

Biochemical Markers of Ovarian Cancer and Cysts

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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

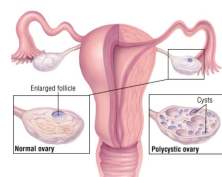
- Types, risk factors
- Diagnosis
- CA-125 biomarker



Polycystic Ovarian Syndrome (PCOS)

It has another name (Stein-Leventhal 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.



Strongly correlated to*

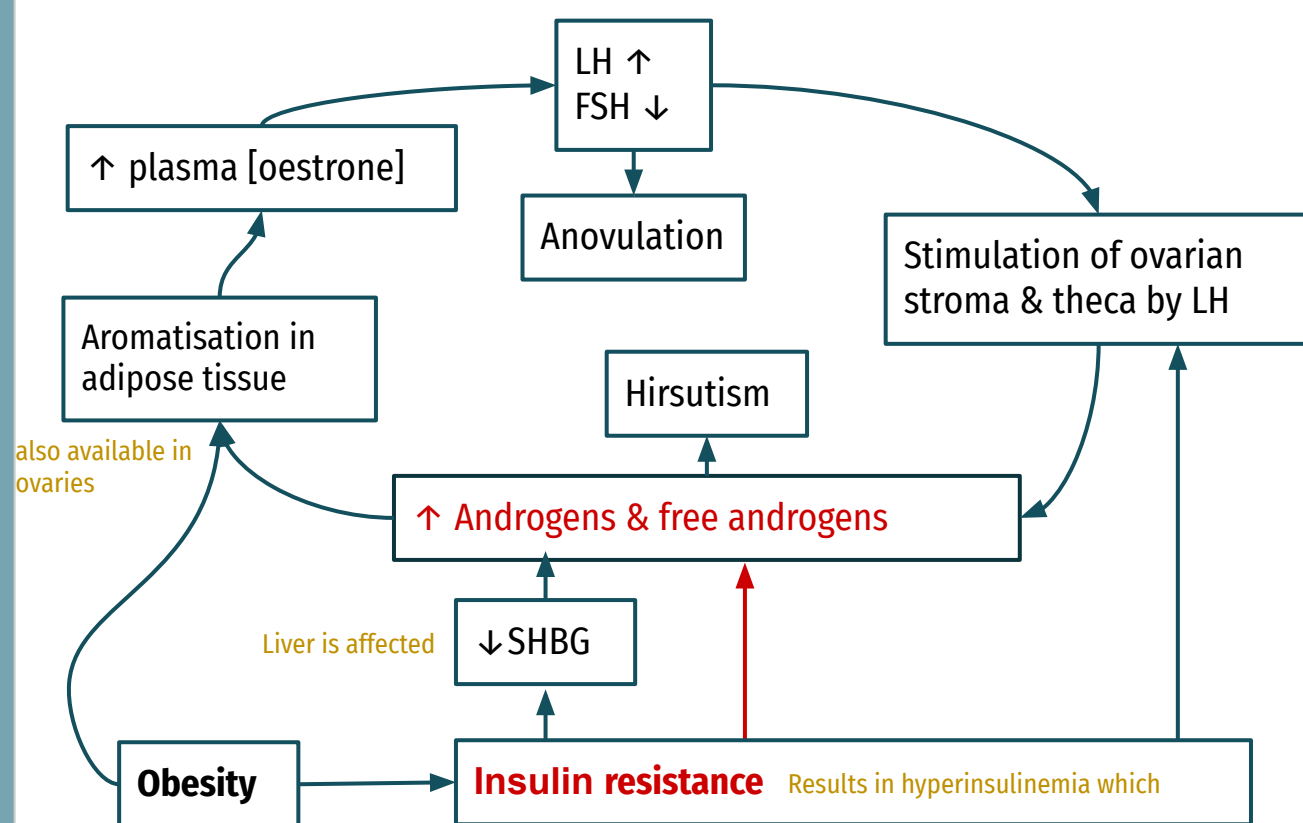
- Family history.
- Obesity (40%).
- Hirsutism. **Because of androgens**
- Chronic anovulation.
- Glucose intolerance.
- Insulin resistance.
- Hyperlipidemia.
- Hypertension.
- Menstrual disorders.
- Hypersecretion of luteinizing hormone (LH) and androgens (testosterone).
- Low levels of SHBG (sex hormone-binding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

PCOS is basically metabolic syndrome with underlying ovarian dysfunction

Cause

- 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. (Problems in the Hypothalamic-Pituitary-Gonadal Axis)

Endocrine changes in PCOS



when the pregnant mother has condition that increase her androgen level (e.g. Cushing syndrome) then the child will expose to this high amount of androgen and she (the child) may develop PCOS later.

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).

