REGULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS:

USE OF GONADOTROPS:

- **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:
    - 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

GONADOTROPINS:

- **FOLLICLE-STIMULATING HORMONE (FSH) & LUTEINIZING HORMONE (LH):**
  - Produced by specialized cells in the anterior pituitary gland
  - Act on FSH and LH receptors in gonads
  - Changes to amino acid sequence that alters their activity

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
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<tbody>
<tr>
<td>FSH</td>
<td>LH</td>
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<tr>
<td>Stimulation of the developing ovarian follicles during the first half of the menstrual cycle, and promotes the synthesis of estrogen (LH also required)</td>
<td>Stimulates 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>
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<th>CG</th>
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<td>Produced by fertilized ovum, then by placenta in pregnancy</td>
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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 alter their activity
- Both used when want to decrease release of Gn and sex steroids

**GnRH AGONISTS:** Buserelin, Leuprolide, Nafarelin

- **Compare to GnRH:**
  - ↑ affinity for GnRH on pituitary gland = ↑ potency
  - Less susceptible to proteolysis = longer duration
  - Anti-fertility when given continuously
    - Physiological GnRH = pulsatile (pro-fertility)

- **MOA**
  1. Initial rise in hormone levels (= “flare” of disease)
  2. Down-regulation of GnRH receptors on pituitary gland
  3. ↓ FSH, LH which then ↓ sex steroids

- **AEs**
  - Largely due to suppression of sex steroid production
    - 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