



Reproductive  
System



**PHARMACOLOGY**  
**432 TEAM**



# DRUGS IN OVULATION INDUCTION

## Learning Objectives:

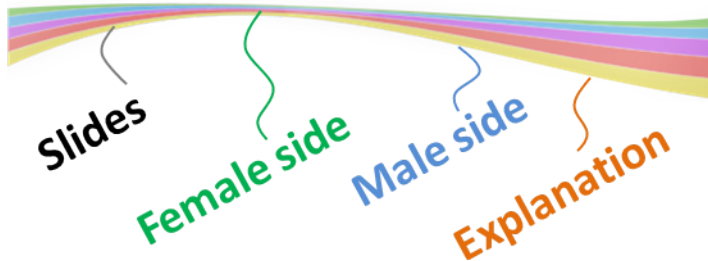
1. Recall how ovulation occurs and specify its hormonal regulation
2. Recognize causes and types of female infertility
3. Classify ovulation inducing drugs in relevance to the existing deficits
4. Expand on the pharmacology of each group with respect to mechanism of action, protocol of administration,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

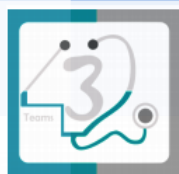
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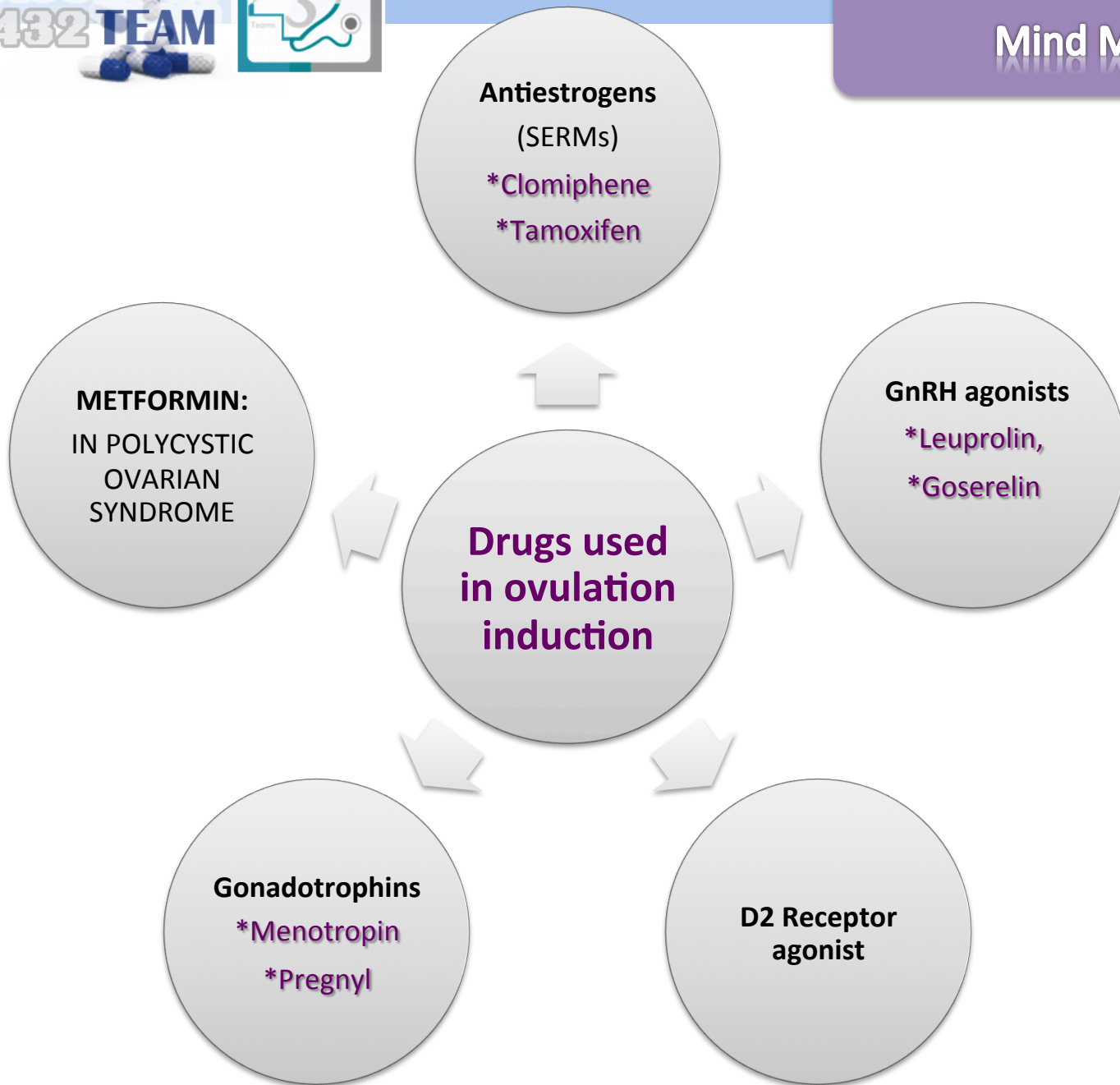
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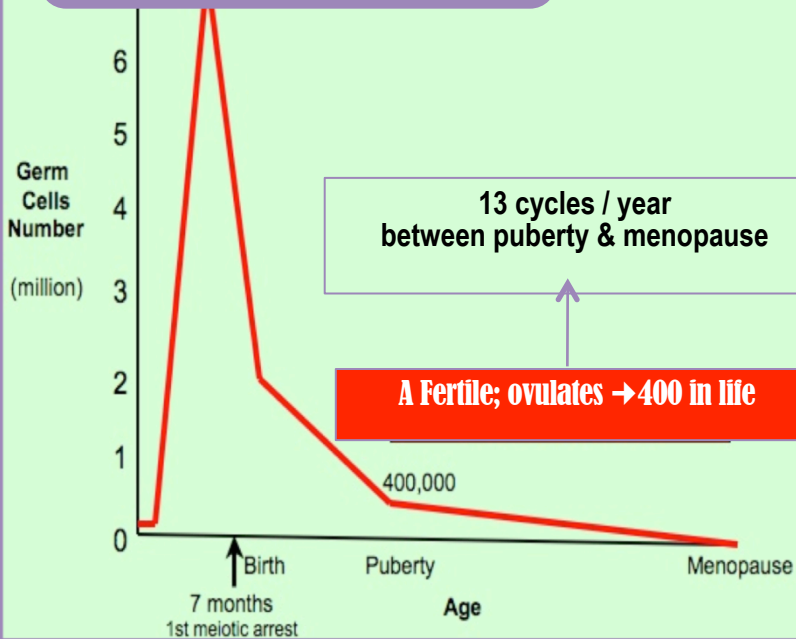


