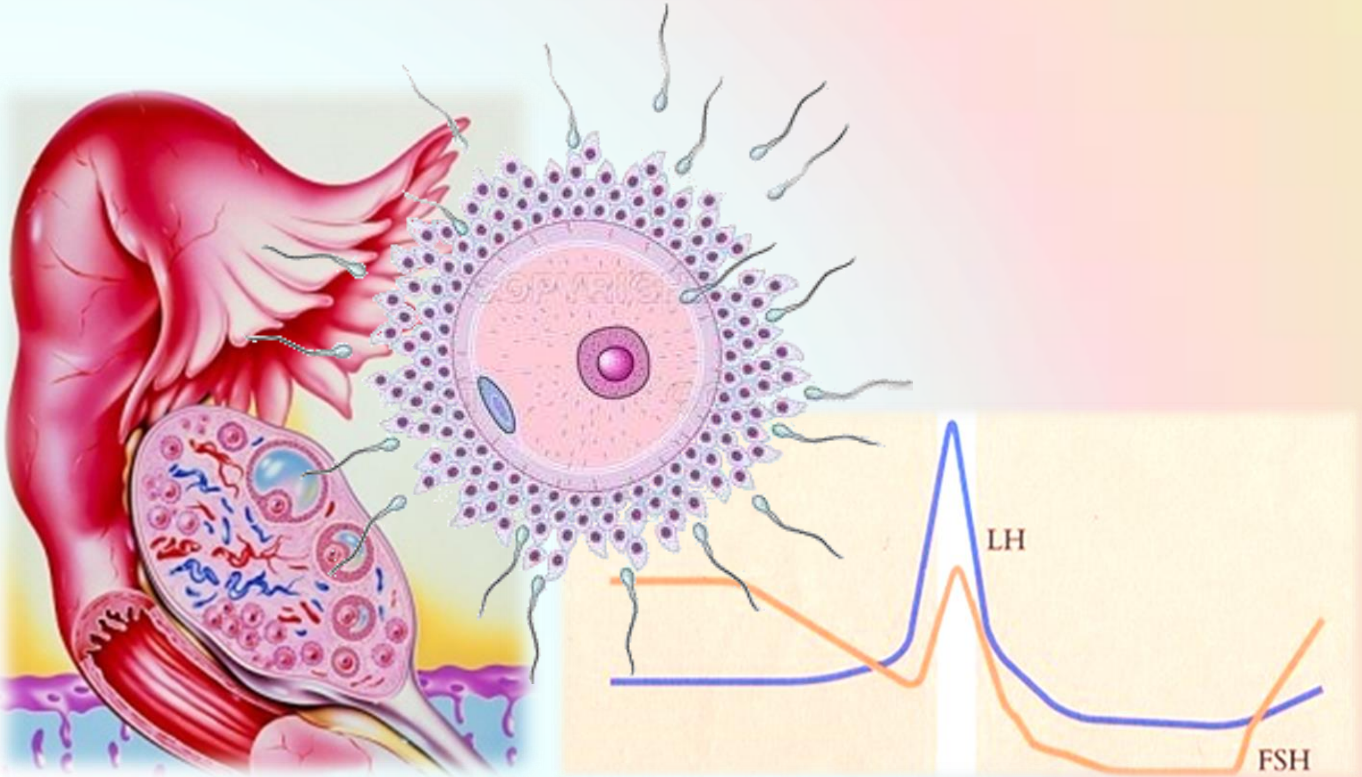
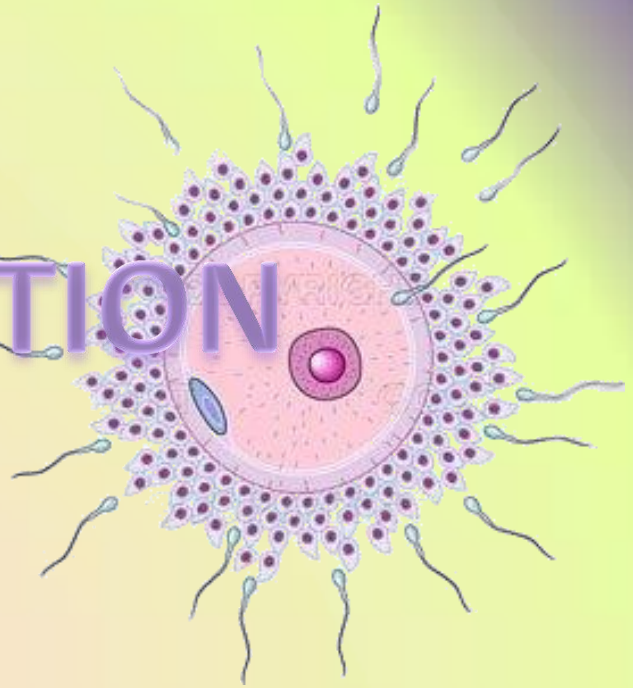
Drugs In OVULATION INDUCTION



