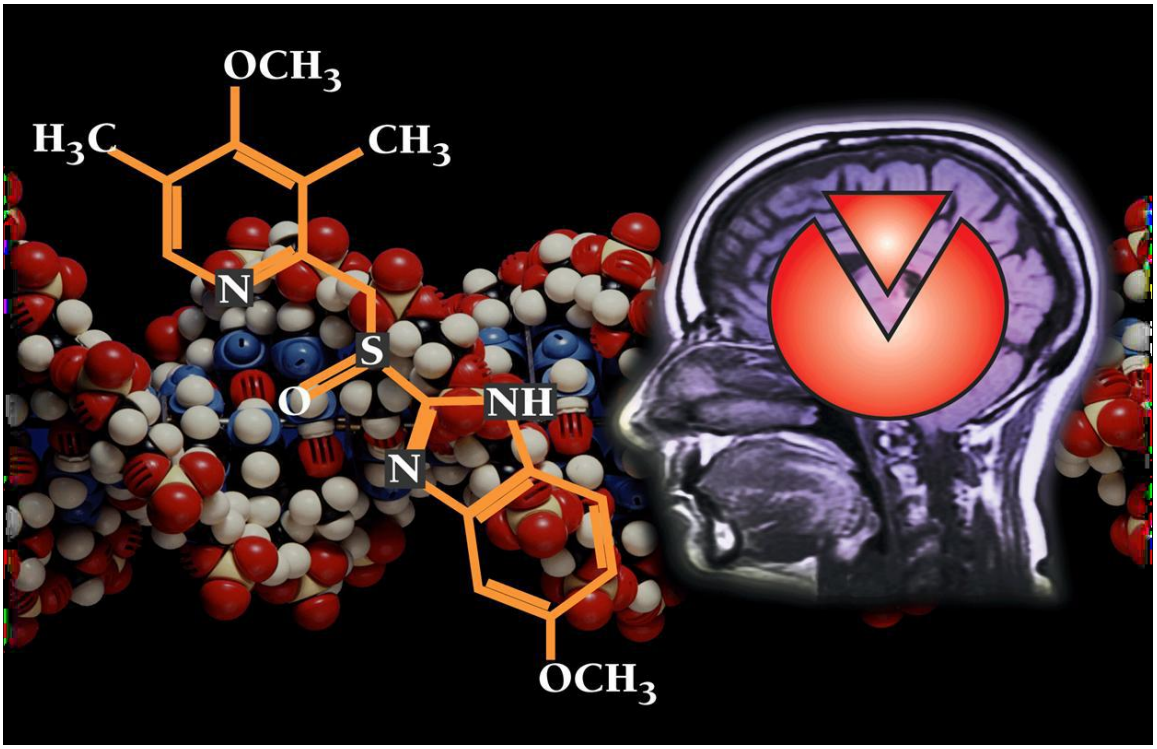
King Saud University
College Of Medicine
Pharmacology Team 430
Reproductive Block

# 05-Induction of ovulation




**Note: First page is an introduction, and text in red is important.**

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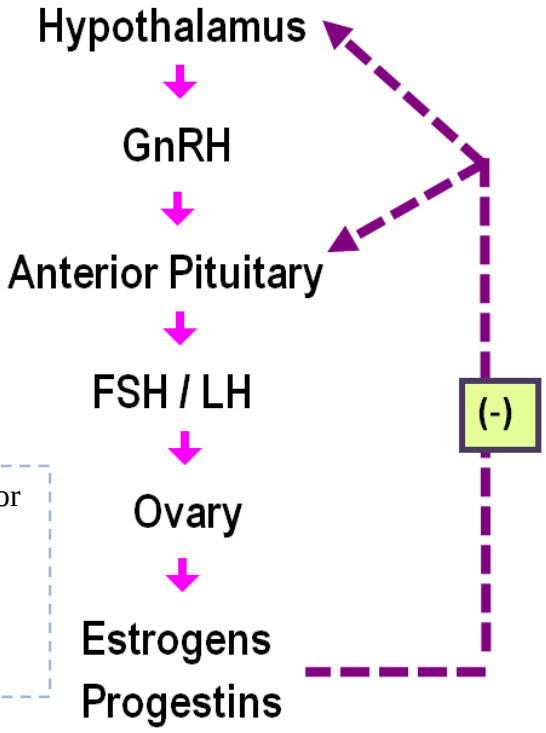
## Introduction:

Causes of Failure to Ovulate (Female infertility)




