BIOMARKERS OF OVARIAN CANCER AND CYSTS.

* **Please check out this link to know if there are any changes or additions.**

Revised by

هشام الغفيلي   &   خولة العماري

Color index: Important | Doctors notes | Further explanation.

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

Polycystic ovarian syndrome

What is it?	Formation of **multiple small** cysts in the <u>ovaries.</u>
Epidemiology:	• Affects **5-10%** of women (20% in some populations). Percentage of PCOS depends upon the race • A **major** cause of infertility in women.
Causes:	• <u>Exact</u> cause of the syndrome is **unknown.** • May be **multifactorial** (genetic and environmental - lifestyle-) • <u>**Probable causes:**</u> o **Insulin resistance** causes excessive <u>androgen</u> production in ovaries (common). o **Abnormalities in: ovaries, adrenal** and **pituitary glands.** Leading to increased production of androgens and luteinizing hormone

Strongly correlated to:	Metabolic syndrome related:		
	Obesity (40% of women with PCOS are obese)	**Insulin resistance.** And type 2 DM	**Glucose intolerance.**
	Hyperlipidemia.	**Hypertension.**	**Family history. (genetic predisposition)**
	Hormonal related:		
	Chronic anovulation.	**Menstrual disorders.**	**Hirsutism.**
	<u>Hyper</u>secretion of luteinizing hormone (**LH**) and androgens (**testosterone**)	<u>Low</u> levels of **SHBG** (sex hormone-binding globulin.) Levels of free testosterone will go up.	

Polycystic ovarian syndrome – Diagnosis:

❖ **DIAGNOSIS DONE BY MEASURING:**

Free testosterone (Total testosterone)	Less sensitive; androgens are **increased** in PCOS.
Sex hormone-binding globulin (SHBG)	**Decreased** in PCOS.
Leutinizing hormone (LH)	**High** in 60% cases. (so it leads to –ve feedback on GnRH)
Follicle stimulating hormone (FSH)	**Normal** or decreased in PCOS.
Fasting blood glucose	Since PCOS is strongly correlated with glucose intolerance.
Insulin	Since PCOS is strongly correlated with insulin resistance.
Lipids	Since PCOS is strongly correlated with hyperlipidemia.

Ovarian ultrasound:30% of patients do not have ovarian cysts despite having symptoms.(which means you can't confirm the diagnosis by ultrasound).

❖ **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:		
Oligo-ovulation or anovulation	**Hyper-androgenism**	**Polycystic ovaries**
Manifested as **oligo**menorrhea or **a**menorrhea	<u>Clinical</u> and <u>biochemical</u> evidence of androgen excess	As defined by **ultrasonography.** In some women with PCOS(about 30%The cysts are so small that they do not show on ultrasound) do not show ultrasound findings if Polycystic ovary That is why we have these other criteria

Endocrine changes in PCOS & treatment

❖ **Endocrine changes in PCOS:**

Let's start with obesity → insulin resistance → hyperinsulinemia:

- liver → low SHBG → high Free androgen. → Hirsutism.
- It also affects the ovaries:
- → more androgens → adipose tissue → **oestrone** → increase LH (normally decrease it) → Anovulation + stimulation of ovarian stroma + theca cells → further androgen is being produced → hirsutism.
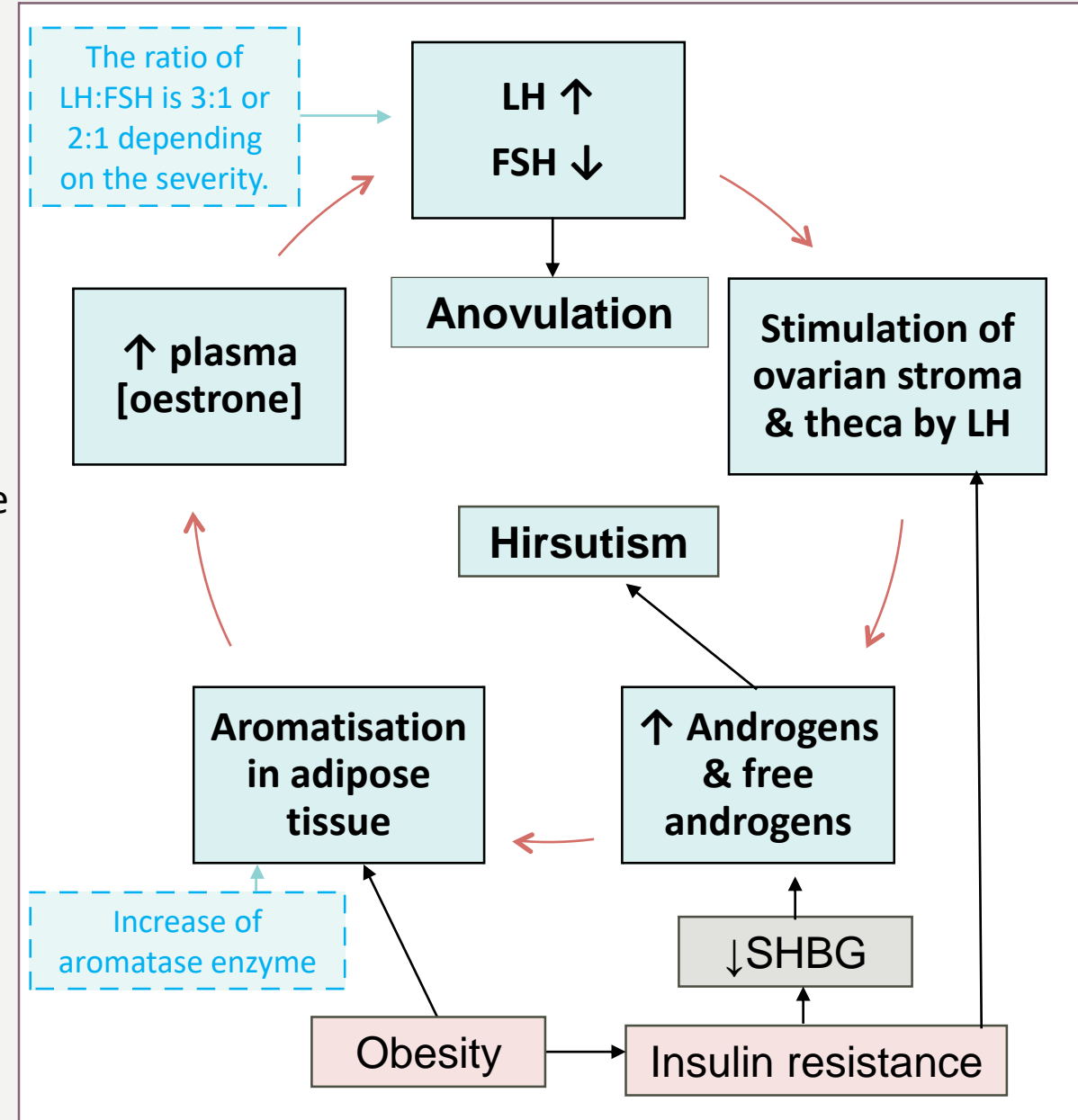
❖ **Treatment of PCOS:**

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

- **Reduce LH levels (by <u>oral contraceptives</u>)**
- **Reduce body weight**
- **Increase FSH levels (by <u>clomiphene</u>, etc.)**
- Estrogen replacement therapy
  - In select women after careful risk counseling
  - Metformin for insulin resistance(increase sensitivity)

- Insulin resistance leads to decrease the levels of SHBG (some hypothesis says that the diet may influence the levels of SHBG by causing down-regulation of its gene).
- Estrogens are used as a treatment of PCOS. But estrone is high, why do we give estrogen ? Well, estrogens include: estrone, estradiol, estriol. So we use estrogens other than estrone.

The ratio of LH:FSH is 3:1 or 2:1 depending on the severity.

LH ↑ FSH ↓

Anovulation

Stimulation of ovarian stroma & theca by LH

↑ plasma [oestrone]

Hirsutism

Aromatisation in adipose tissue

↑ Androgens & free androgens

Increase of aromatase enzyme

↓SHBG

Obesity

Insulin resistance

OVARIAN CANCER

What is it?	o <u>malignant</u> transformation of ovarian <u>epithelial cells</u>.
Epidemiology:	o A **leading** cause of <u>death</u> because of gynecologic cancer. o **Most common** type of ovarian cancer.