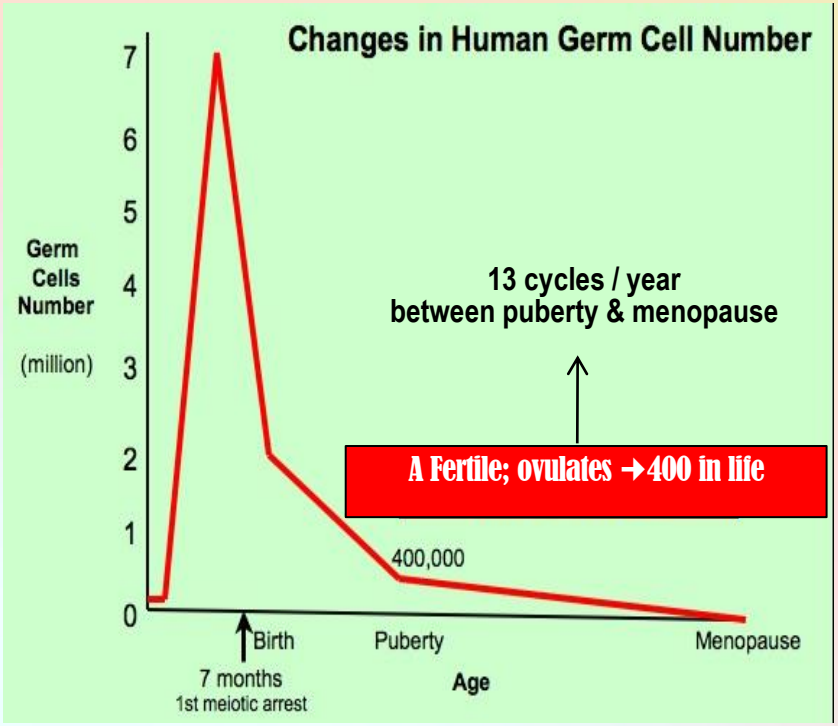
Drugs In OVULATION INDUCTION

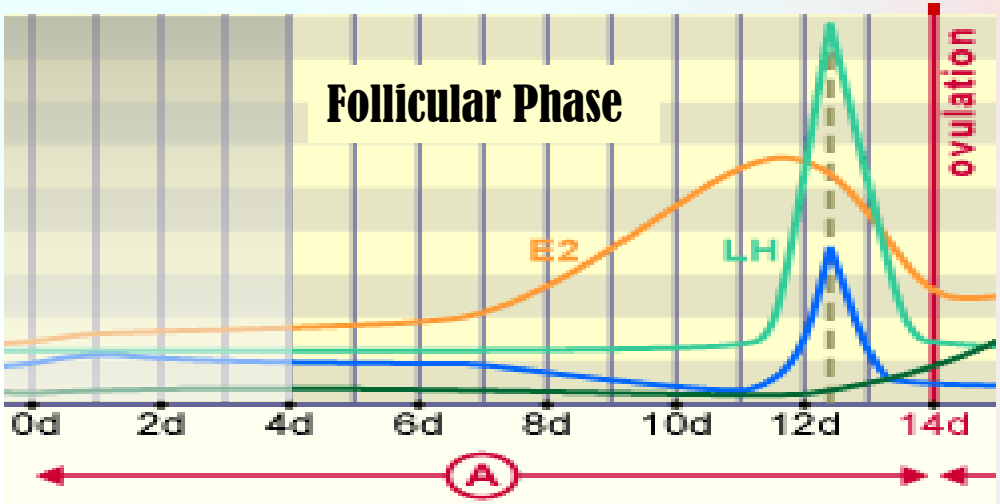


ILOs

By the end of this lecture you will be able to:

- Recall how ovulation occurs and specify its hormonal regulation
- Recognize causes and types of female infertility
- 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.