**Mind Map**

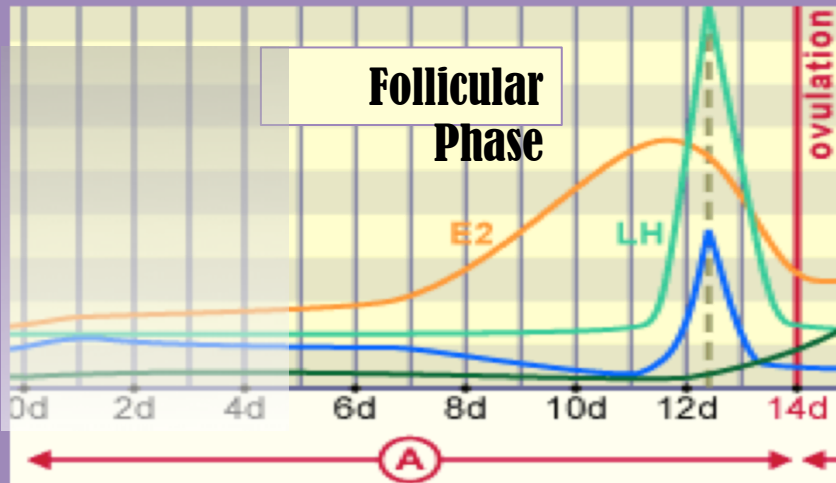


# physiology

Germ Cell Number



## Follicular Phase



## Follicular Phase

Recruitment  
Gn-independent

Selection  
Gn-responsive

Little estrogen

Maturation  
Hormone-dependent

High estrogen

LH > FSH SURGE

~~X~~ OVULATION  
INFERTILITY

Primordial

2/3-7 d

Prim

Sec

Preantral

Antral

7/8-12 d

Graffian Follicle

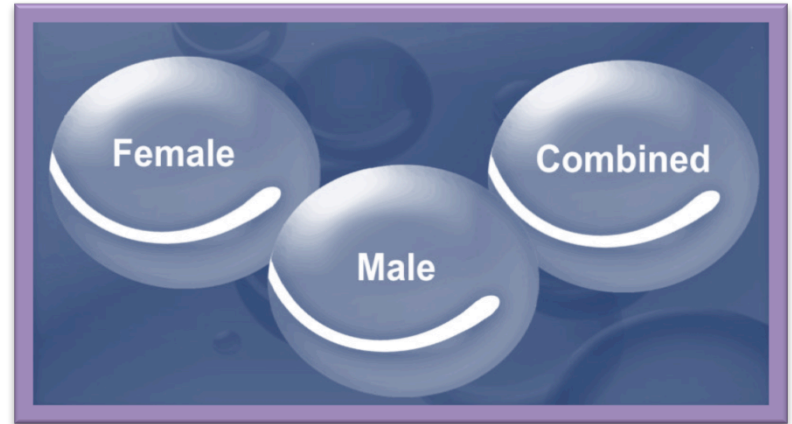
12-14 d

ovulation

# INFERTILITY

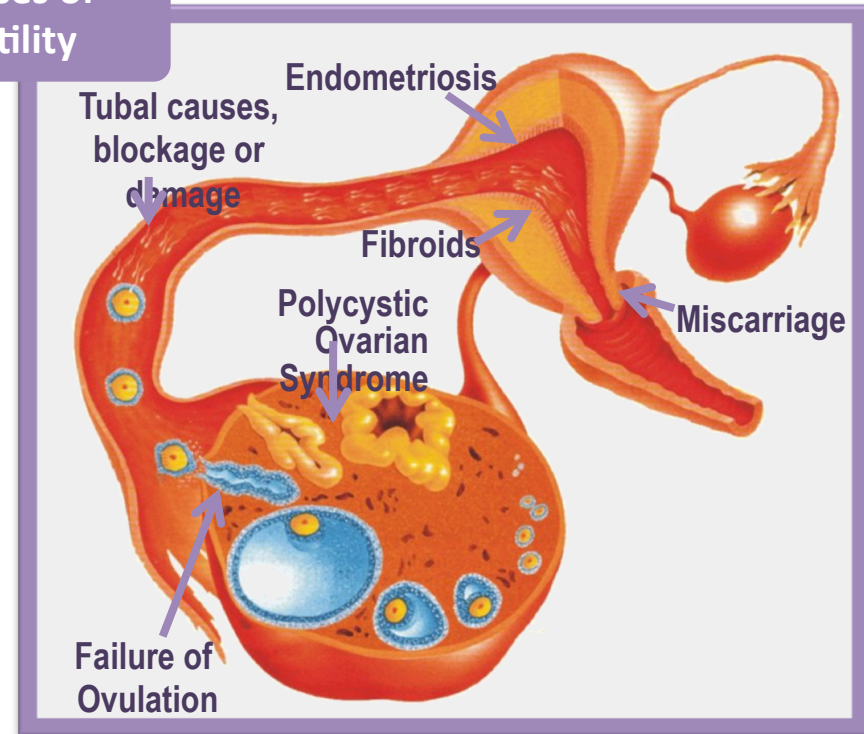
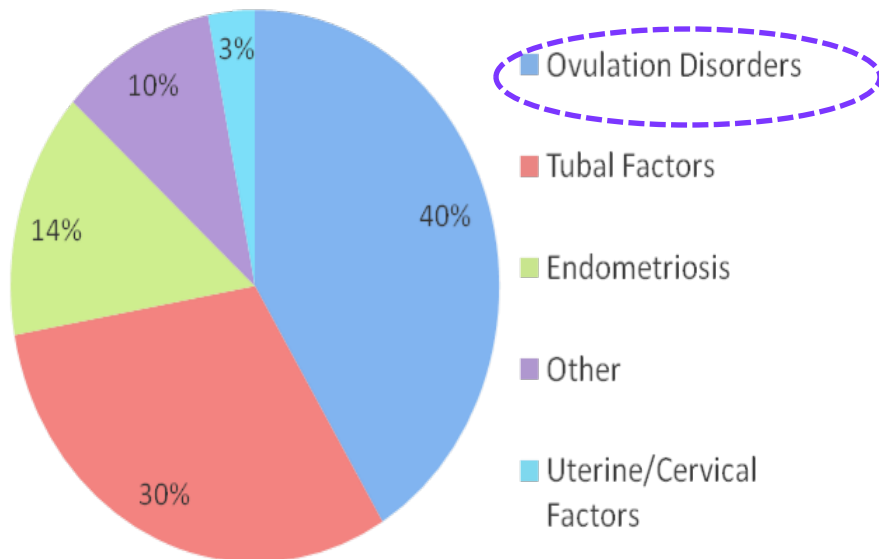
Not important