Subtypes:	**Serous**	46%	surface epithelial tumors
	Mucinous	36%	mucinous epithelial tumors
	Endometrioid	8%	endometrial tumors

د. عثمان سحب عليها وقال هذا شغل الباثولوجي :)

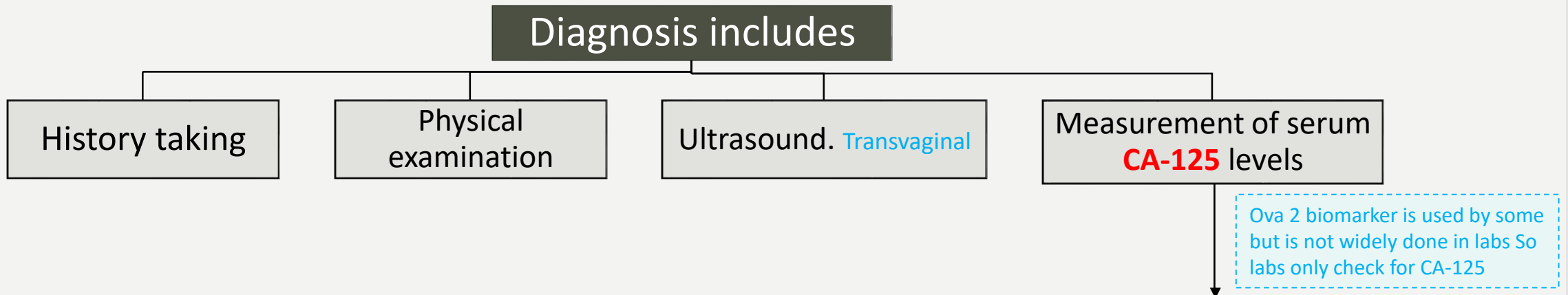| **Risk factors:**	**Nulliparity** (woman with no child birth or pregnancy). **Family history of <u>breast</u>**, <u>ovarian</u>, <u>colorectal</u> cancer. - Mutations in **BRCA1** and **BRCA2** genes (most common) ✓ Carriers of BRCA**1** mutations have a cancer risk of 44%. ✓ <u>**Pre**</u>menopausal **breast cancer** or ovarian cancer indicates higher risk for hereditary or breast cancer. If the women in the family had breast cancer before menopause then this type of cancer will make the next generation more prone cancer much more For example : the women in our PBL case were 38,36 (premenopausal)when they were diagnosed with cancer So in this family, the result is that the hereditary passage of cancer is much more prevalent because they were diagnosed before menopause **Ashkenazi Jews** have <u>higher</u> risk of ovarian cancer.

تذكرون وش كان يجيهم بعد بالسي ان اس؟!

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.(the symptoms of late stage indicate metastasis)

Diagnosis includes

History taking	Physical examination	Ultrasound. Transvaginal	Measurement of serum **CA-125** levels

Ova 2 biomarker is used by some but is not widely done in labs So labs only check for CA-125

What is it?	• A **cell surface** glycoprotein expressed in the epithelium of all tissues. • Normally **absent** in serum.
Uses:	• The **only** serum marker of epithelial ovarian cancer. • CA-125 is **elevated** in ovarian cancer (**>35 U/ml** is considered positive).

CA-125 is associated with stages of ovarian cancer: Elevated in:		
50% of patients with	**90% of patients with**	**>90% of patients with**
stage **I**	stage **II**	stage **III** and **IV**

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

High false-positive rate.

- A **non-specific** marker (the BIGGEST drawback for this biomarker)
- **False positive** CA-125 conc. are found in benign conditions (so it's not specific):
  1. **Endometriosis**
  2. **Uterine leiomyomas** (Fibroids).
  3. **Pelvic inflammatory disease**
  4. **During the first trimester of pregnancy**
  5. **During menstruation**
- Some patients (< 50 years) have elevated CA-125 due to <u>un</u>related malignant mass. So in some patients above 50 will have a malignant cancer which will cause high levels of CA-125 but is not associated with ovarian cancer

Low prevalence of ovarian cancer

High false-positive rate means: when we do a screening for the biomarker the woman may have positive CA-125 although she doesn't have ovarian cancer, because CA-125 is positive for some other benign conditions.

