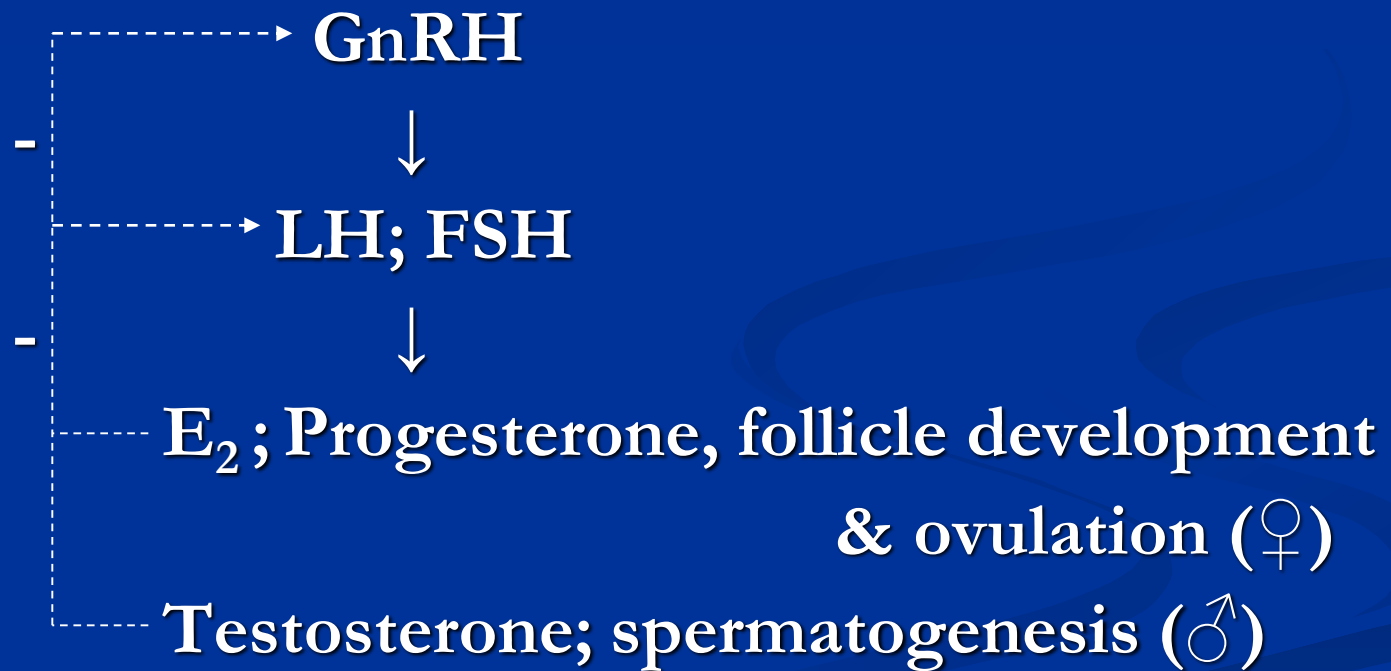# GnRH, LH, FSH

- **GnRH (Gonadotropin Releasing Hormone; Gonadorelin)**

- A small peptide (decapeptide= 10 a.a peptide)

- Stimulates synthesis and release of two different complex glycoprotiens (LH & FSH)

- Has unique pattern of release from hypothalamus

- Has interesting structure activity relationship

- Has many clinical uses

- **Negative feedback mechanisms**

$$\text{GnRH}$$
$$\downarrow$$
$$\text{LH; FSH}$$
$$\downarrow$$

E_2 ; Progesterone, follicle development

& ovulation (♀)

Testosterone; spermatogenesis (♂)

** Structure-activity relationship:

pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2

** Pattern of release and MOA:

- Pulsatile (Ca^{++} second messenger) → ↑ LH & FSH

- Large doses or continuous administration (down regulation of pituitary GnRH receptors) → ↓ LH & FSH

- **GnRH synthetic preparations:**

Leuprolide acetate, Triptorelin, Goserelin, Histrelin, Nafarelin, Busereline...

