



Drugs in Ovulation Induction

Objectives:

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

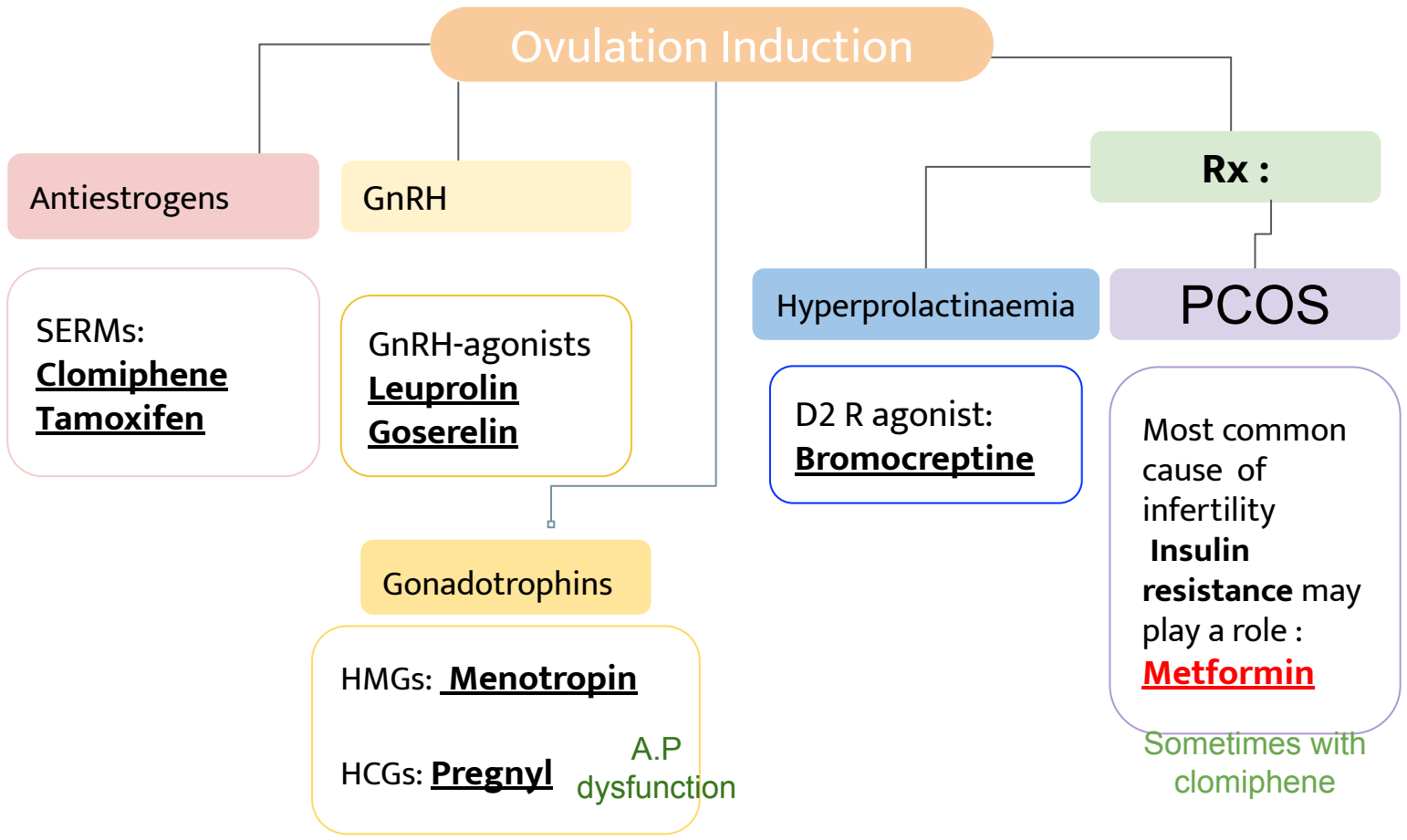
