Ovulation induction

Objectives:

- **Recall** how ovulation occurs and specify its hormonal regulation
- **Classify** ovulation inducing drugs in relevance to the existing deficits
- **Expand** on the pharmacology of each group with respect to mechanism of action, protocol of administration, indication, efficacy rate and adverse effects.

Done by:

Editing file

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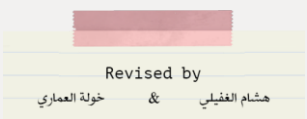
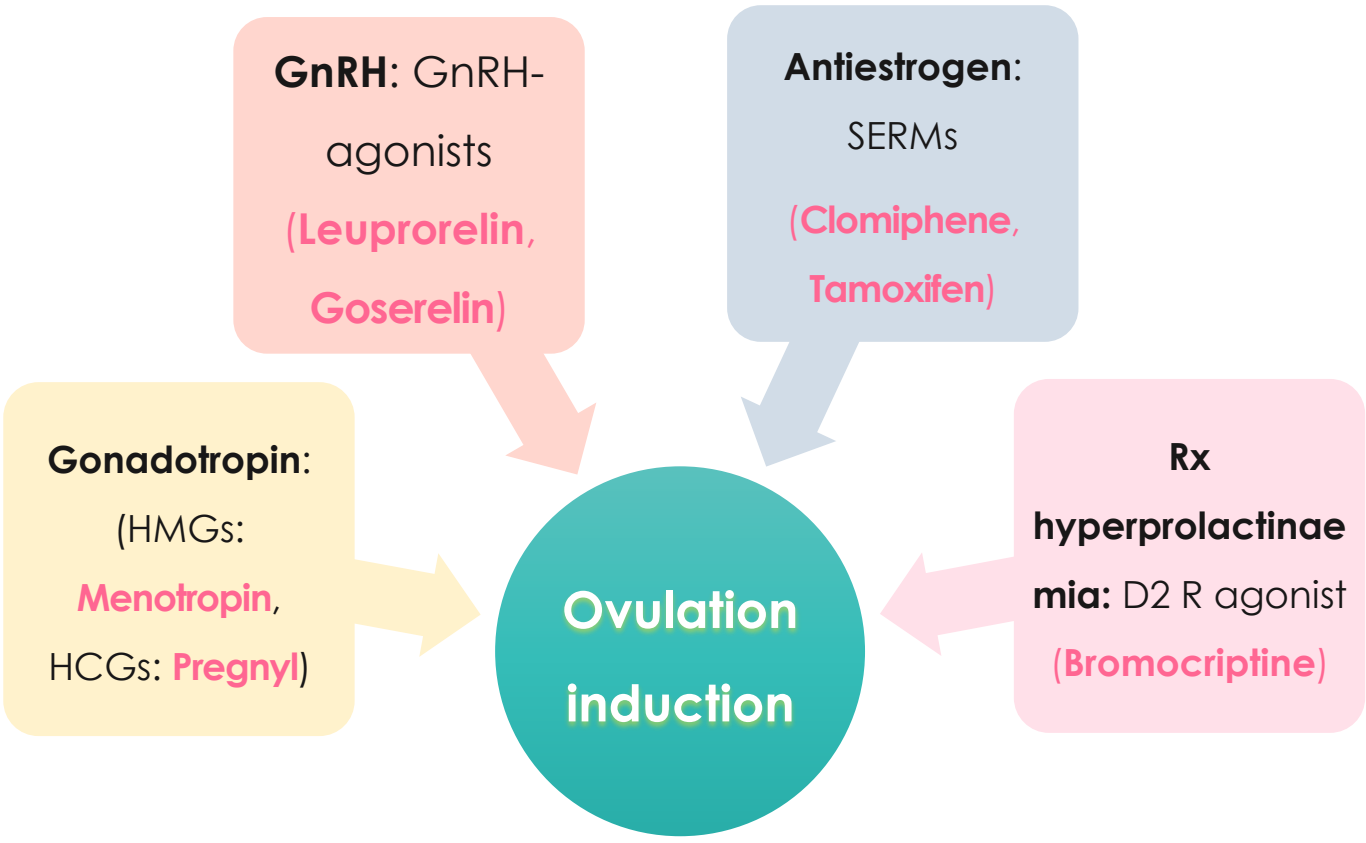


Drug's name | Doctors' notes | Important | Extra

« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

سورة العنكبوت

Mind Map



Rx Polycystic ovarian syndrome (PCOS) → Metformin

* **Rx**: is a symbol meaning "prescription".

