جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

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Biomarkers of Ovarian Cancer

Biochemistry Team 437

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Reproductive block

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Objectives & Overview:

شرحنا لكم المحاضرة كاملة شوفو الفيديو بالدرايف

Objectives:

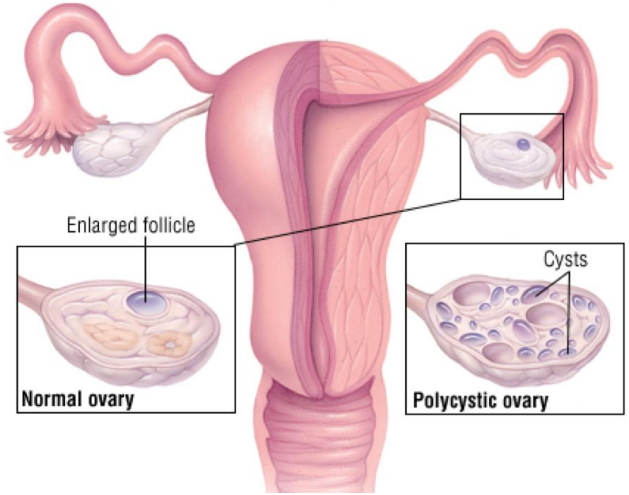
- Discuss the risk factors and possible causes of polycystic ovarian syndrome (PCOS) and ovarian cancer
- Comprehend the role of insulin resistance and hypersecretion of androgens in the development of PCOS
- Identify avenues for the diagnosis and treatment of PCOS and ovarian cancer
- Assess the diagnostic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



Multiple cysts which are formed of immature follicles with arrested growth during development**(Due to constant secretion of LH rather than LH Surge)** affecting menstrual cycle and causing infertility.

Polycystic Ovarian Syndrome

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Strongly correlated to:

Family History	Obesity (40%)	Hirsutism	Chronic Anovulation	Glucose Intolerance	Insulin Resistance
Hyperlipidemia	Hypertension	Hypersecretion of LH & androgens (testosterone)[1]		Low levels of SHBG (sex hormone binding globulin)[2]	

[1]Common feature

[2]SHBG binds mainly to testosterone

Causes:

Exact cause of the syndrome is **unknown,** may be multifactorial (genetic and environmental).

Probable causes:

- Insulin resistance (usually starts with obesity) causes excessive androgen production in ovaries (common)
- Abnormalities in ovaries, adrenal and pituitary glands

Endocrine Changes in PCOS

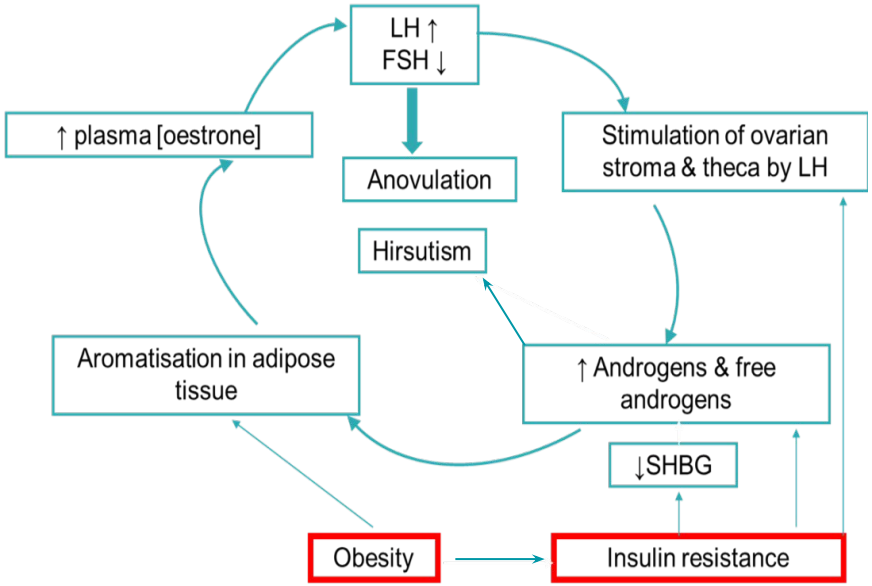
Obesity leads to 2 things:
A) Insulin resistance, which will lead to hyperinsulinemia.
B) The increase in adipose tissue will increase aromatisation of androgens to estradiol by the aromatase present in adipose tissue.

