Reviewed By
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Polycystic Ovary Disease

Objectives:

- → Describe the pathogenesis of PCOS
- → Identify the clinical picture of PCOS
- → List The investigations required to diagnose PCOS
- → List The health hazards associated with PCOS
- → Describe the management options of PCOS

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Kaplan Video

Editing File

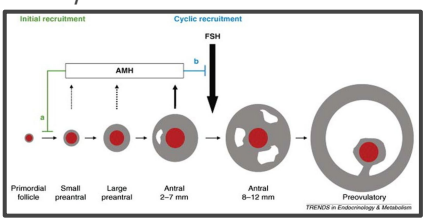
Polycystic Ovarian Syndrome

History:

→ **First clinical description:**
  → 1935.
  → By Stein & Leventhal.
  → **Description:**
    → Long cycles or even amenorrhea.
    → Hirsutism.
    → Large ovary without macrocysts.
    → Obesity.

Definition:

→ **Polycystic Ovarian Syndrome:** an excess of growing ovarian follicles, not cysts or a microcysts.
  → **Normal number of ovarian follicles:** 6 M.
→ **Polycystic Ovarian Syndrome:** a set of symptoms caused by anovulation and ↑ androgens in women.
→ **Primarily characterized by:** ovulatory dysfunction and **hyperestrogenism**.
→ **Cause:** a combination of genetic and environmental factors.
  → **PCOS:** a genetically heterogeneous syndrome.
    → Genetic contributions remain incompletely described.
    → **Studies of family members with PCOS:** an **autosomal dominant** inheritance mode occurs for many families (*between sisters, relatives and first degree cousins*).
→ **Most frequent etiology:**
  → Oligo-ovulation/anovulation.
  → Hyperandrogenism.
  → Female infertility.
→ One of the leading causes of poor fertility.
→ The most common endocrine disorder amongst women between 18 - 44 years old.
  → Affects ≈ 2 - 20% of this age group.
→ **Prevalence:** 7 - 15% of women worldwide.



Hormonal Changes of PCOS:

01 Luteinizing Hormone
→ Stimulates ovarian theca cells.

02 Follicular Stimulating Hormone
→ Main hormone for follicular genesis, triggers follicle to grow.
→ ↓ FSH relative to LH.

03 Anti-Müllerian Hormone
→ Oocytes number indicator.
→ 🚫 FSH + ↑ LH.
→ 🚫 initial recruitment.
→ 🚫 FSH stimulating effect on pre-antral & small antral follicles growth (*cyclic recruitment*).
→ Multiple small follicles → ↑ AMH → 🚫FSH action + ↑ LH.

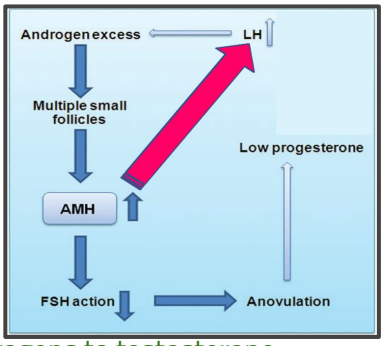
04 Lack of Aromatization
→ Lack of aromatization of androgens to estrogens.

05 Androgens
→ ↑ androgen production (*testosterone & androstenedione*).

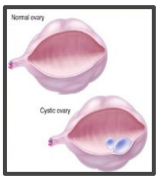
06 Estrogen
→ ↓ estrogen levels → anovulation.
→ Most cases have hyperestrogenism.

Polycystic Ovarian Syndrome

Pathophysiology:



→ Exact etiopathophysiology is unclear.
→ **Result from:** abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis.
  → ↑ LH secreted by anterior pituitary → ovarian theca cells stimulation → ↑ androgen production (*androstenedione & testosterone*) → ↓ FSH relative to LH → lack of aromatization of androgens to estrogens → ↓ estrogen levels → anovulation.
→ **Abnormalities in androgens & estrogen metabolism** & in androgen production control.
→ Androgens will not metabolize to estrogen → ↑ androgen levels → androgens to testosterone → high androgen levels symptoms.
→ **Biochemical features of PCOS:**
  → ↑ androgen production (*testosterone "leading to virilization" - androstenedione - DHEA-S*).
    → Only 50% have a change in testosterone or androgen level.
    → Individual variation is considerable → normal androgen levels doesn't rule out PCOS.
  → Peripheral insulin resistance → hyperinsulinemia (*secondary to androgen affect*) + obesity (*abnormal glucose metabolism → ↑ insulin production*) → T2D (*persistent high glucose levels*) → ↑ the degree of both abnormalities.
  → Polycystic ovaries are enlarged bilaterally and a smooth thickened capsule.
  → **Cut section:** subcapsular follicles in various stages of atresia are seen at the periphery, with hyperplasia of theca stromal cells (*due to LH secretion*).