Could be given SC, IM, IV

Mainly given S.C

Ineffective orally

Available in intranasal, suppositories, subdermal implants and vaginal pessaries dosage forms (? contraceptive)

- **Leuprolide acetate**

pGlu-His-Trp-Ser-Tyr-Leu-Leu-Arg-Pro-NHEt

- **Busereline**

pGlu-His-Trp-Ser-Tyr-Ser(tBu)-Leu-Arg-Pro-NHEt

- **Nafarelin**

pGlu-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH2

- **Triptorelin**

pGlu-His-Trp-Ser-Tyr-Trp-Leu-Arg-Pro-Gly-NH2

- **Goserelin**

pGlu-His-Trp-Ser-Tyr-Ser(tBu)-Leu-Arg-Pro-NHNHCONH2

- **Histrelin**

pGlu-His-Trp-Ser-Tyr-His(1-Bn)-Leu-Arg-Pro-NHEt

■ **GnRH clinical uses:**

a. Pulsatile administration

- Diagnostic use

- GnRH deficiency (Kallman's syndrome)

R_x of ♂ & ♀ hypogonadism; induction of ovulation (infertility), delayed puberty, amenorrhea, cryptorchidism…

b. Continuous administration or large doses or the use of a GnRH superagonists:

- Ca prostate; Ca breast (depo IM injection dosage forms are available and could be given every month or 3 months)

- Endometriosis

- IVF

- Precocious puberty

- Uterine fibroids or uterine leiomyomas, polycystic ovarian syndrome (PCOS)
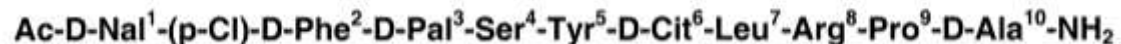
- ?? Contraceptive

- **Side effects to GnRH:**

- Production of GnRH Abs → resistance to treatment
- Headache and abdominal pain (tolerance develops to these side effects)
- Sweating, facial flushing, hot flushes
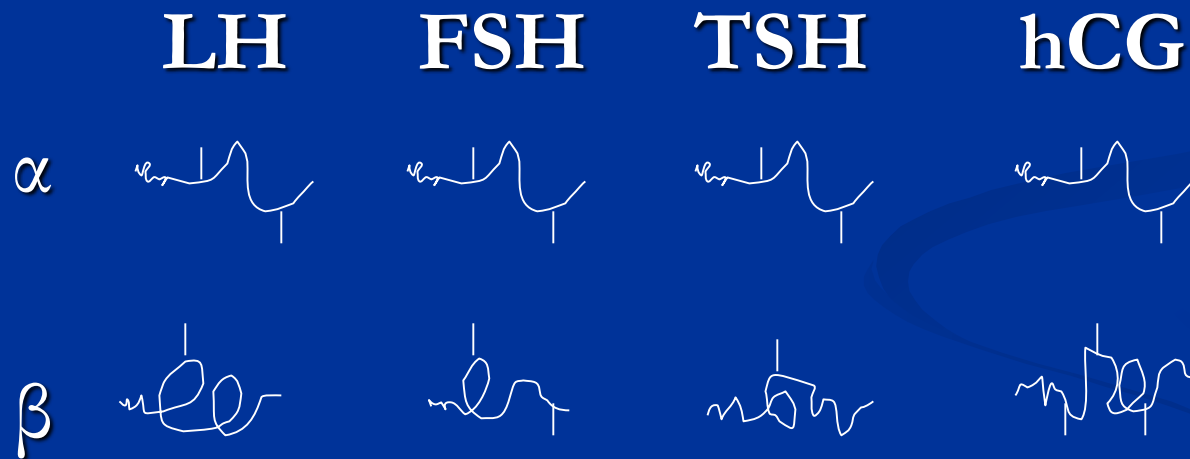- **Osteoporosis**

