[Color index: Important | Notes | Extra]

POLYCYSTIC OVARIAN SYNDROME

Objectives:

- Describe the pathogenesis of PCO
- Identity the clinical picture of PCO
- List the investigation required to diagnosis PCO
- List the health hazard associated with PCO
- Describe the management option to treat PCO

Done by : Afnan AlMalki.
Revised by: Haifa Almohsen , lina alshehri.

Definition

Polycystic ovarian syndrome (PCOS) is a condition of chronic anovulation with resultant infertility. The patient presents typically with irregular vaginal bleeding. Other symptoms include obesity and hirsutism.

Epidemiology

- affects about 6-10% of women worldwide. which is true here because of obesity
- one of the most common human disorders and the single **most common** endocrinopathy among women of reproductive age (18-44), It affects 2-20% of them.
- PCOS is the leading cause of female anovulatory infertility.

Clinical sign & symptoms

The clinical symptoms of PCOS usually develop at the time of puberty.

- Menstrual dysfunction (amenorrhea, oligomenorrhea and menorrhagia). the main compline the patient present with in gynecology. Oligomenorrhea = periods are every 2-3 months
- Anovulation.
- Infertility.
- Sign of hyperandrogenism (hirsutism, acne and hair fall) the main compline the patient present with in dermatology. So most of the time the dermatologist referred the patient to gynecologist. Hirsutism (excessive hair in upper lip, chest and suprapupic area)
- Hair thinning and hair loss.
- Obesity: 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.
- Metabolic syndrome: along with its underlying insulin resistance, occurs two to three times more frequently in women with PCOS
- Obstructive and sleep apnea. women with PCOS are more likely to have sleep disordered breathing and daytime sleepiness than healthy women.
- Depression & stress as a result of the symptoms
- On examination: if it doesn't there it doesn't rollout the diagnosis.
  - Virilizing sign
  - Hypertension
  - Acanthosis nigrican (due to increased insulin resistance)
  - Enlarged ovaries (may or may not be present) by US not by pelvic exam.

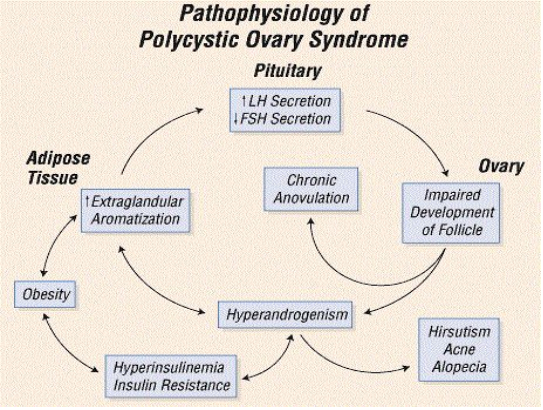
Pathophysiology video ★ main abnormalities behinds PCO is raised androgen.

The exact etiopathophysiology of PCOS is **unclear**.

It is due to combination of genetic and environmental factors.

Studies of family members with PCOS indicate that autosomal dominates mode of inheritance occurs for many family with the disease.

It can result from abnormal function of HPO axis.



- ➔ **LH:FSH ratio increased**: normal ratio (1.5:1) in PCOS Increased (3:1).
- ➔ **Hyperandrogenism :** The hyperandrogenism (such as: testosterone, androstenedione and DHEA-S) of PCOS results from an overproduction of male hormones by the ovary and often from the adrenal gland.
  Sometimes patient will have normal androgen levels due to "individual variations".
- ➔ **Insulin resistances**

Chronic anovulation

- women with PCOS have abnormalities in metabolism of androgen and estrogen and in the control of androgen production.
- Instead of showing the characteristic hormone fluctuation of the normal menstrual cycle, **PCOS gonadotropins and sex steroids are in a steady state**, resulting in anovulation and infertility.
- Without ovulation, there is no corpus luteum to produce progesterone.
- Without progesterone there is unopposed estrogen.
- Endometrium, which is chronically stimulated by estrogen, without progesterone ripening and cyclic shedding, becomes hyperplastic with **irregular bleeding.**
- With time endometrial hyperplasia can result, which could progress to endometrial cancer.

Increased testosterone

- **Increased LH levels** cause increased ovarian follicular theca cell production of androgens. 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.
- The increased levels of androstenedione and testosterone **suppress hepatic production of SHBG by 50%**.
- The combined effect of increased total testosterone and decreased SHBG leads to mildly **elevated levels of free testosterone.**
- This results in **hirsutism**.
- PCOS is one of the most common causes of hirsutism in women.
- there is an association between hyperandrogenism and hyperinsulinemia because of insulin resistance. 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.
  - **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. Enhanced serum IGF-1 bioactivity results due to suppressed IGF-binding protein production.

