3- Biomarkers of ovarian cancer and cysts

Polycystic ovarian syndrome (PCOS)

Overview

- Formation of multiple small cysts in the ovaries affecting 5-10% of women (20% in some populations).
- It is a major cause of infertility in women

Correlates to:

- Family history
- Obesity (40%)
- Hirsutism - Chronic anovulation
- Glucose intolerance - **Insulin resistance**
- Hyperlipidemia - Hypertension
- Menstrual disorders
- Hypersecretion of luteinizing hormone (**LH**) and **androgens** (testosterone),
- Low levels of **SHBG** (sex hormone-binding globulin)

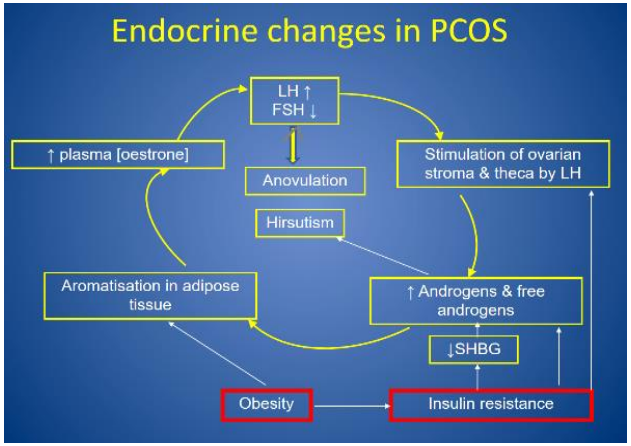
Causes

Exact cause of the syndrome is unknown. May be multifactorial (genetic and environmental). **Probable causes:**

- Insulin resistance causes excessive androgen production in ovaries (common)
- **Abnormalities in ovaries, adrenal and pituitary gland**

Diagnosis

European Society for Human Reproduction & Embryology (**ESHRE**) and American Society for Reproductive Medicine (**ASRM**) recommendation:



- **At least two of the following features are required for PCOS diagnosis:**
  1. Oligo-ovulation or anovulation: manifested as oligomenorrhea or amenorrhea
  2. Hyperandrogenism (clinical and biochemical evidence of androgen excess)
  3. Polycystic ovaries (as defined by ultrasonography)
- **PCOS diagnosis done by measuring:**
  - High Free testosterone (total testosterone is less sensitive)
  - Low Sex hormone-binding globulin (SHBG)
  - High Luteinizing hormone (LH) in 60% cases
  - Normal or decreased Follicle stimulating hormone (FSH)
  - Fasting blood glucose, Insulin, and Lipids
- **Ovarian ultrasound** (30% of patients do **not** have ovarian cysts despite having symptoms)

Treatment

- Aim of treatment: interrupt the cycle of obesity, insulin resistance, excess androgens.
  - Reduce LH levels (by oral contraceptives)
  - Reduce body weight
  - Increase FSH levels (by clomiphene, etc.)
  - Estrogen replacement therapy (In selected women after careful risk counseling)

Ovarian cancer

Overview

- Ovarian cancer is a leading cause of death because of gynecologic cancer
- Most common type of ovarian cancer is due to malignant transformation of ovarian **epithelial cells**, Subtypes:
  - Serous (46%): surface epithelial tumors
  - Mucinous (36%): mucinous epithelial tumors
  - Endometrioid (8%): endometrial tumors

Risk factors

- Nulliparity (woman with no child birth or pregnancy)
- Family history of breast, ovarian, colorectal cancer
  - **Mutations** in BRCA1 and BRCA2 genes (most common)
  - **Carriers** of BRCA1 mutations have a cancer risk of 44%
  - **Premenopausal** breast cancer or ovarian cancer indicates higher risk for hereditary or breast cancer
  - **Ashkenazi Jews** have higher risk of ovarian cancer.

Biomarkers and diagnosis

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

CA-125

- The only serum marker of **epithelial ovarian cancer**
- It is a cell surface glycoprotein expressed in the epithelium of all tissues. But normally absent in serum.
- CA-125 is elevated in ovarian cancer (>35 U/ml is considered positive)
- Recommended as **an annual test** for women with family history of ovarian cancer
- **CA-125 is associated with stages of ovarian cancer.** Elevated in:
  - 50% of patients with stage I
  - 90% of patients with stage II
  - >90% of patients with stage III and IV
- **A non-specific marker**, as false positive CA-125 conc. are found in **benign conditions**:
  - Endometriosis - Uterine leiomyomas - Pelvic inflammatory disease
  - During the first trimester of pregnancy - During menstruation
  - Some patients (< 50 years) have ↑ CA-125 due to unrelated malignant mass
- **CA-125 is not a marker of choice for ovarian cancer screening due to:**
  - Low prevalence of ovarian cancer, and high false-positive rate
- **Useful in Monitoring:**
  - patient's response to chemotherapy
  - Success of surgery (de-bulking procedures)

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