The Gonadotropins

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The Gonadotropins

1. Follicle-stimulating hormone (FSH).
2. Luteinizing hormone (LH).
3. Human chorionic gonadotropin (hCG).
4. Human menopausal gonadotropins (hMG).

Gonadotropins Available for Use

1. **Urofollitropin (uFSH): extracted from the urine of postmenopausal women.**
2. **Recombinant FSH (rFSH), follitropin.**
3. **Recombinant human LH (rLH), or Lutropin.**
4. **Choriogonadotropin alfa is a recombinant form of hCG (rhCG), which is a combination of FSH and LH.**

The Gonadotropins

Therapeutic Uses:

1. **Induction of ovulation: needs progesterone support of the luteal phase.**
2. **Male infertility: for hypogonadal men.**

The Gonadotropins

Adverse effects:

1. **Ovarian hyper-stimulation syndrome:**

a) **Ovarian enlargement, ascitis, hydrothorax, hypovolemia and sometimes shock.**

b) **Hemoperitoneum (from a ruptured ovarian cyst).**

c) **Fever and arterial thromboembolism can occur.**

The Gonadotropins

2. **Multiple pregnancies (15-20% vs 1%).**
3. **Headache, depression, edema.**
4. **Production of antibodies against hCG.**
5. **Gynecomastia in males.**
6. **Possible association with ovarian cancer.**

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs

- It is secreted by neurons in the hypothalamus.
- Pulsatile GnRH secretion stimulates the gonadotrophs to produce and release FSH and LH.
- Sustained, nonpulsatile administration of GnRH (or its analogs) inhibits the release of FSH & LH by the pituitary in both women and men → hypogonadism.

(GnRH) & Its Analogs

- **Gonadorelin is an acetate salt of synthetic human GnRH.**
- **Synthetic analogs include: Goserelin, Leuprolide.**
- **Duration of clinical use varies from few days to years, therefore, preparations have been developed with a range of duration of action from several hours to months.**

(GnRH) & Its Analogs

- **Lower pulse frequencies favor FSH secretion, whereas higher pulse frequencies favor LH secretion.**

Pharmacologic use:

1. **Pulsatile IV administration of gonadorelin every 1-4 hours stimulates FSH and LH secretion.**

(GnRH) & Its Analogs

2. **Continuous administration of gonadorelin or its analogs produces a biphasic response:**

A. **During the first 7-10 days, an agonist effect occurs that results in increased concentration of gonadal hormones in males and females – called a flare.**

(GnRH) & Its Analogs

B. **After that, the continued presence of GnRH results in inhibitory action leading to decreased concentrations of gonadotropins and gonadal steroids.**

- **The inhibitory action is due to receptor down-regulation and changes in the signaling pathway.**

(GnRH) & Its Analogs

Therapeutic Uses:

A. Stimulation:

1. **Female and Male infertility: Less commonly used, and less convenient method than gonadotropins.**
2. **As an "LH responsiveness test" to diagnose the cause of delayed puberty.**

(GnRH) & Its Analogs

B. Suppression of gonadotropin production:

1. **Controlled ovarian hyperstimulation: When multiple mature oocytes are produced in the course of assisted reproduction to suppress endogenous LH surge that could prematurely trigger ovulation.**

(GnRH) & Its Analogs

2. **Endometriosis (ectopic estrogen-sensitive tissue): The pain of endometriosis is reduced by abolishing exposure to the cyclical changes in the concentration of estrogen and progesterone which are part of the menstrual cycle.**

(GnRH) & Its Analogs

3. **Uterine leiomyomata (fibroids): Estrogen-sensitive fibrous growths.**
4. **Central (pituitary or hypothalamic) precocious puberty (onset of secondary sex characteristics before 8 years in girls and 9 years in boys).**

(GnRH) & Its Analogs

Adverse effects:

1. **Headache, light-headedness, nausea and flushing.**
2. **Local swelling at injections site.**
3. **Hypersensitivity reactions: bronchospasm and anaphylaxis.**
4. **The syndrome of menopause in women.**
5. **Ovarian cysts.**

(GnRH) & Its Analogs

6. **Sudden pituitary apoplexy: Abrupt hemorrhage or infarction of the pituitary gland within a pituitary adenoma, leading to abrupt onset of severe headache, neck stiffness, visual disturbances, and oculomotor palsies.**
7. **Reduced bone density and osteoporosis.**

GnRH Receptor Antagonists

Ganirelix, Cetrorelix (Synthetic decapeptides):

- **They inhibit FSH and LH secretion in a dose-dependent manner.**

Therapeutic uses:

1.Prevention of the LH surge during controlled ovarian hyperstimulation.

GnRH Receptor Antagonists

- **An advantage over continuous treatment with GnRH agonists is immediate action, and shorter duration of administration.**
- **Their use can be delayed until day 6–8 of the in vitro fertilization cycle.**

GnRH Receptor Antagonists

On the other hand:

1. **Adherence to treatment regimen is more critical because effect reverses quickly after discontinuation.**
2. **They produce more complete suppression of gonadotropin secretion.**

GnRH Receptor Antagonists

3. **Suppression of LH may inhibit ovarian steroidogenesis to an extent that impairs follicular development when FSH is used during the follicular phase of IVF cycle.**
4. **Lower rate of pregnancy in IVF cycles compared with those using GnRH agonists.**

GnRH Receptor Antagonists

B. **Treatment of advanced prostate cancer: Degarelix reduces concentrations of gonadotropins and androgens more rapidly than GnRH agonists and avoids the testosterone surge seen with GnRH agonist therapy.**

GnRH Receptor Antagonists

Adverse effects:

1. **Nausea and headache are the most common.**
2. **During the treatment of men with prostate cancer, degarelix may cause injection-site reactions and may increase liver enzymes.**
3. **Signs and symptoms of androgen deprivation, including hot flushes and weight gain.**

Prolactin

- **198 aa peptide, similar in structure to growth hormone.**
- **Principal hormone responsible for lactation.**
- **Hyperprolactinemia → amenorrhea, galactorrhea and infertility in women; AND loss of libido and infertility in men.**
- **The hypogonadism and infertility associated with hyperprolactinemia is due to inhibition of GnRH release.**

Prolactin

- **The prolactin-inhibiting hormone is dopamine.**
- **Dopamine agonists are used to treat hyperprolactinemia.**
- **Adenomas that secrete excess prolactin retain sensitivity to dopamine.**

Dopamine Agonists

Dopamine agonists (D_2 receptor):

1. **Ergot derivatives: Bromocriptine, cabergoline, pergolide.**
2. **Nonergot derivatives: Quinagolide.**

Pharmacodynamics:

1. **Suppress prolactin release effectively in patients with hyperprolactinemia.**
2. **Also suppress GH release in acromegaly.**
3. **Improve motor function in Parkinsonism.**

Dopamine Agonists

Therapeutic uses:

1. **Hyperprolactinemia:**

- **Shrink pituitary prolactin-secreting tumors.**
- **Lower circulating prolactin levels.**

2. **Restore ovulation in ~ 70% of women with microadenomas and ~ 30% of those with macroadenomas.**
3. **Acromegaly.**
4. **4. Parkinsonism.**

Dopamine Agonists

Adverse effects:

1. **Nausea, vomiting, headache, fatigue and lightheadedness.**
2. **Orthostatic hypotension.**
3. **Psychiatric manifestations.**
4. **Erythromelalgia (paroxysmal throbbing and burning pain in the skin).**

Dopamine Agonists

5. **Ergots → cold-induced peripheral digital vasospasm.**
6. **Pulmonary infiltrates with chronic high dose therapy.**
7. **Stroke or coronary thrombosis in postpartum women taking bromocriptine to suppress postpartum lactation.**