Pharmacology 439

MED439

Revised & Approved

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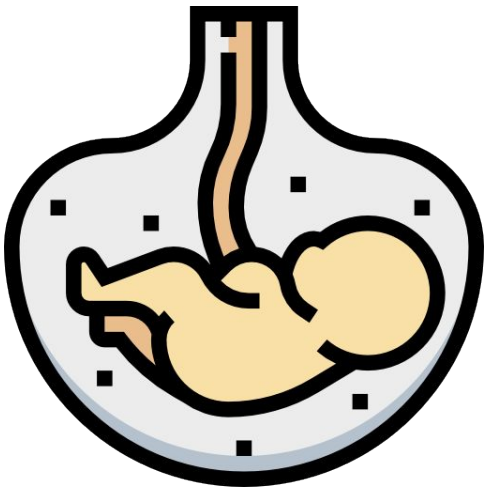

Editing File

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Pharmacology team 439

Drugs Inducing Ovulation

Objectives:

By the end of the lecture , you should know:

- 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

Color index:

Black : Main content
Red : Important
Blue: Males' slides only

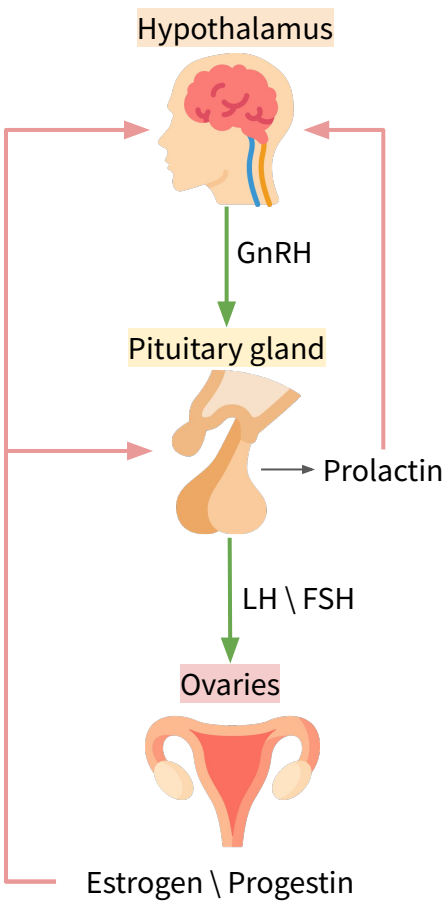
Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)

Green: Dr. notes (438)

Overview

Drugs Used to Induce Ovulation

- **1) Antiestrogen (SERMs)**
  1. Clomiphene
  2. Tamoxifen
- **2) GnRH agonists**
  1. Leuprolin
  2. Goserelin
- **3) Gonadotrophin**
  1. HMGs: Menotropin
  2. HCGs: Pregnyl
- **4) D2 receptors agonists**
  Hyperprolactinaemia
  1. Bromocriptine
- **5) Treatment of Polycystic Ovarian Syndrome (PCOS)**
  PCOS is the most common cause of infertility and insulin resistance may play a role → use Metformin, Tamoxifen, Clomiphene[1]



Recall Hypothalamic pituitary gonadal axis

1. Hypothalamus secretes Gonadotropin Releasing Hormone (GnRH) to stimulate the pituitary gland
2. Pituitary gland secretes Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH) which act on ovaries to stimulate it.
3. Ovaries produce estrogen and progestin, they have a -ve feedback on pituitary and hypothalamus
4. It is also important to mention that the prolactin released from the anterior pituitary gland and have an inhibitory effect on GnRH → Hyperprolactinemia causes infertility
   a. The main inhibitor of prolactin is dopamin

- To induce ovulation, there is a need for more LH and FSH. so, drugs act by:

1. Inhibiting the -ve feedback → Antiestrogen
2. Stimulating GnRH release → GnRH agonists
3. Mimic LH and FSH → Gonadotrophs
4. Inhibiting prolactin secretion → D2 agonist

Special thanks to 436 pharmacology team

1- Clomiphene is 1st choice, if obese or diabetic choose metformin, Reminder: Metformin reduces insulin resistance and improves lipid profile.

