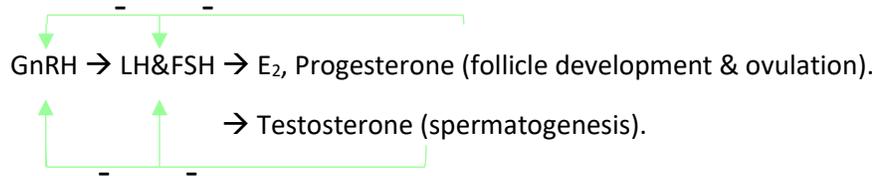


GnRH, LH, FSH

Gonadotropins (Glycoprotein hormones): FSH, LH, hCG and TSH. They have α subunit (identical for all hormones) and β subunit (unique and provide biological specificity), each subunit is encoded by a different gene.

GnRH (Gonadotropin Releasing Hormone; Gonadorelin): A small 10 a.a peptide that stimulates synthesis and release of two different complex glycoproteins (LH & FSH). Has unique pattern of release from hypothalamus.

Negative feedback mechanisms:



Structure-activity relationship: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂

10 amino acids; the first 3 are stable, the rest will be changed producing different modified structures which are used in similar function of GnRH.

Pattern of release and MOA	- Pulsatile (Ca ⁺⁺ second messenger): \uparrow LH & FSH - Large doses or continuous administration (down regulation of pituitary GnRH receptors): \downarrow LH & FSH
GnRH synthetic preparations	Leuprolide acetate, Triptorelin, Goserelin, Histrelin, Nafarelin, Busereline...
Administration	Given S.C (mainly), I.M, I.V. but Ineffective orally.
Dosage form	Intranasal, suppositories, subdermal implants and vaginal pessaries (?contraceptive).
GnRH clinical uses	a. Pulsatile administration: - Diagnostic use. - GnRH deficiency (Kallman's syndrome): Treatment of male and female hypogonadism (induces ovulation), delayed puberty, amenorrhea, cryptorchidism (the absence of one or both testes from the scrotum). (Hypogonadism: diminished functional activity of the gonads). b. Continuous administration or large doses or the use of a GnRH superagonists: prostate and breast cancer, Endometriosis, in-vitro fertilization (IVF), Precocious puberty, Uterine fibroids (benign smooth muscle tumors of the uterus), 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, SC); Degarelix (prostate cancer, SC); Elagolix (endometriosis, oral)

Gonadotropins:

1. 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.

2. LH & FSH: Glycoproteins regulated by GnRH

MOA of LH & FSH: - Surface receptors; cAMP 2nd messenger.

- LH stimulates desmolase enzyme: \uparrow steroidogenesis in gonads.

- LH helps in the descent of testes during fetal life.

Source of LH & FSH: Natural human source.

Clinical uses of gonadotropins	<ul style="list-style-type: none"> - Infertility in females and males due to LH & FSH deficiency - I.V.F - Cryptorchidism (hCG; I.M)
Side effects of gonadotropins	<ul style="list-style-type: none"> - Allergy - Ovarian hyperstimulation syndrome (fever; abdominal pain, ovarian enlargement, ascites, shock...) - Multiple births - Production of specific antibodies - Precocious puberty - ? Ovarian tumors - abortion

General rules:

- If the problem is sexual function: give estrogen or testosterone.
- If the problem is infertility:
 - GnRH in pulses.
 - LH, FSH, hCG
 - Estrogen or testosterone.
 - Clomiphene citrate or Tamoxifen (estrogen antagonists) in females and males.

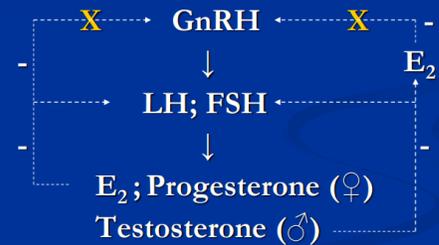
Estrogen antagonists as anti-infertility agents:

Highly effective in inducing ovulation in females and restoring fertility in males. (Inhibit the negative feedback).

Major side effects:

Menopausal manifestations in females, nausea and vomiting, multiple birth, allergies, headache, insomnia, fatigue, ovarian enlargement, and cyst formation.

■ MOA of estrogen antagonists as anti-infertility agents:



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