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.

## Common causes of female infertility



# causes of female infertility:

**Hyperprolactin –  
aemia.**

**D2 R Agonists**  
(Bromocriptine)

**Hypogonado-  
tropic: lack of**  
(FSH) and (LH).

**GONADOTROPHINS**  
(Menotropin ,Pregnyl)  
**GnRH agonists**  
(Leuprolin ,Goserelin)

**Normogonado-  
trophic.**  
anovulatory cycle

**ANTIESTROGENS:**  
Clomiphene  
Tamoxifen

**Hypergonado-  
trophic: primary**  
ovarian failure.

**No therapy**

## **METFORMIN:**

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

\* decrease Androgen.



## Antiestrogens (SERMs)

- ❖ Selective Estrogen Receptor Modulators [SERMs] → compete with estrogen on estrogen receptors in the nucleus.
- ❖ 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**.

**Note:** SERMs are **selectively** into different tissue and variable to some extent .

**Agonist** on selective thing and **antagonist** on others thing.

As long as the drug has more **antagonistic** action on the brain center → it'll be more efficient in inducing ovulation.

## Pharmacological effects of clomiphene:

- ❖ **On hypothalamus:**

**decreases** negative feed back of endogenous estrogen on hypothalamus → increases **pulsatile** secretion of GnRH → **increases gonadotropins production [FSH & LH]** → cause growth maturation & rupture of follicles → **OVULATION**.

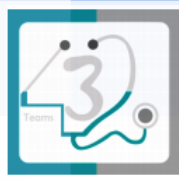
- ❖ **On pituitary:**

↑ response of gonadotrophins to GnRH.

**Clomphene is more potent than tamoxiffen because it has more antagonistic action.**



Indication of clomiphene	Method of administration of clomiphene	ADRs Of clomiphene
<ul style="list-style-type: none"> <li>❖ In female infertility which is not due to ovarian or pituitary failure → <b>Normogonadotrophic.</b> ( <b>increase gonadotrophin</b> )</li> <li>❖ The success rate for : <b>ovulation → 80% .</b> <b>pregnancy → 40% .</b></li> <li>❖ The discrepancy between 2 rates is due to antiestrogenic effects of clomiphene on uterus, cervix &amp; vagina (lead to impaired implantation) .</li> <li><b>Note:</b> it can be used in some hypogonadotropic cases . It has some opposing effects on cervix and uterus so it is not 100% successful rate of pregnancy. But worth to try!</li> </ul>	<ul style="list-style-type: none"> <li>❖ Clomiphene given → 50 mg/d for <b><u>5 days from 5<sup>th</sup> day of the cycle to the 10<sup>th</sup> day.</u></b></li> <li>❖ If no response give 100 mg for 5 days again from 5<sup>th</sup> to 10<sup>th</sup> day</li> <li>❖ The drug can be repeated <b><u>not more than 6 cycles.</u></b></li> <li>❖ During therapy it ↑ FSH &amp; LH</li> </ul> <div style="border: 2px dashed purple; border-radius: 15px; padding: 10px; margin-top: 10px;"> <ul style="list-style-type: none"> <li>1- In the 1<sup>st</sup> month 50 mg/d from day 5 to day 10 of the cycle.</li> <li>2- If there is no response double the dose in the 2<sup>nd</sup> month.</li> <li>3- BUT not more than 6 months.</li> <li>4- There must be sexual intercourse on day 12 to 14.</li> </ul> </div>	<ul style="list-style-type: none"> <li>1) Hot Flashes &amp; breast tenderness. (<b>anti estrogenic effect</b>).</li> <li>2) Gastric upset (nausea and vomiting) .</li> <li>3) Visual disturbances (<b>reversible</b>).</li> <li>4) ↑ nervous tension &amp; depression.</li> <li>5) Skin rashes .</li> <li>6) Fatigue.</li> <li>7) Weight gain .</li> <li>8) Hair loss (<b>reversible</b>).</li> </ul> <ul style="list-style-type: none"> <li>❖ <b>N.B. ↑ incidence of multiple ovulation (over stimulation) → twins in 10% birth</b></li> </ul>