→ **Figure 1 Notes:**
  → Obesity → more production of androgen (fat cells produce androgen by aromatization).
  → LH & FSH levels are measured in the follicular phase.
    → Before the LH surge; normally FSH levels are higher, but PCOS it's the opposite.
  → Androgen excess is one of the major contributors of the symptoms.
  → No ovulation → no corpus luteum → no progesterone → unopposed estrogen.

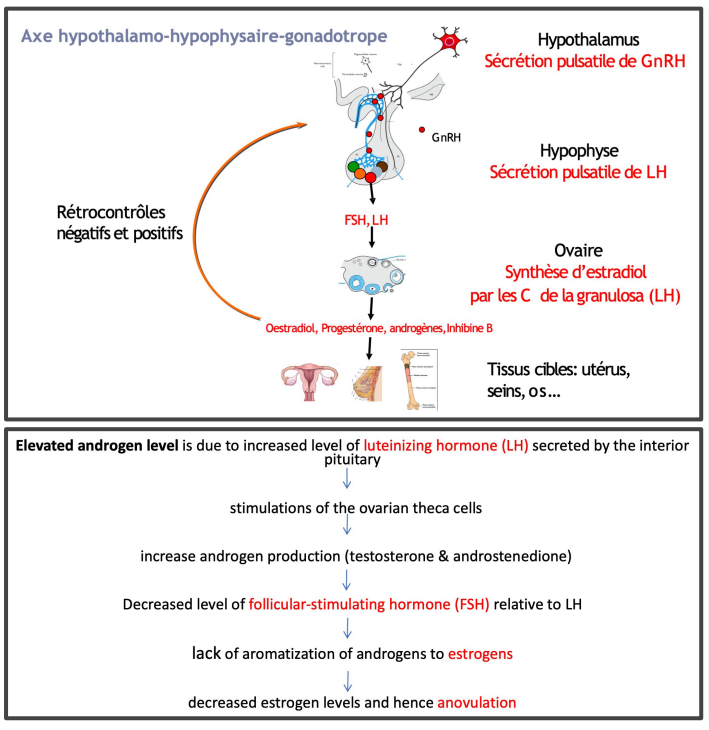


Figure 1

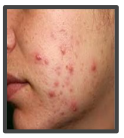
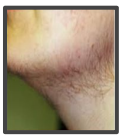
Polycystic Ovarian Syndrome

Oligo-Anovulation (OA):

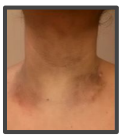
- → Primary (**onset:** time of menarche) | Secondary amenorrhoea.
- → Oligomenorrhea.
- → < 8 episodes of menses a year.
- → **Cycle length:** exceeds 35 days.
  - → **Normal cycle length:** 21 - 35 days.
- → Regular cycle → normal ovulation.
  - → **Regular cycle:** the days between the 1st day of two menstrual cycles is from 27 - 35 days.
- → Complications polycystic ovary morphology (PCOM) diagnosis on US → No longer recommended in the presence OA.

Signs & Symptoms:

- → **Menstrual dysfunction:** amenorrhea - oligomenorrhea - menorrhagia.
- → **Chronic anovulation:**
  - → **normal menstrual cycle:** characteristic hormone fluctuation.
  - → **PCOS:** gonadotropins and sex steroids are in a steady state → anovulation + infertility.
    - → No ovulation → no corpus luteum to produce progesterone → unopposed estrogen → hyperplastic endometrium (*chronically stimulated by estrogen, without progesterone ripening and cyclic shedding*) → irregular bleeding.
      - → Endometrial hyperplasia → endometrial cancer (with time).
- → **Signs of hyperandrogenism:**
  - → **Hirsutism**[1] in the face, chest, back, neck, pubic area, under the umbilicus.
    - → PCOS is one of the most common causes of hirsutism in women.
  - → Severe acne.
  - → Hair fall.

- → ↑ **total & free testosterone:**
  - → ↑ LH levels → ↑ ovarian follicular theca cell production of androgens → ↑ androstenedione and testosterone → ↓ SHBG hepatic production by 50%.
  - → ↑ total testosterone + ↓ SHBG → mildly ↑ levels of free testosterone → hirsutism.
- → **Infertility:**
  - → Subfertility, because it still can be treated.
- → **Obesity & metabolic syndrome:**
  - → Obesity in up to 70% of patients.
  - → Insulin resistance → fat deposition → no break down of fat → gain weight.
- → Obstructive sleep apnea.



1. Check free testosterone level even if the patient doesn't have hairstism.

Polycystic Ovarian Syndrome

Diagnosis:

Physical Examination:

- → **Virilizing signs:** hirsutism - acne - temporal alopecia.
- → **Acanthosis nigricans:** sign of insulin resistance, more with obese.
- → Hypertension.
- → **Enlarged ovaries (*may or may not be present*):** not palpable only seen by US.

