic CAH, in women with hyperandrogenism. Nonclassic CAH is more commonly seen in women of Ashkenazi Jewish, Italian, or Slavic descent.2,6
			- Consider DHEAS if there is concern for androgen-secreting tumor (adrenal or ovarian) in the case of very high testosterone levels or rapid virilization.2,4,6
			- Consider midnight salivary cortisol to evaluate for Cushing’s (in the case of other physical findings such as striae, hypertension, proximal myopathy).
			- Cushing’s and androgen-secreting tumors are rare and should be considered only if there is clinical concern.2,3,6
2. Menstrual irregularities – There is a broad differential for menstrual irregularities.
	* All patients with oligomenorrhea or amenorrhea should be ruled out for pregnancy and hypothalamic or pituitary diseases that might cause hyperprolactinemia (prolactinoma, thyroid disorders). Initial laboratory testing should include **TSH** ± **free T4**, **β-HCG**, **prolactin levels**. Clinical history should rule out functional hypothalamic amenorrhea caused by extreme exercise or an eating disorder.
	* Structural abnormalities such as polyps, adenomyosis, leiomyoma, malignancy, endometrial hyperplasia can be associated with menstrual irregularities. A pelvic ultrasound could be considered for evaluation of structural abnormalities.2,3
	* LH and FSH can be considered in patients where there is concern for hypothalamic dysfunction or premature ovarian insufficiency or early menopause. PCOS is associated with an increased LH/FSH ratio but because LH secretion is pulsatile, absence of an increased ratio does not rule out diagnosis.3
3. Polycystic ovaries – can be seen in normal ovulatory cycle. Some studies have estimated that more than 50% of women meet follicle number per ovary criteria. Similar appearance of polycystic ovaries has also been seen in female-to-male trans-people after testosterone therapy.3

**Objective 3: Identify gynecologic and non-gynecologic co-morbidities commonly associated with PCOS. *(Complications)***

There are many co-morbidities associated with PCOS. We will review them in two categories –non-gynecologic and gynecologic co-morbidities. *Depending on your audience, you may tailor the content covered about each individual risk factors.*

**Non-Gynecologic:** *Ask your learners to list what broad categories of non-gynecologic comorbidities associated with PCOS.**Click to reveal different organ systems that are affected (brain, hair, cardiac, and pancreas). Click on each of these organ system icons to reveal additional information about the risk factors. Click on “Management” buttons to reveal management and screening options.*

* Mood disorders (Brain): PCOS is independently associated with multiple psychiatric conditions including depression, anxiety, and eating disorders, especially binge eating disorder.2 Even when controlling for weight, hirsutism, and infertility, PCOS still confers an increased risk of a concurrent mood disorder.
	+ *Management*: Patients should be screened normally with a PHQ9 and a GAD7. All patients with PCOS should also be asked about disordered eating habits, then referred accordingly.
* Hyperandrogenism (Chin hairs):
	+ *Management:* Treatment of hyperandrogenism requires controlling levels of circulating androgens. Treatment of choice for hirsutism is combined oral contraceptive pills (OCPs) and/or spironolactone.2
		- *OCPs:* Although no oral contraceptive pill is FDA approved specifically to treat hirsutism, they work by lowering androgens via suppression of ovarian androgen production and increasing sex hormone binding globulin (SHBG). They are first line for treatment of hyperandrogenism. Combination pills include ethinyl estradiol and a progestin. Third and fourth generation progestins (e.g., norgestimate, desogestrel, and drospirenone) are less androgenic and have fewer metabolic side effects. However, these benefits need to be weighed against a potential increase in risk of venous thromboembolism especially in patients with other risk factors for thromboembolism.2,4
		- *Anti-androgens:* There may be an additional benefit when OCPs are prescribed with anti-androgens. Spironolactone is the most used anti-androgen and works by binding the androgen receptor, inhibiting ovarian and adrenal steroid creation, competing for androgen receptors in hair follicles, and inhibiting 5α reductase activity, decreasing terminal hair growth. It is typically started at 50 mg daily but can be titrated up to 100 mg BID. All anti-androgens are teratogenic, so women on these medications should be using another form of contraception.2
		- *Cosmetic:* Another treatment option is cosmetic, like laser hair removal.
* Cardiovascular (CV) risk (Heart): PCOS is associated with lower HDL and higher LDL levels compared to BMI and age matched controls. However, the cardiovascular implications of this is not clear.5 There are conflicting studies about whether PCOS is associated with increased CV events and mortality.5 There is some evidence that increasing degree of oligomenorrhea is associated with both non-fatal and fatal CV events.
	+ *Management:* Screen all patients with PCOS for hypertension and with a fasting lipid panel to assess cardiovascular risk. Statins should be started based on calculated cardiovascular risk.7
* Insulin resistance (*Pancreas*): Insulin resistance is thought to play a critical role in the pathogenesis of PCOS. Insulin resistance is present regardless of weight compared to age-matched controls. This is thought to be in addition and unrelated to the elevated androgen levels.5 Patients with PCOS are at a far higher risk of having or developing type 2 DM (T2DM). Patients with PCOS have a 7.5-10x higher prevalence of undiagnosed type 2 diabetes compared to women of similar age.2 Other studies show a 5-15% risk of progression to T2DM within 3 years in patients with normal glucose tolerance.5
	+ *Management*: To test for insulin resistance, obtain a 2 h oral glucose tolerance test (or fasting blood glucose or HgbA1c). Because of the high risk of progression to T2DM, patients should be screened at least every 1-2 years.5
		- The primary treatment is lifestyle modifications (diet and exercise) should also be recommended to patients with impaired glucose tolerance. Even 5 to 10% weight loss can reduce metabolic risk factors.2.5
		- In patients with demonstrated impaired glucose tolerance, starting an insulin sensitizer like metformin can help with glucose tolerance and decrease risk of conversion to T2DM. Metformin can also improve symptoms of hyperandrogenism, menstrual irregularity, and fertility.5,7
* Other metabolic complications associated with PCOS include obstructive sleep apnea and non-alcoholic fatty liver disease.2