1) Antiestrogens

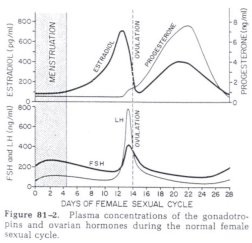
Drugs	Clomiphene	Tamoxifen
MOA	• **Compete with estrogen on the hypothalamus and anterior pituitary gland**: decrease the negative feedback of endogenous estrogen ⟶ increase GnRH ⟶ increase production of FSH & LH ⟶ OVULATION	
P.K	• Clomiphene given 50 mg/d for 5 days from 5th day of the cycle to the 10th day. • If no response give 100 mg for 5 days again from 5th to 10th day chance to be pregnant with a twin • Each dose can be repeated **not more than 3 cycles**	• Similar and alternative to clomiphene but differ in being non Steroidal
Uses	• Female infertility due to anovulation or oligoovulation[1]; • **Not due to** ovarian or pituitary failure (**Normogonadotrophic**) • The success rate for ovulation is 80% & pregnancy is 40%	★ Tamoxifen is a good alternative to clomiphene in women with polycystic ovarian syndrome and clomiphene-resistant cases ★ Used in palliative treatment of estrogen receptor- positive breast cancer (why not Clomiphene?[2])
ADR	★ Hyperstimulation of the ovaries and high incidence of multiple birth (75% twins) • Hot Flushes & breast tenderness • Gastric upset (nausea and vomiting) • Visual disturbances (reversible) • ↑ nervous tension & depression • Skin rashes • Fatigue • Weight gain • Hair loss (reversible)	-

2) GnRH Agonists

Drug	Leuprolin & Goserelin
MOA	• Analogous with agonist activity
P.K	• GnRH and agonists, given S.C. in a **pulsatile (drip)**[3] (1 – 10 µg / 60 – 120 min as drip) to stimulate gonadotropin release • Start from day 2-3 of cycle up to day 10
Uses	★ Induction of ovulation in patients with **hypothalamic amenorrhea** (GnRH deficient) • Given <u>continuously</u> (paroxidal opposite effect) when gonadal <u>suppression</u> is desirable e.g. **precocious puberty** and **advanced breast cancer** in women and **prostatic cancer** in men.very serious side effect be careful with dosing
ADR	• GIT disturbances, abdominal pain, nausea...etc • Hypoestrogenism (with long term use): ○ Hot flashes , ↓ libido, osteoporosis, rarely ovarian hyperstimulation (ovarian swelling and enlargement) • Headache

1) Anovulation: failure of the ovary to release an ova.
Oligoovulation: irregular ovulation.
2) Because tamoxifen has stronger anti-estrogen activity against cancers caused by elevated Estrogen with more efficacy to compete with Estrogen receptors, Estrogen may cause breast cancer after metabolic activation
3) Pulsatile administration ⟶ stimulates gonadotropin release.
Continuous administration ⟶ suppresses gonadotropin release.

3) Gonadotrophins

Drugs	Menotropin	Pregnyl
MOA	• FSH and LH are naturally produced by the pituitary gland • For therapeutic use, extracted forms are available as:	
	• Human Menopausal Gonadotrophin (hMG) → extracted from postmenopausal urine → contains LH & FSH usually used in low FSH	• Human Chorionic Gonadotrophin (hCG) extracted from urine of pregnant women → contains mainly LH testing hormone for pregnancy
P.K	• hMG is given I.M every day starting at day 2-3 of cycle for 10 days followed by hCG on (10th - 12th day)[1] for ovum retrieval and that will trigger the eggs production from the ovary at the day 14 so ovulation happened  Figure 81–2. Plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.	
Uses	★ Stimulation & induction of ovulation in infertility secondary to gonadotropin deficiency **(pituitary insufficiency)** • Success rate for inducing ovulation (not fertilization) is usually >75 %	
ADR	• FSH containing preparations: ○ Fever ○ Ovarian enlargement (Hyperstimulation) ○ multiple pregnancy (~20%) • LH containing preparation: ○ Headache ○ edema	

