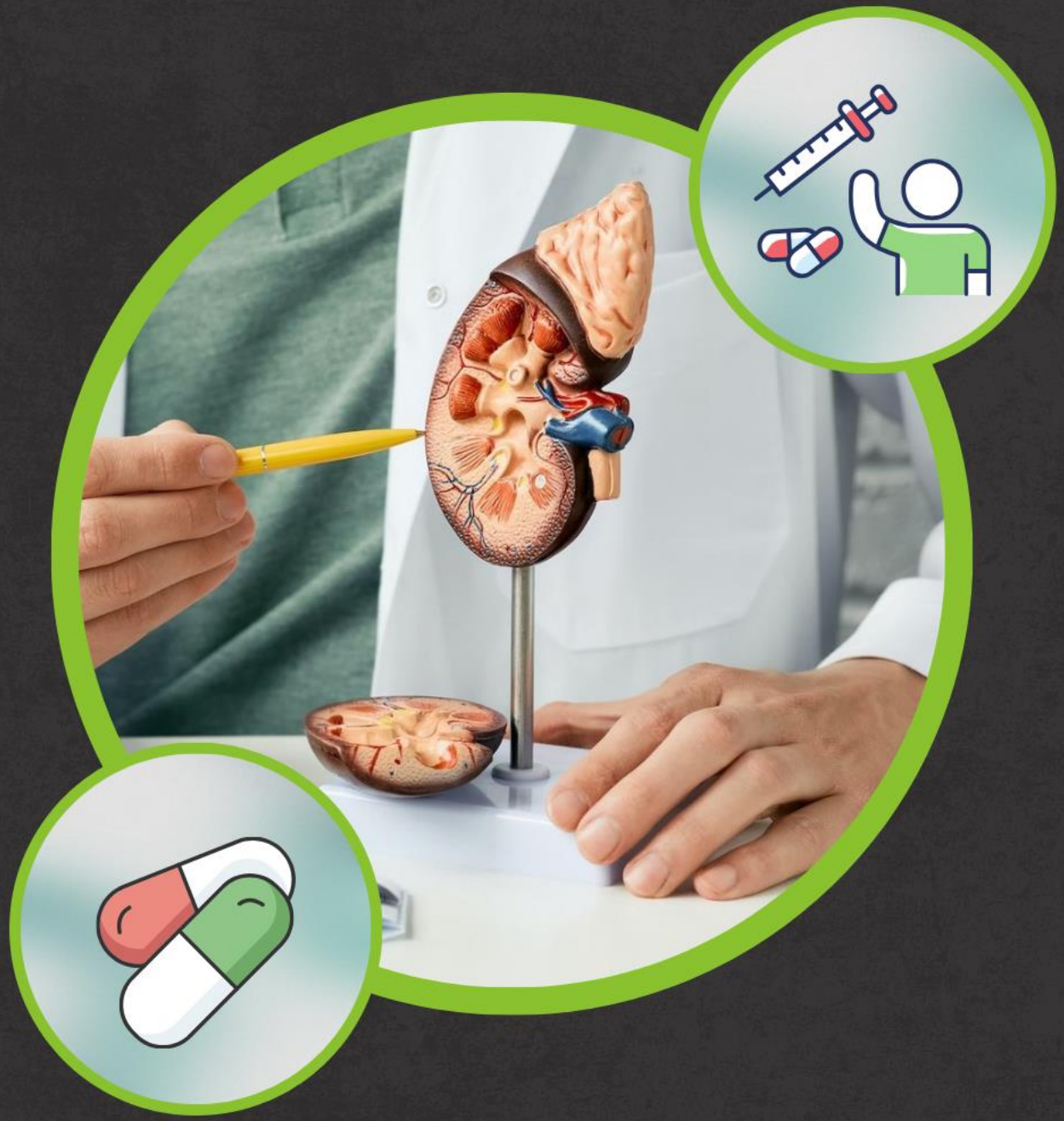

PHARMA

MODIFIED NO. 9

الكُتّاب: صهيب زعيتر و فرح عليان

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The Gonadotropins

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The Gonadotropins From Pituitary

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

The second most important adverse reaction

2. Multiple pregnancies (15-20% of patients receiving gonadotropins vs 1% in natural pregnancies).
3. Headache, depression (hormonal depression), edema.
4. Production of antibodies against hCG.
5. Gynecomastia in males.
6. Possible association with ovarian cancer. Because they increase hormone levels, there is a risk of hormone-dependent cancers.