A) The hyperinsulinemia has 2 effects:
1- Insulin affects the ovary directly and stimulates androgen production.
2- Affects the liver to decrease the formation of SHBG.
⇒ *Net results:* increase in the amounts of free androgens leading to:

- Hirsutism and other symptoms.
- Increase in the pulsatile secretion of GNRH, which favors the production of LH over FSH. LH will be very high while FSH is low/normal.
- Increase in androgen conversion to estrogen in adipose tissue, which will increase estrogen → affects GNRH secretion→ decrease the secretion of FSH from AP

⇒ So in PCOS, the ratio between FSH and LH is important. LH is at least double FSH.

B) the continuous high levels of LH and the decrease in FSH and progesterone will lead to anovulation and arrested growth of the follicles leading to PCOS



Diagnostic Criteria for PCOS

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

At least <u>two</u> of the following features are required for PCOS diagnosis:

1- Oligo-ovulation or anovulation	2- Hyperandrogenism	3- Polycystic ovaries[2]
manifested as oligomenorrhea or amenorrhea	clinical and biochemical evidence of androgen excess[1]	as defined by ultrasonography

1- Clinical: acne, hirsutism, alopecia
Biochemical : hyperandrogenemia " increase androgens in blood"
2- Not always clear. this is why 2 out of these symptoms is sufficient for diagnosis

Diagnosis for PCOS Done by Measuring

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Free testosterone (total testosterone is less sensitive; androgens are increased in PCOS)

Sex hormone-binding globulin (SHBG; decreased in PCOS)

Luteinizing hormone (LH; high in 60% cases)

Follicle stimulating hormone (FSH); usually normal in PCOS

Fasting blood glucose or 2H OGTT

- Insulin
- Lipids

- LH: FSH ration is at least 2
- Glucose is measured to check for insulin resistance

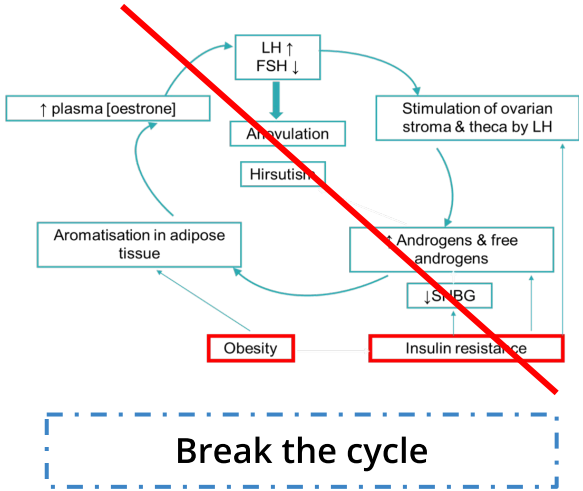
Ovarian Ultrasound

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

Treatment of PCOS

Aim of treatment:
Interrupt the cycle of obesity, insulin resistance, excess androgens

- Reduce LH levels[1] (by oral contraceptives)
- Reduce body weight[2]
- Increase FSH levels (by clomiphene,etc.)
- Estrogen replacement therapy[3]
  – In select women after careful risk counseling "risk of cancer"
- Give combined oral contraceptives which have estrogen and progesterone[4]
- Provide metformin "oral hypoglycemic" for insulin resistance



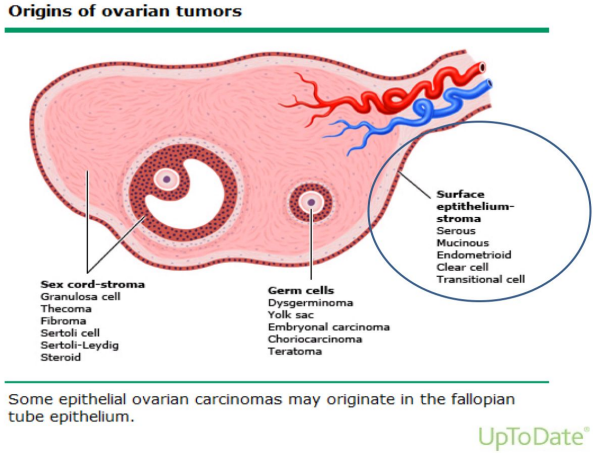
1| can be done by Decreasing androgens → decreases LH
2| More sensitive to insulin → lower insulin levels in the blood - androgen excess decreased
3| Increase FSH production and increase synthesis of SHBG → decreases free testosterone
4| To make the cycle ovulatory

Ovarian Cancer

- A leading cause of death because of gynecological cancer
- Due to **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



Ovarian Cancer

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Risk factors:

- Nulliparity (woman with no childbirth or pregnancy)
- Family history of breast, ovarian, colorectal cancer
- Mutations in BRCA1 and BRCA2 genes (most common, they are tumor suppressor genes associated with cancer)
- **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

Biochemarkers and diagnosis

- **Epithelial ovarian cancer** is commonly diagnosed at a later stage.
- Due to **nonspecific symptoms** such as abdominal pain, bloating, 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 *a biomarker discussed next slide*

Cancer Antigen in 125 (CA-125)

- A cell surface glycoprotein expressed in the epithelium of all tissues.
- The only serum marker of epithelial ovarian cancer.
- CA-125 is elevated in ovarian cancer.
- Normally absent in serum.
- It is usually not present in the serum, if its present >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 & IV
- A non-specific marker.
- Some patients (< 50 years) have elevated CA-125 due to unrelated malignant mass* .

*If a postmenopausal woman has a high serum level of CA125, she has a high chance of having an ovarian cancer.

Cancer Antigen in 125 (CA-125)

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

1. High false-positive rate

False positive CA-125 conc. are found in benign conditions and are usually not associated with postmenopausal women:

- Endometriosis
- Uterine leiomyomas
- Pelvic inflammatory disease
- During the first trimester of pregnancy
- During menstruation

2. Low prevalence of ovarian cancer

- **Useful in:**
  - Monitoring patient's response to chemotherapy.
  - Success of surgery (de-bulking procedures removing a tumor mass).
  - Annual testing for women with family history of ovarian cancer.

Take Home Messages

- 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.

Extra resource suggested by the doctor:
Mcmaster pathophysiology review - PCOS

Summary

POS: Is the formation of multiple small cysts in the ovaries, due to idiopathic causes, however the probable causes are Insulin resistance or Abnormalities in the glands regulating the ovaries.

Diagnostic criteria (Atleast two of the following)	Polycystic on the ovaries		Oligo-ovulation or anovulation		Hyperandrogenism	
Diagnosis measurements	Free testosterone	LH	Sex hormone binding globulin (SHBG)	FSH	-Insulin -Lipids	Fasting blood glucose
Treatment	Reduce LH levels[1] (by oral contraceptives)		Reduce body weight[2]	Increase FSH levels (by clomiphene)	Estrogen replacement therapy[3] In select women after careful risk counseling	
Ovarian cancer Risk factors	Nullparity		Family history	Jews	GENETIC **-BRACA 1** **-BRACA 2**	
Ovarian cancer biomarkers **(CA-125)**	CA-125 is not a marker of choice for ovarian cancer screening due to: • High false positive • Low prevelance with ovarian cancer				Uses: • Monitoring patient's response to chemotherapy. • Success of surgery (de-bulking procedures removing a tumor mass). • Annual testing for women with family history of ovarian cancer.	

MCQs:

1) Oligo-ovulation or anovulation manifested
A. Amenorrhea
B. Hypomenorrhea
C. Menorrhagia
D. Dysmenorrhea

2) The only serum marker of epithelial ovarian cancer
A. CA-135
B. CA-125
C. CA-120
D. CA-130

3) Which of the following is wrong about the diagnostic methods for polycystic ovarian syndrome
A. Measuring Sex hormone-binding globulin
B. Measuring LH
C. Measuring FSH
D. Measuring free estrogen

4) Which one of the following is not a subtype of ovarian cancers
A. Serous
B. Mucinous
C. Endometrioid
D. Fibroid

5) Carriers of BRCA1 mutations have a cancer risk of
A. 44%
B. 70%
C. 91%
D. 15%

6) Which one of the following is not recommended during the treatment of polycystic ovarian syndrome
A. Oral contraceptives
B. Exogenic androgen intake
C. Reduce body weight
D. Interrupt insulin resistance

1- A
2- B
3- D
4- D
5- A
6- B

تم بحمد الله ..

بنهاية هذه المحاضرة، نكون قد أتممنا بحمدالله جميع محاضرات مادة الكيمياء الحيوية في سنوات العلوم الأساسية، إن أصبنا فمن الله وإن اخطأنا فمن أنفسنا والشيطان.
نسأل الله أن نكون قد وفقنا لعمل نافع ومفيد.

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نسأل الله لكم التوفيق جميعاً في مسيرتكم العلمية و العملية.

رهام الحلبي ، معاذ الحمود

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Girls team

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- مشاعل القحطاني
- نورة بن حسن
- رهف الشنيبر
- ارجوانة العقيل
- شهد الجبرين
- ريناد الغريبي

Boys team

Team leaders

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