MOA of all of these drugs is very important in this lecture.

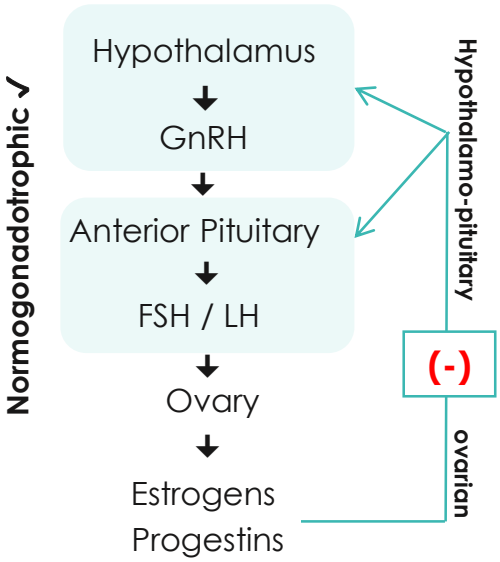
Ovulation Induction

- **Antiestrogens**
  - **SERMs:** Clomiphene, Tamoxifen
- **GnRH**
  - **GnRH-agonists:** **Leuprorelin**, Goserelin
- **Gonadotrophins**
  - **HMGs;** Menotropin
  - **HCGs;** Pregnyl
- **D2 R agonists**
  - **Bromocreptine**
    - **Used for:** Hyperprolactinemia

Rx: Polycystic ovarian syndrome (PCOS):

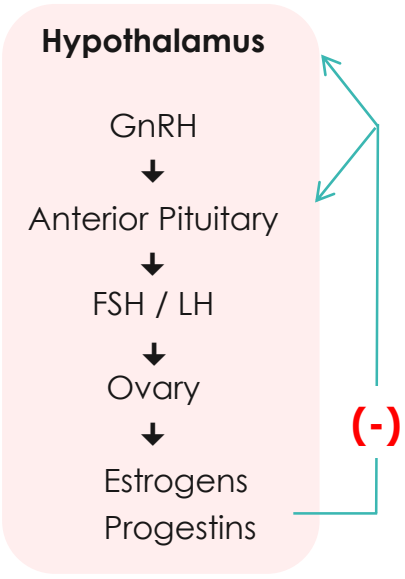
- Most common cause of infertility
- Inulin resistance may play a role.
  - ✓ We give **Metformin**

PCOS is the most common cause of infertility.

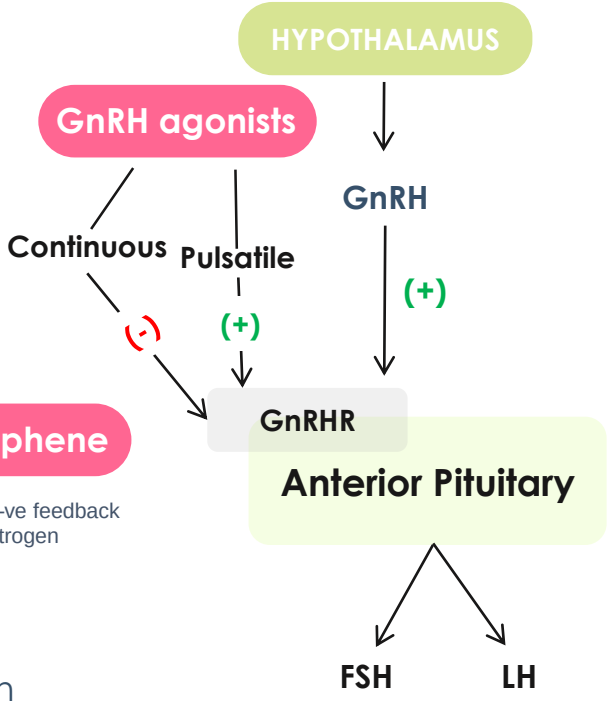


The effect of each drug in the HPG-axis:

Go back to these diagrams with studying each drug



Inhibit the –ve feedback effect of estrogen



Why pulsatile secretion? See the beginning of this video: 5 min

Anti-estrogens

Drug: Clomiphene

MOA

- **Compete with estrogen** on the hypothalamus and anterior pituitary gland; ↓ the negative feed-back of endogenous estrogen → ↑ **GnRH** → ↑ production of FSH & LH → OVULATION
- **Clomiphene** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

Administration

مش بسألكم في هذي الأشياء

- Clomiphene given → 50 mg/d for 5 days from 5th day of the cycle to the 10th day.
- If no response give 100 mg for 5 days again from 5th to10th day
- Each dose can be repeated not more than 3 cycles .