Ref: PCOS Consensus Workshop Group. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. Jan 2004;81(1):19-25

This is the criteria in adult females. In adolescent females, all 3 features(not just 2) are required for a diagnosis of PCOS. The presence of only 2 of the features in an adolescent female puts her at an increased risk for PCOS, and lifestyle modifications should be recommended

Diagnosis

Diagnosis done by measuring:

- 1- Free testosterone**
(total testosterone is less sensitive; androgens are **increased** in PCOS)
- 2- Sex hormone-binding globulin**
(SHBG; **decreased** in PCOS) → excess free androgens → symptoms(hirsutism etc).
- 3- Luteinizing hormone**
(LH; **high** in 60% cases) LH::FSH is more than 2. Using this ratio is more helpful than using either LH or FSH alone
- 4- Follicle stimulating hormone**
(FSH); usually normal in PCOS (low according to pathology, but clinically it's usually on the lower end of normal, that's why we use LH:FSH)
- 5- Fasting blood glucose.**
- 6- Insulin.**
(insulin resistance)
- 7- Lipids.**

Ovarian ultrasound:

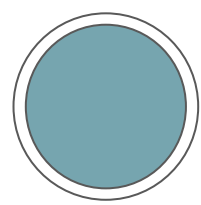
- 30% of patients do **not** have ovarian cysts despite having symptoms.

Treatment of PCOS

Aim of treatment: interrupt (break) the cycle above of obesity, insulin resistance, excess androgens.

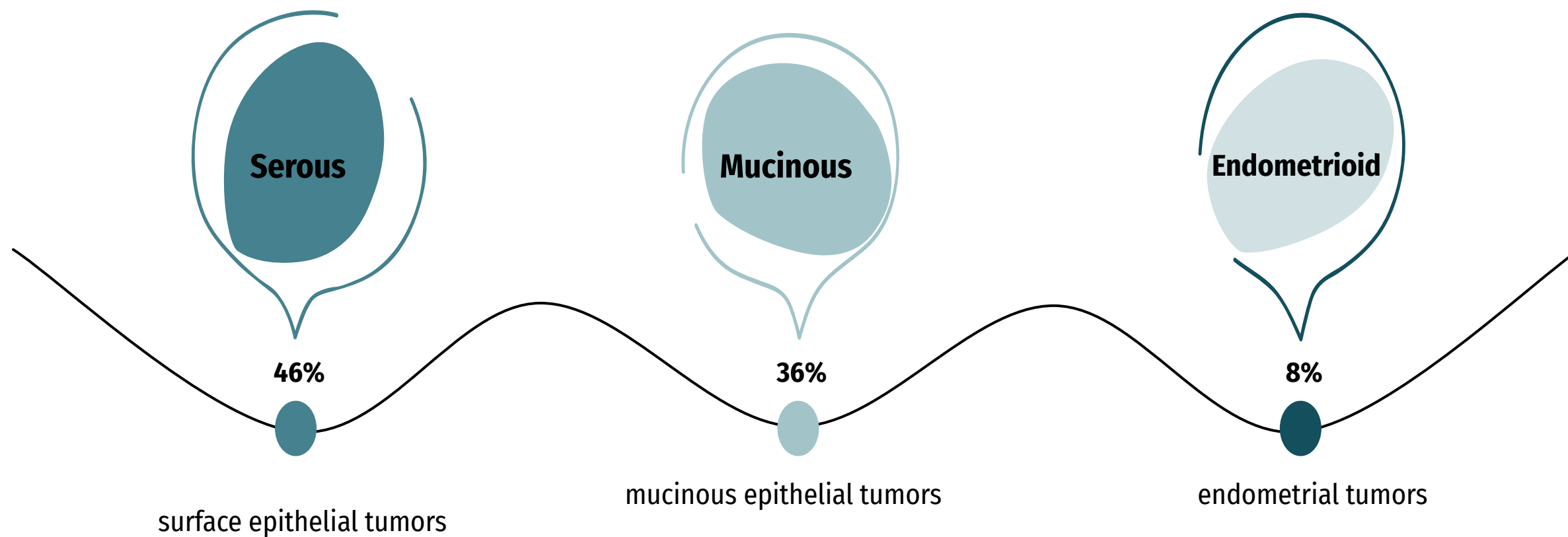
- Reduce LH levels** (by oral contraceptives) **Androgens**
- Reduce body weight**
Insulin Sensitivity
Adipose tissue (Aromatase)
- Increase FSH levels** (by clomiphene, etc.)
- Estrogen replacement therapy:**
- In select women after careful risk counseling

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



Ovarian Cancer Risk Factors

- Nulliparity (woman with no childbirth or pregnancy)
Increase in Age is a risk factor and its important.
- Family history of breast, ovarian, colorectal cancer (first degree relatives)
- Mutations in **BRCA1** 44% higher chance to develop cancer 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
- Ashkenazi Jews have higher risk of ovarian cancer