4) D2 receptor agonists

Drug	Bromocriptine
MOA	• Is an ergot derivative (not a hormone) • D2 receptors agonists binds to dopamine receptors in the anterior pituitary gland & **inhibits prolactin secretion** prolactin have a negative feedback on th hypothalamus to lower GnRH
Uses	★ Female infertility **secondary to hyperprolactinemia**[2]
ADR	• GIT disturbances: nausea, vomiting, constipation • Headache dizziness & orthostatic hypotension • Dry mouth & nasal congestion • Insomnia

Drug & uses (extra)

- **Clomiphene** → infertility due to anovulation or oligoovulation, PCOS (with metformin)
- **Tamoxifen** → alternative to clomiphene (PCOS and resistant cases), estrogen receptor- positive breast cancer
- **Leuprolin & Goserelin** → hypothalamic amenorrhea (pulsatile), precocious puberty (continuous)
- **Menotropin (hMG), Pregnyl (hCG)** → induce ovulation in gonadotropin deficiency (pituitary insufficiency)
- **Bromocriptine** → secondary to hyperprolactinemia

1) Remember that ovulation occur at day 14 of the cycle, so Pregnyl (which mainly contains LH) is given between day 10-12 so the body level of LH reaches the optimum level by day 1 4 to induce a successful ovulation
2) Remember that antipsychotics (anti-schizophrenia) can cause hyperprolactinemia.

Quiz

MCQ

Q1- A 27-year-old woman with amenorrhea, infertility, and galactorrhea (caused by hyperprolactinemia) was treated with a drug that successful restored ovulation and menstruation. Before being given the drug, the woman was carefully questioned about previous mental health problems, which she did not have. She was advised to take the drug orally. The drug used to treat this patient was probably.

A- Bromocriptine. B- Leuprolide. C- Human gonadotropin hormone. D-Clomiphene

Q2- A 29-year-old woman has a 3 years history of anovulatory infertility. She has undergone a year of treatment with Clomiphene which was successful. What is the mechanism of action of the drug she was using?

A- GnRH Agonist B- Human Chorionic Gonadotrophin
C- Antiestrogen D- Dopamine receptor Agonist

Q3- A doctor wants to induce ovulation in a woman with hypothalamic amenorrhea. What's the treatment of choice for this condition?

A- Continuous Administration of Goserelin B- Tamoxifen pills
C- I.M injections of Menotropin D- Pulsatile Administration of Leuprolin

Q4- A 31-year-old woman with infertility secondary to pituitary insufficiency is taking gonadotrophins for treatment. Which one of the following is given on (10th - 12th day) for Ovum retrieval?

A- Bromocriptine B- Pregnyl C- Clomiphene D- Menotropin

SAQ

- A 23-year-old woman has failed to become pregnant after 2 years of unprotected intercourse.

Q1-Which drug would be effective in treating infertility due to anovulatory cycles?

Q2-What is the M.O.A of that drug?

- A 26-years-old married couple has been unable to conceive after 3 years of unprotected intercourse, the husband's sperms count is normal but the wife labs show infertility is secondary to pituitary insufficiency and they both agree that they would like the wife to undergo fertility treatment.

Q3-Which drug can be used in this case?

Q4-list 2 ADR of that drug.

- A 24-year-old woman with infertility due to hyperprolactinemia and her 29-year-old husband desires to start a family. She is currently taking a fertility medication but is troubled by some side effects. She couldn't sleep at night and she feels dizzy most of the day, and this makes her depressed.

Q5- Which drug is she most likely taking?

Answers:

MCQ

Q1	A
Q2	C
Q3	D
Q4	B

SAQ

Q1	clomiphene
Q2	Compete with estrogen on the hypothalamus and anterior pituitary gland leading to ovulation
Q3	Menotropin & Pregnyl
Q4	Headache - edema - fever
Q5	Bromocriptine

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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