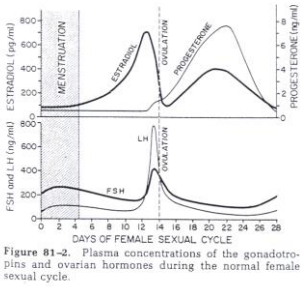


Figure 81–2. Plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.

Indications

- Female infertility; due to **anovulation or oligoovulation** not due to ovarian or pituitary failure → **Normogonadotrophic =** يعني ما عندها مشاكل في الهيبوثالمس ولا في البتيوتاري.. ال HPG axis حقها سليم
- The success rate for ovulation → 80% & chance to get pregnant → 40% .

ADRs

1. Hot Flushes & breast tenderness
2. Gastric upset (nausea and vomiting)
3. Visual disturbances (reversible)
4. ↑ nervous tension & depression
5. Skin rashes
6. Fatigue
7. Weight gain
8. Hair loss (reversible)
9. **Hyperstimulation of the ovaries & high incidence of multiple birth**

Drug: Tamoxifen

MOA

- Is similar & alternative to clomiphene, But differ in being **Non Steroidal**
- Clomiphene is the 1st choice.

Indications

- Tamoxifen is a good alternative to **clomiphene** in women with **PCOS** and **clomiphene-resistant cases**.
- Used in palliative* treatment of **estrogen receptor- positive breast cancer**.
  - * = relieving the pain without treating the cause.
  - Metastatic breast cancer, or as adjuvant therapy following mastectomy or radiation for breast cancer

ADRs

- The most frequent → hot flashes and nausea.
- Endometrial hyperplasia and malignancies have been reported

Gonadotropin releasing hormone (GnRH)

Drug

Analgoues with agonist activity:
Leuprorelin, Goserelin

Mech. of action

- **Pulsatile secretion of gonadotropin-releasing hormone** (GnRH) from the hypothalamus is **essential for the release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH)** from the anterior pituitary. However, **continuous administration of GnRH inhibits gonadotropin release** through down-regulation of the GnRH receptors on the pituitary. Continuous administration of synthetic GnRH analogs, such as leuprolide, goserelin, nafarelin, and histrelin, is effective in suppressing production of the gonadotropins
- **MOA is very imp in MCQs!!!** → **answer: GnRH agonist**. للتوضيح، شوفوا الدياقرام في سلايد ٣

Administration

مش مهم الدوز

- GnRH and agonists, given **S.C**. in a **pulsatile (drip)** to **stimulate** gonadotropin release (1 – 10 µg / 60 – 120 min). Start from day 2-3 of cycle up to day 10.
- Given **continuously**, when gonadal **suppression** is desirable e.g. **precocious puberty** and advanced breast cancer in women and prostatic cancer in men.

Indications

- Induction of ovulation in patients with **hypothalmic amenorrhea** (GnRH deficient)
- Endometriosis

ADRs

- GIT disturbances, abdominal pain, nausea….etc
- Headache
- Depression
- **Hypoestrogenism** on long term use → في حال استخدمناه لمدة طويلة وخصوصًا إذا given continuously
  راح يقلل عندنا FSH & LH بالتالي بيقل الإستروجين، وبنشوف مثل ال typical symptoms of menopause
  - Hot flashes and sweating
  - ↓ Libido
  - Osteoporosis
  - Rarely ovarian hyperstimulation → (ovaries swell & enlarge) - Ovarian cysts

C.I

- Contraindicated in pregnancy and breast-feeding.

Gonadotrophins [FSH & LH]

Are glycoproteins naturally produced by the anterior pituitary gland

Drug

hMGs; **Menotropin**
hCGs; **Pregnyl**

❖ **For therapeutic use, extracted forms are available as;**

1. Human Menopausal Gonadotrophin (hMG) → extracted from **postmenopausal** urine → contains **LH & FSH** → **MENOTROPIN**

ليش يصير مستواهم عالي في البوستمينوز؟ لأن ما عندهم إستروجين وبروجستيرون يسوون النيقاتف فيدباك إنهبشن.

2. Human Chorionic Gonadotrophin (hCG) extracted from urine of **pregnant** women → contains mainly **LH**) → **PREGNYL**

Administration

- **hMG** is given i.m every day starting at day 2-3 of cycle for 10 days followed by **hCG** on (10th -12th day) for **OVUM RETRIEVAL** (ovulation).

