

Biochemistry Team

Biomarkers of
ovarian cancer and cysts

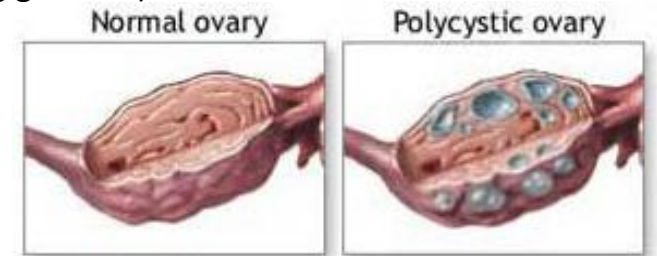


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- is for team notes
- is for important notes

POLYCYSTIC OVARIAN SYNDROME (PCOS)

- Formation of multiple small cysts in ovaries
- Affects 5-10% of women (*or even higher: 20% in some populations*)
- A major cause of infertility in women. associated with:
 - Obesity (40% of cases) (*or overweight*)
 - Hirsutism
 - Chronic anovulation (*with or without normal menstruation*)
 - Glucose intolerance (*insulin resistance*)
 - Hyperlipidemia (*high LDL&VLDL, low HDL*)
 - Hypertension
 - Menstrual disorders
 - Hypersecretion of leutinizing hormone (LH) and androgens (testosterone) (*causing hirsutism*).
 - Low levels of SHBG (sex hormone-binding globulin)
- Exact cause of the syndrome is unknown
- **May be multifactorial:**
 - Genetic factors and
 - Environmental factors
- **Suggested causes:**
 - Insulin resistance (*in 50% of patients*) and excessive androgen production are very common
 - Abnormalities in ovaries, adrenal & pituitary glands.



DIAGNOSIS DONE BY MEASURING: (Biochemical Tests)

- **Free testosterone** (*total testosterone is less sensitive than free testosterone, androgens are often moderately increased in PCOS*)
- **Sex hormone-binding globulin (SHBG)** (*often decreases in PCOS → tends to ↓ [total testosterone] & ↑ [free testosterone]*)
- **Leutinizing hormone (LH)** (*↑ in 60% of cases*)
- **Follicle stimulating hormone (FSH)** (*often normal in PCOS*) (*usually the lower end of the normal range*)
- **LH/FSH Ratio** (*↑ in > 90% of patients*)
- **Fasting glucose**
- **Insulin**
- **Lipids**
 - Ovarian ultrasound