Revised By

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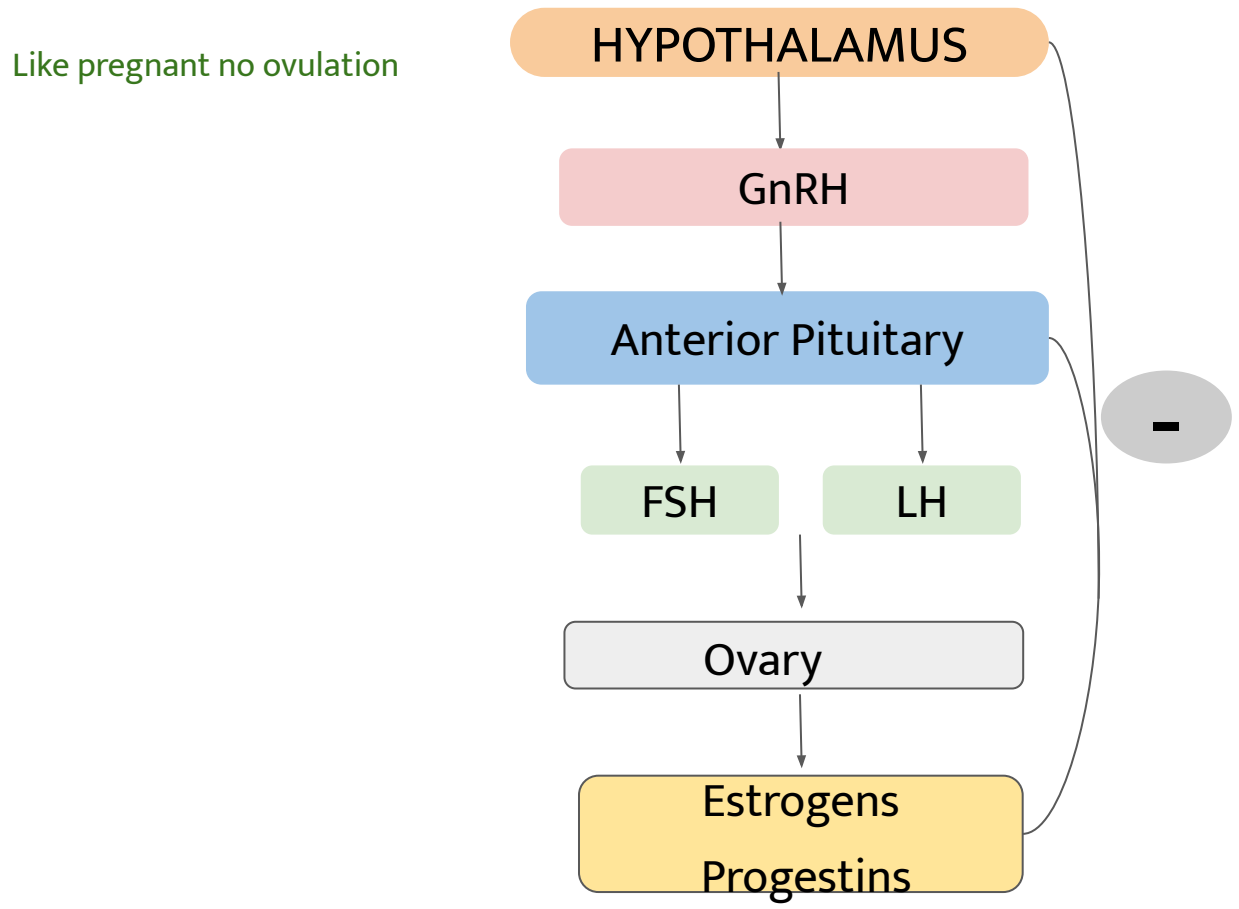
Color index:
Important Note Extra