**Gynecologic:**

* Endometrial hyperplasia: Women with PCOS have a 3x higher risk of endometrial cancer due to chronic anovulation, which leads to lack of endometrial shedding. This chronic estrogen stimulation can lead to endometrial carcinoma. Other risk factors for endometrial hyperplasia/cancer include hyperinsulinemia, hyperandrogenism, and obesity.
	+ *Management:* Treatment is any agent that decrease endometrial stimulation and promotes regular endometrial turnover. Options include OCPs, progestin IUDs, or cyclic progesterone usage. All patients should have a withdrawal bleed at least every 90 days to promote endometrial shedding and prevent hyperplasia.
	+ Current guidelines do not recommend routine US screening for endometrial cancer.2
* Menstrual irregularities: Patients with PCOS have an increased risk of abnormal uterine bleeding. This is disruptive, impairs quality of life, and can even cause dysfunctional uterine bleeding causing anemia. The most common and well-tolerated way to treat these menstrual irregularities in a patient not desiring pregnancy is combined oral contraceptives.
	+ *Management:* OCPs suppress gonadotropin release, also improving other co-morbidities associated with PCOS like hirsutism. We recommend choosing a progestin that is less androgenic in this patient population (examples: desogestrel, norgestimate, and drosperinone).
* Infertility: PCOS is the most common cause of anovulatory infertility in the US. Infertility is an extremely common in women with PCOS, independent of BMI! While a normally ovulating woman has about a 10-15% chance of conceiving each cycle, a woman with PCOS has a conception rate about half that, at 5-10% per cycle.
	+ *Management:* It is also important to discuss fertility goals regularly with these patients to connect them with resources early and refer patients with PCOS to OB/Gyn or Reproductive Endocrinology and Infertility (REI) when they are considering childbearing for additional counseling.
		- Weight loss is the first line treatment in overweight and obese patients. Five to 10% weight loss can improve menstrual irregularities and ovulation frequency.2,7
		- BONUS: Clomiphene, a selective estrogen receptor modulator, is first line for ovulation induction in women with PCOS. It binds estrogen receptors in the hypothalamus and inhibits negative feedback of estrogen on the hypothalamus.2,5
* Pregnancy complications: PCOS is associated with negative pregnancy outcomes. Many studies also describe an increased rate of early pregnancy loss in PCOS, up to 20-40% higher risk. The etiology of this is unclear. Patients with PCOS will also have increased odds ratio of gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, and pre-term labor. The risk of GDM in patients with PCOS is unrelated to BMI.

**Take Home Points**

1. PCOS is defined by the Rotterdam Criteria, which include hyperandrogenism, menstrual irregularities, and polycystic ovaries on ultrasound. You need two of three to meet diagnostic criteria.
2. PCOS is a diagnosis of exclusion, and you must rule out other causes of menstrual irregularities and/or hyperandrogenism before assigning this diagnosis.
3. There are multiple gynecologic and medical co-morbidities associated with PCOS to screen patients for, including abnormal uterine bleeding, endometrial hyperplasia/neoplasia, insulin resistance and type 2 diabetes, cardiovascular disease, hyperandrogenism, infertility, and pregnancy complications.

**References**

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