## TAMOXIFEN

- ❖ Is similar & alternative to clomiphene but differ in being **Non Steroidal**.
- ❖ Used in palliative treatment of **hormone-dependent / estrogen receptor-positive advanced breast cancer**.

*Q: why clomiphene not used in such cases of cancer breast?*

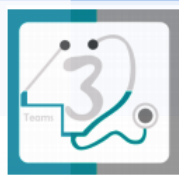
**Because it is steroidal.**

**Note :**

**1- it is weaker in ovulation induction than clomiphene.**

**2-it is more selective to the breast and used more in breast cancer ( Hormone dependent) than in ovulation induction.**





# Gonadotropins (FSH & LH)

## Source

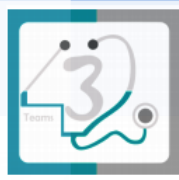
Natural	Therapeutic: extracted forms	
Are naturally produced by the pituitary gland (cyclical release).	<b>Human Menopausal Gonadotropins (hMG )</b>	<b>Human Chorionic Gonadotropins (hCG)</b>
	<ul style="list-style-type: none"> <li>• Extracted from <u>postmenopausal urine</u></li> <li>• Contains LH &amp; FSH</li> <li>• <b>Menotropin</b></li> </ul>	<ul style="list-style-type: none"> <li>• Extracted from urine of <u>pregnant women</u></li> <li>• Contains <b>mainly (LH)</b></li> <li>• <b>Pregnyl</b></li> </ul>
<b>N.B. Now new available preparations by recombinant technology.</b>		

## Mechanism (given sequentially the FSH then LH)

Preparations of FSH ( <u>hMG</u> ) in the first part	Preparations of LH ( <u>hCG</u> ) must be high on 12 <sup>th</sup> day
act on ovary directly, stimulating growth & maturation of Graafian Follicle(s).	act just to induce ovulation within 36 hours

## Indication

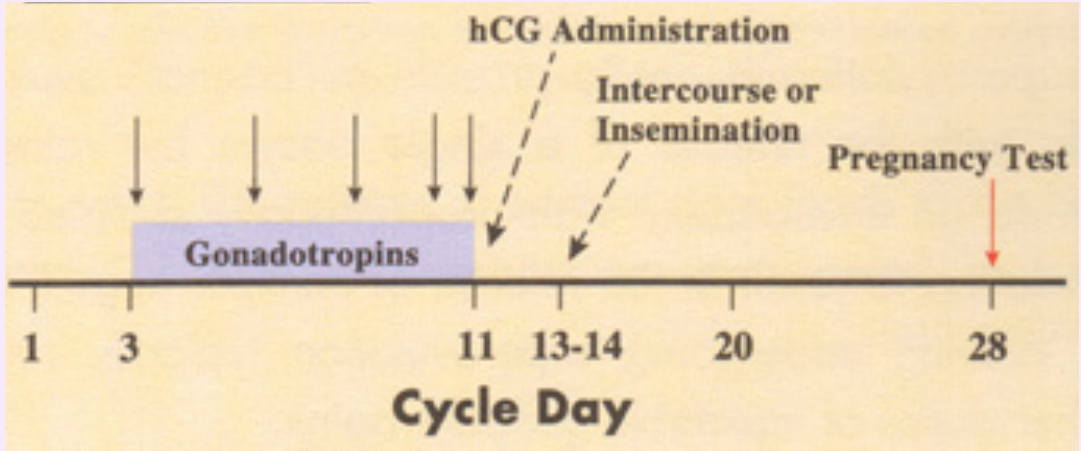
- Stimulation & induction of ovulation in infertility 2<sup>nd</sup>ry to gonadotropin deficiency (pituitary insufficiency or hypothalamic even) (hypogonadotropic hypogonadism)
- Success rate for inducing ovulation is usually  $\geq 75\%$



