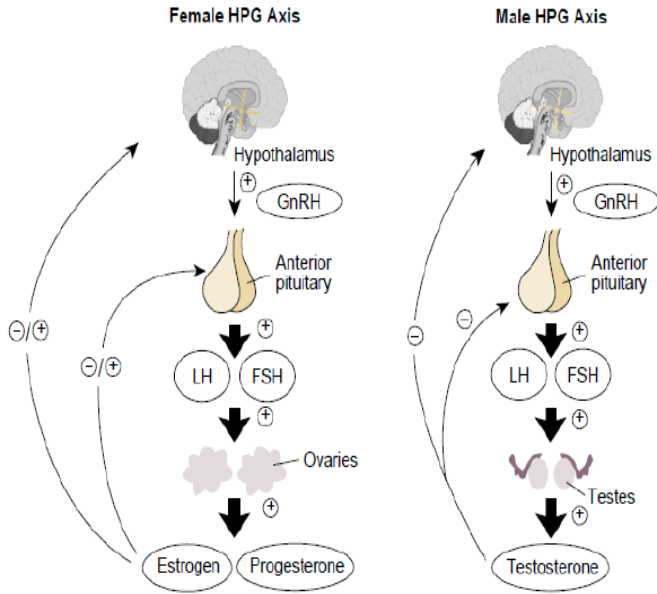


REGULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS:



• NOTE: pre-ovulatory surge of estrogen actually has a stimulatory effect on GnRH and Gn production (i.e. positive feedback)

GONADOTROPINS:

FOLLICLE-STIMULATING HORMONE (FSH) & LUTEINIZING HORMONE (LH):

<ul style="list-style-type: none"> Produced by specialized cells in the anterior pituitary gland Act on FSH and LH receptors in gonads 					
Females	<table border="1"> <tr> <td>FSH</td> <td> <ul style="list-style-type: none"> Stimulates the growth of the developing ovarian follicles during the first half of the menstrual cycle, and promotes the synthesis of estrogen (LH also required) </td> </tr> <tr> <td>LH</td> <td> <ul style="list-style-type: none"> Induces ovulation, and stimulates progesterone and estrogen synthesis by the corpus luteum (formed from the remaining cells of the ruptured follicle) during the second half of the menstrual cycle </td> </tr> </table>	FSH	<ul style="list-style-type: none"> Stimulates the growth of the developing ovarian follicles during the first half of the menstrual cycle, and promotes the synthesis of estrogen (LH also required) 	LH	<ul style="list-style-type: none"> Induces ovulation, and stimulates progesterone and estrogen synthesis by the corpus luteum (formed from the remaining cells of the ruptured follicle) during the second half of the menstrual cycle
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CHORIONIC GONADOTROPIN (CG):

<ul style="list-style-type: none"> Produced by fertilized ovum, then by placenta in pregnancy Sequence similar to LH, interacts with LH receptors in both men and women 	
Females	<ul style="list-style-type: none"> Acts to maintain the corpus luteum when ovum is fertilized
Males	<ul style="list-style-type: none"> Not produced Exogenous CG acts like LH

USE OF GONADOTROPINS:

DIAGNOSTIC:

Pregnancy testing:	CG levels in maternal blood and urine
Prediction of ovulation:	Ovulation occurs about 36 hours after onset of LH surge, and 10-12 hours after peak
Determining cause of impaired sex hormone:	<ul style="list-style-type: none"> Primary gonadal failure: ovaries or testes fail to respond to stimulation by gonadotropins Secondary gonadal failure (hypogonadotropic hypogonadism): failure of hypothalamus to secrete GnRH or pituitary to secrete gonadotropins

THERAPEUTIC USE:

- Treatment of infertility in women – component of assisted reproductive technologies programs in ovulatory patients
 - Possible SEs:
 - Multiple births
 - Ovarian hyperstimulation syndrome (massive ovarian enlargement, fluid accumulation leading to pain & renal failure)

GONADOTROPIN PREPARATIONS:

- Purified from human urine:
 - Menotropins: roughly equal amounts FSH and LH
 - Chorionic gonadotropin
- Recombinant versions of FSH, LH and CG have also been developed

GONADOTROPIN RELEASING HORMONE (GnRH):

- Acts on specific GnRH receptors on anterior pituitary gland to increase production and release of LH and FSH (in pulses):
- Decapeptide with very short half-life (2-4 min)
- Gonadorelin acetate** = synthetic GnRH identical to the native hormone
 - Used to investigate delayed puberty, and treatment of infertility in both men and women

GnRH ANALOGUES:

- Both **GnRH agonists** and **GnRH antagonists** now available
- Both groups of drugs are analogues of GnRH with changes to amino acid sequence that alters their activity
- Both used when want to **decrease** release of Gn and sex steroids

GnRH AGONISTS: Buserelin, Leuprolide, Nafarelin

Compare to GnRH:	<ul style="list-style-type: none"> ↑ affinity for GnRH on pituitary gland = ↑ potent Less susceptible to proteolysis = longer duration Anti-fertility when given continuously <ul style="list-style-type: none"> Physiological GnRH = pulsatile (pro-fertility)
MOA	<ol style="list-style-type: none"> Initial rise in hormone levels (= "flare" of disease) Down-regulation of GnRH receptors on pituitary gland ↓ FSH, LH which then ↓ sex steroids
AEs	Largely due to suppression of sex steroid production <ul style="list-style-type: none"> Women: hot flashes, vaginal dryness, memory impairment, decreased bone density (can be reduced by "add back therapy" with estrogen + progesterone) Men: hot flashes, decreased libido, erectile dysfunction, increased risk of osteoporotic fractures, type 2 diabetes and CVD
Forms	SC injection and nasal spray

GnRH ANTAGONISTS: Ganirelix, Cetrorelix, Degarelix

- Analogues of GnRH that are competitive reversible antagonists of GnRH at its receptor on pituitary cells
- Induce a rapid, reversible inhibition of LH and FSH secretion, with no agonist phase at beginning of treatment
- Approved to prevent premature LH surge and ovulation in *in vitro* fertilization cycles and for use in advanced prostate cancer
- Adverse effects appear to be similar to GnRH agonists