

Biomarkers of ovarian cancer and cysts

Reproduction System Block

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Objectives

By the end of this lecture, the Second Year students will be able to:

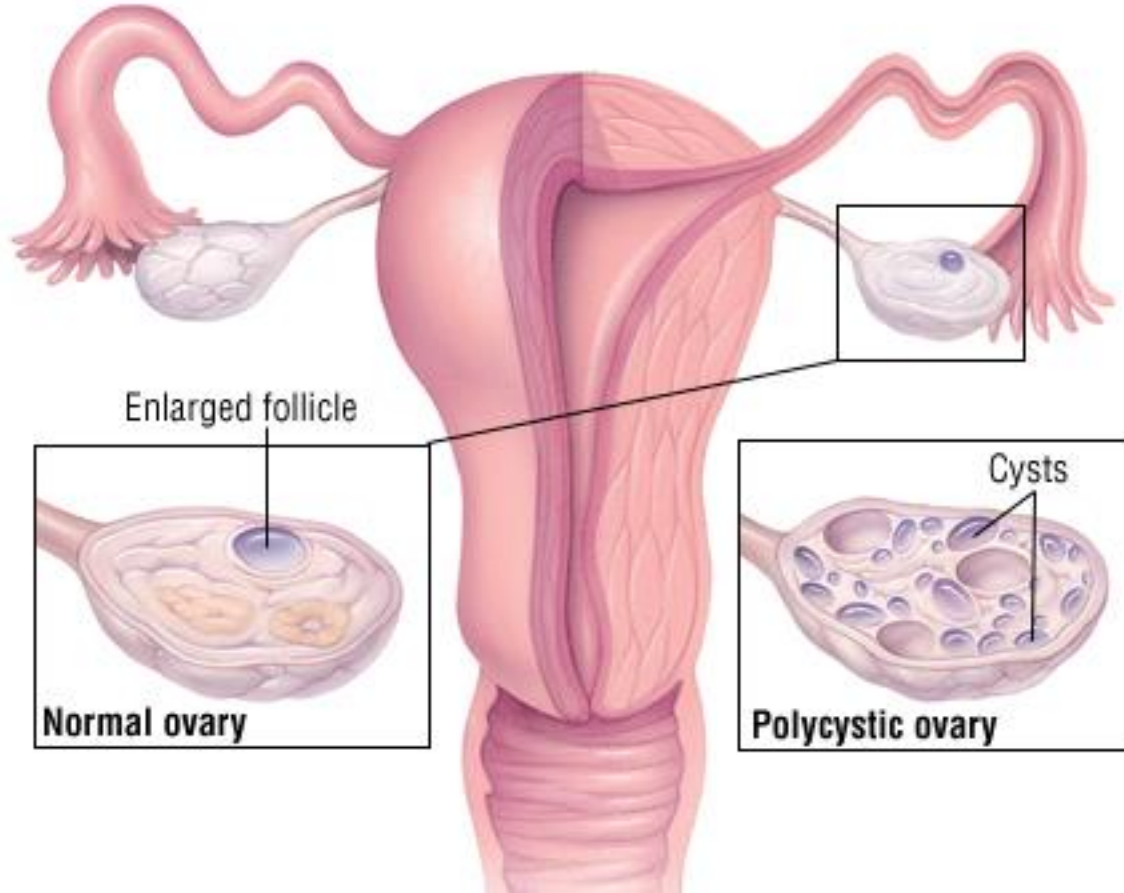
- Discuss the risk factors and possible causes of polycystic ovarian syndrome (PCOS) and ovarian cancer
- Comprehend the role of insulin resistance and hypersecretion of androgens in the development of PCOS
- Identify avenues for the diagnosis and treatment of PCOS and ovarian cancer
- Assess the diagnostic significance of CA-125 in ovarian cancer

Overview

- Polycystic ovarian syndrome (PCOS)
 - Causes
 - Endocrine changes
 - Diagnostic criteria
 - Treatment
- Ovarian cancer
 - Types, risk factors
 - Diagnosis
 - CA-125 biomarker

Polycystic ovarian syndrome

- Formation of multiple small cysts in the ovaries
- Affects 5-10% of women (20% in some populations)
- A major cause of infertility in women



Polycystic Ovarian Syndrome

Polycystic ovarian syndrome

Strongly correlated to:

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

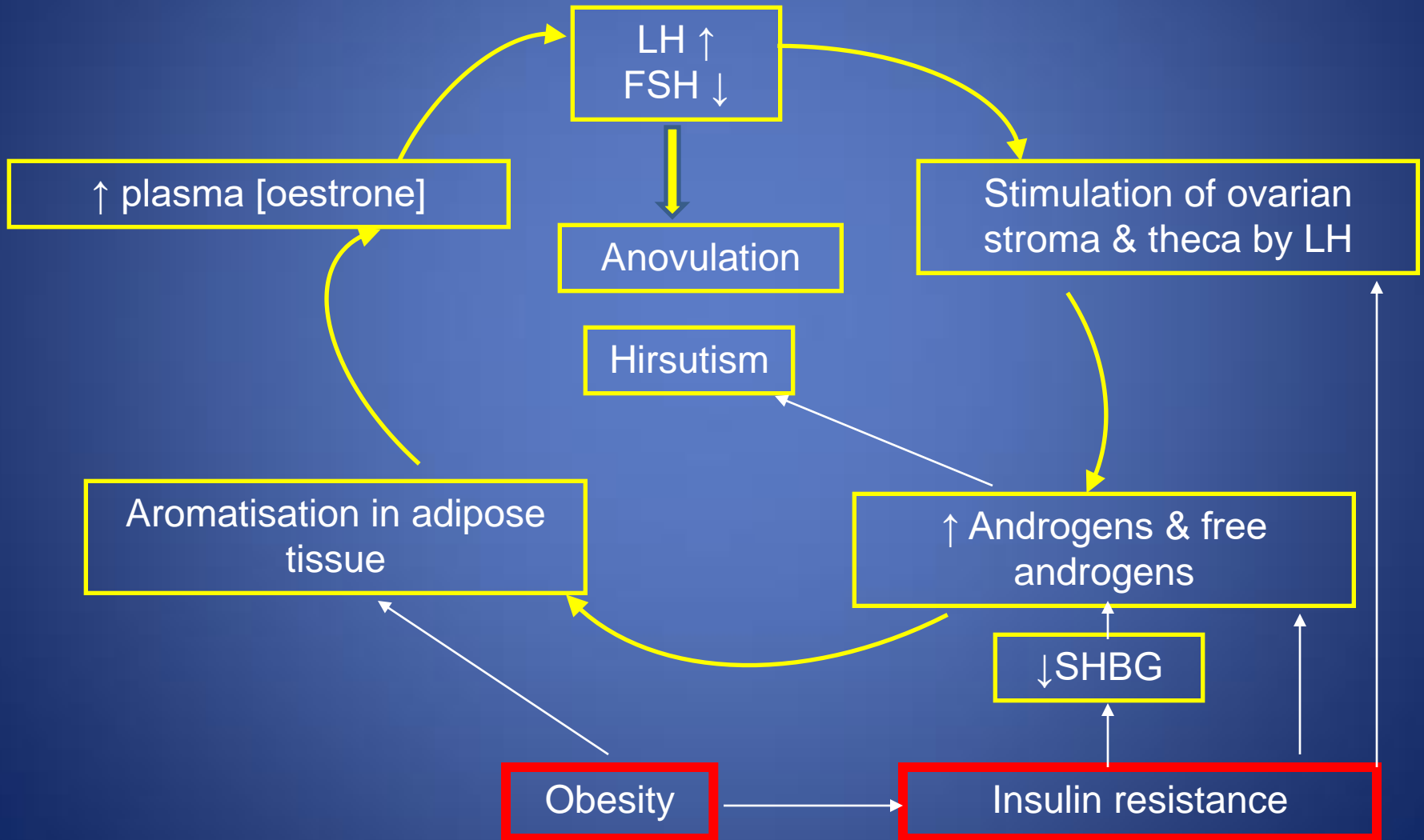
Polycystic ovarian syndrome

- 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 glands

Endocrine changes in PCOS



Diagnostic criteria for PCOS

- 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)