# Gonadotropins (FSH & LH)

## Method of Administration **very important**

- **hMG** is given **i.m** or **subcut.** every day starting at day **2-3 of cycle** (because in the first three days the follicle grows **autonomously** (programmed growth no dependent in FSH) for 10 days followed by
- **hCG** on **(10<sup>th</sup> - 12<sup>th</sup> day)** then within **36 hrs**:
  - Ovum retrieval.
  - intrauterine insemination.
    - to bypass the cervical plug they put the semen inside the uterus
  - Intercourse.



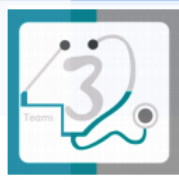
## ADRs

### FSH containing preparations

- Fever / flu-like symptoms.
- Ovarian enlargement (hyper stimulation).
- Multiple Pregnancy **more than one follicle matures** (approx. 20%).

### LH containing preparations

- Headache.
- Edema.



# Gonadotropin-Releasing Hormone Agonists

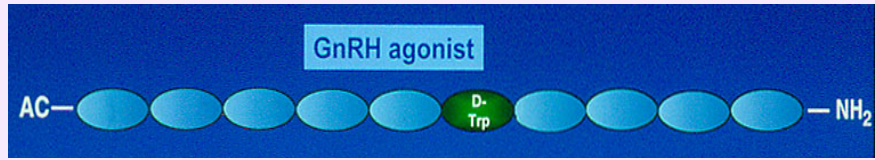
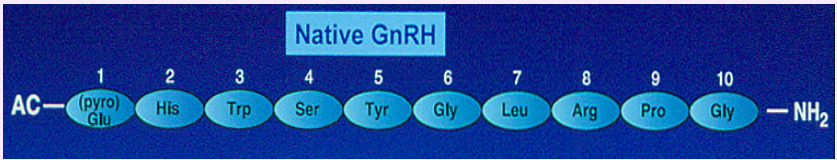
## Mechanism

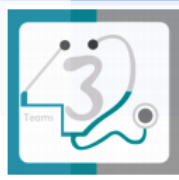
### Native GnRH

- 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 **in the pituitary** & mimic the native hormones provided it is given **PULSATILE**





# Gonadotropin-Releasing Hormone Agonists

## Drugs

**Leuprolin**

**Goserelin**

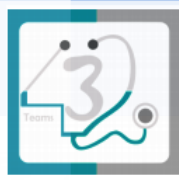
## Administration

**Pulsatile**  
(this is the one we're concerned with in the lecture)

**Continuous**

- **Mimics Native GnRH.**
- **Mechanism:** Binds to receptor → activates signaling → Stimulates gonadotropin synthesis and secretion → **Dissociates from the receptor** → **GnRH receptor responsive to next GnRH pulse** → **FSH & LH** → **Growth, maturation & rupture (Ovulation Induction)** (the dissociation/association activates the receptor)
- **Preparations:**
  - Intranasal
  - **Injectable best one**
  - Implant formulations

- **Block GnRH Receptors**
- **Mechanism:** Binds to receptor → activates signaling → Stimulates gonadotropin synthesis and secretion → **desensitization of GnRH receptor** → **GnRH receptor non-responsive to GnRH** → **Stop gonadal activation acts as antagonist (inhibitory)**
- **Uses:** (long term indications) **to prevent estrogen release**
  - cancer (prostate & breast)
  - precocious puberty
  - Endometriosis
  - fibroids