Follicular Phase

Recruitment
Gn-independent

Selection
Gn-responsive
Little estrogen

Dominance=Maturation
Hormone-dependent
High estrogen

Primordial

Pry

Sec

Preantral

Antral

Graffian Follicle

2/3-7 d

7/8-12 d

12-14 d

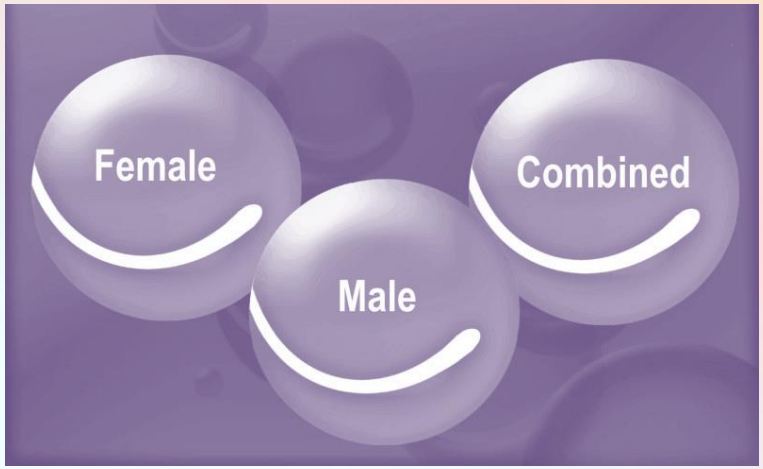
LH > FSH SURGE

X OVULATION

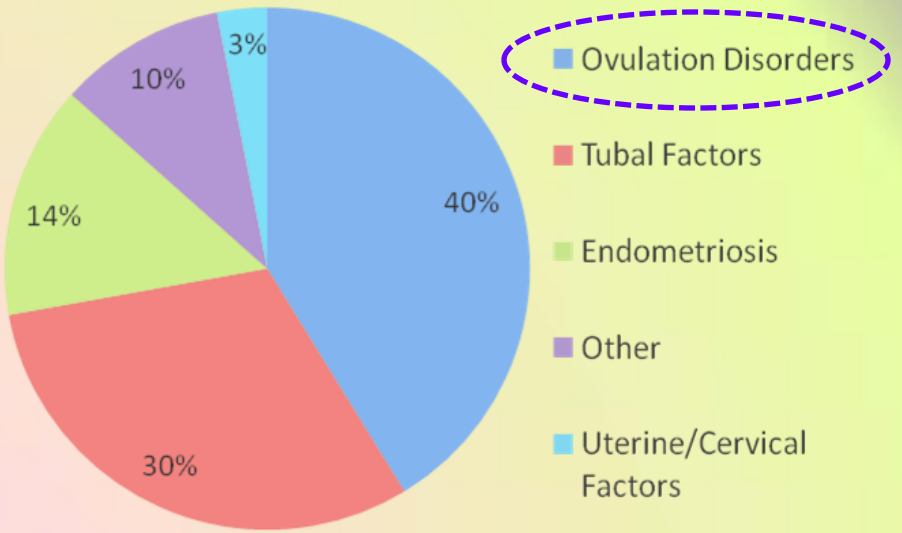
INFERTILITY

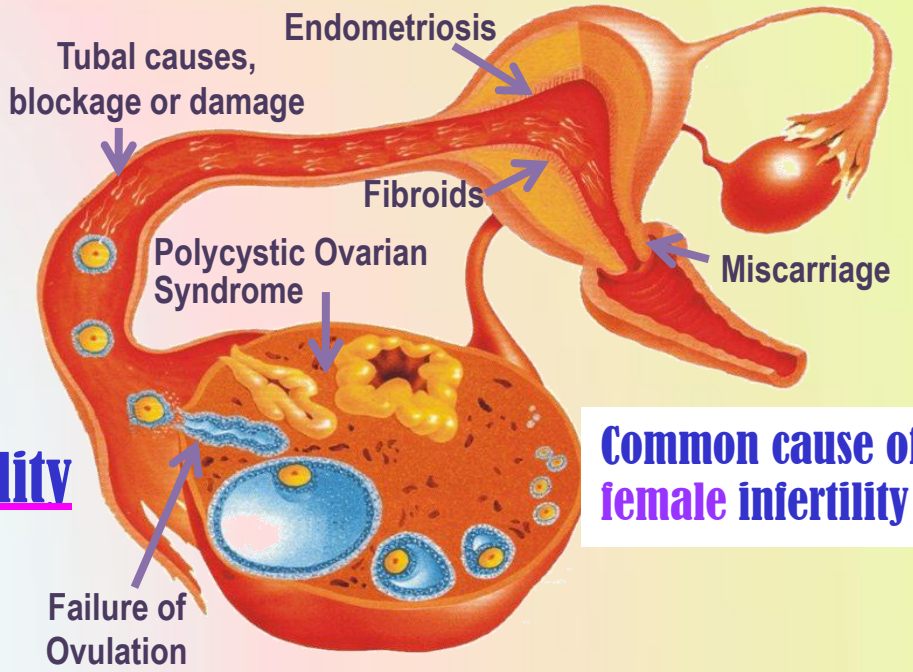
INFERTILITY

A condition characterized by a reduction in ability to reproduce or to achieve conception



- 1/3 attributed to women.
- 1/3 attributed to male factors
- 1/3 both or unexplained





Most common cause of female infertility

Common cause of female infertility

Ovulation Induction

ANTIESTROGENS

SERMs;
Clomiphene
Tamoxifen

D_2 R Agonists

Bromocreptine

GONADOTROPHINS

HMGs; Menotropin
HCGs; Pregnyl

GnRH

GnRH-agonists
Leuprolin
Goserelin

METFORMIN; IN POLYCYSTIC OVARIAN SYNDROME
to ↓ body weight &
↑ response to ovulation induction drugs

➢Conception remote, no place for therapy←

Hyperprolactinaemia

Hypogonadotropic ☑

Hypothalamus
↓
GnRH
↓
Anterior Pituitary
↓
FSH / LH
↓
Ovary
↓
Estrogen
Progestins

Hypothalamo-pituitary

(-)

Ovarian

(-)