M.O.A of every drug is IMP



Normogonadotrophic



ANTIESTROGENS

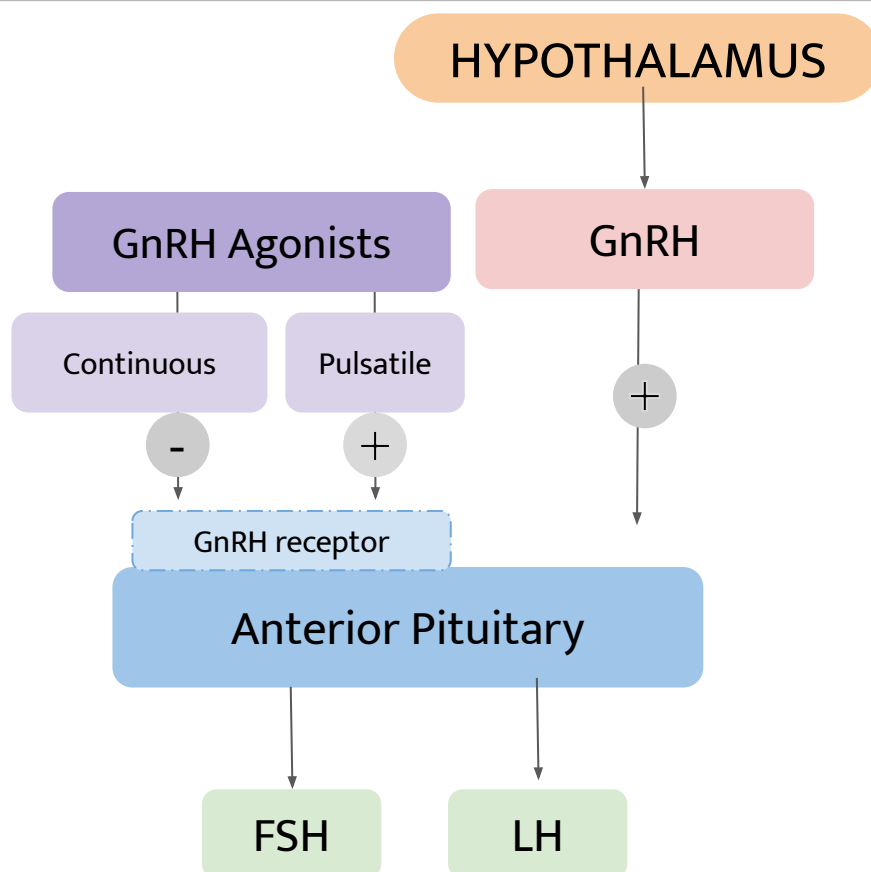
Clomide/clomidene		CLOMIPHENE	
M.O.A	<p>Compete with estrogen on the hypothalamus and anterior pituitary gland; ↓negative feed back of endogenous estrogen ↑GnRH ↑production of FSH & LH → OVULATION Clomiphene acts as partial estrogen agonist and interferes with negative feedback of estrogen. Imp MOA</p>		
P.K	<ul style="list-style-type: none"> ❖ Method of administration <ul style="list-style-type: none"> ○ 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 to 10th day ○ Each dose can be repeated not more than 3 cycles . 		
Indications	<ul style="list-style-type: none"> ❖ Female infertility; due to anovulation or oligoovulation . not due to ovarian or pituitary failure (Normogonadotrophic) ❖ The success rate for ovulation : 80% & pregnancy: 40% . <small>Hypothalamus and pituitary are fine</small> 		
ADR	1.Hot Flashes & breast tenderness <small>Due to estrogen</small> 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.
TAMOXIFEN			
M.O.A	Is similar & alternative to clomiphene <u>But</u> differ in being <u>Non Steroidal</u>		
Indications	<ul style="list-style-type: none"> ● 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. <p style="text-align: right;"><small>Better for breast</small></p>		