Testing & Investigations:

- → **Exclude other disorders that can result in menstrual irregularities and hyperandrogenism:**
  - → Adrenal tumor
  - → **Ovarian tumor:** ↑ estrogen level.
    - → **Granulosa cell tumor:** can cause ↑ estrogen.
  - → **Thyroid dysfunction:** hypothyroidism → irregularity of cycle + weight gain.
  - → **Congenital Adrenal Hyperplasia:** similar presentation of PCOS but totally different management.
  - → Hyperprolactinemia.
  - → Acromegaly.
  - → Cushing syndrome.

Diagnosis (Rotterdam Criteria):

- → **Diagnosis by exclusion or 2 out of 3 following:**
  - → Hyperandrogenemia → hirsutism - acne.
  - → Ovarian dysfunction → endometrial shedding secondary to ↑ estrogen level → irregular cycles.
  - → **Polycystic ovarian morphology by US[1] (ideally:** transvaginal US**):** higher ovarian volume, a lot of follicles the number isn't important.

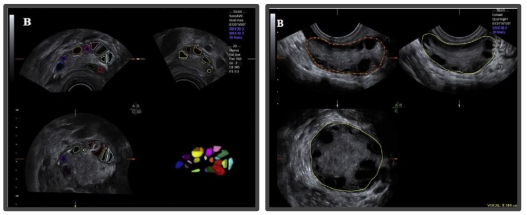


TABLE 1

Evolution of the diagnostic criteria for polycystic ovarian syndrome.

Parameter	NIH 1990 (18)	ESHRE/ASRM 2003 (19, 20)	AE-PCOS 2006 (24, 25)	NIH 2012 extension of ESHRE/ASRM 2003 (23)
Criteria	HA OA	HA OD PCOM	1. HA 2. Ovarian dysfunction (OD and/or PCOM)	1. HA 2. OD 3. PCOM
Limitations	1.Two of two criteria required	1. Two of three criteria required	1. Two of two criteria required	1. Two of three criteria required; and 2. Identification of specific phenotypes included: A: HA + OD + PCOM B: HA + OD C: HA + PCOM D: OD + PCOM
Exclusion of related or mimicking etiologies				

Note: AE-PCOS = Androgen Excess & PCOS Society; ASRM = American Society for Reproductive Medicine; ESHRE = European Society for Human Reproduction and Embryology; HA = hyperandrogenism; NIH = National Institutes of Health; OA = oligo-anovulation; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

Ultrasound and polycystic ovarian morphology (PCOM)		
CCR	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 incidence of multi-follicular ovaries in this life stage.	****
CCR	The threshold for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined.	****
CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.	****
CCR	Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8 MHz, the threshold for PCOM on either ovary, a follicle number per ovary of ≥20 and/or an ovarian volume ≥10 ml on either ovary, ensuring no corpora lutea, cysts or dominant follicles are present.	***
CPP	If using older technology, the threshold for PCOM could be an ovarian volume ≥10 ml on either ovary.	–
CPP	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.	–
CPP	In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥10 ml, given the difficulty of reliably assessing follicle number with this approach.	–

1. Healthy women may also have polycystic-appearing ovaries, particularly in adolescence, when the ovaries normally contain a large number of follicles.

Polycystic Ovarian Syndrome

Screening:

→ **First tests (even before FSH & LH):** TSH - prolactin - US.

Screening

Lab Studies

→ **Thyroid function test:** TSH +/- free thyroxine.
→ Serum prolactin level.
→ **Total & free testosterone level:** free testosterone reflects androgen symptoms → higher than normal.
  → Free testosterone levels are more important.
→ Free androgen index.
→ **Serum hCG level:** if 2° amenorrhea or oligo → rule out pregnancy.
→ **FSH levels:** if 1° amenorrhea.

Other Tests

→ Androstenedione level.
→ **FSH and LH levels:** the most important test.
→ Normal levels don't exclude PCO.
→ GnRH stimulation levels.
→ Glucose level.
→ **Insulin level.**
→ **Lipid level:** may develop dyslipidemia.

Imaging Tests

→ **Ovarian ultrasonography:** preferably transvaginal approach especially if obese.
→ **Pelvic CT scan or MRI:** visualize the adrenals and ovaries.
→ **AFC → transvaginal US:**
  1. Ovarian volume of both the ovaries is calculated.
  2. Number of small antral follicles in both the ovaries is calculated.