CA-125 is not used for screening for ovarian cancer, it's used for staging & monitoring (check for recurrence after treatment) only.
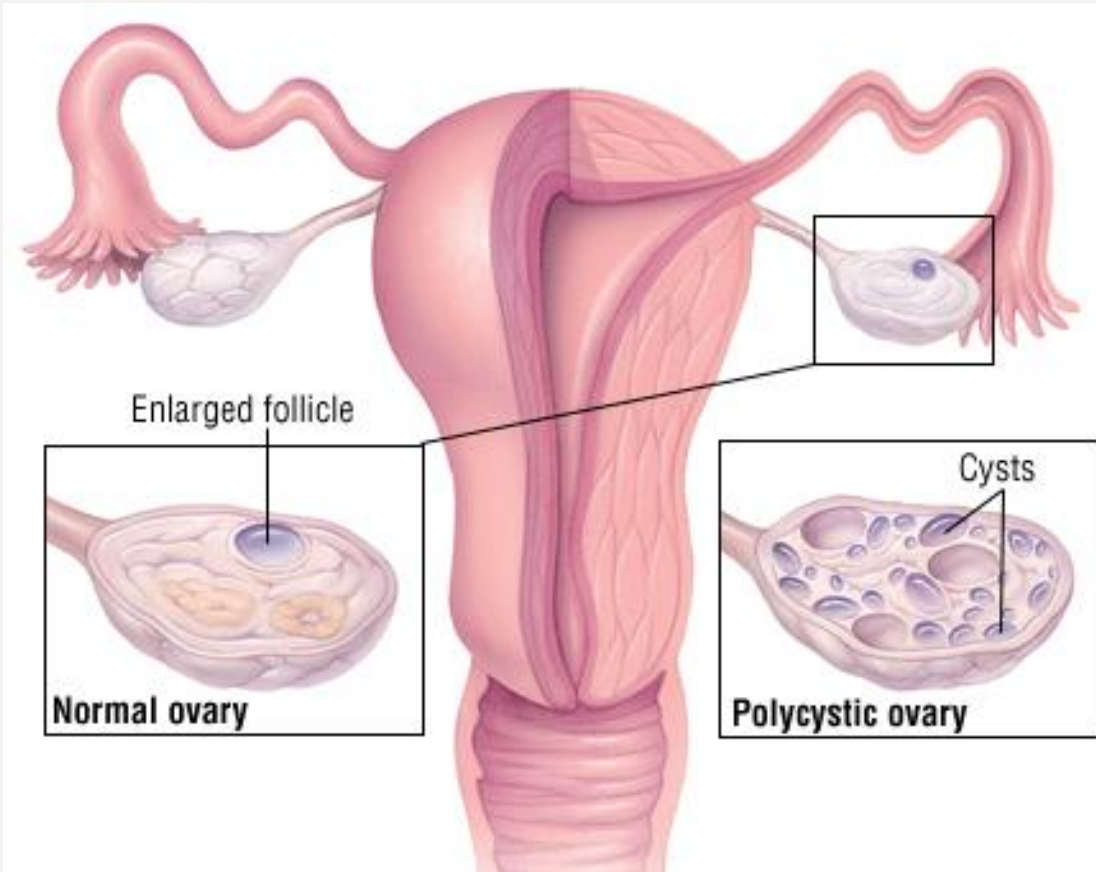
So it's useful in

Useful in:

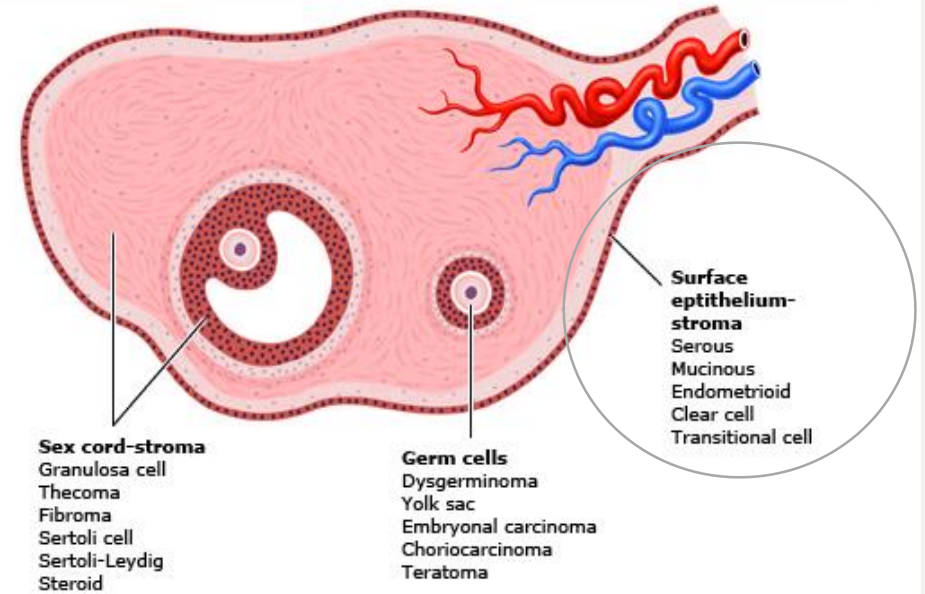| **Monitoring** patient's response to chemotherapy	**Success of surgery** (de-bulking procedures)	**Annual testing** for women with family history of ovarian cancer

Measure multiple times along the course of treatment   Check for CA-125 after surgery to remove the cancer

Polycystic Ovarian Syndrome

Origin of Ovarian tumors

Check your understanding!

Q1:Which of the following is diagnostic criteria PCOS :
A. Oligo-ovulation or anovulation.
B. Hyperandrogenism.
C. Polycystic ovaries.
D. All of the above.

Q2:Which of the following hormones is measuring in diagnosis of PCOS:
A. Free testosterone.
B. Leutinizing hormone.
C. Follicle stimulating hormone.
D. All of the above.

Q3:Which of the following hormones is treatment of PCOS:
A. Reduce LH levels.
B. Increase body weight.
C. Decrease FSH levels.
D. Androgen replacement therapy.

Q4:Which of the following ovarian cancer is originate from surface epitheliaum:
A. Serous.
B. Mucinous.
C. Endometrioid.
D. none of the above.

Q5:Which of the following genes mutation are common in ovarian cancer:
A. BRCA 1&2.
B. P53.
C. CYP21.
D. None of the above.

Q6: Why CA-125 is not a marker of choice for ovarian cancer screening:
A. Low prevalence of ovarian cancer.
B. High prevalence of ovarian cancer.
C. Low false-positive rate.
D. None of the above.

1.D 2.D 3.A 4.A 5.A 6.A

تم بحمدالله !

وبهذا نكون قد أتممنا محاضرات فريق مادة الكيمياء الحيوية للسنوات النظرية !
نتمنى أن يكون عملنا قد حاز على رضاكم ☺
و نود أن نوجه كلمة شكرٍ لجميع أعضاء الفريق ولكل من ساعدنا في السنتين الماضيتين،
فخورون جدًا بما أنجزناه معكم!
ونود أن نشكر أيضًا: عبدالعزيز المالكي و نوف العبدالكريم
على جهودهما في قيادة الفريق في أوقات سابقة، وحرصهما على أن يكون العمل على أكمل وجه.
كتب الله أجر الجميع، ونفع بعلمكم وجعله شفيعًا لكم.
تم بحمد الله.

قادة فريق الكيمياء الحيوية:
شهد العنزي & عبدالله الغزي

Done by:

– شهد العنزي.

– عبداللّه الغزي.

– نورة الرميح.

– ريفان هاشم.

– ابراهيم الشايع.

Revised by:

– فارس المطيري.

Resource:

- 435's slides.

لا تَعِش حياةً لا تُشبِهُك ،
ولا تَقُل كلاماً لا يُمثِلُك
ولا تَقبل أنْ تُشارك بِمعرَكة ليستْ لكْ
وكُنْ أنتَ دوماً ، والسَلامْ .

@435biochemteam

435biochemistryteam@gmail.com

@biochemteam435