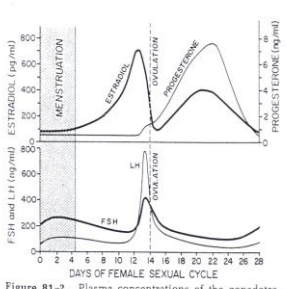


Figure 81–2. Plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.

هنا إحنا كأننا نطابق اللي يصير في الأوفارين سايكل بالضبط اللي يحصل في الأنثى الطبيعية.. بحيث إننا في بداية السايكل نعطي hMG اللي يحتوي على FSH & LH لمدة ١٠ أيام، و FSH هو أكثر شيء بنحتاجه في ال proliferative phase
بعدها نبدأ نعطي hCG اللي يطابق LH من اليوم العاشر إلى ١٢، وهنا نحتاج LH عشان يسوي لنا ال ovulation

Indications

- Stimulation & induction of ovulation in **infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)** (not Normogonadotrophic) Success rate for inducing ovulation is usually >75 %.

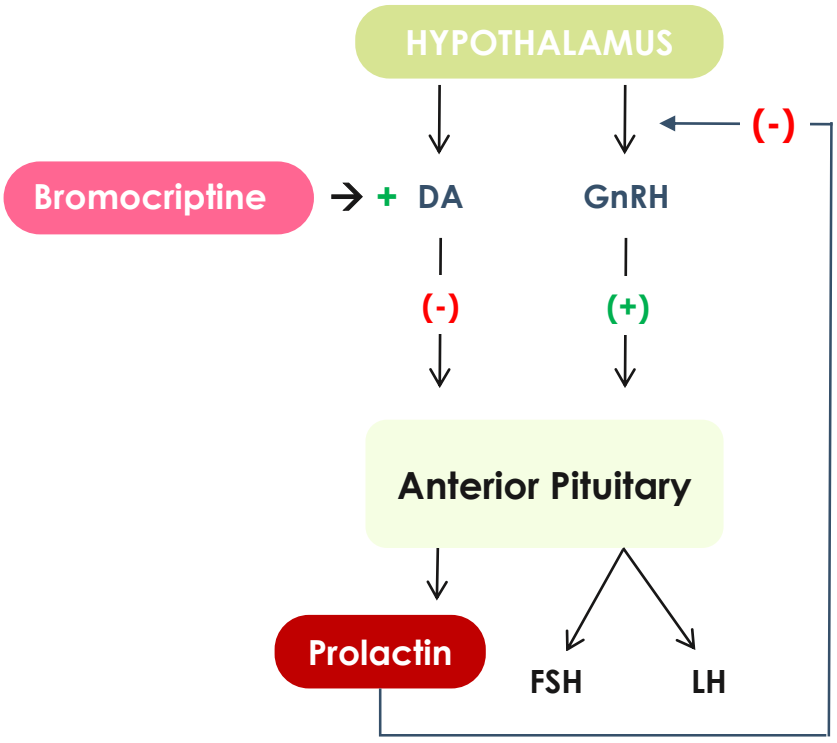
ADRs

- **FSH containing preparations;**
  - Fever
  - Ovarian enlargement (ovarian **hyperstimulation** syndrome)
  - **Multiple Pregnancy** (approx. 20%)
- **LH containing preparations** → Headache & edema

حتى في بعض الإناث الطبيعيات، وقت الأوفيوليشن ممكن يحسون بالheadach & edema

D2 R Agonists

Drug	**Bromocriptine** Is an **ergot** derivative (not a hormone)
MOA	○ D2 R Agonists binds to dopamine receptors in the anterior pituitary gland → **inhibits prolactin secretion**. ○ Prolactin is a peptide hormone that is also secreted by the anterior pituitary. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. Its secretion is inhibited by dopamine acting at D2 receptors. [Note: Drugs that act as dopamine antagonists (for example, metoclopramide and antipsychotics such as risperidone) can increase the secretion of prolactin.] Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D2 receptor agonists, such as **bromocriptine and cabergoline.**
Indications	○ **Female infertility 2ndry to hyperprolactinaemia**
ADRs	○ **GIT disturbances**; nausea, vomiting, constipation ○ Headache dizziness & **orthostatic hypotension** ○ Dry mouth & nasal congestion ○ **Insomnia**



Summary

Antiestrogens (SERMs)

Drug

clomiphene (steroidal)

Tamoxifen (non-steroidal)

MOA

Compete with estrogen on the hypothalamus and anterior pituitary gland; ↓negative feed back of endogenous estrogen → ↑GnRH → ↑production of FSH & LH → OVULATION

P.K

50 mg/d for 5 days from 5th day of the cycle to the 10th day.
- If no response give 100 mg for 5 days again from 5th to10th day

Indications:

Female infertility in Normogonadotrophic

Used as an alternative in:

- in women with PCOS and clomiphene **resistant cases**.
- in palliative treatment of estrogen receptor-positive breast cancer.