Health Hazards & Prognosis:

→ ↑ risk for cardiovascular & cerebrovascular disease.
→ Often associated with android obesity (≈70%),
  → **Normal BMI:** 20 - 30% of patients.
→ ↑ serum lipoprotein levels similar to those of men.
→ Insulin resistance in 50 - 70% of PCOS → ↑ type 2 diabetes and cardiovascular complications risk.
→ Chronic anovulation in PCOS → constant endometrial stimulation with estrogen without progesterone → ↑ endometrial hyperplasia and carcinoma risk.

Polycystic Ovarian Syndrome

Management:

Lifestyle Modifications:
- → First-line treatment.
- → Diet
- → Exercise
- → Weight Loss → might regulate the cycle.
- → ↓ Weight → ↓ fat → ↓ conversion of androgen to estrogen.

Multidisciplinary Team:
- → Gynecologists.
- → Dieticians.
- → Physician / Endocrinologist.
- → Fertility specialist.
- → Support group (unfortunately not here in KSA).

Pharmacotherapy:
- → **Metabolic derangements:** anovulation - hirsutism - menstrual irregularities.
  - → **Oral contraceptive pills (OCP):**
    - → First-line medical therapy.
    - → Induce regular menses.
    - → **Why we give OCPs?**
      - → Untreated pcos → ↑ estrogen → ↑ endometrium thickness → endometrial hyperplasia → endometrial cancer.
    - → **OCPs contraindications:**
      - → Smoking.
      - → Migraine.
    - → **Diane - Marvelon:**
      - → 3rd generation.
      - → Most commonly used.
      - → Antiandrogen effect.
    - → **Ethinylestradiol - Medroxyprogesterone:**
      - → 3rd generation.
      - → Progestin component will prevent endometrial hyperplasia.
      - → Normalize bleeding
      - → Low dose of estrogen and progesterone → ↓ thromboembolic risk.
      - → No antiandrogen effect.
    - → Obese patient wants to regulate their period → give progesterone from days 15 - 25 of their menstrual cycle (10 days & stop after that) → after the 10 days, they will have their period.
  - → Second-line cyclical oral progesterone (if she's not seeking for ovulation)
- → Hyperandrogenism **(Hirsutism):**
  - → **Androgen blocking agent: spironolactone** - leuprolide - finasteride.
  - → **Can be suppressed two ways:**
    - → **OCPs:** ↓ testosterone production by ↓ LH stimulation of ovarian follicle theca cells.
    - → **OCPs:** ↑ SHBG → ↓ free testosterone (takes time).
    - → **Spironolactone:** ↓ hair follicle 5-α reductase enzyme (↓ *androstenedione & testosterone* → *dihydrotestosterone*).
- → **Anovulation:**
  - → **Clomiphene citrate:** antiestrogen.
  - → **Letrozole:** selective estrogen receptor modulators.
  - → Ultrasound follow up is necessary
- → **Obesity:**
  - → **Hypoglycemic agents: metformin** - insulin.
  - → **Myo-inositol:** natural, less side effect than metformin, weight loss.
- → **Topical hair-removal agents:** eflornithine.
- → **Topical acne agents:**
  - → Benzoyl peroxide.
  - → Tretinoin topical cream (0.02 - 0.1%) / gel (0.01 - 0.1%) / solution (0.05%).

Polycystic Ovarian Syndrome

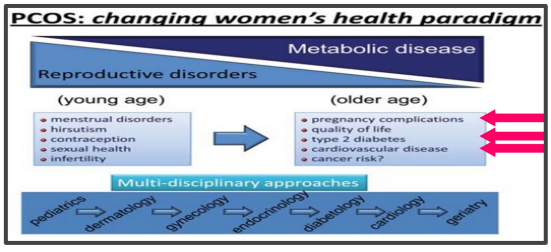
Management:

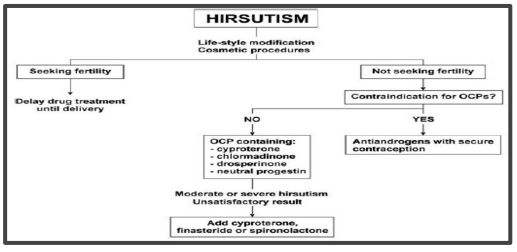
Surgery

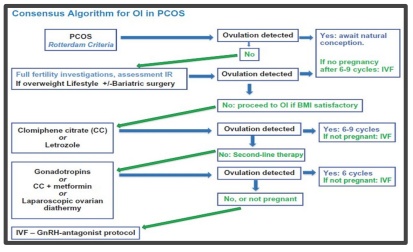
- → **Aim:** restore ovulation method (*laparoscopically*).
- → Electrocautery.
- → **Laser drilling:**
  - → **Ovarian drilling:** ovary perforation to decrease the ovarian reserve.
  - → Not practiced anymore because if the doctor overdo it, it will cause lower ovarian follicles then normal.
- → Multiple biopsy

Infertility Cases:

- → **After systematic verification of the uterine, tubal, spermogram, hygienic and dietary measures:**
  - → Spermogram (semen analysis) is really important to do even if the patient have irregular cycles.
  - → **1st line:** *antiestrogens*:
    - → Clomiphene citrate (Clomid).
    - → Letrozole.
    - → Femara.
    1. Give them progesterone for 10 days to get their period.
    2. Give an antiestrogen in day 3 of menstrual cycle for 5 days.
       - → To decrease estrogen so the cycle hormones regulate after 2 - 3 days.
    3. See the follicle by US.
    4. Redo up to 6 cycles.
       - → After 3 cycle usually pregnancy rate is up to 80%.
    - → Usually result in natural ovulation but we can give induction ovulation for sertanty.
  - → **2nd line:** *Either*:
    - → Ovulation induction with gonadotropins (+/- IUI according to spg).
    - → Ovarian drilling.
  - → **3rd line:** *IVF*:
    - → PCOS patients have excellent prognosis.
  - → **Metformin (***hypoglycemic agent***):**
    - → ↑ insulin sensitivity.
    - → Enhance the likelihood of ovulation both with and without clomiphene.







439 Summary

Polycystic Ovarian Syndrome

Pathophysiology:

- Strong association with obesity → ↑ in peripheral estrogen synthesis from adipose tissue and ↓ in peripheral sensitivity to insulin
- Reduced insulin sensitivity (peripheral insulin resistance) and the consequent hyperinsulinemia result in:
  - Epidermal hyperplasia and hyperpigmentation (acanthosis nigricans)
  - ↑ Androgen production in ovarian theca interna cells → imbalance between androgen precursors and the resulting estrogen produced in granulosa cells (abnormalities in the metabolism of androgens and estrogen)
    - ↑ LH secretion disrupts the LH/FSH balance → impaired follicle maturation with cyst formation due to lack of follicle rupture and anovulation/oligoovulation → infertility
    - ↑ Androgen precursor release and ↑ estrogen production in adipose tissue
  - Inhibition of SHBG in the liver → ↑ free androgens and estrogens
    - ↑ Unopposed estrogen (lack of progesterone) during anovulatory cycles → endometrial hyperplasia → ↑ risk of endometrial carcinoma

Symptoms:

Onset of symptoms typically occurs during adolescence.

- **Menstrual irregularities**
  - Primary or secondary amenorrhea
  - Oligomenorrhea
  - Menorrhagia
  - **Infertility** or difficulties conceiving
- Insulin resistance and associated conditions:
  - Metabolic syndrome, especially obesity → ↑ risk of obstructive sleep apnea (OSA)
- Skin conditions
  - Hyperandrogenism:
    - Hirsutism
    - Androgenic alopecia (hair fall)
    - Acne vulgaris
    - Oily skin
  - Hyperinsulinemia: Acanthosis nigricans
- Virilization:
  - Hirsutism, Male-pattern hair loss, Acne, Increased muscle mass, Voice deepening, Clitoromegaly

Investigations:

Laboratory studies

- ↑ Testosterone/androgens
- ↑ Estrogen
- Anti-Müllerian hormone:
  - **Elevated LH (with LH:FSH ratio > 2:1)** (high but no LH surge)
  - Inhibits FSH
- Lack of aromatization
- ↑ Insulin
- Other labs to order to rule out differential diagnoses and evaluate for comorbidities:
  - rule out pregnancy FIRST
  - thyroid, prolactin, GnRH stimulation levels
  - glucose level, insulin level, lipid level
  - free androgen index, androstenedione level.

Imaging studies

- Pelvic ultrasound (initial test)

Diagnostics:

by exclusion or Rotterdam criteria (⅔ of the following):

Rotterdam criteria

1. **Oligoovulation and/or anovulation**-irregular cycles due to shedding of the endometrium secondary to ↑ estrogen
2. **Hyperandrogenism** (based on clinical features or laboratory studies)
   a. Rule out other causes of hyperandrogenism like:
      1. Adrenal tumor: order DHEA-S
      2. Androgen-secreting ovarian tumor: order pelvic U/S
      3. Non-classical congenital adrenal hyperplasia: order 17-OH progesterone
3. **Enlarged and/or polycystic ovaries on U/S**

Treatment:

- Weight loss (target BMI < 25 kg/m2 can reduce estrone production in the adipose tissue)
- **Menstrual Irregularity:**
  - Combined oral contraceptives (COCs). First-line. Additional benefits:
    - ↓ Endometrial hyperplasia → ↓ risk of endometrial carcinoma
    - ↓ Menstrual bleeding
    - ↓ Acne
    - Treatment of hirsutism
- **Hyperandrogenism (hirsutism):**
  - Androgen blocking agent (e.g., spironolactone aka aldactone, leuprolide, finasteride)
  - Combined oral contraceptives (COCs).
    - By increasing sex hormone binding globulin
- **Patients planning to conceive/Anovulation:** Medical induction of ovulation: letrozole, clomiphene citrate, human menopausal gonadotropins (HMG), and metformin
  - **Letrozole**: aromatase inhibitor first-line therapy for ovulation induction
  - **Clomiphene:** SERM (Selective Estrogen Receptor Modulators)
  - Exogenous gonadotropins(Hcg): The low-dose regimen is the second-line treatment for ovulation induction.
- **Obesity: (Hypoglycemic agents)**
  - Insulin
  - **Metformin:**
    - Can be used as second-line monotherapy for fertility treatment.
    - Combination with clomiphene may increase pregnancy rates, especially in obese women.

Complications:

Women with PCOS are at ↑ risk of:

- Type 2 diabetes mellitus
- Metabolic syndrome
- Cardiovascular diseases
- Malignancies: breast and endometrial cancer, because of unopposed estrogen secretion
- **Obstetric complications:** Miscarriage and gestational DM

Approach to PCOS (Hacker & Moore)

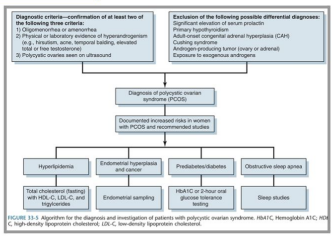


FIGURE 33-5 Algorithm for the diagnosis and investigation of patients with polycystic ovarian syndrome. HbA1C, Hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Quiz

Question 1:

→ **A 22-year-old woman consults you for treatment of hirsutism. She is obese and has facial acne and hirsutism on her face and periareolar regions and a male escutcheon. Serum LH level is 35 mIU/mL and FSH is 9 mIU/mL. Androstenedione and testosterone levels are mildly elevated, but serum DHAS is normal. The patient does not wish to conceive at this time. Which of the following single agents is the most appropriate treatment of her condition?**

A. Oral contraceptives
B. Corticosteroids
C. GnRH
D. Parlodel
E. Wedge resection

Question 2:

→ **A 26-year-old G0P0 comes to your office with a chief complaint of being too hairy. She reports that her menses started at age 13 and have always been very irregular. She has menses every 2 to 6 months. She also complains of acne and is currently seeing a dermatologist for the skin condition. She denies any medical problems. Her only surgery was an appendectomy at age 8. Her height is 5 ft 5 in., her weight is 180 lb, and her blood pressure is 100/60 mm Hg. On physical examination, there is sparse hair around the nipples, chin, and upper lip. No galactorrhea, thyromegaly, or temporal balding is noted. Pelvic examination is normal and there is no evidence of clitoromegaly. Which of the following is the most likely explanation for this patient's problem?**

A. Idiopathic hirsutism
B. Polycystic ovarian syndrome
C. Late-onset congenital adrenal hyperplasia
D. Sertoli-Leydig cell tumor of the ovary
E. Adrenal tumor

Question 3:

→ **Your patient is a 23-year-old woman with primary infertility. She is 5 ft 4 in tall and weighs 210 lb. She has had periods every 2 to 3 months since starting her period at age 12. She has a problem with acne and hair growth on her chin. Her mother had the same problem at her age and now has adult-onset diabetes. On physical examination of the patient, you notice a few coarse, dark hairs on her chin and around her nipples. She has a normal-appearing clitoris. Her ovaries and uterus are normal to palpation. Which of the following blood tests has no role in the evaluation of this patient?**

A. Total testosterone
B. 17 α-hydroxyprogesterone
C. DHEAS
D. Estrone
E. TSH

A	B	D
1	2	3

Quiz

Question 1:

→ **You have just diagnosed a 21-year-old infertile woman with polycystic ovarian syndrome. The remainder of the infertility evaluation, including the patient's hysterosalpingogram and her husband's semen analysis, were normal. Her periods are very unpredictable, usually coming every 3 to 6 months. She would like your advice on the best way to conceive now that you have made a diagnosis. Which of the following treatment options is the most appropriate first step in treating this patient?**

A. Dexamethasone
B. Gonadotropins
C. Artificial insemination
D. Metformin
E. In vitro fertilization

Question 2:

→ **With regard polycystic ovary syndrome (PCOS), which of the following statements is true?**

A. PCOS is an unusual cause of anovulation.
B. Ultrasonic evidence of polycystic ovaries is present in 50% of all women.
C. PCOS is associated with obesity in 10% of women.
D. PCOS is associated with acanthosis nigricans.
E. The diagnosis of PCOS can only be made with biochemical evidence of hyperandrogenism.

