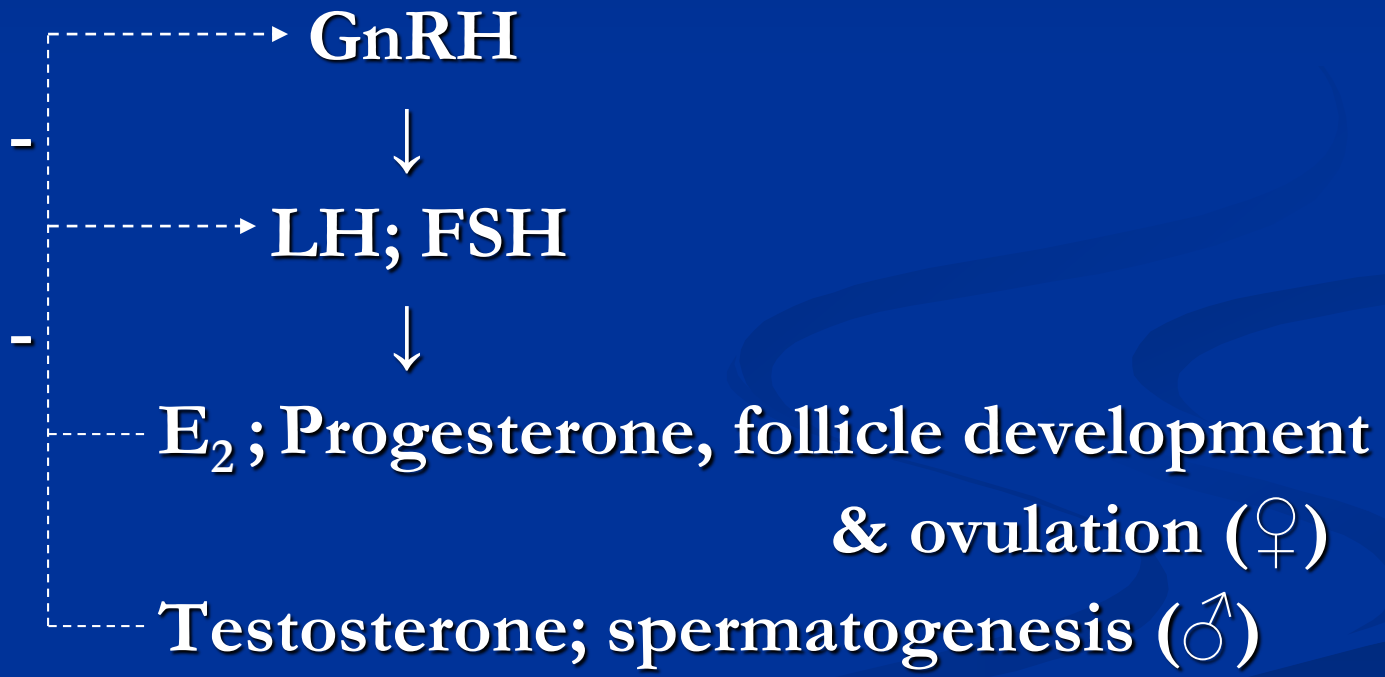
GnRH, LH, FSH

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



** Structure-activity relationship:

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

** Pattern of release and MOA:

- Pulsatile (Ca^{++} second messenger) → ↑ LH & FSH
- Large doses or continuous administration (downregulation of pituitary GnRH receptors) → ↓ LH & FSH

- **GnRH synthetic preparations:**

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

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)

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
- 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

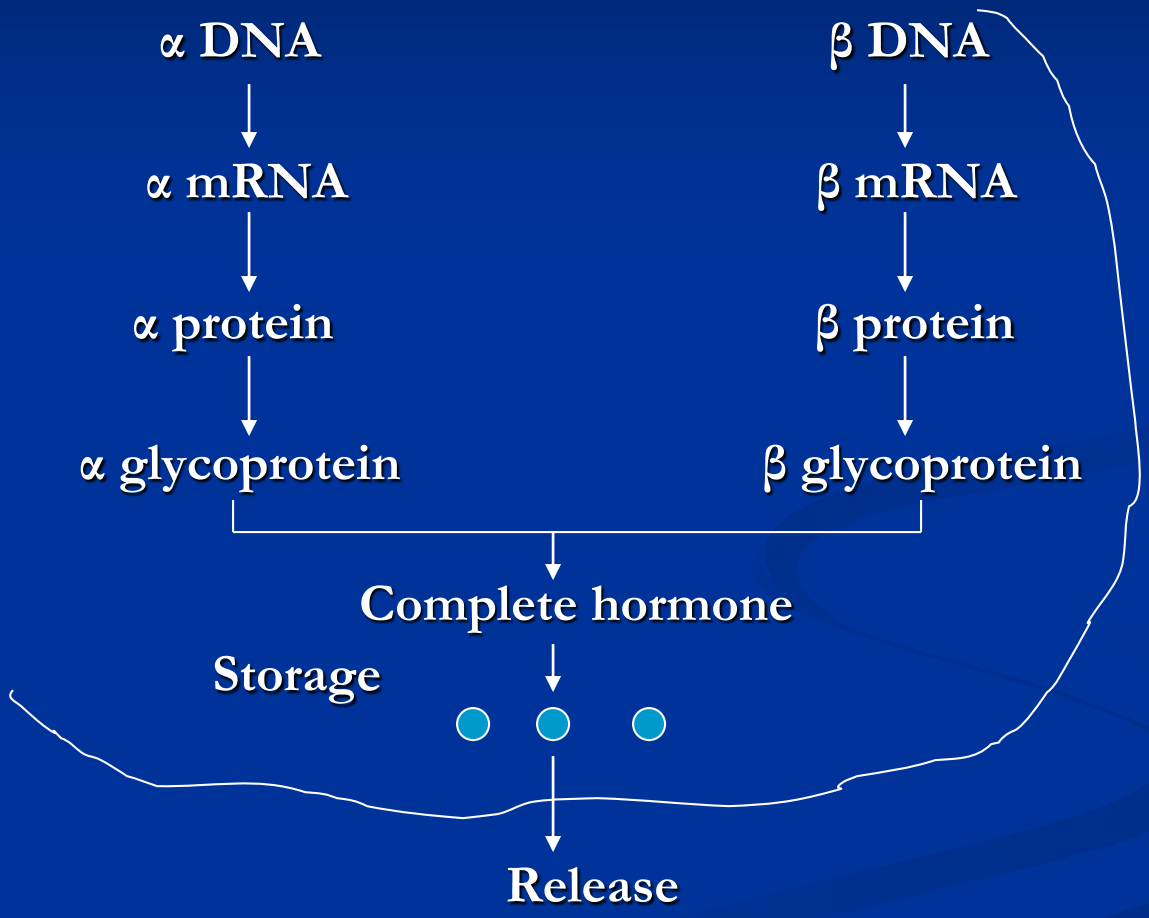
- **GnRH specific antagonist:**

  Ganirelix; given SC (IVF)

Gonadotropins: LH & FSH

Glycoproteins; under regulation by GnRH

	LH	FSH	TSH	hCG
α				
β				


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

- **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:**