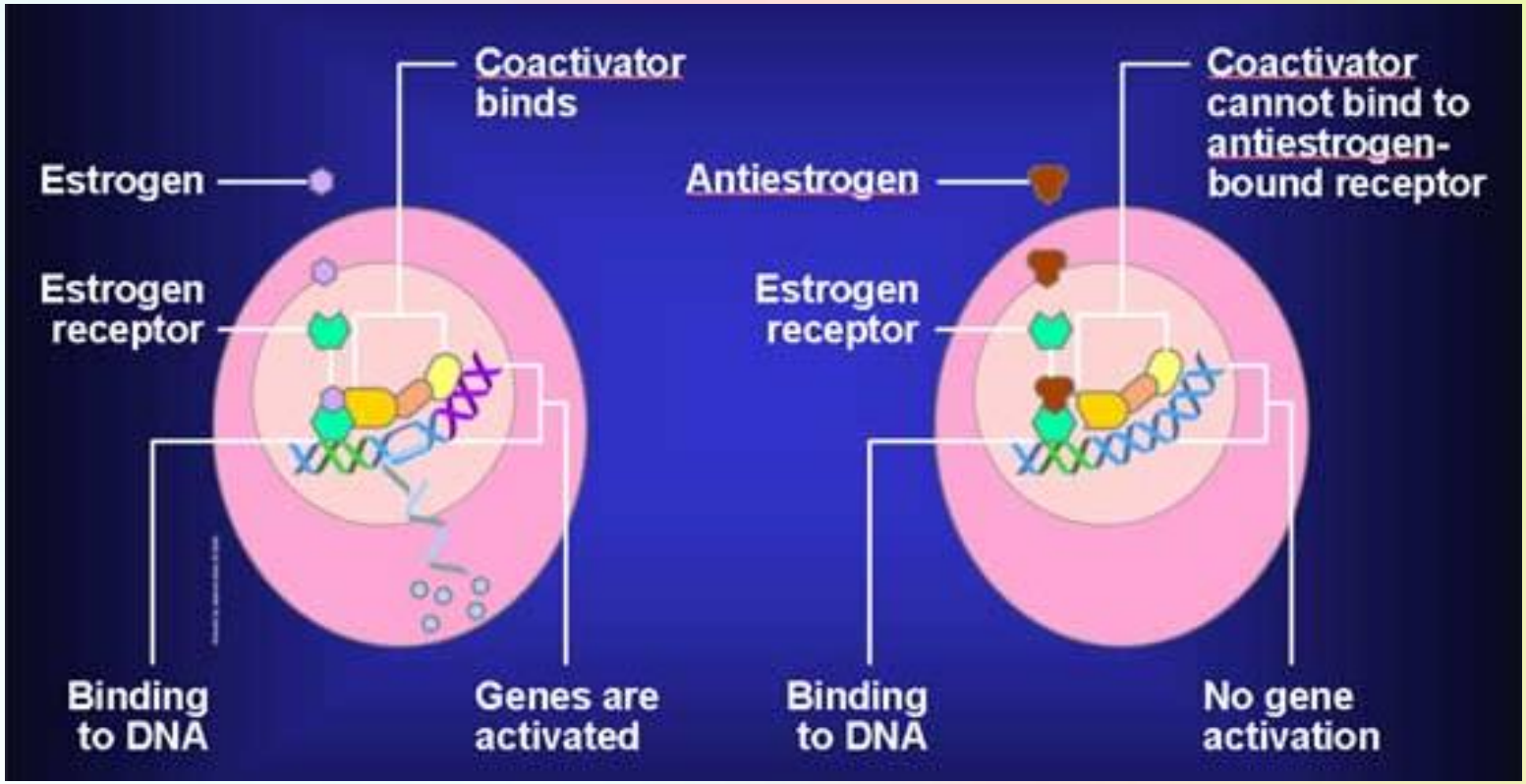
Normogonadotrophic ☑

Hypergonadotrophic ☒

ANTIESTROGENS

SERMs

Selective Estrogen Receptor Modulators [SERMs] ➔ compete with estrogen on estrogen receptors in the nucleus
Doing so they act as antagonists or partial agonists depending on how they bind & the different target tissue of action.
In the hypothalamus & pituitary they have ANTAGONISTIC ACTION



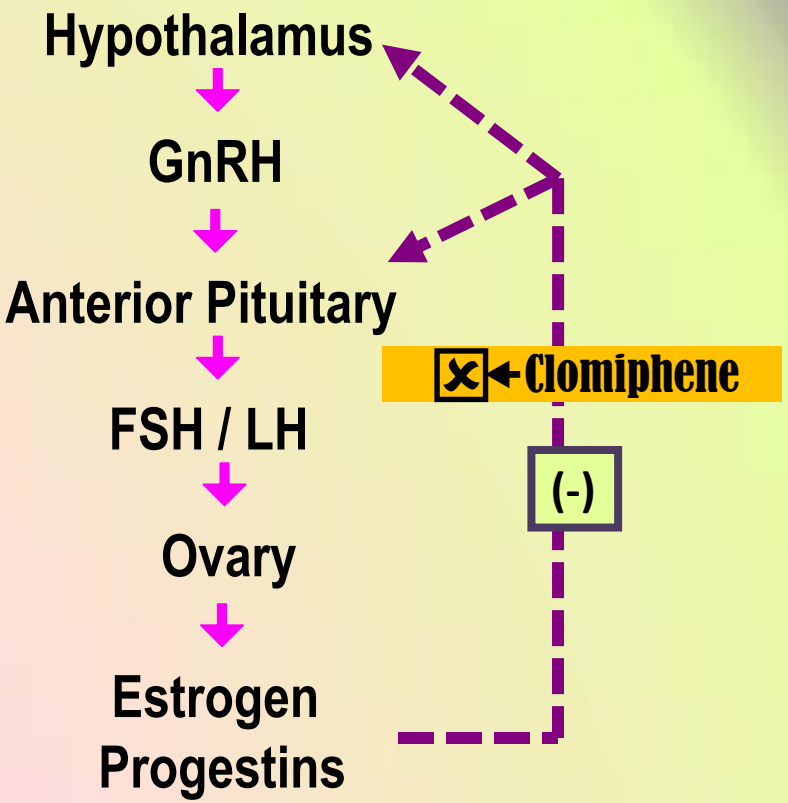
ANTIESTROGENS

SERMs

1. CLOMIPHENE

Pharmacological effects

- On hypothalamus; ↓negative feed back of endogenous estrogen on hypothalamus→ pulse ↑GnRH → ↑ gonadotrophin production [FSH & LH] → cause growth maturation & rupture of follicles→ **OVULATION**
- On pituitary; ↑response of gonadotrophins to GnRH



Indication

- Female infertility;
  not due to ovarian or pituitary failure → **Normogonadotrophic**
- The success rate for ovulation →80% & pregnancy →40% .
  The discrepancy between 2 rates is due to the antiestrogenic effects of clomiphene on uterus, cervix & vagina

CLOMIPHENE cont.