Ovarian enlargement

- On **ultrasound** the ovaries demonstrate the presence of the **necklace like pattern** of multiple peripheral cysts (20–100 cystic follicles in each ovary). It doesn't mean a cyst in ovaries as tumor.
- The increased androgens prevent normal follicular development, inducing premature follicle atresia.
- **Grossly**, these multiple follicles, in various stages of development and atresia, along with stromal hyperplasia and a **thickened** ovarian capsule, result in ovaries that are bilaterally enlarged and more smooth . Normal size of ovary is 3x2x2cm ,it almonds(oval) in shape and pinkish in color.
- On **microscopic** examination luteinized theca cell are seen.

Diagnosis

Rotterdam criteria : inclusion of at least two of the following three features

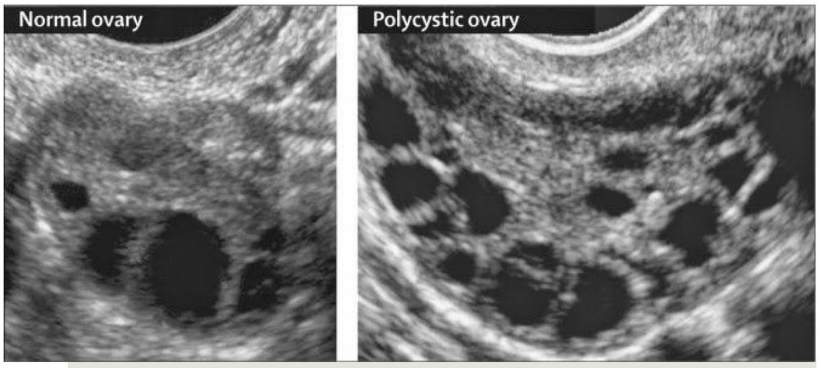
1) clinical or biochemical **hyperandrogenism**.
2) menstrual dysfunction or oligomenorrhea.
3) polycystic ovaries.

Excluding other endocrine disorders that mimic PCOS.

Investigation

- ➔ Exclude other disorders that result in menstrual irregularities and hyperandrogenism:
  - Adrenal tumor, ovarian tumor
  - Thyroid dysfunction
  - Congenital Adrenal hyperplasia
  - Hyperprolactinemia, Acromegaly and Cushing syndrome
- ➔ Screening Labs study: to exclude other endocrine disorders or to confirm diagnosis. You shouldn't go through all of these lab test because PCO is clinically diagnosed rather than biochemical so, if you have 3 clinical sign and 1 lab test + that diagnostic of PCO.
  - **TFT** (TSH, free thyroxine).
  - **total and free testosterone level , free androgen index , Androstenedione level.**
  - **serum prolactin level**. High prolactin means menstrual abnormalities.
  - GnRH level , FSH and LH levels. If LH is normal it doesn't rollout the diagnosis but if + it confirmed the diagnosis. Don't measure the LH level in the middle of the cycle either at the **beginning** or the end of it.
  - Serum hCG level.
  - Cosyntropin stimulation test (The ACTH test)
  - Serum 17-hydroxyprogesterone (17-OHPG) level.
  - Urinary free cortisol and creatinine level, low dose dexamethasone test.
  - Glaucos level , Serum insulin like growth factor, insulin level. Because in PCO Increased risk of DM2
  - lipid level.
- ➔ Imaging test

- Ovarian US: simple test to do, preferably using intravginal approach in married women but in un married girl do suprapupic or Abdominal pelvic US. Importantly, healthy women may also have polycystic appearing ovaries, particularly in adolescence, when the ovaries normally contain a large number of follicles. In the picture there is multiple small cyst less than 8mm in diameter.
- Pelvic CT scan or MRI: to visualized Adrenals and ovaries. To rellout other problem like tumor.



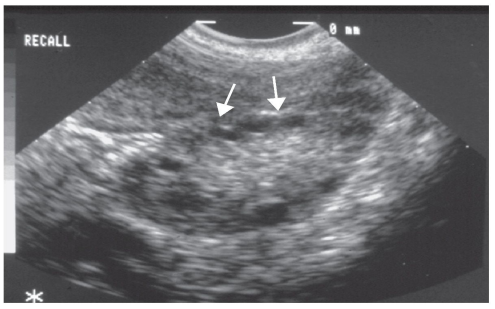
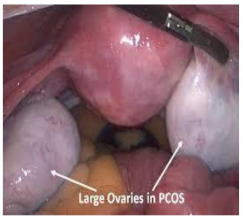


FIGURE 33-3 Transvaginal ultrasonogram of a woman with polycystic ovarian disease. The multiple subcapsular cysts, with their "string of pearls" appearance *(arrows)*, are common in this syndrome.

