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بسم الله الرحمن الرحيم

Gonadotropins and Analogues

FINAL | Lecture 9

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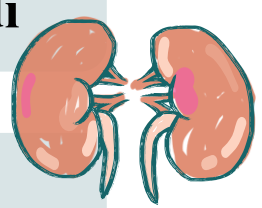
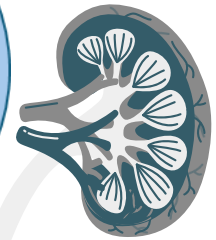


﴿ قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ ﴾



The Gonadotropins

Yacoub M. Irshaid, MD, PhD, ABCP

The doctor noted that there is some general information that everyone should pay close attention to, regardless of whether they intend to specialize in obstetrics and gynecology or not. However, we will also go through many detailed topics that are especially beneficial for those planning to pursue this specialty.

The Gonadotropins

1. Follicle-stimulating hormone (***FSH***).
2. Luteinizing hormone (***LH***).
3. Human chorionic gonadotropin (***hCG***).
4. Human menopausal gonadotropins (***hMG***).
   - ✓ hCG and hMG are both isolated from women urine.

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.

Recall: **chorio** means of placental origin.

The Gonadotropins

Therapeutic Uses

- Used for infertility:
  1. **Induction of ovulation:** needs progesterone support of the luteal phase to prepare the uterus for implantation. Progesterone supplementation is typically continued until placental steroidogenesis becomes adequate to sustain pregnancy, usually after the luteo-placental shift in early gestation.
  2. **Male infertility**: for hypogonadal men.

The Gonadotropins

Adverse effects(1)

1. Ovarian hyper-stimulation syndrome:

a) Ovarian enlargement, **ascites** (fluid accumulation in the abdomen), **hydrothorax** (fluid accumulation in the chest cavity), **hypovolemia** and sometimes **shock**, renal damage, coma, brain damage (if oxygen levels drop severely due to compromised breathing or circulation).

b) **Hemoperitoneum** (bleeding into the peritoneal/abdominal cavity). This typically occurs from a **ruptured ovarian cyst**, because fertility medications can cause multiple ova (eggs) and fluid-filled follicles to mature and enlarge simultaneously.

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

The Gonadotropins

Adverse effects(2)

2. **Multiple pregnancies** (>2) (15-20% vs 1%) as they may pose serious risks to the embryos, although successful survival is still possible.
3. **Headache**, **depression** (steroid associated depression as they interfere with biogenic amines), **edema**.
4. **Production of antibodies against hCG,** see next slide.
5. **Gynecomastia in males.**
6. Possible association with **ovarian cancer** see next slide.

The doctor emphasized the importance of distinguishing between **side effects** and **adverse effects**, as side effects can sometimes be beneficial, unlike adverse effects.

The Gonadotropins

Adverse effects(2) - Explanation

4. Production of antibodies against hCG:

- Due to residual non-human protein contaminants introduced during the purification process, which can potentially trigger allergic or immunogenic responses.

6. Possible association with ovarian cancer:

- It's more of an **adverse event** than an adverse reaction.
- An **adverse event** refers to any undesirable medical occurrence that follows the use of a drug, **regardless of whether a causal relationship exists.** It **may** or **may not** be caused by the drug
- Whereas an adverse drug reaction is a harmful effect in which a causal link with the drug is suspected or established, with the degree of certainty varying rather than being absolute. The doctor said that it's **100%** proven to be caused by the drug which is not entirely accurate.

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs

- It is secreted by neurons in the **hypothalamus**.
- **Pulsatile** GnRH secretion or administration **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**.
- Gonadotropin secretion is regulated by GnRH and influenced by estrogen or testosterone through negative feedback.

Gonadotropin-Releasing Hormone (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.

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs

- Lower pulse frequencies favor FSH secretion, whereas higher pulse frequencies favor LH secretion. This rule also applies to analogues.

❖ **Pharmacologic use:**

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

Gonadotropin-Releasing Hormone (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**.

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.
- **Down-regulation:** Reduction in the number of receptors on the surface of the cell either due to endocytosis or inhibition of receptor synthesis.

Recall that agonists cause receptor downregulation, while antagonists cause the opposite (upregulation).

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs - Therapeutic Uses(1):

A. Stimulation:

1. **Female and Male infertility:** Less commonly used, and less convenient method than gonadotropins, because we are not sure whether the gonads and pituitary will response to GnRH.
2. As an "**LH responsiveness test**" to diagnose the cause of **delayed puberty**.

B. Suppression of gonadotropin production by sustained administration:

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.
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.