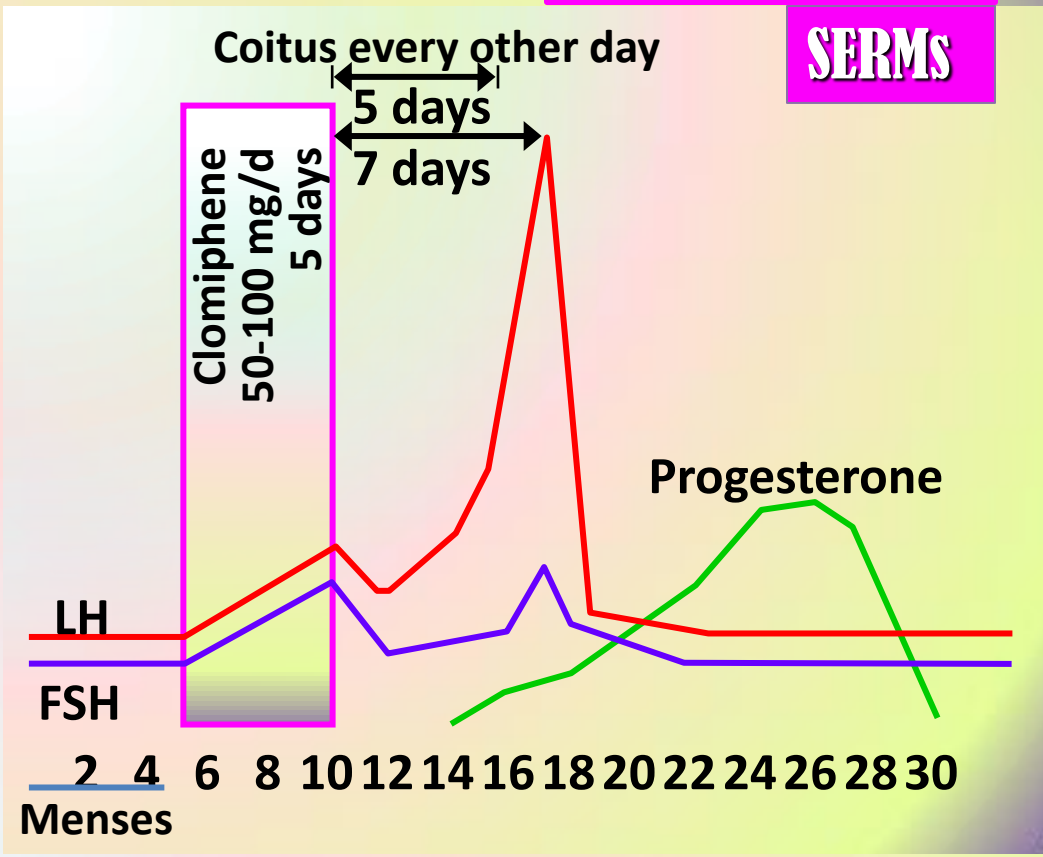
ANTIESTROGENS

SERMs

Method of administration

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

The drug can be repeated not more than 6 cycles .



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)

N.B. ↑ *incidence of multiple ovulation* ➔ twins in 10% *birth*

2. TAMOXIFEN

ANTIESTROGENS

SERMs

Is similar & alternative to clomiphene
But differ in being Non Steroidal

- Used in palliative treatment of hormone-dependent / estrogen receptor- positive advanced breast cancer

- *But why clomiphene not used in such cases of cancer breast?*

GONADOTROPHINS → [FSH & LH]

Are naturally produced by the pituitary gland

For therapeutic use, extracted forms are available as;

1. Human Menopausal Gonadotrophins (hMG)➔ extracted from postmenopausal urine ➔ contains LH & FSH ➔**MENOTROPIN**
2. Human Chorionic Gonadotrophins (hCG) extracted from urine of pregnant women ➔contains mainly LH) ➔**PREGNYL**

N.B. Now new available preparations by recombinant technology

Mechanism

- Preparations of FSH ➔ act on ovary directly, stimulating growth & maturation of Graafian Follicle(s)
- Preparations of LH ➔ act just to induce ovulation

Given sequentially

Indication

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

Success rate for inducing ovulation is usually ≥75 %

GONADOTROPHINS

[FSH & LH]