➔ Procedure
- Ovarian biopsy for histological confirmation of PCOS. By laparoscopy.
- US diagnostic for PCOS. "strings of pearls sign"
- Endometrial biopsy to evaluate for endometrial disease (malignancy)



Health hazard/ prognosis

➔ Increase risk of cardiovascular & cerebrovascular disease: In the long term, the **insulin resistance a**ssociated with PCOS may lead to an increased risk of cardiovascular disease, most likely mediated through **increased total and abdominal adiposity**.

➔ 2.7 fold increased risk of developing endometrial cancer, increased malignancy risk preceding development of **endometrial hyperplasia** caused by prolonged exposure to estrogen unopposed by progesterone in the absence of ovulation.

➔ Elevated serum lipoprotein level similar to men.

➔ 40% have insulin resistance which increase the risk of **DM2** & cardiovascular complication.

Management

➔ **Lifestyle modification** is the **first line of treatment**: Diet, Exercise, Weight loss.

➔ Treatment is directed toward the primary problem and the patient's desires. **OCPs** is the first line pharmacotherapy (ethinyl estradiol, medroxyprogesterone)

➔ If she comes with hyperandrogenism problem the dermatologist will deal with that.
- **Irregular bleeding : OCPs** will normalize her bleeding. The progestin component will prevent endometrial hyperplasia.
- **Hirsutism**: Excess male-pattern hair growth can be suppressed 2 ways.
  - **OCPs** will lower testosterone production by suppressing LH stimulation of the ovarian follicle theca cells. OCPs will also increase SHBG, thus decreasing free testosterone levels.

- Androgen blocking agent (**Spironolactone**, leuprolide, finasteride) Spironolactone suppresses hair follicle 5-α reductase enzyme conversion of androstenedione and testosterone to the more potent dihydrotestosterone.

◆ **Infertility**: If she desires pregnancy, ovulation induction can be achieved through selective estrogen receptors modulator (**clomiphene citrate** (Clomid) or Letrozole) ovulation induction as first line of treatment. or gonadotrophic hormones.

- **Metformin**, a hypoglycemic agent that increases insulin sensitivity, can enhance the likelihood of ovulation both with and without. Metformin is a magical drug, I give it to all of my patients. It can also help in weight reduction due to its side effects (N/V). many of the cases improves with metformin only (Sx disappears and ovulation regulates)
- clomiphene. It causes ovarian stimulation.
  - MOA : antagonizes estrogen receptor in hypothalamus > prevents normal feedback inhibition > ↑ release of LH, FSH

◆ Topical hair removal agent (eflornithine).

◆ Topical acne agent (benzoyl peroxide, tretinoin topical cream

➔ Surgery: aim to restore ovulation laparoscopically. Last option.

◆ Electrocutare

◆ Laser drilling

◆ Multiple biopsy .

★ **Q1: 27-year-old Pregnant lady is diabetic on insulin, which one of the following complication she might have?**

A. Intrauterine growth restriction (IUGR).
B. Polycystic ovarian disease (PCO).
C. Respiratory distress syndrome.

★ **Q2: 19 years old single lady presented with oligomenorrhea, hirsutism and acne, Her luteinizing hormone is double the level of follicle stimulating hormone. What is the most likely diagnosis?**

A. Androgen sensitivity syndrome.
B. Congenital adrenal hyperplasia.
C. Polycystic ovarian syndrome.
D. Premature Menopause.

★ **Q3: A 15-year-old girl presented with normal secondary sexual characteristics but she has not seen her period yet. She used to have periodic monthly abdominal pain. Which one of the following is the most likely cause?**

A. Imperforated hymen.
B. Polycystic ovarian syndrome.
C. Testicular feminization syndrome.
D. Turner syndrome.

Q4: 19 years old girl with BMI of 36 presented with hirsutism, irregular menstruation and acne. She is worried about why she is not yet getting her menstrual period like others. What is the initial step for management of this patient ?

A. Anti androgen medication.
B. Estrogen / progestogen pills.
C. Laser hair ablation.
D. Weight reduction.

(The patient seems to have PCOS due to the high BMI, acne and hirsutism so initially we start with weight reduction by diet and exercise if it didn't work we put her on Metformin or OCPs)

Answers:
1-B/2-C/3-A/4-D