Question 3:

→ **In polycystic ovary syndrome estrogen levels are elevated,increasing the risk of which of the following?**

A. Metabolic syndrome.
B. Endometrial cancer.
C. Hirsutism.
D. Hypertension.

Question 4:

→ **Which of the following is not a criterion for PCOS according to the Rotterdam criteria?**

A. Menstrual irregularity/chronic anovulation.
B. Obesity and metabolic syndrome.
C. Polycystic ovarian on US.
D. Hyperandrogenism.

1	2	3	4
D	D	B	B

Reference

OVARIAN DISORDERS

Polycystic Ovarian Syndrome

According to recent guidelines **(Rotterdam criteria),** PCOS is defined by the inclusion of **at least two of the following three features: (1) clinical or biochemical hyperandrogenism, (2) oligomenorrhea or amenorrhea, and (3) polycystic ovaries,** excluding other endocrine disorders that mimic PCOS. The various PCOS phenotypes vary in severity, with the classic PCOS form (i.e., clinical or biochemical hyperandrogenism with oligo-ovulation) having the most severe reproductive and metabolic abnormalities. **PCOS affects about 6-10% of women worldwide on the basis of classic PCOS criteria, and even more individuals on the basis of the new Rotterdam criteria,** making it one of the most common human disorders and the single most common endocrinopathy among women of reproductive age. The clinical symptoms of PCOS usually develop at the time of puberty. PCOS is more prevalent among family members (20-40% of first-degree female relatives affected) than in the general population (prevalence: 6-10%), suggesting that **genetic factors influence development of the syndrome.** Because adolescent girls may have some of the features of PCOS without having the disorder, it is recommended that all three of the Rotterdam criteria be met in them (see Chapter 32).

The hyperandrogenism of PCOS results from an overproduction of male hormones by the ovary and often from the adrenal gland. A common clinical sign of hyperandrogenism in PCOS is hirsutism. Visual assessment of hirsutism is valuable because most women with PCOS of white or black race demonstrate excessive hair growth, although **hirsutism is less likely in women who have used hormonal contraceptives for prolonged intervals** and for many East Asian women. Obesity per se is not necessarily intrinsic to PCOS. Rather, the worldwide prevalence of obesity in most female populations has increased over the past two decades, and hyperinsulinemia caused by obesity-related insulin resistance worsens the symptoms of PCOS.

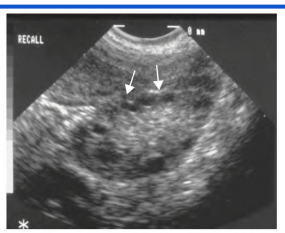


FIGURE 33-3 Transvaginal ultrasonogram of a woman with polycystic ovarian disease. The multiple subcapsular cysts, with their "string of pearls" appearance *(arrows),* are common in this syndrome.

In patients with PCOS, **ovarian hyperandrogenism, hyperinsulinemia caused by insulin resistance, and altered intraovarian signaling can disrupt follicular growth.** The consequent follicular arrest in PCOS is accompanied by menstrual irregularity, anovulatory subfertility, and the accumulation of small antral follicles within the periphery of the ovary, giving it a polycystic morphology (Figure 33-3). The ovarian stroma contains abundant theca cells that overproduce androgens. **Importantly, healthy women may also have polycystic-appearing ovaries, particularly in adolescence, when the ovaries normally contain a large number of follicles.**

LH hypersecretion increases serum LH levels in up to 70% of patients with PCOS, with elevated LH pulse amplitude and frequency inducing a two- to threefold elevation in circulating LH over FSH levels. Increased LH pulse frequency in PCOS, from enhanced hypothalamic GnRH pulsatile release, occurs as the result of reduced steroid hormone negative feedback on LH secretion from hyperandrogenism. As a result, **LH hypersecretion promotes ovarian hyperandrogenism in a feedforward mechanism, with androstenedione and testosterone undergoing peripheral aromatization to create tonic estrogen production without progesterone in the absence of ovulation.**

In women with PCOS, there is an association between hyperandrogenism and hyperinsulinemia because of insulin resistance. In approximately 60-70% of patients with PCOS, insulin sensitivity is impaired, leading to hyperinsulinemia. Consequently, the excessive amount of insulin perpetuates ovarian hyperandrogenism in several ways. The excess insulin stimulates the activity of CYP17A (cytochrome P450, 17A) in the theca cell. CYP17A is the enzyme responsible for androgen production in the theca cell. The excessive insulin also amplifies insulin-like growth factor 1 (IGF-1)–stimulated androgen production, elevating serum free testosterone levels through decreased hepatic SHBG production, which binds testosterone. Less binding results in more free testosterone. And finally, enhanced serum IGF-1 bioactivity results due to suppressed IGF-binding protein production. Thus, the physical manifestations of hyperandrogenism in PCOS may be dramatic in relation to the serum level of total testosterone.