30% of patients do not have ovarian cysts despite having symptoms

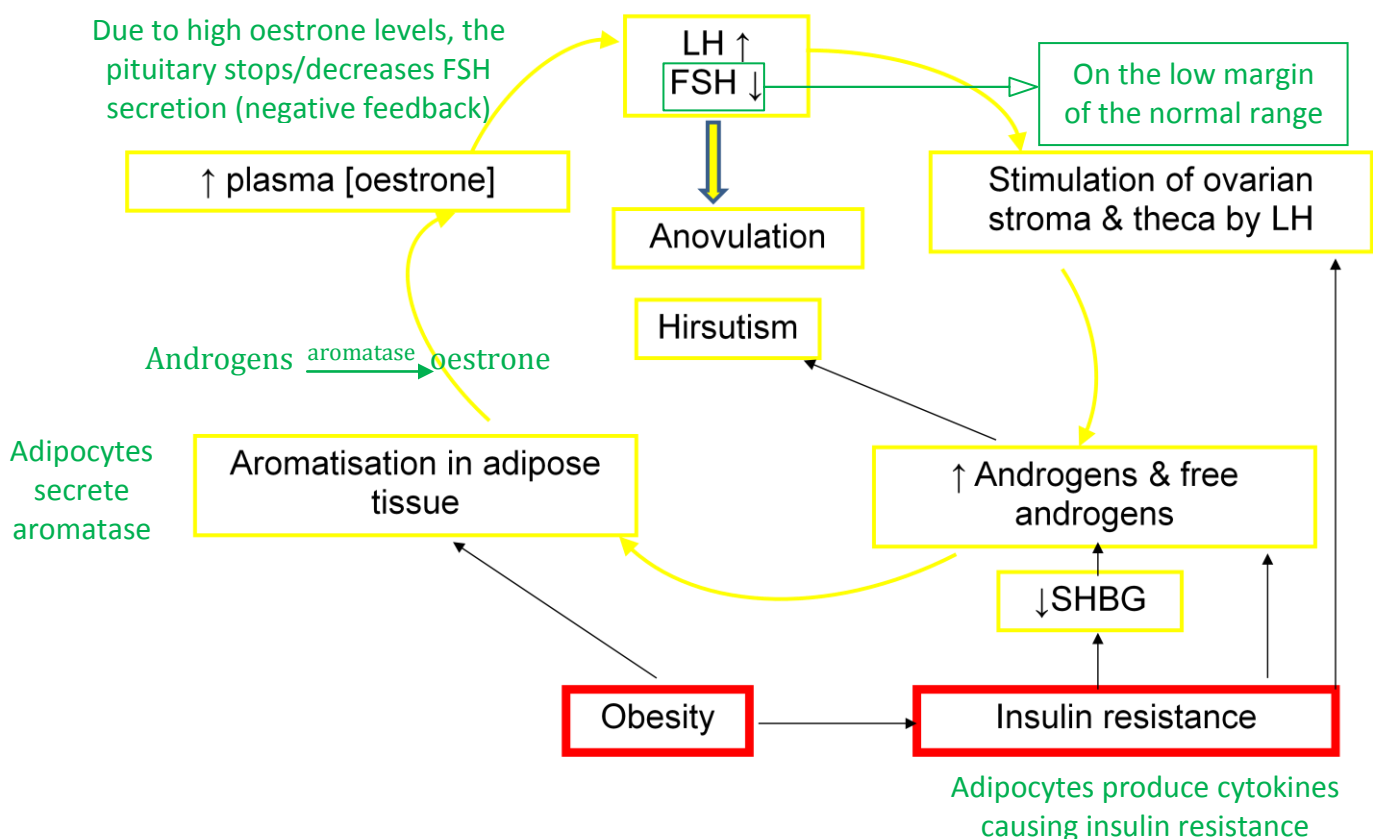
- Diagnosis cannot be based on TOTAL testosterone levels only. Free (active) testosterone is more sensitive.
- Calculating LH\FSH ratio is more sensitive than measuring LH or FSH separately.
- Hormones are usually measured in the mid-follicular phase.

DIAGNOSIS OF PCOS (CRITERIA)

The European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recommended that **at least 2 of the following 3 features are required for PCOS to be diagnosed:**

1. Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea (rule out pregnancy)
2. Hyperandrogenism (clinical evidence of androgen excess) → e.g. Hirsutism, acne, baldness...etc or hyperandrogenemia (biochemical evidence of androgen excess)
3. Polycystic ovaries (as defined on ultrasonography)

Biochemical, metabolic & endocrine changes in PCOS



Treatment of PCOS → try to break the cycle

Aim: interrupt the previous cycle (*obesity, insulin resistance, excess androgens...*)

- The management of PCOS depends on:
 - The severity of the condition
 - Individual circumstances (e.g. fertility is required or not)
- ↓ weight
- ↓ [LH] with oral contraceptives
- ↑ [FSH] with clomiphene, etc
- Estrogen replacement therapy in select women after careful risk counseling

OVARIAN CANCER



- A leading cause of death from gynecologic cancer (in USA)
- Results from malignant transformation of ovarian epithelial cells (*Most common type of ovarian cancer*)

Subtypes:

- Serous (46%): surface epithelial tumors
- Mucinous (36%): mucinous epithelial tumors
- Endometrioid (8%): endometrial tumors
- Other types of ovarian cancer:
 - Sex cord tumors
 - Stromal tumors
 - Germ cell tumors