# Gonadotropin-Releasing Hormone Agonists

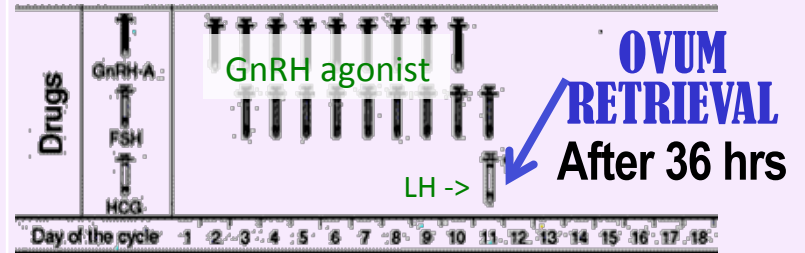
## Uses

### In Ovulation Induction

- Given in (hypothalamic amenorrhea GnRH deficient) → S.C. pulsatile(drip) (1–10 µg / 60 – 120 min) → ↑ GnHs release
- Start from day **2-3** of cycle (as if we're giving it instead of hMG) up to **day 10** (after that we give LH (hCG) to induce ovulation)

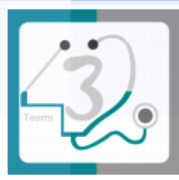
### In Assisted Reproduction

As part of a protocol for **Ovum Retrieval**



## ADRs

- GIT disturbances, abdominal pain, nausea....etc
- Headache
- Hypoestrogenism on long term use (because in long-term use it starts to give the same effect as continuous administration and so inhibits estrogen release so never use more than 6 months) which causes:
  - Hot flashes
  - ↓ Libido
  - Osteoporosis
  - Vaginal bleeding
- Rarely ovarian hyperstimulation → (ovaries swell & enlarge)



## D<sub>2</sub> Receptor Agonists

### Preparation

- **Bromocriptine**
- Is an ergot derivative

### Mechanism

D<sub>2</sub> R Agonists bind to dopamine receptors in anterior pituitary → -ve PRL secretion **shuts down prolactin secretion**

### Indications

Female infertility 2ndry to hyperprolactinaemia **in both male and female** (hypogonadotrophic)

### ADRs

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



**Antiestrogens**  
(clomiphene):

- decreases negative feed back on hypothalamus ,incerase gonadotrophin.
- Given from **day 5 to day 10** of the cycle, no response **double the dose**, but not more than **6 monthes**.

**Tamoxifen**

- **Non Steroidal.**
- Used in palliative treatment of hormone-dependent / estrogen receptor- positive advanced **breast cancer**.

**Gonadotropins (FSH & LH)**  
(hMG/Menotropin, hCG/  
Pregnyl)

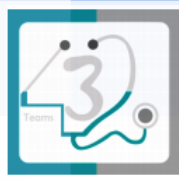
- are used to **stimulate follicular growth and induce ovulation** respectively to treat infertility secondary to gonadotropin deficiency
- **hMG** is given for **10 days** followed by **hCG** for **2 days** then the ovum can be retrieved in 36 hours

**GnRH-agonists**  
(Leuprolin, Goserelin)

- given in hypothalamic amenorrhea to stimulate the release of gonadotropins

**D2 Receptor agonists**  
(Bromocriptine)

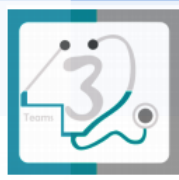
- is used to inhibit prolactin secretion in cases of hyperprolactinemia.



1. **Which one of the following drugs is used in treatment of Hormone dependent breast cancer?**
  - A. Leuprolin
  - B. Goserelin.
  - C. Tamoxiffen.
  - D. Metformin.
  
2. **We use clomiphene in:**
  - A. Hyperprolactinaemia.
  - B. Hypogonadotropic.
  - C. Normogonadotrophic.
  - D. Hypergonadotrophic.
  
3. **24 year old female came the clinic complaining of infertility , she was diagnosed with Polycystic Ovary Syndrome. Which of the following is the best drug for treatment ?**
  - A. Clomphene.
  - B. Tamoxiffen.
  - C. Goserelin.
  - D. Metformin.

Answers: C, C, D.





**4. The Drug Menotropin contains:**

- A. FSH
- B. LH
- C. FSH & LH

**5. When should you retrieve the ovum after giving hCG:**

- A. Immediately
- B. 36 h
- C. 60 h
- D. A week

**6. In which of the following cases should you NOT give continuous GnRH-agonists as treatment:**

- A. Prostatic Cancer
- B. Fibroid
- C. Infertility
- D. Precocious puberty



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**PHARMACOLOGY**  
**432 TEAM**



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