EXTRA:
Blue FILM
B = Breast Cancer
F = Family history
I = Infertility
L = Low parity
M = Mumps

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

Early stages could be discovered by chance in other surgeries

Extra from robbins :

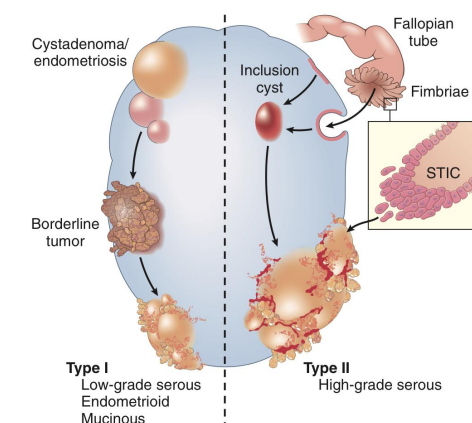


Fig. 19.15 Derivation of various ovarian neoplasms. Type I tumors progress from benign tumors through borderline tumors that may give rise to a low-grade carcinoma. Type II tumors arise from inclusion cysts/fallopian tube epithelium via intraepithelial precursors that are often not identified. They demonstrate high-grade features and are most commonly of serous histology. STIC, serous tubal intraepithelial carcinoma.

Biomarkers and diagnosis



❖ **Diagnosis** includes:

- History taking Age of menarche, Pregnancy, Family history
- Physical examination pelvic mass
- Ultrasound cysts maybe not detected cuz very small
- Measurement of serum CA-125 levels should be significantly high along with the previous factors

Cancer antigen 125 (CA-125) (Mucin 16)

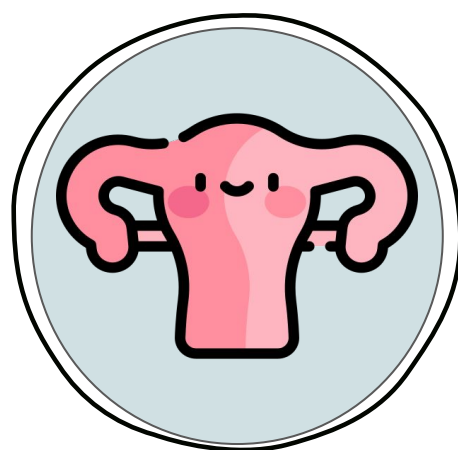
CA-125 + HE4 both done along the menopausal status of the female

HE4 (human epididymis protein) is another marker used. Both HE4+CA-125 help in determining whether a lump found in a pelvic exam is likely to be malignant or not. In Addition use of HE4 and CA-125 is as part of a Risk of Ovarian Malignancy Algorithm (ROMA).

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 associated with stages of ovarian cancer.



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 levels are Elevated in :

50% of patients with **stage I**

90% of patients with **stage II**

>90% of patients with **stage III and IV**

Basically, the greater the stage of ovarian cancer, the higher the probability of finding CA-125 in the serum. Make sure you know which number are for which stage

Useful in:

- ❖ **Monitoring patient's response to chemotherapy**
- ❖ Success of surgery (de-bulking procedures) how successful was the surgery in tumor removal?
- ❖ Annual testing for women with family history of ovarian cancer

Cancer antigen 125 (CA-125)

❖ **A non-specific marker**

False positive CA-125 conc. are found in benign conditions such as:

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

False= benign condition
Positive= elevated 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

Basically, because of all of its problems (non-specific, high-false positive rate etc.) we DON'T use it for diagnosis/screening. CA-125 is used only for:
-staging of ovarian cancer
-follow-up of ovarian cancer treatment (chemo, surgery)
-Annual testing for women with history of ovarian cancer
-Recurrence and relapse of the cancer

Some patients (< 50 years) have elevated CA-125 due to unrelated malignant mass.

Take Home Messages



PCOS is strongly correlated to insulin resistance and endocrine abnormalities



Although a nonspecific marker, CA-125 is important for staging and follow-up of ovarian cancer treatment

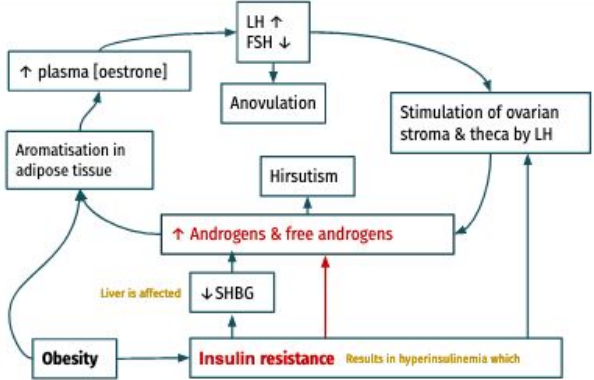


Goodbyes are usually hard, but this one isn't.
ADIOSSSSS basic years!!



