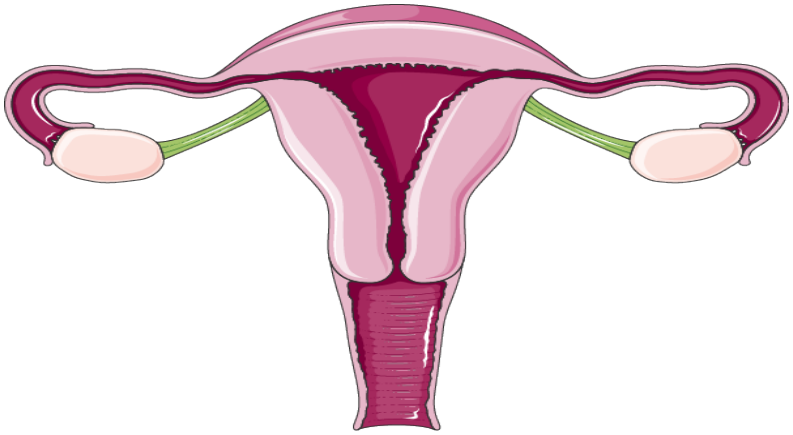
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



6: 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.

Color index

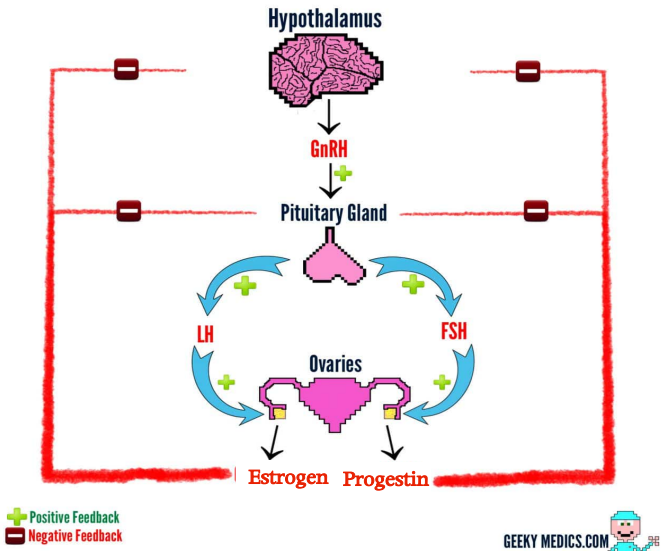
- Doctors' notes
- Drugs names
- Extra information and further explanation
- Important
- Mnemonics

Kindly check the editing file before studying this document

Overview

Drugs used to induce ovulation[1]

Antiestrogens (SERMs[2])	GnRH-agonists	Gonadotrophins[3]	D_2 receptors agonists	Treat polycystic ovarian syndrome (PCOS)
Clomiphene	Leuprolin	HMGs[4]: Menotropin	Bromocreptine	* Most common cause of infertility * Insulin resistance may play a role ??? e.g. Metformin[6]
Tamoxifen	Goserelin	HCGs[5]: Pregnyl		



The hypothalamus produce GnRH to stimulate pituitary, which produce FSH + LH, they will go to the ovaries to stimulate them to produce estrogen + Progestin which will give negative feedback to pituitary and hypothalamus
In ovulation we need more FSH & LH, so we either give drugs that: (1) inhibit the negative feedback 'Antiestrogens' or (2) stimulate GnRH release 'GnRH-agonists' or (3) mimic the FSH + LH 'Gonadotrophins' or (4) we will discuss them later ☺

[1] If the cause of infertility is due to ovarian or testicular failure it can't be treated. So, these treatments are only used if the ovaries are well functioning but the problem is in ovulation
[2] selective estrogen receptors modulators
[3] Gonadotrophin = LH & FSH
[4] Human Menopausal Gonadotrophin
[5] Human Chorionic Gonadotrophin
[6] Polycystic ovarian syndrome induce high androgen which will cause acne and hirsutism. Patients also become obese → obesity cause Insulin resistance. Treating insulin resistance by Metformin will highly increase the possibility of pregnancy. We also use Clomiphene for the infertility in case of PCOS