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs - Therapeutic Uses(2):

B. Suppression of gonadotropin production by sustained administration:

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).

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs - Adverse effects[1]:

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; suppression results in early menopause.
5. **Ovarian cysts.**
6. **Sudden pituitary apoplexy**: Abrupt hemorrhage or infarction (stroke) of the pituitary gland within a pituitary adenoma, leading to **abrupt onset** of severe headache, neck stiffness, visual disturbances, and oculomotor palsies, a presentation that is similar to meningitis.

Gonadotropin-Releasing Hormone (GnRH) & Its Analogs - Adverse effects(2):

7. **Reduced bone density and osteoporosis** can result from decreased sex steroid production, such as declining androgen levels in men. Whereas in females, particularly after menopause, estrogen deficiency is the major contributor to bone loss.
   - In some cases, osteoporosis in males can result from the absence or scarcity of androgen receptors.

GnRH Receptor Antagonists

- **Ganirelix, Cetrorelix** (Synthetic decapeptides [of 10 peptides]):

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

❖ Therapeutic uses:

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

   To induce ovulation and achieve pregnancy, ovarian stimulation is used to promote the development of mature oocytes. However, excessively elevated luteinizing hormone (LH) levels can lead to premature luteinization and early progesterone production, which may impair follicular development and endometrial receptivity. Therefore, GnRH antagonists are used to suppress LH secretion, thereby preventing premature progesterone elevation and premature ovulation.

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.

❖ **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.
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

Therapeutic uses

2. Treatment of advanced prostate cancer:

   In **Androgen-dependent prostate cancer, Degarelix** reduces concentrations of gonadotropins and androgens more rapidly than GnRH agonists and avoids the testosterone surge (tumor flare) seen with GnRH agonist therapy.

GnRH Receptor Antagonists

Adverse effects

1. Nausea and headache are the most common and important.
2. During the treatment of men with prostate cancer, **degarelix** may cause injection-site reactions and may **increase liver enzymes.**
   - Elevation of liver enzymes is **not always due to liver toxicity**. Sometimes it reflects enzyme induction or simple leakage from hepatocytes, not necessarily cellular damage. If they are low, that relates more to liver function.
   - The enzymes mainly indicate the integrity of hepatic cells. Conventionally, however, they are grouped under ***liver function tests.*** True liver function is more directly reflected by synthesis of proteins such as **albumin** and **clotting factors**. So, when you order LFTs, remember they do not all measure the same thing.
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**.
- Excess prolactin secretion, as in prolactin-secreting tumors, in both males and females causes **hyperprolactinemia** → amenorrhea, galactorrhea (milk production from the breast) 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

- Prolactin is regulated by dopamine, and this regulation is mainly inhibitory.
  - ✓ The prolactin-inhibiting hormone/factor is **dopamine**.
- Prolactin is continuously inhibited by dopamine, and when stimulation occurs - for example, breast stimulation during breastfeeding - prolactin secretion increases because dopaminergic inhibition is reduced.
- **Dopamine agonists are used to treat hyperprolactinemia.**
- Adenomas that secrete excess prolactin retain sensitivity to dopamine.
  - Pituitary adenomas are classified as **microadenomas** and **macroadenomas**.
    - Macroadenomas often require surgical management in addition to medical therapy, whereas microadenomas are frequently managed medically.
    - These tumors are not fully regulated by normal endogenous physiological inhibitory mechanisms. For example, prolactin-secreting adenomas exhibit reduced sensitivity to physiological dopaminergic inhibition; however, **pharmacologic dopamine agonists can still effectively suppress prolactin secretion and reduce tumor activity.**

Dopamine Agonists

- Dopamine itself is not used because its half-life in circulation is very short. Clinically, dopamine may be **administered by continuous IV infusion** in selected conditions such as cardiogenic shock, not as routine bolus therapy.
- D2 receptors are the major receptors involved in prolactin inhibition.

❖ Dopamine agonists (D_2 receptor):

1. **Ergot derivatives**: Bromocriptine (prototype), cabergoline, pergolide.
2. **Non-ergot 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. **Infertility treatment**: in women with hyperprolactinemia who wish to become pregnant, dopamine agonists can restore ovulation in ~ 70% of women with microadenomas and ~ 30% of those with macroadenomas.
3. **Acromegaly.**
4. **Parkinsonism.**

Dopamine Agonists

Adverse effects(1)

1. Nausea, vomiting, headache, fatigue and lightheadedness.
2. **Postural (Orthostatic) hypotension**, if suddenly standing upright, blood pressure may fall; dizziness or faintness may occur.
3. **Psychiatric manifestations**, particularly psychosis, can also occur. Psychosis is classically associated with disorders such as schizophrenia.
4. **Erythromelalgia** (paroxysmal throbbing and burning pain in the skin).
5. **Ergots → cold-induced peripheral digital (related to digits) vasospasm.**

   - Ergot derivatives affect smooth muscle in structures such as the GI tract, ureters, gallbladder, and vascular system.