ADRs

1.Hot Flushes & breast tenderness
2. Gastric upset
3. Visual disturbances
4. ↑ nervous tension & depression
5. Skin rashes
6. Fatigue
7. Weight gain
8. Hair loss (reversible)
9. Hyperstimulation of the ovaries & high incidence of multiple birth.

(GnRH) analouges with agonist activity

Drug

leuprolin

goserelin

MOA

GnRH agonist

P.K

GnRH and agonists, given S.C. in a pulsatile (drip) → to stimulate gonadotropin release.
Given continuously→ when gonadal suppression is desirable.

Indications:

Induction of ovulation in patients with hypothalmic amenorrhea (GnRH deficient).

ADRs

1-GIT disturbances, abdominal pain, nausea….etc
2.Headache
3.Hypoestrogenism on long term use →
Hot flashes
-↓Libido
-Osteoporosis
-Rarely ovarian hyperstimulation → (ovaries swell & enlarge)

Gonadotropins (FSH & LH)

Drug

Menotropin (hMG) contain LH&FSH

Pregnyl (hCG) contain mainly LH

P.K

(hMG) i.m every day starting at day 2-3 of cycle for 10 days followed by (hCG) on (10th - 12th day) for OVUM RETRIEVAL

Uses

Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)

ADRs

FSH containing preparations:
-Fever
-Ovarian enlargement (hyper stimulation)
-Multiple Pregnancy (approx. 20%)
LH containing preparations:
-Headache & edema

D2 R Agonists

Drug

Bromocreptine

MOA

D2 R Agonists binds to dopamine receptors in the anterior pituitary gland & inhibits prolactin secretion.

Uses

Female infertility 2ndry to hyperprolactinaemia

ADRs

-**GIT disturbances**; nausea, vomiting, constipation
-Headache dizziness & **orthostatic hypotension**
-Dry mouth & nasal congestion
-**Insomnia**

MCQs

1- Clomiphene acts through:

A. Blocking Negative feedback of estrogen on hypothalamus and pituitary
B. Acting synergistically with estrogen
C. Inhibit gonadotropin secretion

2- In order to to stimulate gonadotropin release, Leuprorelin must be given:

A. Continuously
B. Orally
C. S.C in a Pulsatile secretion
D. non of the above

3- Bromocriptine is considered as:

A. D2 receptor blocker
B. D2 receptor agonist
C. H2 receptor blocker
D. H2 receptor agonist

4- What is true of tamoxifen:

A. It can induce endometrial proliferation in postmenopausal women
B. It exerts antiestrogenic activity in bone
C. It raises LDL-cholesterol levels
D. It is ineffective in estrogen receptor-positive breast cancer

5- A 23-year-old woman has failed to become pregnant after 2 years of unprotected intercourse. Which of the following would be effective in treating infertility due to anovulatory cycles?

A. A combination of an estrogen and progestin.
B. Estrogen alone.
C. Clomiphene.
D. Tamoxifen

6- A 26-year-old woman with infertility and her 23-year- old husband with a history of bilateral undescended testicles desires to start a family. She is currently taking a fertility medication but is troubled by some unusual and troubling side effects. She experiences heat and cold intolerance and mood swings. She com- plains of visual changes, and this makes her depressed. Which of the following medications is she most likely taking?

A. Clomiphene citrate
B. Human chorionic gonadotropin
C. Pulsatile GnRH
D. Pergonal (human gonadotropins)

7- A young married couple has been unable to conceive after 3 years of unprotected intercourse. The husband's sperm count is normal. They both agree that they would like the wife to undergo fertility treatment. Which of the following drugs has the ability to either stimulate or inhibit ovulation depending only on the dosing schedule?

A. Bromocriptine
B. Clomiphene
C. hCG
D. Leuprolide

8- Menotropins is a preparation of:

A. FSH + LH obtained from urine of menstruating women
B. LH obtained from urine of pregnant women
C. FSH + LH obtained from urine of menopausal women
D. LH obtained from serum of pregnant mare

9- Bromocriptine causes the following:

A. Prolactin release
B. Vomiting
C. Uterine contraction
D. Impotence

Answers: 1-A 2-C 3-B 4-A 5-C 6-A 7-D 8-C 9-B

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 25, 5th edition.