- **GnRH specific antagonist:**

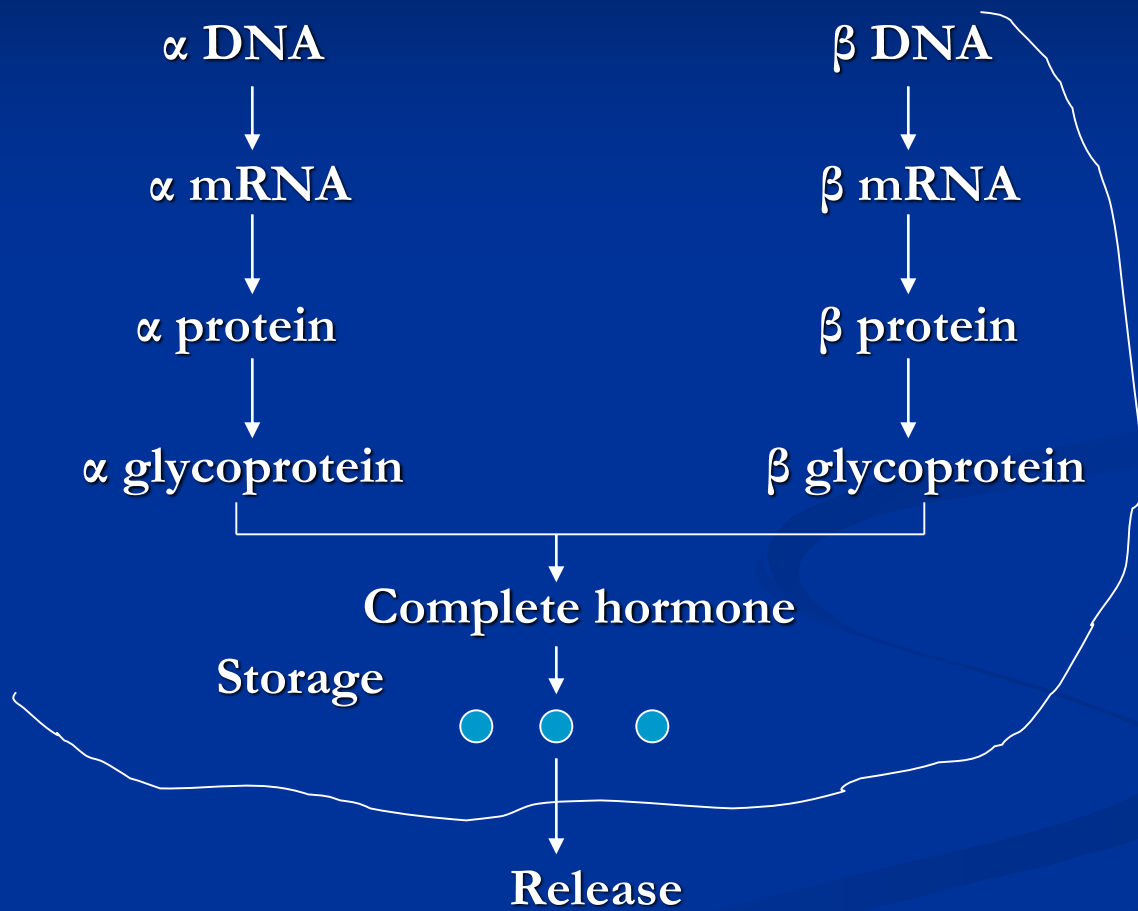Ganirelix; (IVF, SC); Degarelix (Ca prostate, SC); Elagolix (endometriosis, oral)

Histamine release

$$\text{Ac-D-Nal}^1\text{-(p-Cl)-D-Phe}^2\text{-D-Pal}^3\text{-Ser}^4\text{-Tyr}^5\text{-D-Cit}^6\text{-Leu}^7\text{-Arg}^8\text{-Pro}^9\text{-D-Ala}^{10}\text{-NH}_2$$

Gonadotropins: LH & FSH

Glycoproteins; under regulation by GnRH

	LH	FSH	TSH	hCG
α				
β				

- ■ **MOA of LH & FSH:**

- Surface receptors; cAMP 2nd messenger

- LH stimulates desmolase enzyme → ↑ steroidogenesis in gonads

- LH helps in the descent of testes during fetal life

- ■ **Source of LH & FSH:**

- Natural human source. Human menopausal gonadotropins (HMG; Menotropin) (Mainly FSH)

- rDNA preparations (rβ-FSH; rLH+FSH)

- **Human Chorionic Gonadotropin (hCG)**

A product of the placenta

Has similar pharmacological properties to LH

Obtained from the urine of pregnant ladies

Recombinant preparations are also available

- **Clinical uses to gonadotropins:**

- Infertility in ♂'s and ♀'s due to LH & FSH
  deficiency

- IVF

- Cryptorchidism (hCG; IM)

