GnRH, LH, FSH
GnRH (Gonadotropin Releasing Hormone; Gonadorelin) A decapeptide

- GnRH → LH; FSH
  ↓
- E₂; Progesterone, follicle development & ovulation (♀)
- Testosterone; spermatogenesis (♂)
** Structure-activity relationship:

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

** Pattern of release and MOA:

- Pulsatile (Ca^{++} second messenger) $\rightarrow$ $\uparrow$ LH & FSH
- Large doses or continuous administration (downregulation of pituitary GnRH receptors) $\rightarrow$ $\downarrow$ LH & FSH
GnRH synthetic preparations:

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

Could be given S.C, I.M, I.V
Mainly given S.C
Ineffective orally
Available in intranasal, suppositories, subdermal implants and vaginal pessaries dosage forms
GnRH clinical uses:

a. Pulsatile administration

- Diagnostic use

- GnRH deficiency (Kallman’s syndrome)

Rx 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
- Endometriosis
- IVF
- Precocious puberty
- Uterine fibroids or uterine leiomyomas, polycystic ovarian syndrome (PCOS)
- ?? Contraceptive
**Side effects to GnRH:**

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

**GnRH specific antagonist:**

Ganirelix (IVF)
Gonadotropins: LH & FSH

Glycoproteins; under regulation by GnRH

LH  FSH  TSH  hCG

α

β
α DNA
↓
α mRNA
↓
α protein
↓
α glycoprotein
↓
Complete hormone
↓
Storage
↓
Release

β DNA
↓
β mRNA
↓
β protein
↓
β glycoprotein
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)
- **Human Chorionic Gonadotropin (hCG)**

  A product of the placenta

  Has similar pharmacological properties to LH

  Obtained from the urine of pregnant ladies

- **Clinical uses to gonadotropins:**
  - Infertility in ♂’s and ♀’s due to LH & FSH deficiency
  - I.V.F
  - Cryptorchidism (hCG; I.M)
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)
*** 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
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.
MOA of estrogen antagonists as anti-infertility agents:

- $X \rightarrow$ GnRH $\rightarrow X$
- $\rightarrow$ LH; FSH $\rightarrow E_2$
- $E_2$; Progesterone ($\♀$)
- Testosterone ($\♂$)