**Hormonal Problems**
these are the most common causes of anovulation. The process of ovulation depends upon a complex balance of
hormones and their interactions to be successful, and any disruption in this process can hinder ovulation. There are three
main sources causing this problem

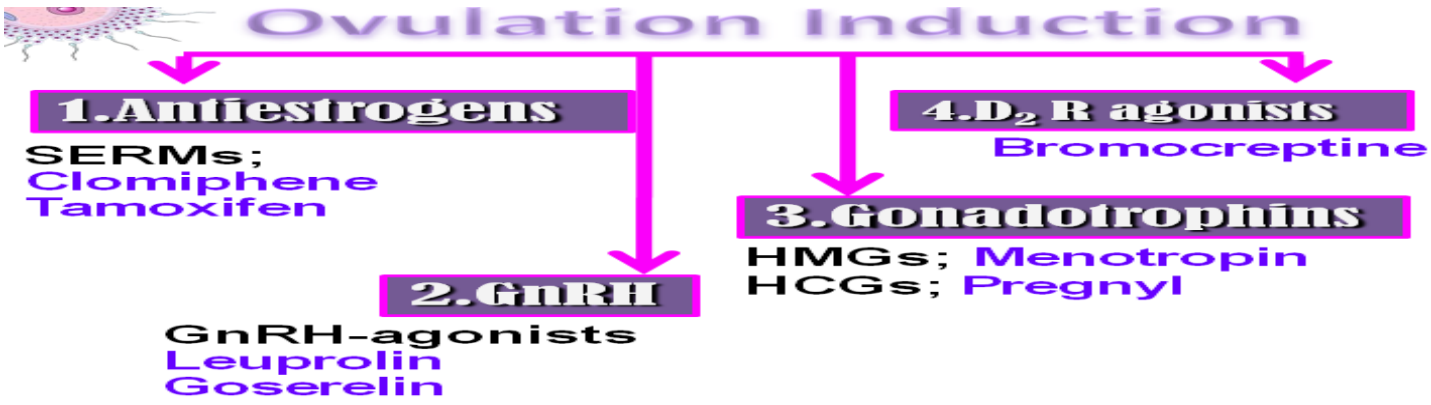
- ***Failure to produce mature eggs***
  In approximately 50% of the **cases of anovulation**, the ovaries do not produce normal follicles in which the eggs can mature. Ovulation is rare if the eggs are immature and the chance of fertilization becomes almost nonexistent.

**Note:** Polycystic ovary syndrome, the most common disorder responsible for failure to produce mature eggs, includes symptoms such as amenorrhoea, hirsutism, anovulation and infertility. This syndrome is characterized by a reduced production of FSH, and normal or increased levels of LH, estrogen and testosterone.

- ***Malfunction of the hypothalamus*** **(Low GnRH) Hypogonadotropic**
  The hypothalamus is the portion of the brain responsible for sending signals to the pituitary gland, which, in turn, sends hormonal stimuli to the ovaries in the form of FSH and LH to initiate egg maturation. If the hypothalamus fails to trigger and control this process, immature eggs will result.

- ***Malfunction of the pituitary gland*** **(Low LH & FSH) (Hypogonadotropic)**
  The pituitary's responsibility lies in producing and secreting **FSH and LH**. The ovaries will be unable to ovulate properly if either too much or too little of these substances is produced. This can occur due to physical injury, a tumor or if there is a chemical imbalance in the pituitary.

- ***Hyperprolactinaemia:*** it is usually caused by Prolactin secreting pituitary tumors. High prolactin levels would inhibit the action of **Gonadotrophs (FSH & LH)**




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

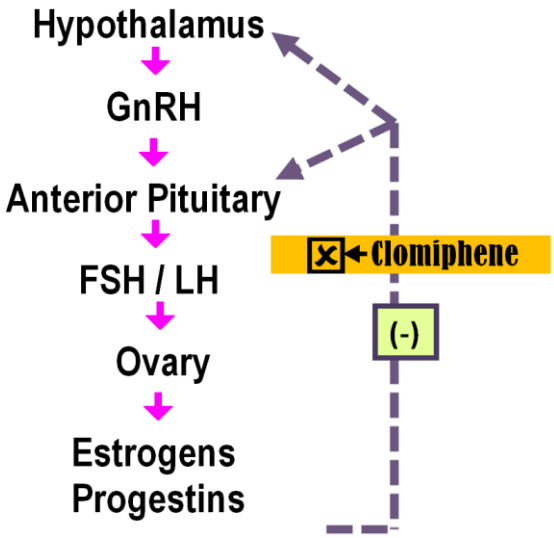
# Drugs used to induce ovulation

## 1-ANTIESTROGENS (SERMs)

**E.g. Clomiphene & Tamoxifen**

**MOA:**

**Selective Estrogen Receptor Modulators [SERMs] ➔ compete with estrogen on estrogen receptors & antagonise the action of estrogen on the hypothalamus & anterior pituitary gland.**