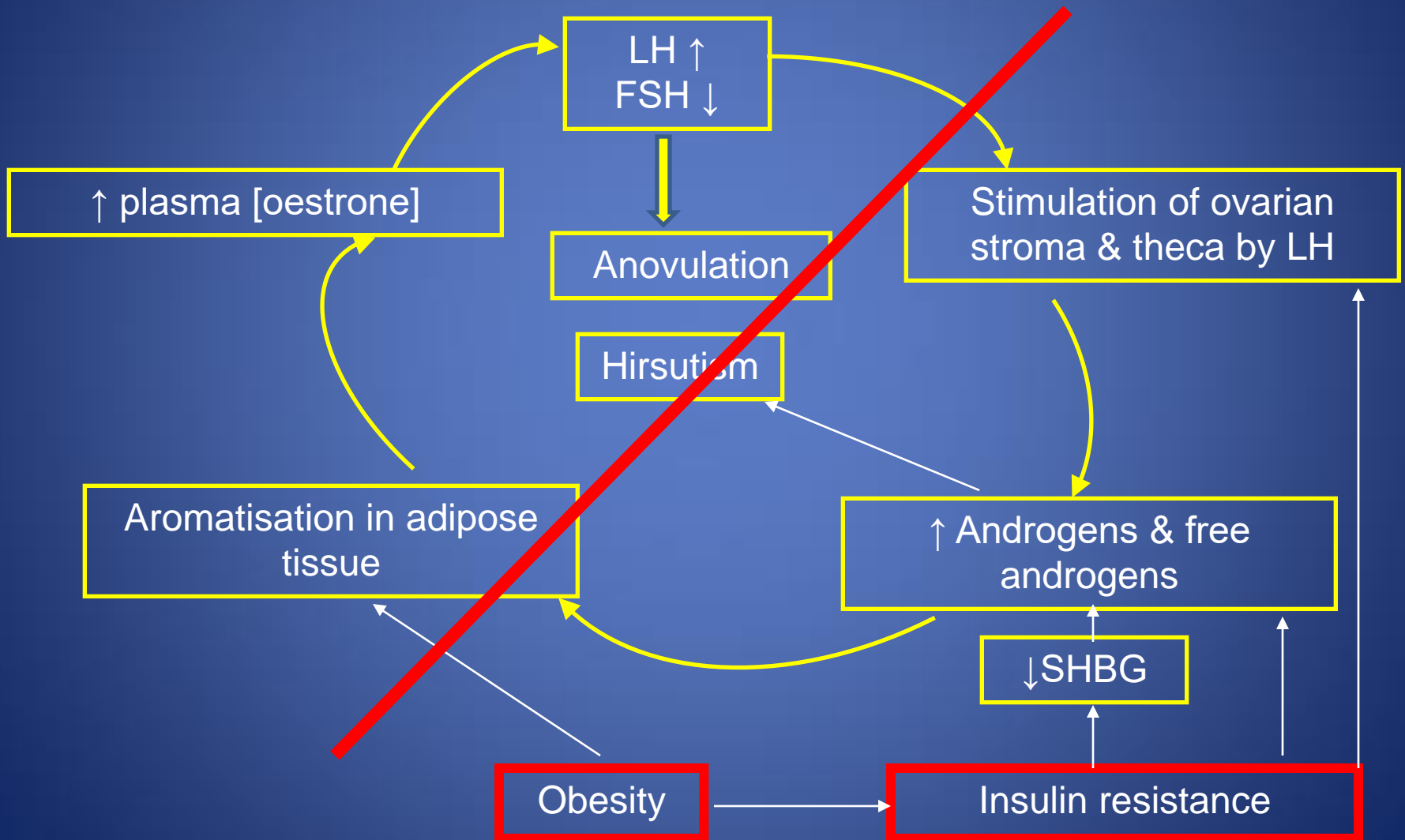
Polycystic ovarian syndrome

- Diagnosis done by measuring:
 - Free testosterone (total testosterone is less sensitive; androgens are increased in PCOS)
 - Sex hormone-binding globulin (SHBG; decreased in PCOS)
 - Leutinizing hormone (LH; high in 60% cases)
 - Follicle stimulating hormone (FSH); usually normal in PCOS

Polycystic ovarian syndrome

- Diagnosis done by measuring:
 - Fasting blood glucose
 - Insulin
 - Lipids
- Ovarian ultrasound
 - 30% of patients do not have ovarian cysts despite having symptoms

Treatment of PCOS: Break the cycle



Treatment of PCOS

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 select women after careful risk counseling

