Outline and Objectives:

- Polycystic ovarian syndrome (PCOS)
  - Biomarkers and diagnosis
- Ovarian cancer
  - Types
  - Risk factors
  - Biomarkers and diagnosis (CA-125)

- **Blue = extra info from the book**

Biochemistry of the Reproductive Block

Biomarkers of ovarian cancer and cysts

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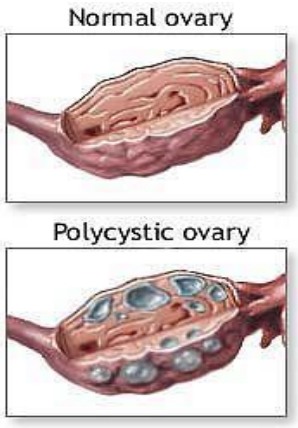
Polycystic ovarian syndrome: (mostly benign)



- Formation of multiple small cysts in the ovaries (affects the ovarian functions)
- Affects 5-10% of women worldwide (the rate increase in white women)
- A major cause of infertility in women
- The onset of PCOS is perimenarchial, chronic and progress slowly.

Associated with (this disorder can present by many ways):

- Obesity (40% of cases)
- Hirsutism (hair growth)

Obese: Married → infertility

Single → hirsutim (androgen)

- Chronic anovulation
- Glucose intolerance [The patient could be diabetic (also could be due to obesity → insulin resistance or just GIT glucose intolerance]
- Insulin resistance
- Hyperlipidemia or dyslipidemia.
- Hypertension
- Menstrual disorders
- Hypersecretion of leutinizing hormone (LH) and androgens (testosterone) Why?*
- *the ovaries are not responsive to LH, as a result, decreasing the –ve feedback to the anterior pituitary. This also explain the increased secretion of androgens.
- Low levels of SHBG (sex hormone-binding globulin) which increases the effects of androgens since the free form is the active form.

Polycystic ovarian syndrome it is not a single disease it is a combinations of factors which will cause this disease.

Etiology:

- Exact cause of the syndrome is unknown (idiopathic)
- May be multifactorial (genetic and environmental) (lifestyle)
- Excessive androgen production and insulin resistance in *in* 50% of patients is very common in patients

Peripheral tissue Insulin resistance → pancreas will secret more insulin to compensate→ Hyperinsulinemia →↑ Androgens

- Abnormalities in ovaries, adrenal and pituitary glands are also observed

Diagnosis and investigation: confirm the diagnosis by clinical examination and ovarian scan

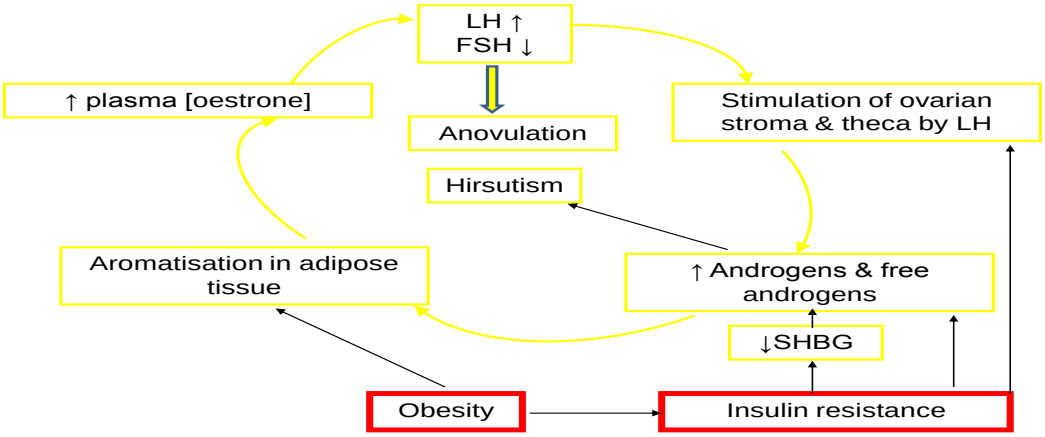
- Measuring free testosterone.
- Sex hormone-binding globulin *(SHBG; often decreases in PCOS and hirsutism → tends to ↑ [total testosterone]& ↓ [free testosterone])* [SGBG is decreased because of the insulin resistance]
- Leutinizing hormone *(LH; ↑ in 60% of cases)*