■ **Side effects to gonadotropins:**

- **Allergy**

- **Ovarian hyperstimulation syndrome (fever; abdominal pain, ovarian enlargement, ascites, pleural effusion, arterial thrombosis, hemoperitoneum, shock...)**

- **Multiple births**

- **Production of specific antibodies**

- **Precocious puberty and gynecomastia**

- **? Ovarian tumors**

- **Failure of Rx (abortion)**

Estrogen antagonists

E-antagonists (Clomiphene citrate or Tamoxifen) are highly effective in inducing ovulation in ♀'s and restoring fertility in ♂'s
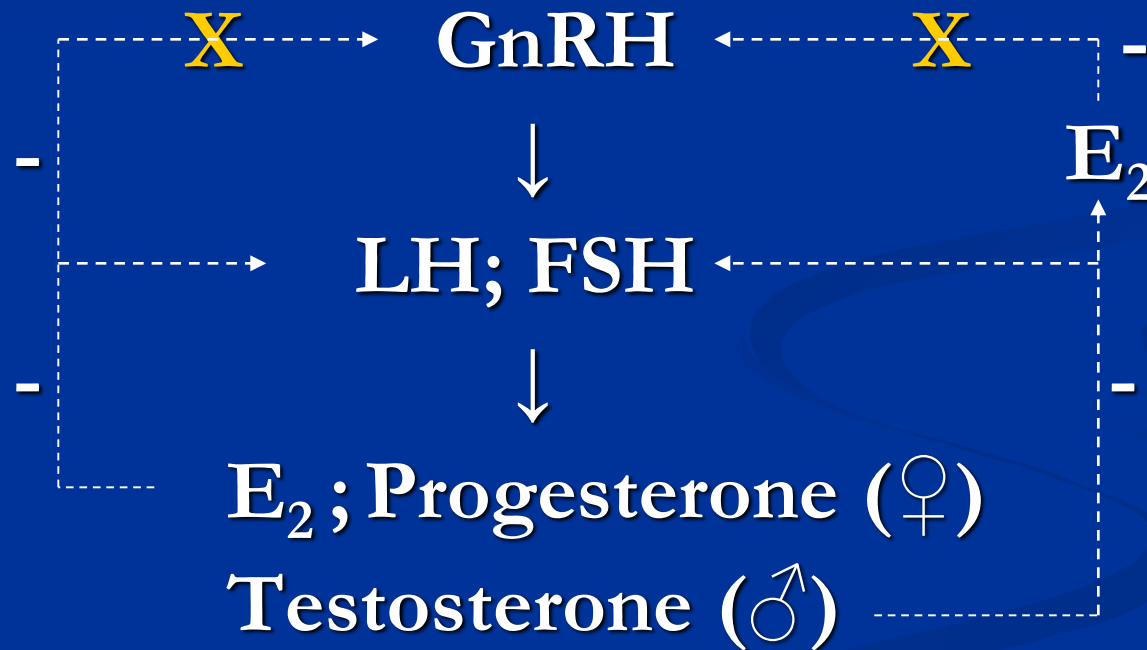
Also E-antagonists are used with HMG and hCG to regulate ovulation in IVF

Major side effects:

Menopausal manifestations in ♀'s, N & V, multiple birth, allergies, headache, insomnia, fatigue, ovarian enlargement and cyst formation

*** Assisted reproductive technology (IVF; IVM; GIFT; ZIFT)

- **MOA of estrogen antagonists as anti-infertility agents:**

$$X \dashrightarrow \textbf{GnRH} \dashleftarrow X \cdots -$$

$$\downarrow$$

$$\textbf{LH; FSH} \dashleftarrow \textbf{E}_2$$

$$\downarrow$$

$$\textbf{E}_2 \text{; Progesterone } (\female)$$

$$\textbf{Testosterone } (\male)$$

*** If the problem is sexual function

Give estrogen or testosterone

*** If the problem is infertility:

- GnRH in pulses

- LH, FSH, hCG

- Estrogen (♀'s); testosterone (♂'s)

- Bromocriptine

- Clomiphene citrate or Tamoxifen (estrogen antagonists) in ♀'s & ♂'s

*** IVF, IVM, ZIFT, GIFT… If above management fail