Risk factors

- Nulliparity (*woman with no child birth or pregnancy*)
- Family history of ovarian cancer
- Family history of breast, ovarian, endometrial, or colon cancer (*may indicate a familial cancer susceptibility syndrome*)
- Mutations in **BRCA1** and **BRCA2** genes are the most common inherited ovarian cancer susceptibility syndrome.
- **Carriers of BRCA1 mutations have a risk of ovarian cancer approaching 44%**
- Premenopausal breast or ovarian cancer indicates higher risk for hereditary ovarian or breast cancer
- **Ashkenazi Jews** (endogamous ethnoreligious group): **have higher risk of ovarian cancer**
endogamy: is the custom of marrying within the limits of a clan or tribe.

BIOMARKERS AND DIAGNOSIS

- Epithelial ovarian cancer is commonly diagnosed at a **later stage** (**it is a silent cancer**)
 - Due to non-specific symptoms such as abdominal pain, bloating, early satiety, nausea
 - Most patients (75%) have advanced-stage tumor upon diagnosis
- **Diagnosis includes:**
 - History taking
 - Physical examination
 - Ultrasound
 - Determination of serum **CA-125** levels

Cancer antigen 125 (CA-125)

- The only serum marker of epithelial ovarian cancer
- A cell surface glycoprotein
- Normal ovarian epithelial cells do not express CA-125
- Normally absent in serum
- CA-125 is elevated in ovarian cancer
- >35 U/ml is considered positive

Any level <35 U/ml is considered normal due to physiological changes (it is considered absent)
High levels of CA-125 do NOT always indicate ovarian cancer (not sensitive)

- Recommended as an **annual test** for women with family history of ovarian cancer
- **CA-125 correlates with ovarian cancer stage**
- Elevated in:
 - 50% of patients with stage I (**NOT elevated in the other 50%**)
 - 90% of patients with stage II (**NOT elevated in the other 10%**)
 - >90% of patients with stage III and IV

It is not specific enough:

- False positive CA-125 conc. are found in benign conditions:
 - Endometriosis
 - Uterine leiomyoma
 - Pelvic inflammatory disease
 - During the first trimester of pregnancy
 - During menstruation
- Some patients (< 50 years) have elevated CA-125 due to unrelated malignant mass (**other than ovarian cancer**)

CA-125 is not a marker of choice for ovarian cancer screening in asymptomatic individuals due to:

- Low prevalence of ovarian cancer
- High false-positive rate

Useful in:

- Monitoring chemotherapy
- Monitoring success of surgery (de-bulking procedures)
- Annual testing for women with family history of ovarian cancer

CA-125 measurement is not usually used for diagnosis of ovarian cancer (not sensitive or specific)

- If it is used for diagnosis; two readings must be obtained, a baseline and another one (to check for changes of the levels)

It is not used in screening tests either.

Best use of CA-125 measurement is for monitoring a patient's recovery after treatment.

Questions:

1. The biomarker of ovarian cancer is:

- a) AFT
- b) CA-125
- c) HCG
- d) CEA

2. Breast cancer and ovarian cancer is commonly caused due to mutation in which one of the following genes:

- a) p35
- b) PTEN
- c) HER2
- d) BRCA 1&2

3. All of the following are elevated in Polycystic ovarian syndrome EXCEPT:

- a) LH
- b) Androgens
- c) SHBG (Sex hormone-binding globulin)
- d) b+c

4. Regarding the serum marker of epithelial ovarian cancer (CA125), which ONE of the following statements is correct:

- a) Normally present in serum
- b) Less 35 U/ml is considered positive
- c) CA-125 is not elevated in ovarian cancer
- d) CA-125 is associated with stages of ovarian cancer

5. False positive CA-125 concentration are found in all of the following conditions EXCEPT:

- a) Endometriosis
- b) Uterine leiomyoma
- c) Ovarian cancer
- d) Pelvic inflammatory disease

Answers:

1.b 2.d 3.c 4.d 5.c