### *A. Clomiphene: compete with the endogenous estrogen receptors in:*

hypothalamus; it inhibits the **negative feedback of endogenous estrogen on hypothalamus ➔ This will lead to the increased pulsatile release of GnRH ➔ ↑ gonadotrophin production [FSH & LH] ➔ cause growth maturation & rupture of follicles ➔** OVULATION

- Ant.pituitary; **↑response of gonadotrophins to GnRH**

## Indications

- **Female infertility that is not due to ovarian or pituitary failure ➔ Normogonadotrophic**
- **The success rate for ovulation ➔80% & pregnancy ➔40% .**

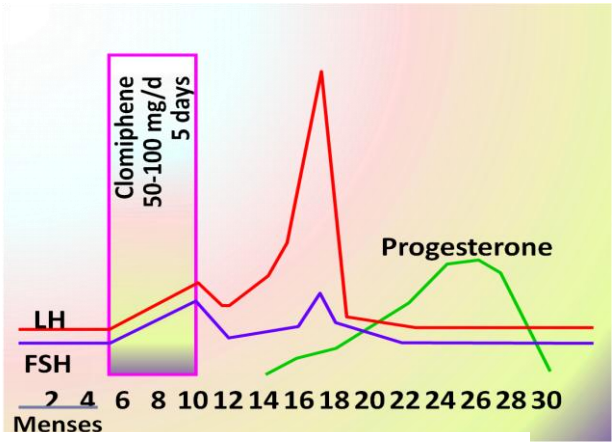
**The discrepancy between 2 rates is due to the antiestrogenic effects of clomiphene on uterus, cervix & vagina**

## Method of administration imp

**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 (double the dose)**

**The drug can be repeated not more than 6 cycles .**




## ADRs

**1.Hot Flushes & breast tenderness (Anti-estrogenic effect)**

**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. (10%)**

**Note:** variety of other symptoms such as nausea and vomiting increased nervous tension, depression, fatigue, breast soreness. However, these appear to result from the hormonal changes associated with an ovulatory menstrual cycle rather than from the medication.

## *2. 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**

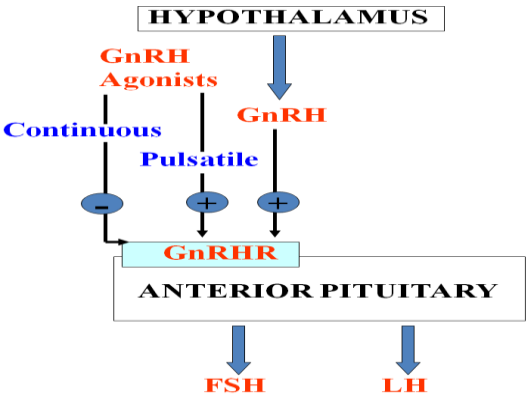
- ***But why not clomiphene used in such cases of breast cancer?***

**Tamoxifen** has an **antiestrogenic effects** in the **breast** while ***clomiphene doesn't; it is actually has a weak estrogen agonist effect in the breast.***

Note: Tamoxifen **has a potent antiestrogenic effects in the breasts** (But maybe **estrogen agonist in the uterus**). That is why it must be used with caution while treating a female with breast cancer and has a history of endometrial hyperplasia.

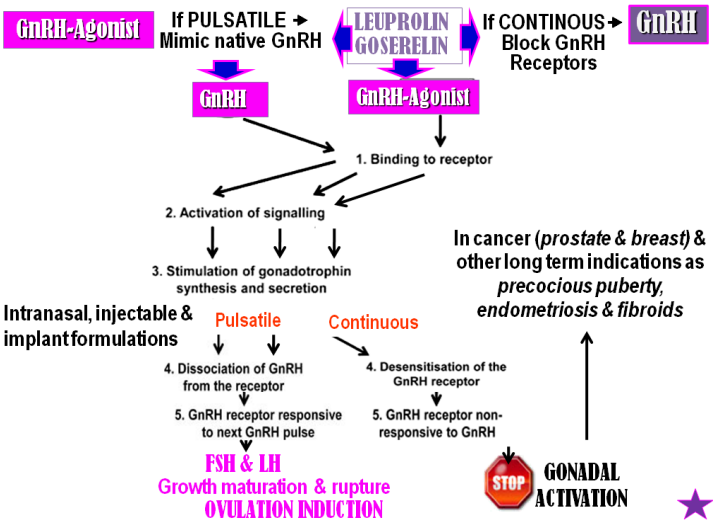
## 2. GONADOTROPIN RELEASING HORMONE (GnRH)