Ovarian cancer

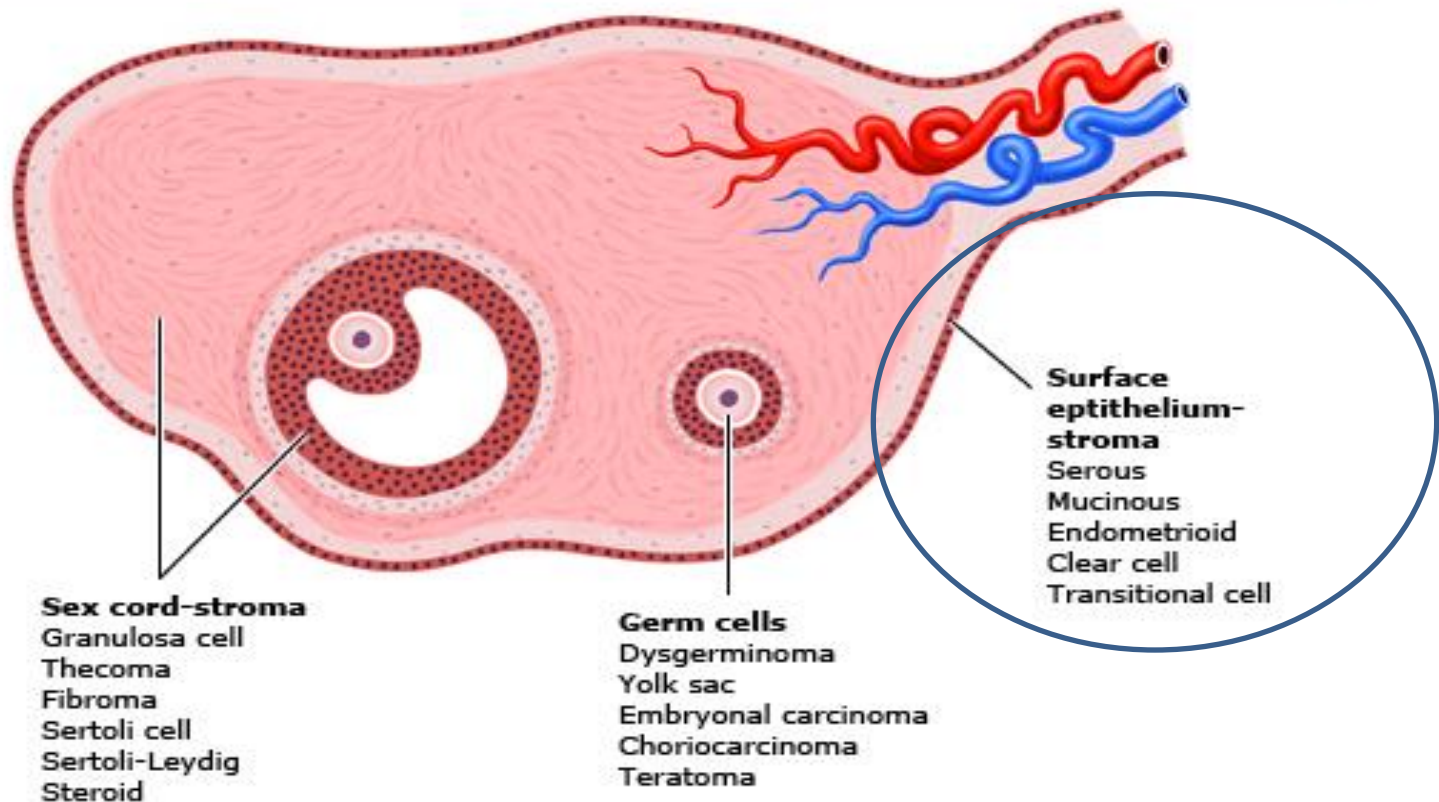
- A leading cause of death because of gynecologic cancer
- Due to malignant transformation of ovarian epithelial cells
- Most common type of ovarian cancer

Ovarian cancer

Subtypes:

- Serous (46%): surface epithelial tumors
- Mucinous (36%): mucinous epithelial tumors
- Endometrioid (8%): endometrial tumors

Origins of ovarian tumors



Some epithelial ovarian carcinomas may originate in the fallopian tube epithelium.

Ovarian cancer

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%

Ovarian cancer

- Premenopausal breast cancer or ovarian cancer indicates higher risk for hereditary or breast cancer
- Ashkenazi Jews have higher risk of ovarian cancer

Ovarian cancer

Biomarkers and diagnosis

- Epithelial ovarian cancer is commonly diagnosed at a later stage
- Due to non-specific symptoms such as abdominal pain, bloating, early satiety, nausea, etc.
- Most patients (75%) have advanced-stage tumor upon diagnosis

Ovarian cancer

- Diagnosis includes:
 - History taking
 - Physical examination
 - Ultrasound
 - Measurement of serum CA-125 levels

Cancer antigen 125 (CA-125)

- The only serum marker of epithelial ovarian cancer
- A cell surface glycoprotein expressed in the epithelium of all tissues
- Normally absent in serum
- CA-125 is elevated in ovarian cancer
- >35 U/ml is considered positive

Cancer antigen 125 (CA-125)

- 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

Cancer antigen 125 (CA-125)

- A non-specific marker
- 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 elevated CA-125 due to unrelated malignant mass

Cancer antigen 125 (CA-125)

- CA-125 is not a marker of choice for ovarian cancer screening due to:
 - Low prevalence of ovarian cancer
 - High false-positive rate
- Useful in:
 - Monitoring patient's response to chemotherapy
 - Success of surgery (de-bulking procedures)
 - Annual testing for women with family history of ovarian cancer

Take home message

- PCOS is strongly correlated to insulin resistance and endocrine abnormalities.
- Although a nonspecific biomarker, CA-125 is important for staging and follow-up of ovarian cancer treatment

References

- Sheehan, MT. Polycystic ovarian syndrome: diagnosis and management. *Clin. Med. Res.*, 2003, 2(1): 13-27
- Sundar, S. Diagnosis of ovarian cancer, *BMJ*, 2015, 351:h4443.