Antiestrogens

	Clomiphene	Tamoxifen
M.O.A	Compete with estrogen on the hypothalamus and anterior pituitary gland: decrease (or inhibits) the negative feed back of endogenous estrogen → increase GnRH → increase production of FSH & LH → OVULATION	
	Week, reversible antiestrogen	alternative to clomiphene But differ in being Non Steroidal
P.K	• Clomiphene given 50 mg/d for 5 days from 5th day of the cycle to the 10th day. • If no response after 3 months give 100 mg for 5 days again from 5th to 10th day • Each dose can be repeated not more than 3 cycles .	
indication	• Female infertility, due to anovulation or oligoovulation. not due to ovarian or pituitary failure (Normogonadotrophic) Given when the ↑ levels of estrogen causes anovulation • The success rate for ovulation is 80% & The success rate for pregnancy is 40% .	• Tamoxifen is a good alternative to clomiphene in women with polycysts ovarian syndrome (PCOS[7]) and clomiphene-resistant cases • Used in palliative treatment of estrogen receptor- positive breast cancer (relieve symptoms but do not cure the disease) why we don't use clomiphene? bc it's steroid and weak antiestrogen
ADRs[8]	• High incidence of multiple birth. (10% incidence of multiple birth, 75% of them are twins, the rest are 3 babies or more). • Hot Flushes & breast tenderness • Gastric upset (nausea and vomiting). • Visual disturbances (reversible) • ↑ nervous tension & depression • Skin rashes • Fatigue • Weight gain • Hair loss (reversible) • Hyperstimulation of the ovaries	

[7] don't forget the most important drugs in PCOS is metphormine (☺ بروف يلذز عادتها يمكن عشر مرات)

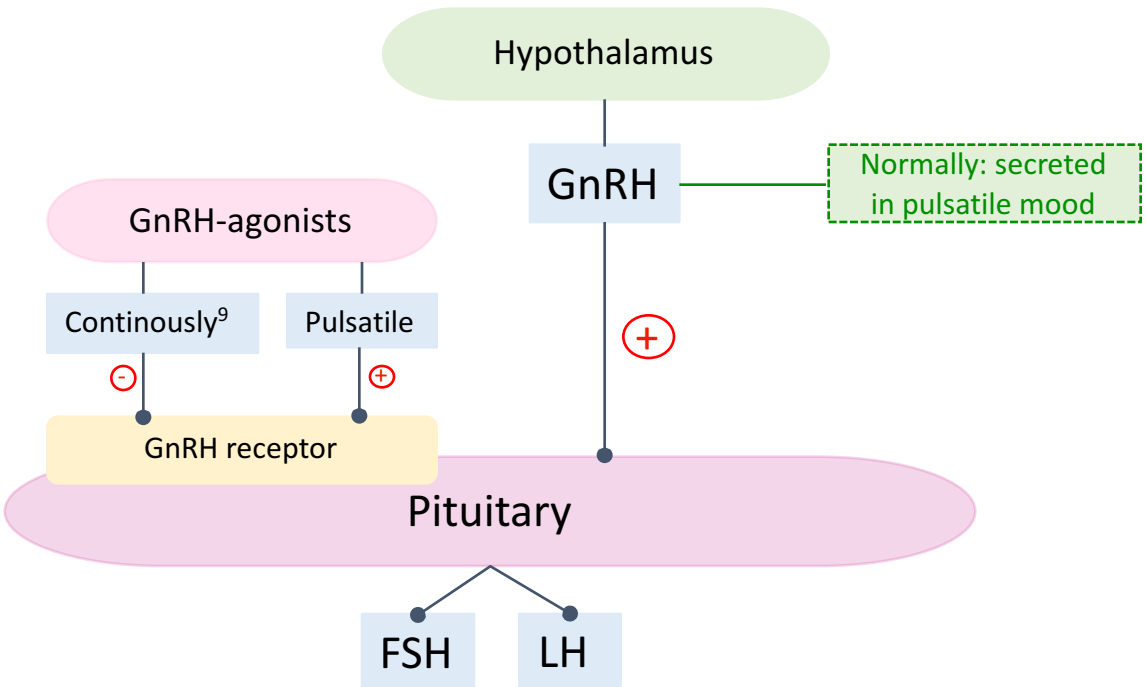
[8] The side effects are due to the hormonal changes and not the drug itself; all are reversible

