Pharmacology Lecture Notes Summary

Gonadotropins, GnRH Modulators, and Prolactin Modulators

1. The Gonadotropins

The gonadotropins include **Follicle-stimulating hormone (FSH)**, **Luteinizing hormone (LH)**, **Human chorionic gonadotropin (hCG), and Human menopausal gonadotropins (hMG).**

Available Formulations

- **Urofollitropin (FSH):** Extracted from the **urine of postmenopausal women**.
- **Recombinant FSH (rFSH): Follitropin.**
- **Recombinant human LH (rLH): Lutropin.**
- **Choriogonadotropin alfa (rhCG):** A recombinant form of hCG of placental origin, combining FSH and LH activity.

Therapeutic Uses

- **Induction of Ovulation (Female Infertility): Requires progesterone support during the luteal phase**.
- **Male Infertility: Used to treat hypogonadal men.**

Adverse Effects

- **Ovarian Hyper-stimulation Syndrome (OHSS):** Characterized by **ovarian enlargement (Could predispose to ovarian cancer)**, **ascites, hydrothorax, hemoperitoneum (**Bleeding into the abdominal cavity, typically from a ruptured ovarian cyst caused by the simultaneous maturation of multiple follicles) and **hypovolemia** (sometimes leading to shock),
- **Multiple Pregnancies: Rates rise to 15–20%** (compared to 1% in natural cycles), presenting risks to embryos.
- **Male-Specific Effects: Gynecomastia in males.**
- **Antibody Production: Production of antibodies against hCG** can occur due to residual non-human protein contaminants from the purification process.
- **Systemic Symptoms:** Fever, arterial thromboembolism, headache, edema, and steroid-associated depression (due to interference with biogenic amines).

2. Gonadotropin-Releasing Hormone (GnRH) & Its Analogs

GnRH is secreted by neurons in the hypothalamus to regulate gonadotrophs **via negative feedback from estrogen or testosterone. Gonadorelin** is an **synthetic human GnRH**. **Other Synthetic Analogs** include **Goserelin** and **Leuprolide.**

Mechanisms of Administration (Callout Summary)

Pulsatile Administration (IV every 1–4 hours):
Simulates physiological pulses to **stimulate the release of FSH and LH. Lower pulse frequencies favor FSH secretion**, while **higher pulse frequencies favor LH secretion**.

Continuous (Sustained) Administration (Biphasic Transition):
• **The Flare Phase (First 7–10 days):** Acts as an **agonist, temporarily increasing concentrations of gonadal hormones.**
• **The Inhibitory Phase**: Continuous presence causes **receptor down-regulation** and signaling changes, **severely reducing FSH, LH**, and gonadal steroids.

Therapeutic Uses

Stimulation (Pulsatile) -Stimulatory Effect-

- **Male and female infertility** (**less common/convenient than using gonadotropins directly**).
- An "**LH responsiveness test" to diagnose the etiology of delayed puberty**.

Suppression (Continuous/Sustained) -Contraceptive Effect-

- **In Vitro Fertilization (IVF) (Controlled Ovarian Hyperstimulation): Suppresses endogenous LH surges** that could prematurely trigger ovulation during assisted reproduction.
- **Endometriosis:** Reduces ectopic estrogen-sensitive tissue pain by **abolishing cyclical exposure to estrogen and progesterone.**
- **Uterine Leiomyomata (Fibroids):** Suppresses these estrogen-sensitive fibrous growths.
- **Central Precocious Puberty:** Manages early onset of secondary sex characteristics (**before age 8 in girls, 9 in boys).**

Adverse Effects

- **General:** Headache, light-headedness, nausea, flushing, local injection site swelling, and hypersensitivity reactions (bronchospasm/anaphylaxis).
- **Reproductive: Ovarian cysts** and **early induced menopause syndrome in women**.
- **Pituitary Apoplexy:** Sudden hemorrhage or infarction of a pituitary adenoma, presenting like meningitis with severe headache, neck stiffness, visual disturbances, and oculomotor palsies.
- **Bone Loss: Reduced bone density and osteoporosis from decreased sex steroid production** (estrogen deficiency in females, declining androgen levels or scarcity of androgen receptors in males).

3. GnRH Receptor Antagonists

Examples include **Ganirelix** and **Cetrorelix** (synthetic decapeptides), as well as **Degarelix**. They **inhibit FSH and LH secretion in a dose-dependent manner**.

Agonists vs. Antagonists Comparison Profile

Clinical Advantages vs. Agonists	Clinical Disadvantages vs. Agonists
Immediate action and **shorter overall duration of administration.**	**Strict treatment adherence is vital** because **effects reverse quickly upon discontinuation**.
Can be delayed until day 6–8 of an in vitro fertilization (IVF) cycle.	Can cause a **more complete suppression of LH,** which may **over-inhibit ovarian steroidogenesis → Impaired follicular development in case of IVF → lower rate of pregnancy in IVF cycles compared to GnRH agonists.**
Avoids the initial surge (flare) seen with agonists.	

Therapeutic Uses

- **In Vitro Fertilization (IVF):** Used during **controlled ovarian hyperstimulation** to suppress LH secretion, **preventing premature ovulation.**
- **Advanced Prostate Cancer: Degarelix** rapidly reduces gonadotropins and androgens in androgen-dependent prostate cancer without creating a tumor flare.

Adverse Effects

- Nausea and headache.
- **Signs of androgen deprivation** (e.g., **hot flushes**, **weight gain**).
- **Degarelix Specific: Injection-site reactions** and **elevated liver enzymes** (which reflect hepatocyte integrity/leakage or enzyme induction rather than absolute synthetic liver failure).

4. Prolactin Modulators & Dopamine Agonists

Prolactin is a 198-amino-acid peptide **responsible for lactation**. **Hyperprolactinemia** not only causes **galactorrhea**, but also **inhibits GnRH release**, resulting in **amenorrhea**, and **infertility in women**, alongside a **loss of libido and infertility in men.**

Dopamine acts as the physiological **prolactin-inhibiting factor**. Since dopamine itself has too short of a circulating half-life for routine hyperprolactinemia treatment, synthetic dopamine agonists targeting D2 receptors are used.

Classification of Dopamine Agonists

- **Ergot Derivatives: Bromocriptine** (the prototype), **cabergoline**, and **pergolide.**
- **Non-Ergot Derivatives: Quinagolide.**

Pharmacodynamics & Therapeutic Uses

- **Hyperprolactinemia & Adenomas:** Effectively **suppresses prolactin release** and **shrinks prolactin-secreting pituitary microadenomas and macroadenomas** (retaining sensitivity to external dopamine agonists despite reduced sensitivity to endogenous dopamine).
- **Infertility Treatment:** Restores ovulation in approximately **70% of women with microadenomas** and **30% of those with macroadenomas.**
- **Other Uses: Suppresses growth hormone (GH) release in acromegaly** and **improves motor function in Parkinsonism.**

Adverse Effects

- **General:** Nausea, vomiting, headache, fatigue, lightheadedness, and **orthostatic (postural) hypotension**.
- **Psychiatric Manifestations:** Can trigger psychiatric manifestations, particularly psychosis.
- **Vascular & Dermatological: Erythromelalgia (throbbing and burning skin pain).**
- **Serious Postpartum Risks: Stroke or coronary thrombosis in postpartum women taking bromocriptine to suppress postpartum lactation.**
- **Ergot-Specific Vasospasm: Cold-induced peripheral digital vasospasm**, also high-dose therapy can produce **pulmonary infiltrates that may progress to pulmonary fibrosis.**