Summary

Polycystic ovarian syndrome

Cause	<ul style="list-style-type: none"> • Exact cause unknown. • May be multifactorial (genetic and environmental). <p>Probable causes:</p> <ul style="list-style-type: none"> - Insulin resistance causes excessive androgen production in ovaries (common). - Abnormalities in ovaries, adrenal and pituitary glands.
Endocrine changes in PCOS	
Diagnosis	<ul style="list-style-type: none"> ❖ Diagnostic criteria for PCOS: At least two of the following features: <ul style="list-style-type: none"> → Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea. → Hyperandrogenism. → Polycystic ovaries. ❖ Measurement results: <ul style="list-style-type: none"> -androgens are increased. -SHBG is decreased. -LH is high in 60% cases. -FSH is usually normal. ❖ 30% of patients do not have ovarian cysts on ultrasound.
Treatment	<ul style="list-style-type: none"> -Reduce LH levels (BY oral contraceptives) -Reduce body weight -Increase FSH levels (by clomiphene, etc.) -Estrogen replacement therapy:

Ovarian Cancer

SubTypes	<ol style="list-style-type: none"> 1. Serous 2. Mucinous 3. Endometrioid
Risk factors	<ul style="list-style-type: none"> ❖ 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 ❖ Ashkenazi Jews have higher risk of ovarian cancer
Diagnosis	<ul style="list-style-type: none"> ❖ Diagnosis includes: <ul style="list-style-type: none"> → History taking → Physical examination → Ultrasound → Measurement of serum CA-125 levels
CA-125	<ul style="list-style-type: none"> ❖ 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.



MCQs

1- In which of the following can the levels of CA-125 be useful ?

A- Monitoring patient response to chemotherapy

B- Biomarker for PCOS

C- نقطلوه

D- Marker of choice for ovarian cancer

2- Which of the following stages of ovarian cancer in which 50% of people have high CA-125 ?

A- Stage 1

B- Stage 2

C- Stage 3

D- Stage 5

3- False positive CA-125 concentrations are found in all of the following conditions EXCEPT ?

A- Endometriosis

B- Pelvic inflammatory disease

C- Uterine leiomyoma

D- Ovarian cancer

4- Which of the following is a criterion in the diagnostic criteria of PCOS by ESHRE and ASRM ?

A- Hyperandrogenism

B- Obesity

C- Insulin resistance

D- Hypertension

5- Which of the following can be found in a patient with PCOS ?

A- High LH and High FSH

B- High LH and High androgens

C- High LH and High SHBG

D- Low LH and High FSH

6- Which of the following is not a recommended treatment for PCOS:

A- Estrogen replacement therapy

B- Exogenous androgen intake

C- Oral contraceptives

D- Clomiphene

Answers key

1-A

2-A

3-D

4- A

5- B

6- B



1- CA-125 levels are Elevated in ?

Answer : Page 7

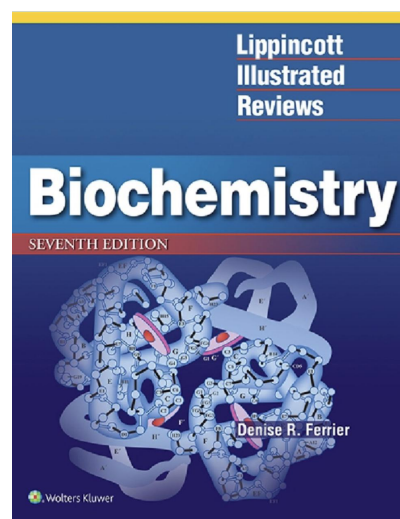
2- What is the cause of anovulation in PCOS patients ?

↑ LH and ↓ FSH

3- What causes hyperandrogenism seen in PCOS patients ?

- Stimulation of ovarian stroma & theca by LH
- insulin resistance → decreased hepatic synthesis of SHBG → ↑ free androgens

Resources [Click on the book to download the resource](#)





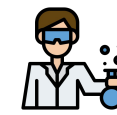
Leaders



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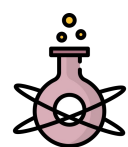


Ghada Alabdi



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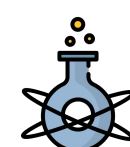
Members



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Yara Alasmari

Yasmine Alqarni

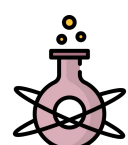


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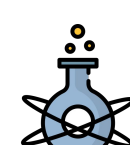
Albara Aldawoud

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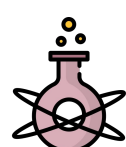


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Special thanks to Fahad AlAjmi for designing our team's logo.