GnRH-agonists

Leuprolin, Goserelin

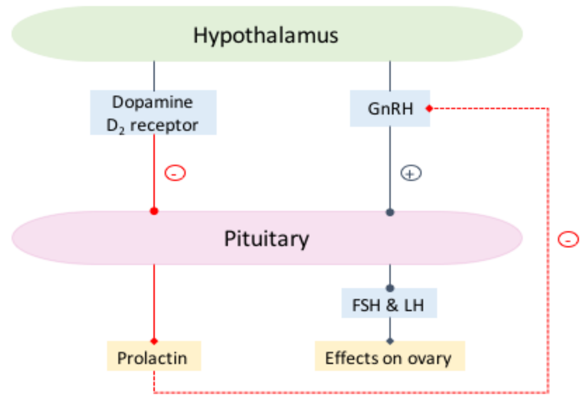
M.O.A	Analgoues with **agonist** activity
P.K	• GnRH and agonists, given S.C. in a **pulsatile** (drip) to stimulate gonadotropin release (1 – 10 µg / 60 – 120 min) to mimic the normal release in the normal situaition • Start from day 2-3 of cycle up to day 10
Indications	• Induction of ovulation in patients with hypothalamic amenorrhea (GnRH deficient) • Given continuously, when gonadal suppression is desirable e.g. precocious puberty and advanced breast cancer in women and prostatic cancer in men
ADRs	GIT disturbances, abdominal pain, nausea….etc Headache • Hypoestrogenism (on long term use): ✓ Hot flashes ✓ ↓ Libido ✓ Osteoporosis ✓ Rarely ovarian hyperstimulation (ovaries swell & enlarge)

مفيش حاجات مهمه في الجزئية دي



[9] Normally GnRH has a pulsatile form of secretion; when given continuously it has a paradoxical effect (suppress the GnRH receptors “down regulation” or “tolerance”)

Ovulation Induction

	Gonadotrophins e.g. **Menotropin**, **Pregnyl**	D_2 receptors agonists e.g. **Bromocreptine**
M.O.A	• FSH & LH Are naturally produced by the pituitary gland ❖ For therapeutic use, extracted forms are available as: 1. Human Menopausal Gonadotrophin (hMG) → extracted from postmenopausal urine → contains LH & FSH (Menotropin) [hMG = FSH+LH / الهمج = فشلة] 2. Human Chorionic Gonadotrophin (hCG) extracted from urine of pregnant women → contains mainly LH (Pregnyl) [hCG= ECG LH / لا ECG سوا]	• Is an ergot derivative (not a hormone) • D_2 receptors Agonists binds to dopamine receptors in the anterior pituitary gland & inhibits prolactin secretion 
P.K	hMG is given I.M every day starting at day 2-3 of cycle for 10 days followed by hCG on (10^{th} - 12^{th} day) for OVUM RETRIEVAL.	Hyperprolactinemia → No Ovulation If there is any stimulation for prolactin (TRH, lactation, stress...etc) prolactin will be produce 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 inhibatory (DA), so we give drugs stimulate dopamine receptors e.g. Bromocreptine
indication	• Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency) • Success rate for inducing ovulation is usually ≥75 %	Female infertility 2ndry to hyperprolactinemia بروف يلدز أنبح حلقها وهي تقول مهم ☺ Hyperprolactinemia in female: amenorrhea and false pregnancy test Hyperprolactinemia in male: gynecomastia + infertility + decrease libido
ADRs	❖ FSH containing preparations - Fever - Ovarian enlargement (hyper stimulation) - Multiple Pregnancy (approx. 20%) ❖ LH containing preparations - Headache - Edema	- GIT disturbances; nausea, vomiting (by stimulating Chemoreceptors Trigging Zone) ,constipation - Headache dizziness & orthostatic hypotension - Dry mouth & nasal congestion - Insomnia