**Analgoues with agonist activity:**
**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 and agonists, given S.C. in a pulsatile(drip) to stimulate gonadotropin release (1 – 10 µg / 60 – 120 min) Start from day 2-3 of cycle up to day 10.**

**Given continuously, when gonadal suppression is desirable e.g. precocious puberty and advanced breast cancer in women and prostatic cancer in men**

### Uses:

- **Induction of ovulation in patients with hypothalmic amenorrhea (GnRH deficient)**
- **In** ASSISTED REPRODUCTION **is part of a protocol for** OVUM RETRIEVAL **(Induction of ovulation**

## ADRs

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

## 3.GONADOTROPHINS (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**

**2. Human Chorionic Gonadotrophin(hCG) extracted from urine of pregnant women ➔contains mainly LH) ➔PREGNYL**

***N.B. Now new available preparations by recombinant technology***

## Mechanism :

Given sequentially

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

## Uses

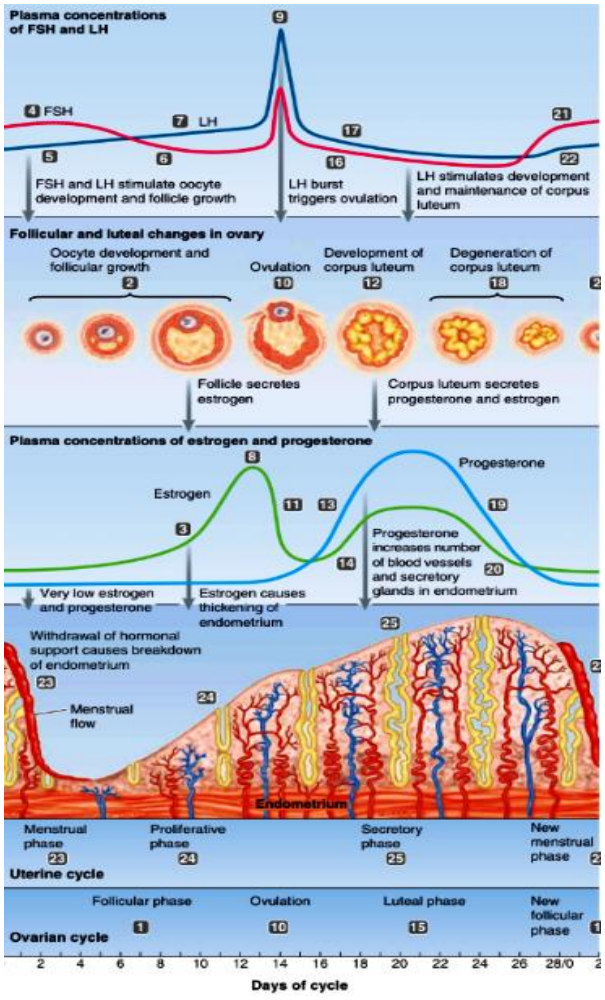
- **Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)**

**Success rate for inducing ovulation is usually ≥75 %**

## Method of administration

**hMG is given i.m or subcutaneous every day starting at day 2-3 of cycle for 10 days (to induce the development of the follicle) followed by**

**hCG on (10th - 12th day) for OVUM RETRIEVAL (Ovulation or rupture of the follicle) within 36 hours when we indicate : intrauterine insemination or intercourse.**




## ADRs

**FSH containing preparations (MENOTROPIN );**

- ✓ **Fever**
- ✓ **Ovarian enlargement (hyper stimulation)**
- ✓ **Multiple Pregnancy (approx. 20%)**