PCOS we can use 1-Clomiphene even 2-Metformin
 After clomiphene we use Tamoxifen

GnRH-agonists

Leuprolin, Goserelin

<p>M.O.A</p>	<p>Analogues with agonist activity. Pulsatile secretion of gonadotropin-releasing hormone from the hypothalamus is essential for the release of gonadotropin follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.</p>
<p>P.K</p>	<ul style="list-style-type: none"> ❖ GnRH and agonists, given S.C. in a pulsatile (drip) to stimulate gonadotropin release (1 – 10 µg / 60 – 120 min) pulsatile=stimulation ❖ Start from day 2-3 of cycle up to day 10
<p>Indications</p>	<ul style="list-style-type: none"> ❖ Induction of ovulation in patients with hypothalamic amenorrhea (GnRH deficient) the problem is the hypothalamus ❖ Given continuously, when gonadal suppression is desirable e.g. <ul style="list-style-type: none"> ○ precocious puberty ○ advanced breast cancer in women ○ prostatic cancer in men
<p>ADR</p>	<ul style="list-style-type: none"> ❖ GIT disturbances, abdominal pain, nausea....etc ❖ Headache ❖ Hypoestrogenism on long term use ☐ : as if u made menopause <ul style="list-style-type: none"> ○ Hot flashes ○ ↓Libido ○ Osteoporosis ○ Rarely ovarian hyperstimulation ☐ (ovaries swell & enlarge) ER

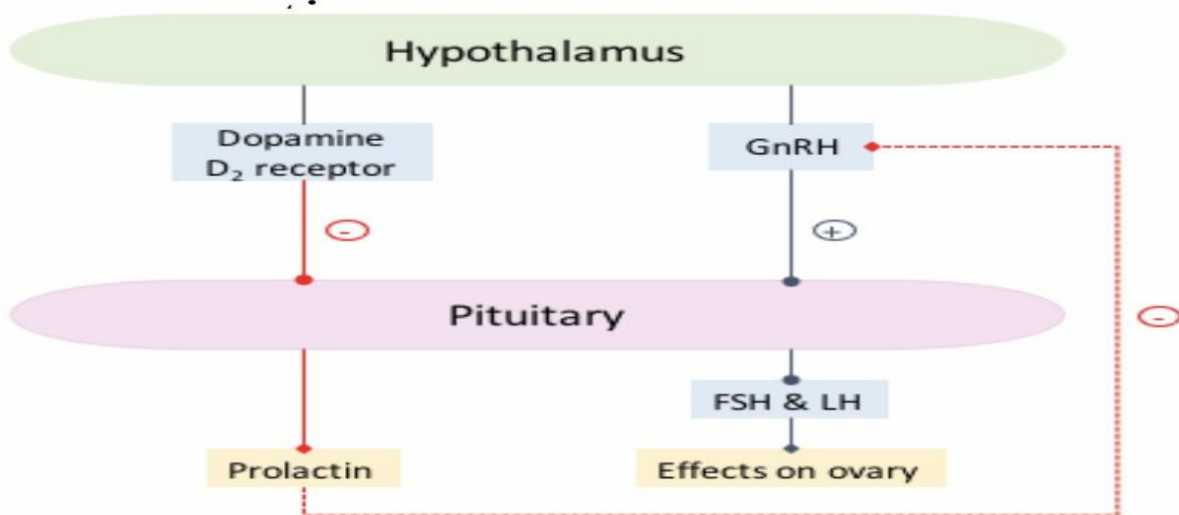


Gonadotropins e.g. Menotropin, Pregnyl

M.O.A	<ul style="list-style-type: none"> ❖ FSH & LH Are naturally produced by the pituitary gland ❖ For therapeutic use, extracted forms are available as: <ul style="list-style-type: none"> 1.Human Menopausal Gonadotrophin (hMG) → extracted from postmenopausal urine → contains LH & FSH (Menotropin) 1ST 2.Human Chorionic Gonadotrophin (hCG) extracted from urine of pregnant women → contains mainly LH (Pregnyl) 2days=ovulate
P.K	<ul style="list-style-type: none"> ❖ 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. <p style="text-align: center; color: green;">هنا نحاكي الطبيعة فكأننا نطابق نفس اللي يصير بالافارين سيكل</p> <p style="text-align: center; color: green;">HMG 1st for 10 days which has FSH and LH; we need FSH more cause the Follicular/proliferative phase</p> <p style="text-align: center; color: green;">HCG 2nd which has the LH hormone which is needed for ovulation</p>
Indications	<ul style="list-style-type: none"> ❖ Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency) Pituitary العيب ❖ Success rate for inducing ovulation is usually >75 %
ADR	<ul style="list-style-type: none"> ❖ FSH containing preparations <ul style="list-style-type: none"> •Fever •Ovarian enlargement (hyper stimulation) ER •Multiple Pregnancy (approx. 20%) clomiphene (clonidine) more ❖ LH containing preparations <ul style="list-style-type: none"> •Headache •Edema