* Both male and female doctors emphasized on the indications of each drug (so please focus on them)

Ovulation Induction

Class	Antiestrogens SERMs		GnRH agonists	Gonado-Trophins		D_2 R Agonists
Drug	Clomiphene	Tamoxifen Non-steroidal	Leuprolin & Goserelin	Menotropin (hMG) Extracted from Postmenopausal urine (contains LH & FSH).	Pregnyl (hCG) Extracted from pregnant women urine (contains mainly LH).	Bromocreptine (Not a hormone)
MOA	↑ Negative feedback of endogenous estrogen on Hypothalamus and anterior pituitry → ↑ GnRH → ↑ FSH & LH → OVULATION!					D_2 R agonists binds to dopamine receptors in the AP gland → inhibits prolactin secretion.
Indication	-Female infertility, due to anovulation or oligoovulation.	Women with PCOS and clomiphene-resistant cases. Estrogen receptor-positive breast cancer.	Female infertility due to hypothalamic amenorrhea GnRH deficient).	Female infertility 2ry to Gonadotropin deficiency (pituitary insufficiency).		Female infertility 2ndary to hyperprolactinemia.
Administration	Given from 5th to 10th day of the cycle. Can not be repeated more than 3 cycles.		Given S.C. in a pulsatile drip to stimulate gonadotropin. -Release Start from day 2-3 of cycle up to day 10. Given continuously when gonadal suppression is desirable e.g.: • Precocious puberty. • Breast cancer in women. • Prostatic cancer in men.	I.M. daily starting at day 2-3 of cycle for 10 days.	Given on 10th - 12th day for Ovum retrieval.	

MCQs

Q1: 33 years old female who is obese, she was diagnosed with PCOS two years ago. Now, she is trying to have and get pregnant. Which of the following drugs can be helpful in her case to induce ovulation ?

A. Leuprolin. B. Menotropin & Pregnyl. C. Bromocriptine. D. Metformin.

Q2: 26 years old female who has breast cancer. Her lab investigation shows it is a positive for estrogen receptors, which of the following drugs can be used in her case ?

A.Clomiphene. B. Menotropin & Pregnyl. C. Tamoxifen. D. Pulsatile Leuprolin.

Q3: Which of the following can be used to treat infertile women due to hypothalamic amenorrhea or 2^{ndry} to GnRH deficiency?

A.Clomiphene. B. Menotropin & Pregnyl. C. Continuous Goserelin. D. Pulsatile Leuprolin.

Q4: Which of the following can be used to treat infertile women due to pituitary insufficiency or gonadotrophic deficiency?

A.Clomiphene. B. Menotropin & Pregnyl. C. Continuous Goserelin. D. Pulsatile Leuprolin.

Q5: 7 years old girl who has precocious puberty, Which of following would be helpful in her case?

A.Clomiphene. B. Menotropin & Pregnyl. C. Continuous Goserelin. D. Pulsatile Leuprolin.

Q6: Which of the following can be used to treat infertile women due to primary anovulation and high level of estrogen ?

A.Clomiphene. B. Menotropin & Pregnyl. C. Bromocriptine. D. Pulsatile Leuprolin.

Q7: In which day of the cycle, hCG should be given for ovum retrieval ?

A. 5th day. B. 5th – 10th day. C. 10th – 12th day. D. Day 21.

Q8: 31 years old female who is failed to have a baby for three years. Her lab investigation shows high level of prolactin and low level of FSH & LH and estrogen and progesterone in her plasma. Which one of the following drugs can be helpful in her case to induce ovulation ?

A.Clomiphene. B. Menotropin & Pregnyl. C. Bromocriptine. D. Pulsatile Leuprolin.

1) D.
2) C.
3) D.
4) B.
5) C.
6) A.
7) C.
8) C.

إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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References :

1- 436 doctor’s slides and notes