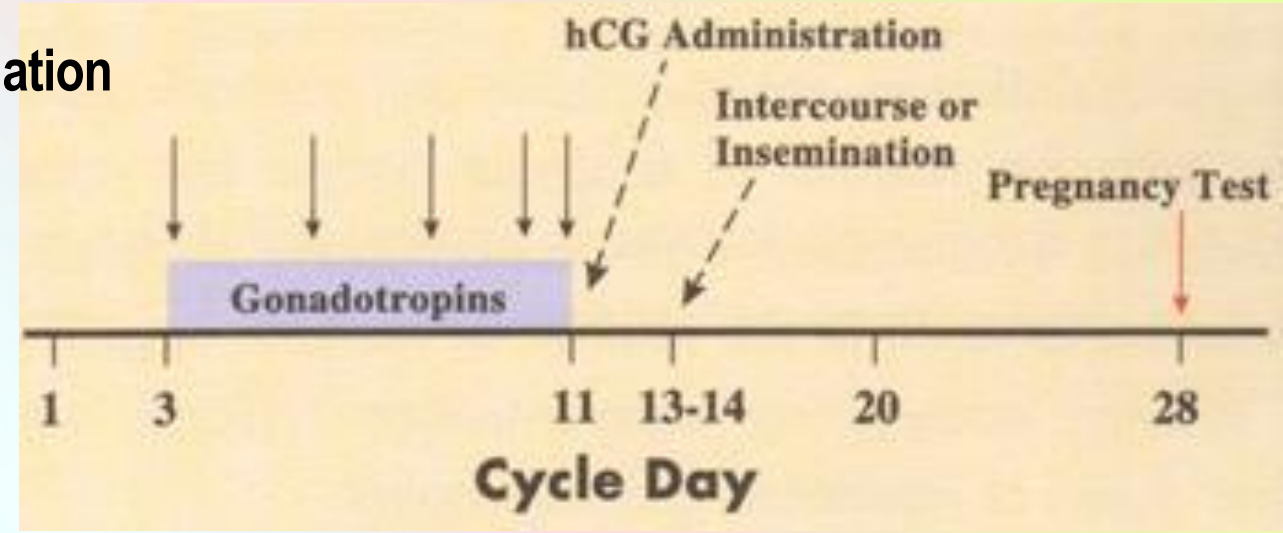
Method of administration

hMG is given i.m or subcut. every day starting at day 2-3 of cycle for 10 days followed by

hCG on (10^{th} - 12^{th} day) for OVUM RETRIEVAL within 36 hrs.

When we indicate:

- intrauterine insemination
- or intercourse

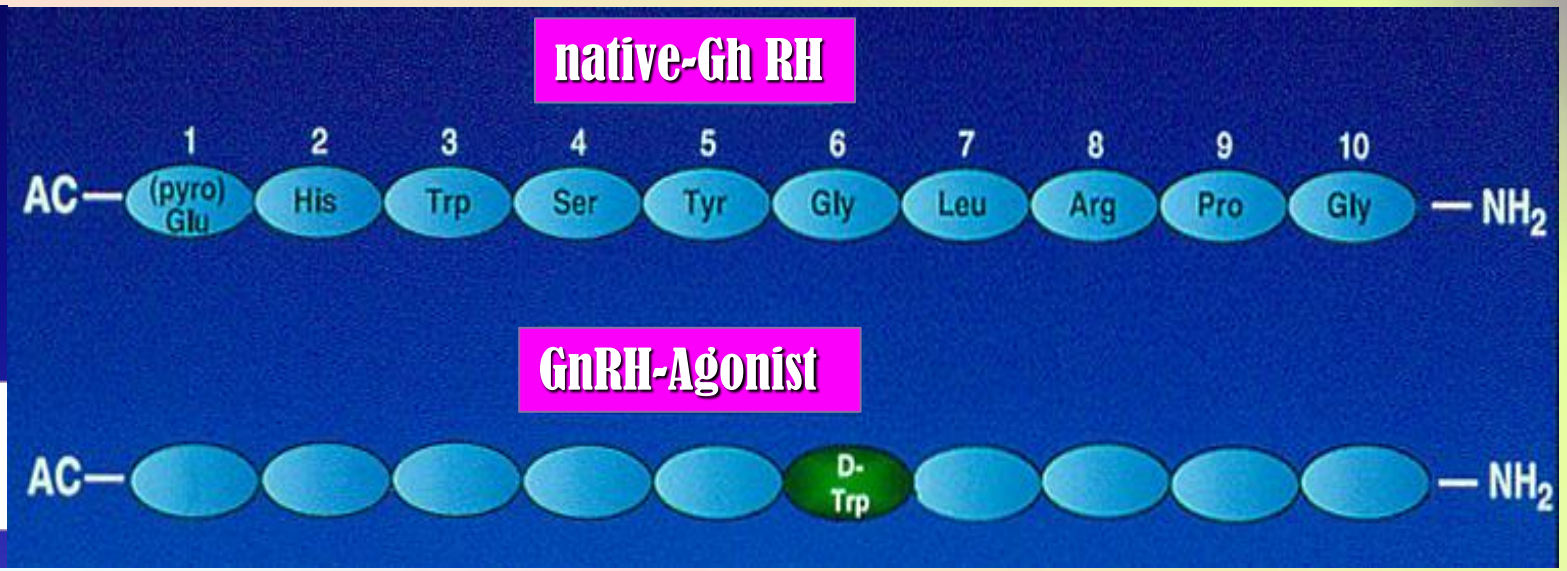


ADRs

FSH containing preparations; Fever
Ovarian enlargement (hyper stimulation)
Multiple Pregnancy (approx. 20%)

LH containing preparations; Headache & edema

GnRH



LEUPROLIN
GOSERELIN

Mechanism

Native GnRH is naturally produced by hypothalamus in a pulsatile manner. It is triggered when the negative feedback inhibition of ovarian hormones is lost by the end of the cycle. This activates FSH release from pituitary that stimulate growth and maturation of ova early during the follicular phase of the cycle. It also mediates estrogen induced LH surge that triggers ovulation.