**LH containing preparations; Headache & edema**

## 4-Dopamine (2) Receptor Agonists (BROMOCREPTINE)

**Is an ergot derivative (not a hormone)**

### MOA

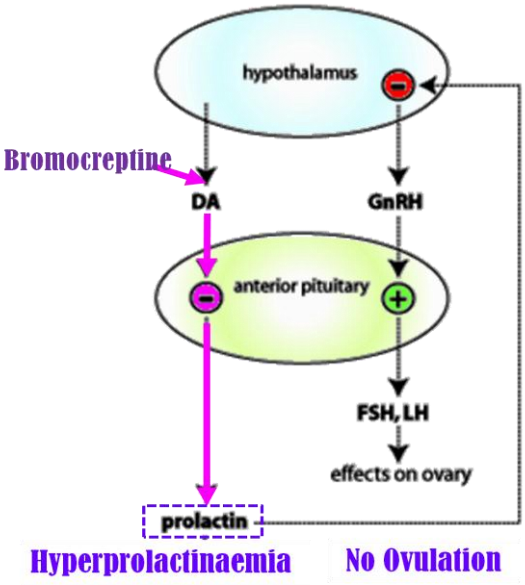
**$D_2$ R Agonists binds to dopamine receptors in the anterior pituitary gland & inhibits prolactin secretion .**

**Uses:** **Female infertility 2$^{ndry}$ to hyperprolactinaemia ( hypogonadotrophic)**

### ADRs

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

**Note:** Orthostatic hypotension is due to stimulating D2 receptors, which are found in peripheral mesenteric and renal vascular beds, that causes vasodilatation.



- ✓ The main Cause of Failure to Ovulate (Female infertility) is hormonal imbalance e.g high estrogen, low gonadotrophs(FSH & LH) due to pituitary or hypothalamic disorders, or high prolactin levels usually due to prolactinoma.
- ✓ **1-Selective Estrogen Receptor Modulators [SERMs] E.g. Clomiphene & Tamoxifen**
- ✓ Clomiphene is a partial agonist at estrogen receptors.
- ✓ **Clomiphene:** compete with the **endogenous estrogen receptors** in hypothalamus & ant.pituitary ,thus removing the negative feedback effect of estrogens from the hypothalamus & Ant.pituitary leading to an increase in gonadotrophs' (FSH & LH) release.
- ✓ Clmoiphene is used in **Female infertility that is not due to ovarian or pituitary failure ➔ Normogonadotrophic**
- ✓ **Clomiphene given ➔ 50 mg/d for 5 days from 5th day of the cycle to the 10th day. (we repeat this method of dosing for 3 cycles)**
- ✓ **If no response for 3 cycles: the dose is doubled in the next 3 cycles with the same method of administration.**
- ✓ **The drug can be repeated not more than 6 cycles .**
- ✓ Its main ADRs : **Visual disturbances, hair loss which can be reversible , .Hot Flushes & breast tenderness that are due to the Antiestrogenic effect of Clomiphene**
- ✓ Tomoxifin **Is similar & alternative to clomiphene ,But differ in being Non Steroidal**
- ✓ Tamoxifin has an **Antiestrogenic effects on the breast** ( Used in cases of breast cancer)
- ✓ **2-Leuprolin, Goserelin are synthetic analogues of GnRH with agonistic activity**
- ✓ **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 and advanced breast cancer in women and prostatic cancer in men**
- ✓ **It's main ADR** is Hypoestrogenism on long term use ➔ **Hot flashes, decreased Libido ,Osteoporosis**
- ✓ **3-Gonadotrophs**
- ✓ **1. Human Menopausal Gonadotrophin(hMG )➔ extracted from postmenopausal urine ➔ contains LH & FSH ➔MENOTROPIN**
- ✓ **2. Human Chorionic Gonadotrophin(hCG) extracted from urine of pregnant women ➔contains mainly LH) ➔PREGNYL**
- ✓ **They are used in Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)**
- ✓ **hMG (MENOTROPIN)is given i.m every day starting at day 2-3 of cycle for 10 days (to induce the development of the follicle) followed by**
- ✓ **hCG (PREGNYL) is given on (10th - 12th day) for OVUM RETRIEVAL (Ovulation or rupture of the follicle) .**
- ✓ **ADRs:**

**FSH containing preparations (MENOTROPIN );**

- ✓ **Fever**
- ✓ **Ovarian enlargement (hyper stimulation)**
- ✓ **Multiple Pregnancy (approx. 20%)**

**LH containing preparations (MENOTROPIN or Pregnyl); Headache & edema**

- ✓ **MENOTROPIN, Leuprolin, and Goserelin may lead to ovarian swelling or enlagement**

- ✓ **4-BROMOCREPTINE: $D_2$ R Agonists binds to dopamine receptors in the anterior pituitary gland & inhibits prolactin secretion .**
- ✓ **Used in Female infertility 2ndry to hyperprolactinaemia**
- ✓ **5-METFORMIN is used in IN POLYCYSTIC OVARIAN SYNDROME to ↓ body weight &↑ response to ovulation induction drugs**