D2 receptors agonists e.g. Bromocriptine

<p>M.O.A</p> <p>v.imp</p>	<ul style="list-style-type: none"> Is an ergot derivative (not a hormone) D2 receptors Agonists binds to dopamine receptors in the anterior pituitary gland & inhibits prolactin secretion the hypothalamus
<p>Indications</p>	<ul style="list-style-type: none"> Female infertility 2ndry to hyperprolactinaemia <p style="text-align: right; color: green;">Caused from : Tumor Drugs;Antipsychotic</p>
<p>ADR</p>	<ul style="list-style-type: none"> GIT disturbances; nausea, vomiting, constipation Headache Dizziness & orthostatic hypotension Dry mouth & nasal congestion Insomnia <p style="color: green;">Loss of libido Gynecomastia Elevated prolactin</p>



Hyperprolactinemia → No Ovulation

If there is any stimulation for prolactin (TRH, lactation, stress...etc) prolactin will be produced and give negative feedback to the hypothalamus, so no GnRH → no FSH & LH → no ovulation. In this lecture we need ovulation, so we need to inhibit prolactin, how? By stimulate the main inhibitory (DA), so we give drugs stimulate dopamine receptors e.g. **Bromocriptine**

Summary

AntiEstrogens(SERMS)

Drugs	Clomiphene (Steriodal)	Tamoxifen (Non steriodal)
M.O.A	➤ Compete with estrogen on the hypothalamus and A.P ↓ negative feedback increase in GNRH then increase in FSH&LH = OVULATION	
PK	500 mg/d for 5 days (5th-10th) day of cycle No response increase to 100 mg/d	
Indications	Female infertility in normogonadotrophic	-Alternative in PCOS and clomihphene resistant cases -Palliative treatment of estrogen receptor- positive breast cancer.
ADRs	-Hot flushes -Hyperstimulation of the ovaries & high incidence of multiple births	

GnRH analogues with Agonist Activity

Drug	Leuprolin	Goserelin
M.O.A	➤ Pulsatile secretion of GnRH from the hypothalamus leading to the release of gonadotropin (FSH) and (LH) from the anterior pituitary.	
Administration	➤ 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 hypothalamic amenorrhea (GnRH deficient)	
ADRs	➤ Hypoestrogenism on long term use □ : Hot flashes, ↓Libido, Osteoporosis, Rarely ovarian hyperstimulation □(ovaries swell & enlarge)	

Summary

Gonadotropins (FSH&LH)

Drugs

Menotropin (hMG)
LH&FSH

Pregnyl (hCG)
LH mainly

PK

- **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**.

Indications

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**

D2 R Agonist

Drug

Bromocriptine

M.O.A

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

Indications

Female Infertility 2ndry to hyperprolactinemia

ADRs

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

Quiz

Q1: A 25 years old female is unable to conceive, and her lab investigations shows hyperprolactinemia. What is the drug of choice?

- A. Bromocriptine
- B. Tamoxifen
- C. Pregnyl
- D. Goserelin

Q2: What is the mechanism of action of Leuprolin:

- A. GnRH antagonist
- B. GnRH agonist
- C. D2 receptor agonist
- D. antiestrogen

Q3: Which of the following is used to treat PCOS:

- A. Bromocriptine
- B. Clomiphene
- C. Menotropin
- D. Tamoxifen

Q4: Which of the following has a high incidence of multiple births:

- A. Menotropin
- B. Clomiphene
- C. Tamoxifen
- D. Leuprolin

Q5: A 25 years old female is unable to conceive. Her labs show her infertility is secondary to pituitary insufficiency. Which of the following drugs can be used in her case:

- A. Tamoxifen
- B. Bromocriptine
- C. Menotropin
- D. Clomiphene

Q6: Which of the following is used to suppress gonads in precocious puberty:

- A. Menotropin
- B. Pulsatile goserelin
- C. Pregnyl
- D. continuous Leuprolin

Answers:
1) A
2) B
3) D
4) B
5) C
6) D



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References:

✓ Doctors' slides and notes



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