The Gonadotropins

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

Gonadotropins Available for Clinical Use:

1. Urofollitropin (uFSH):
- A form of follicle-stimulating hormone (FSH).
- Extracted from the urine of postmenopausal women.

2. Recombinant FSH (rFSH), also called Follitropin
- Lab-made version of FSH

3. Recombinant human LH (rLH), or Lutropin:
- A synthetic form of luteinizing hormone (LH).

4. Choriogonadotropin alfa (rhCG):
- A recombinant form of hCG (human chorionic gonadotropin).
- Mimics the effect of both LH and FSH

✅ Therapeutic Uses of Gonadotropins:

1. Induction of Ovulation
– Used in women with infertility to stimulate ovulation.
– Requires progesterone support during the luteal phase to maintain the endometrium.

2. Male Infertility
– Used in hypogonadal men (men with low pituitary hormone production) to stimulate sperm production.

⚠️ Adverse Effects of Gonadotropins:

1. Ovarian Hyperstimulation Syndrome (OHSS):
a) Ovarian enlargement, fluid in the abdomen (ascites) or chest (hydrothorax), low blood volume (hypovolemia), and shock in severe cases.
b) Hemoperitoneum (bleeding in the abdomen) due to ruptured ovarian cyst.
c) Fever and risk of arterial thromboembolism (blood clots).

2. Multiple Pregnancies:
– Occurs in 15–20% of cases compared to ~1% naturally.

3. Neurological and General Symptoms:
– Headache, depression, fluid retention (edema).

4. Immunologic Reaction:
– Antibody formation against hCG, which may reduce treatment effectiveness.

5. In Men:
– Gynecomastia (breast enlargement).

6. Possible Risk of Ovarian Cancer:
– A potential, though not confirmed, long-term risk.

✅ Basics of GnRH:

- GnRH (Gonadotropin-Releasing Hormone) is a hormone secreted by neurons in the hypothalamus.
- It stimulates the anterior pituitary to release FSH and LH.
- This stimulation occurs only if GnRH is secreted in pulses (not continuously).

✅ Effect of Administration Pattern:

1. Pulsatile GnRH Secretion:

- Stimulates normal FSH and LH release.
- Low-frequency pulses → more FSH.
- High-frequency pulses → more LH.

2. Continuous (Non-Pulsatile) GnRH or Analogs:

- Initially (first 7–10 days): causes a "flare effect" → temporary increase in FSH, LH, and gonadal hormones.
- Afterwards: leads to inhibition of FSH and LH secretion → causing hypogonadism.
- Mechanism: down-regulation of GnRH receptors and signaling changes in the pituitary.

🔬 Examples of GnRH & Analogs:

- Gonadorelin: synthetic GnRH (in acetate form).
- Goserelin, Leuprolide: synthetic long-acting GnRH analogs.
- These can be used in treatments ranging from a few days to several years.

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💊 Pharmacologic Uses:

1. Pulsatile IV administration of Gonadorelin:

- Every 1–4 hours → stimulates FSH & LH → used for infertility treatment.

2. Continuous administration (Gonadorelin or Analogs):

- Used to suppress gonadal hormones in:
- Prostate cancer
- Breast cancer
- Endometriosis
- Precocious puberty

✅ Therapeutic Uses of GnRH & Its Analogs:

🔶 A. Stimulation Purposes: 

1. Infertility (Male & Female):

- Used to stimulate gonadotropin release in some cases, but less commonly than direct gonadotropin therapy (e.g., FSH/LH).

2. Delayed Puberty Diagnosis:

- Used as an "LH responsiveness test" to evaluate if puberty is delayed due to central (hypothalamic/pituitary) causes.

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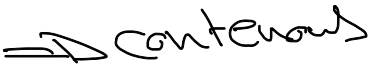
🔶 B. Suppression Purposes: 

1. Controlled Ovarian Hyperstimulation (IVF):

- Used to prevent premature LH surge, which could cause early ovulation during fertility treatments.

2. Endometriosis:

- Suppresses estrogen and progesterone → reduces cyclic hormonal pain associated with ectopic endometrial tissue.

3. Uterine Fibroids (Leiomyomas):

- Fibroids are estrogen-sensitive → reducing estrogen can shrink them and improve symptoms.

4. Precocious Puberty:

- Used in central (true) precocious puberty to delay onset of secondary sexual characteristics.