All of these biochemical tests are not a definitive diagnosis

- Follicle stimulating hormone *(FSH; often normal in PCOS)*
- LH/FSH Ratio *(↑ in > 90% of patients)*
- Fasting glucose [increased]
- Insulin [increased]
- Lipids [Dyslipidimia= decreased HDL & increase LDL+ Total Cholesterol]
- **Ovarian ultrasound** (30% of patients do not have ovarian cysts despite having symptoms).

LH is increased & FSH is either normal or decreased] → 90% of the pt have elevated LH/FSH ratio.

Biochemical, metabolic & endocrine changes in PCOS

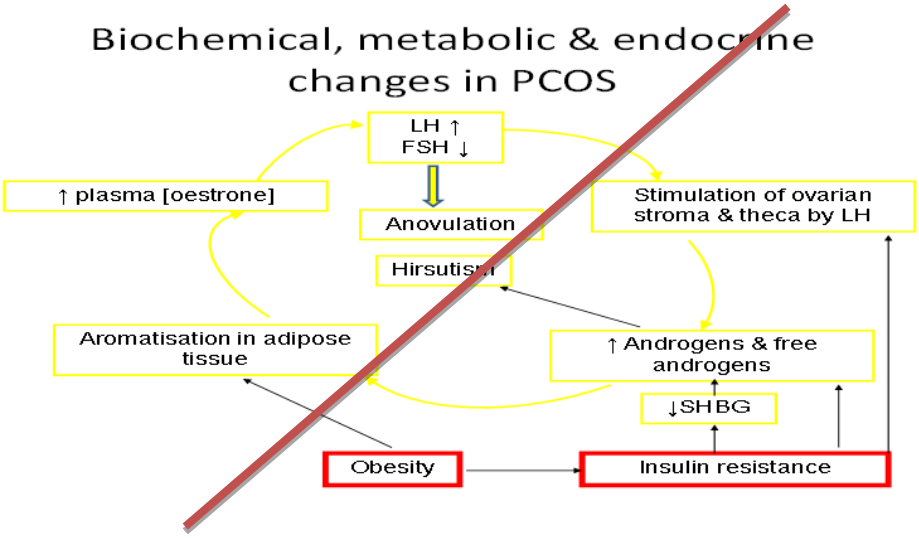


[Obesity → 1. Subcutaneous fats secretes substance that cause insulin resistance→ insulin resistance in turn:
(A)↓Synthesis of hormone binding globins → ↑ Androgens (especially the free form)

(B) stimulate ovaries to release more Androgens (In insulin resistance all peripheral tissue will be resistant except the ovaries→↑ Ovarian Androgen(also due to ↑ LH)

→2. ↑ release of Aromatse (enzyme responsible of converting Androgens into Estrogen)→AP to ↓ FSH or it could be normal]

Treatment of PCOS: try to break the cycle



Treatment: limited treatment (we can consider removal of the ovaries)

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

- ↓ [LH] with oral contraceptives
- ↓ weight
- ↑ [FSH] with clomiphene.
- Replacement therapy in select women after careful risk counseling. (high risk of developing breast and ovarian cancer)

Glucophage (metformin) is commonly used for the treatment of diabetic and non diabetic conditions of PCOS. Also, it normalizes menstrual cycle and improves conception rates.

Estrogen replacement therapy increases the incidence of invasive breast cancer, and venous clot formation. Conversely it reduces bone loss, colon polyp formation, and menopausal symptoms.

Ovarian cancer:

- A leading cause of death in women because of gynecologic cancer
- Due to malignant transformation of ovarian epithelial cells (most common type of ovarian cancer)

Subtypes:

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

epithelial ovarian cancer

- Sex cord tumors
- Stromal tumors
- Germ cell tumors

other ovarian cancer

The transformed epithelial cells are histologically indistinguishable from peritoneal epithelium.