GnRH-Agonists ➔ bind to the receptors & mimic the native hormones provided it is given PULSATILE

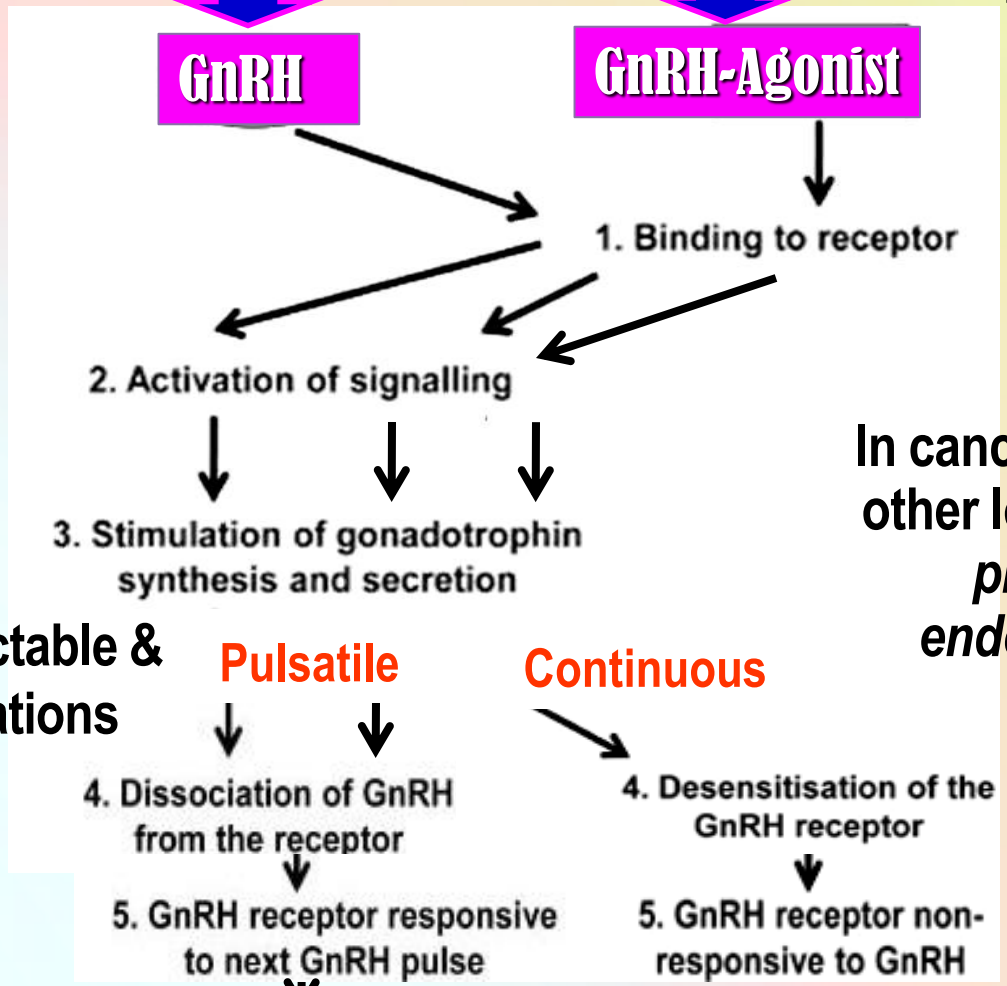
GnRH-Agonist

If PULSATILE → Mimic native GnRH

LEUPROLIN
GOSERELIN

If CONTINOUS → Block GnRH Receptors

GnRH



Intranasal, injectable & implant formulations

In cancer (*prostate & breast*) & other long term indications as *precocious puberty, endometriosis & fibroids*

FSH & LH
Growth maturation & rupture
OVULATION INDUCTION

STOP

GONADAL ACTIVATION

GnRH

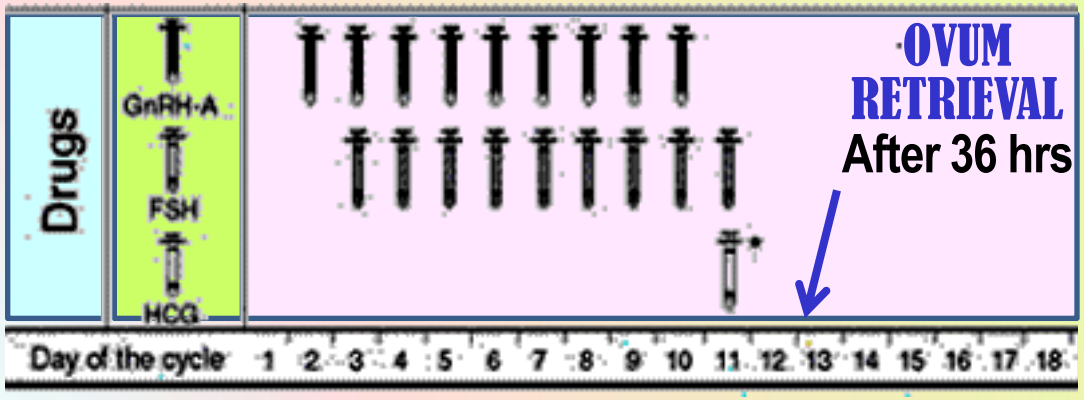
LEUPROLIN
GOSERELIN

Uses

- In **OVULATION INDUCTION** per se

  Given in hypothalmic amenorrhea (GnRH deficient) → S.C. pulsatile(drip) (1–10 µg / 60 – 120 min) → ↑ GnHs release
  Start from day 2-3 of cycle up to day 10