⚠️ Adverse Effects of GnRH & Analogs:

1. Common symptoms:
   - Headache, nausea, flushing, lightheadedness.
2. Injection site reactions:
   - Swelling, discomfort.
3. Hypersensitivity reactions:
   - Bronchospasm, anaphylaxis (rare but serious).
4. Menopausal-like syndrome in women:
   - Hot flashes, mood changes, vaginal dryness due to estrogen suppression.
5. Ovarian Cysts:
   - Especially in early phase (flare).
6. Pituitary Apoplexy:
   - Sudden hemorrhage or infarction of a pituitary adenoma → severe headache, vision issues, cranial nerve palsies.
7. Reduced Bone Density / Osteoporosis:
   - Due to long-term estrogen/testosterone suppression.

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🧠 ***GnRH Receptor Antagonists***

🔷 Examples:

- Ganirelix
- Cetrorelix

(Both are synthetic decapeptides)

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✅ Mechanism of Action:

They directly block GnRH receptors in the pituitary, leading to dose-dependent suppression of FSH and LH secretion.

🟡 Unlike GnRH agonists, they do not cause an initial flare (hormone surge).
They act immediately.

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🔬 Therapeutic Uses:
A. In IVF (Controlled Ovarian Hyperstimulation):

🎯 Goal:
To prevent premature LH surge that could trigger early ovulation before egg retrieval.

✅ Advantages over GnRH agonists:

1. Immediate action (no waiting for downregulation).
2. Shorter duration of administration.
3. Can be started later in the cycle (e.g., day 6–8 of IVF).

⚠️ Disadvantages:

1. Strict adherence is crucial → effect wears off quickly when stopped.
2. May suppress LH too much → impair estrogen production and hinder follicular development (even with FSH support).
3. Lower pregnancy rates in IVF cycles compared to GnRH agonists (in some studies).

B. Advanced Prostate Cancer:
✅ Example: Degarelix

- Rapidly suppresses FSH, LH, and testosterone.
- Advantage: No initial testosterone flare (unlike GnRH agonists).

🧪 GnRH Receptor Antagonists – Adverse Effects

1. Nausea and Headache → most common.
2. Injection-site reactions → especially with degarelix in prostate cancer treatment.
3. Elevated liver enzymes → may occur in men receiving degarelix.
4. Androgen deprivation symptoms:

- Hot flushes (hot flashes)
- Weight gain
- Decreased libido

🧬 Prolactin & Hyperprolactinemia

- ***Prolactin***:

- 198 amino acid peptide.
- Similar in structure to growth hormone.
- Main role: lactation (milk production).

- Hyperprolactinemia leads to:
- **In women**:
- Amenorrhea (no periods)
- Galactorrhea (milk production not related to childbirth)
- Infertility
- **In men**:
- Low libido
- Infertility

- ⚠️ These effects happen because prolactin inhibits GnRH, which ↓ FSH & LH → causes hypogonadism.
- Dopamine is the prolactin-inhibiting hormone.
- So we treat hyperprolactinemia using dopamine agonists (like bromocriptine, cabergoline).
- Good news: Prolactin-secreting adenomas usually respond well to dopamine agonists.

🧠 ***Dopamine Agonists*** (محفزات الدوبامين)

🎯 Target:
They act on D2 receptors.

⚙️ Pharmacodynamics (آلية التأثير):

1. ⛔ Inhibit prolactin release → used for hyperprolactinemia.
2. ⛔ Suppress GH → useful in acromegaly.
3. ✅ Stimulate dopamine receptors in the brain → help in Parkinsonism (improve movement).

🧪 **Types:**

Type	Examples
Ergot derivatives	Bromocriptine, Cabergoline, Pergolide
Non-ergot derivatives	Quinagolide

💊 Therapeutic Uses (الاستخدامات العلاجية):

1. Hyperprolactinemia:

- Shrink prolactin-secreting pituitary tumors.
- Decrease blood prolactin levels.
- Restore ovulation in:
- ~70% of women with microadenomas.
- ~30% with macroadenomas.

2. Acromegaly → Suppress GH secretion.
3. Parkinsonism → Improve motor symptoms.

⚠️ **Adverse Effects (الآثار الجانبية):**

1. 🤢 Nausea, vomiting, headache, fatigue, dizziness.
2. ↓ **Orthostatic hypotension** → drop in BP when standing.
3. 😵 **Psychiatric symptoms** → hallucinations, confusion (especially in Parkinson's patients).
4. 🔥 **Erythromelalgia** → burning/throbbing pain in skin (esp. hands/feet).
5. ❄️ **Vasospasm in fingers/toes** (with **ergots**, e.g. bromocriptine) → gets worse with cold.
6. 🫁 **Pulmonary infiltrates** (with chronic high doses).
7. 💔 **Rare but serious**:
   - **Stroke or heart attack** in **postpartum women** using **bromocriptine** to stop milk production.

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