Because these tumors arise from the ovarian surface epithelium, malignant cells may shed into the peritoneal cavity circulate with peritoneal fluid. Also, surface tumor deposits are identified along the right paracolic gutter, right hemidiaphragm, small and large intestine, and omentum. Tumor spread may occur via pelvic and aortic lymph nodes.

Risk factors:

- Nulliparity (woman with no child birth or pregnancy)
- 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. (BRCA1 and BRCA2 = tumor suppressant or DNA repairing genes)
- Carriers of BRCA1 mutations have a cancer risk of 44%
- Premenopausal breast cancer indicates higher risk for hereditary ovarian or breast cancer
- Ashkenazi Jews have higher risk of ovarian cancer

The mutation is caused by environmental, genetics, and lifestyle factors.

Lynch syndrome II increases the lifetime risk of ovarian cancer.

Diagnosis and prevention by regular ovarian scan

Biomarkers and diagnosis:

- Epithelial ovarian cancer is commonly diagnosed at a later stage (terminal stage) why? Because they grow silently and there is no specific marker for it
- The presenting symptoms of epithelial ovarian cancer are vague. That's why it is diagnosed in the terminal stage
- Due to non-specific symptoms such as diffuse abdominal pain, blotting, early satiety, nausea, dyspepsia and increase abdominal girth.
- Most patients (75%) have advanced-stage tumor upon diagnosis
- Diagnosis includes (History taking, Physical examination, Ultrasound, and Determination of serum CA-125 levels)

Cancer antigen 125 (CA-125): it is not a specific marker

- The only serum marker of epithelial ovarian cancer
- A cell surface glycoprotein expressed in the epithelium of all tissues (means it's not normally found in the serum)
- 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
- Recommended as an annual test for women with family history of ovarian cancer and high risk of developing it for instance people who have mutations in the BRCA genes.
- CA-125 is associated with stages of ovarian cancer [↑stage=↑ positivity of the disease]
- **Elevated in:**
  - 50% of patients with stage I
  - 90% of patients with stage II
  - >90% of patients with stage III and IV (terminal stage)
- **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

- **CA-125 is not a marker of choice for ovarian cancer screening due to:** [not used as screening test]
  - Low prevalence of ovarian cancer
  - High false-positive rate
  - Not used for "asymptomatic screening"
- **Useful in:**
  - Monitoring patient's response to chemotherapy.
  - Success of surgery (de-bulking procedures).
  - De-bulking: is the surgical removal of part of a malignant tumour which cannot be completely excised.
  - Annual testing for women with family history of ovarian cancer.

Case scenario

- Mayar a 28-year-old obese woman presented to her physician with irregular periods, excessive hair growth on her face and abdomen, and family history revealed diabetes in both her mother and paternal grandparents. Hormonal profile and biochemical test were performed. The biochemical result show ↑ free testosterone, LH, glucose and insulin. Whereas, Sex hormone-binding globulin *and FSH were decreased.*

  What is the most likely diagnosis??

  Poly cystic ovarian syndrome

  What the best diagnostic method to justify your answer??

  Ovarian scan (ultrasound)

- Jeeda a 64 year old female came to the local clinic complaining about abdominal pain, bloating, satiety, dyspepsia, nausea, and increase abdominal girth. Jeeda family has a history of maternal endometrial cancer. On further questioning Jeeda has never had children with two failed marriages. The doctor found later that her two sisters have high mutation rate on BRCA genes.

  What is the most likely diagnosis??

  Ovarian cancer

Summary

Polycystic ovarian syndrome:

Associated with:

- Obesity (40% of cases)
- Hirsutism
- Chronic anovulation
- Glucose intolerance
- Hyperlipidemia
- Hypertension
- Menstrual disorders
- Hypersecretion of leutinizing hormone (LH) and androgens

Exact cause of the syndrome is unknown

Treated by: interrupting the cycle

- ↓ [LH] with oral contraceptives
- ↓ weight
- ↑ [FSH] with clomiphene, etc
- Estrogen replacement therapy in select women after careful risk counseling

Ovarian cancer:

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)

Diagnosis includes:

- History taking
- Physical examination
- Ultrasound
- Determination of serum CA-125 levels