- In **ASSISTED REPRODUCTION** is part of a protocol for **OVUM RETRIEVAL**



ADRs

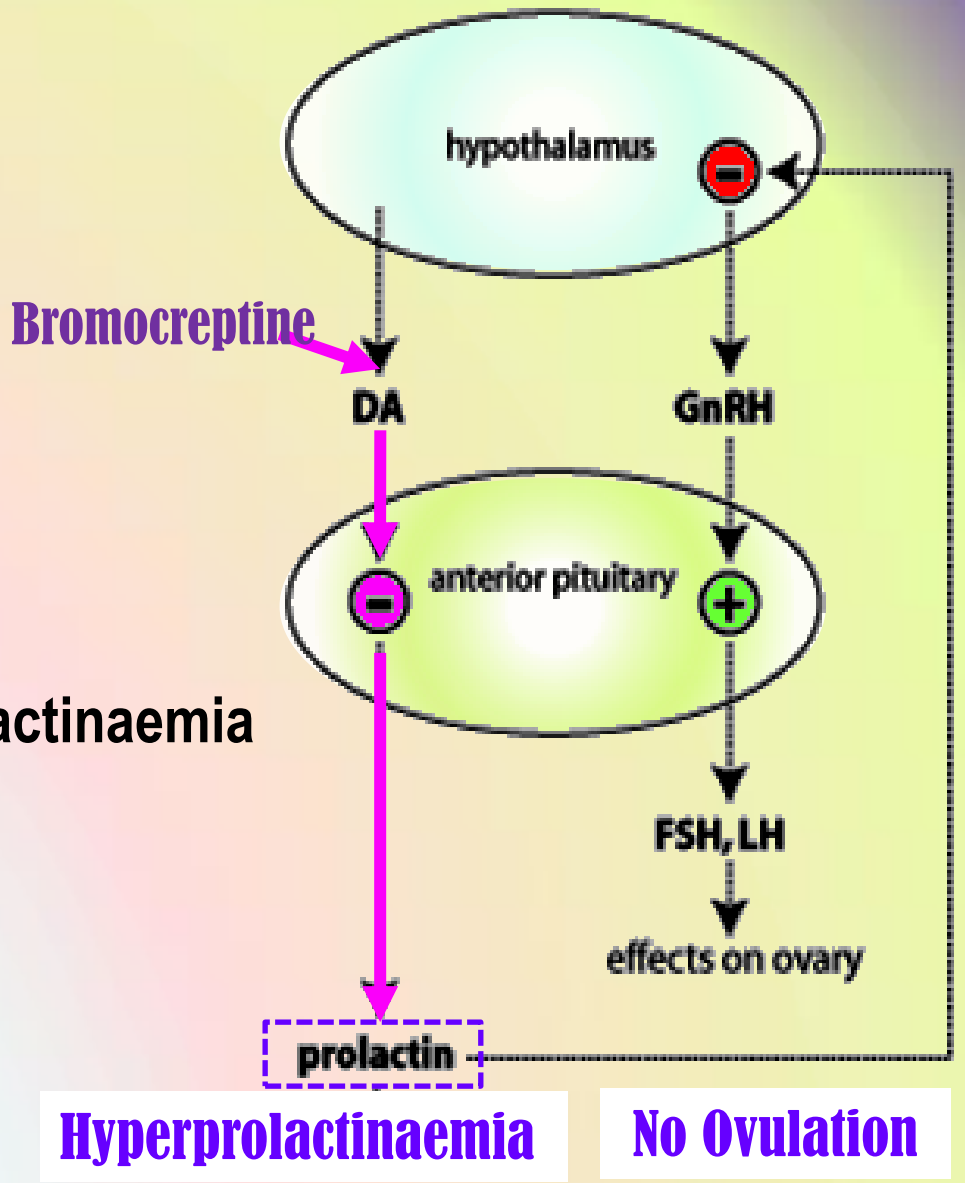
- GIT disturbances, abdominal pain, nausea….etc
- Headache
- Hypoestrogenism *on long term use* →
  - Hot flashes
  - ↓Libido
  - Osteoporosis
  - Vaginal bleeding
- Rarely ovarian hyperstimulation → (ovaries swell & enlarge)

D_2 R Agonists

BROMOCREPTINE

Is an ergot derivative.

Mechanism D_2 R Agonists bind to dopamine receptors in anterior pituitary ➔ -ve PRL secretion



Indications

- Female infertility 2ndry to hyperprolactinaemia (hypogonadotrophic)

ADRs

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

Drugs In OVULATION INDUCTION

GOOD LUCK