Cold-Induced Peripheral Digital Vasospasm

Why Called Digital?

- Because fingers and toes contain end arteries with limited collateral circulation (**limited anastomoses**). Severe vasospasm can therefore compromise blood flow and may progress to **ischemia** or **necrosis**.

Dopamine Agonists

Adverse effects(2)

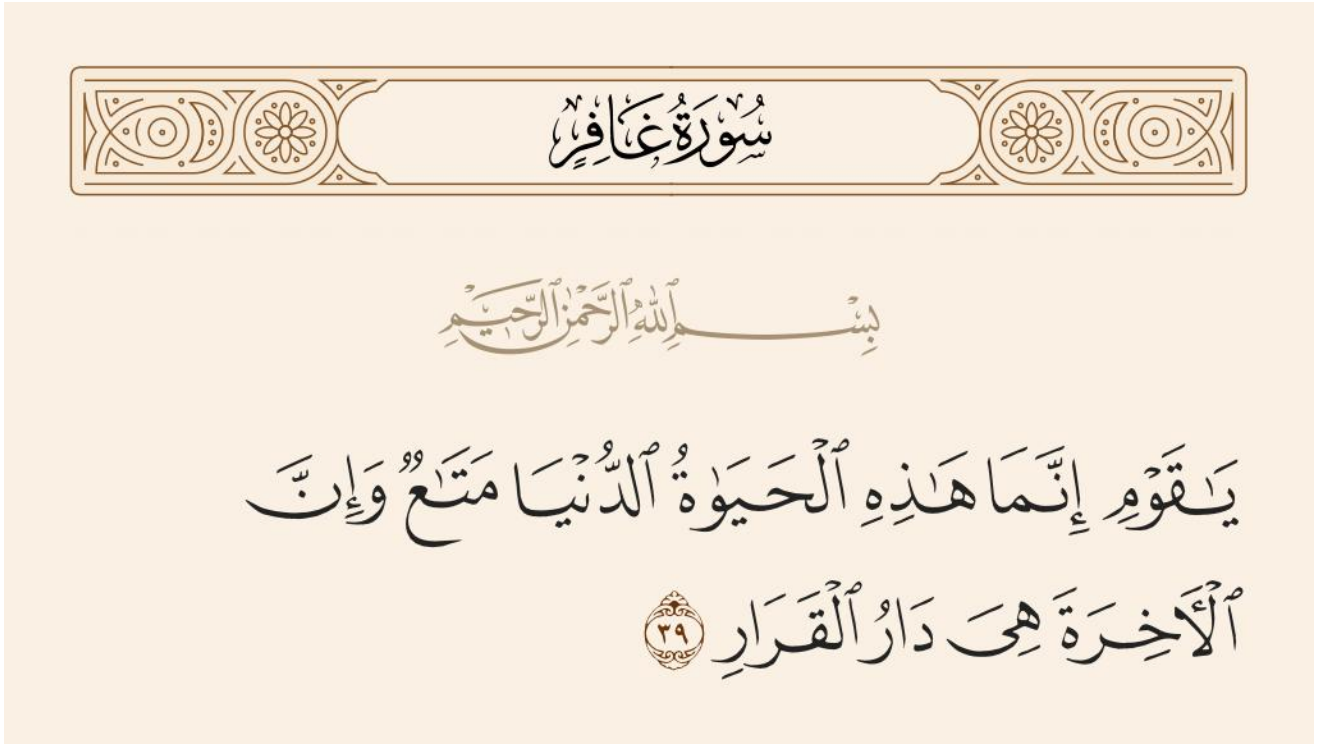
5. Ergot derivatives may also produce **pulmonary infiltrates** with chronic high dose therapy. These infiltrates can progress to **pulmonary fibrosis**.
6. Stroke or coronary thrombosis in postpartum women taking **bromocriptine** to suppress postpartum lactation. Excessive or inappropriate use may be associated with serious vascular adverse effects, including myocardial ischemia and coronary thrombosis. Because of these safety concerns, bromocriptine is generally not used routinely for suppression of lactation and is reserved only for clearly defined medical indications.

PHARMACOLOGY QUIZ LECTURE 9

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



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