Abdominal adiposity in women with PCOS preferentially worsens with weight gain, as does the prevalence of metabolic syndrome (elevated blood pressure and blood glucose with excess body fat around the waist). Metabolic syndrome, along with its underlying insulin resistance, occurs two to three times more frequently in women with PCOS than in age-matched controls, and it is 13.7 times more likely in PCOS women with the highest as opposed to the lowest BMI. **In the long term, the insulin resistance associated with PCOS may lead to an increased risk of cardiovascular disease,** most likely mediated through increased total and abdominal adiposity interacting with PCOS-related hyperandrogenism.

Women with PCOS also have a 2.7-fold increased risk of developing endometrial cancer. A major factor in this increased malignancy risk is the preceding development of endometrial hyperplasia caused by prolonged exposure to estrogen unopposed by progesterone in the absence of ovulation.

INSULIN RESISTANCE AND POLYCYSTIC OVARIAN SYNDROME

Women with PCOS have a type of insulin resistance that is independent of, and additive with, that of obesity. Insulin resistance occurs in 50-70% of women with PCOS and in 95% of obese women with PCOS. Up to 40% of women with classic PCOS develop impaired glucose tolerance or type 2 diabetes mellitus by the fourth decade of life, with age and weight gain worsening glycemic control. **PCOS is associated with a four-fold increased prevalence of type 2 diabetes mellitus. Some patients with PCOS also may have several risk factors for cardiovascular disease, including increased abdominal adiposity, hypertension, hypertriglyceridemia, and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels.** Patients with PCOS with these findings should be counseled regarding weight loss, nutrition, exercise, and other lifestyle changes that will reduce their risk of developing diabetes mellitus and cardiovascular disease. In some cases, insulin-sensitizing agents such as **metformin** may be used to reduce insulin resistance and anovulation (see Chapter 34).

Controlling for body mass index, **women with PCOS are more likely to have sleep-disordered breathing and daytime sleepiness than healthy women,** which are additional risk factors for cardiovascular disease. Screening overweight and obese women with PCOS for symptoms of obstructive sleep apnea should be followed by polysomnography if necessary to make a definitive diagnosis. If obstructive sleep apnea is diagnosed, patients should be referred for appropriate therapy, including continuous positive airway pressure treatment. A flowchart for the diagnosis and investigation of patients with PCOS is shown in Figure 33-5.

Patients with adrenal hyperandrogenism, including late-onset CAH, can be treated with glucocorticoids (e.g., 0.25-mg dexamethasone every other day at bedtime). Many of these women, like those with PCOS, also require suppression of ovarian androgen secretion using combination oral contraceptives and antiandrogens.

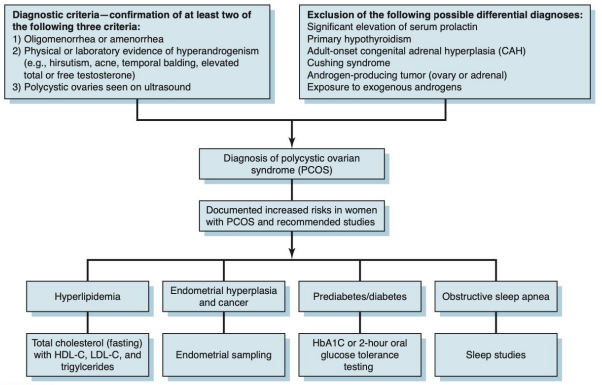


FIGURE 33-5 Algorithm for the diagnosis and investigation of patients with polycystic ovarian syndrome. *HbA1C,* Hemoglobin A1C; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol.

Polycystic Ovarian Syndrome and Puberty

PCOS is the leading cause of female anovulatory infertility and is characterized by ovulatory dysfunction and hyperandrogenism. It is associated with obesity, insulin resistance, and metabolic dysfunction (see Chapter 33). During the transition from adrenarche/pubarche (adrenal androgen production dominance) to menarche, a relatively similar imbalance of hormones leads to irregular menses, polycystic ovaries, and a relative androgen excess. Because of these similar clinical findings, the diagnosis of PCOS in the adolescent population remains controversial.

Recently, it has been suggested that adolescents with congenital virilization, premature pubarche, or central precocious puberty are at higher risk of developing PCOS. **There is growing support for using a modified Rotterdam system to make a diagnosis of PCOS in adolescents.** This requires the presence of all three of the following criteria (rather than the standard two of three criteria): **oligo-ovulation or anovulation, hyperandrogenism, and polycystic ovaries visualized by pelvic ultrasonography.** Adolescent PCOS is associated with metabolic syndrome and sleep disorders, and treatment should include lifestyle modification. Other treatments commonly used to treat PCOS in an older population have not been studied thoroughly in adolescents.

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