How can there be production of antibodies against hCG, since it's a human hormone?

- The answer lies in the **preparation process**. We don't always know exactly what happens during production—**contamination can occur**. During the **development, isolation, and purification** stages, the hormone may **not be completely purified**. As a result, **incomplete or altered hormone molecules** may be present, which can **trigger the immune system** to form **antibodies** against them. These antibodies can then also **react with the fully functional hormone**.

- So, just because hCG is human doesn't mean there will be **no antibody response**. It is possible to develop antibodies against it, although this occurs **much less frequently** than with **animal-derived hCG**, which the immune system more easily recognizes as **foreign**. In such cases, an **error in the preparation process** likely led to the development of these antibodies.

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.

This was explained in the previous modified.

- When you say **GnRH acts as both an agonist and an antagonist at its receptors**, it doesn't mean it's a **partial agonist or antagonist**. Instead, the **mode of secretion or administration determines the effect**.

- If GnRH is given in a **pulsatile manner**, it will **stimulate** the release of FSH and LH, mimicking what naturally happens at **specific times during the menstrual cycle**. But if it is given **continuously**—that is, **sustained and non-pulsatile**—it will actually **inhibit** the release of FSH and LH.

- This distinction is **very important** and applies to **agonists as well**.

(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.**

This means that we don't just use any analog—we must use the appropriate analog based on the specific condition we are treating.

(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.**

Here, we are talking about **gonadorelin**. It may be **similar to other GnRH analogs**, but it is **not exactly the same**.

- When we talk about **low and high pulse frequencies** in the context of **GnRH secretion**, we're referring to **how often** GnRH is released from the hypothalamus into the pituitary over a period of time.

Here's what it means:
- **Low pulse frequency** = GnRH is released **less often** (e.g., one pulse every few hours).
- **High pulse frequency** = GnRH is released **more often** (e.g., one pulse every 30–60 minutes).

Why this matters:
- **Low-frequency GnRH pulses** preferentially stimulate the release of **FSH**.
- **High-frequency GnRH pulses** preferentially stimulate the release of **LH**.

- This difference is **crucial in regulating the menstrual cycle** and **reproductive function**, as the **timing and balance** between LH and FSH affect things like **follicular development, ovulation, and hormone production**.

So, "high" and "low" refer to the **rate of GnRH release over time**, not the hormone quantity or strength of the signal.

(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.**

Agonist effect

(GnRH) & Its Analogs

Antagonist effect

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.**

Decreases their own concentration in the cell.

(GnRH) & Its Analogs

Therapeutic Uses:

A. Stimulation: Agonistic Action

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.** **See next slide**

- **Puberty in children is expected to occur within a specific age range**, but sometimes it may be **slightly delayed**. This can lead to **psychological consequences**, depending on whether the delay is **temporary or ongoing**.

- **Delayed puberty** means that puberty will still occur, but **at a later age**, and then proceed normally. For example, if puberty is expected around **age 14**, delayed puberty means it may happen at **15 or 16**, but still follow a **normal progression** afterward. This delay can have both **physiological and psychological effects** on the individual.

- To determine the cause, we use the **LH responsiveness test**, which helps identify **where the problem lies**. We measure levels of all relevant hormones: **GnRH, gonadotropins, and sex steroids** (such as **estrogen in females** and **testosterone in males**). Then, we administer **GnRH derivatives or agonists** and observe the response.

- If **sex steroid levels increase**, it suggests that the **sex organs are functioning properly**, and the problem lies **higher up**—in the **pituitary or hypothalamus**.
- If **sex steroid levels do not increase**, the issue is likely in the **end organs**—the **ovaries or testes**.

So, this is primarily a **diagnostic test**, **not a therapeutic use**. However, if we follow the formal **definition of a drug**—"a chemical substance used to **prevent, treat, or diagnose disease**"—then in such cases, **diagnosis itself qualifies as a drug use**.

(GnRH) & Its Analogs

B. Suppression of gonadotropin production: Antagonistic Action

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.**

- When we perform **ovarian stimulation**, there is a risk of **hyperstimulation**. We are particularly concerned about **LH causing premature ovulation**, which can lead to **fertilization failure**, as ovulation would occur **before the optimal time**.
- To prevent this, **GnRH analogs are used to suppress gonadotropin production**, thereby **preventing the endogenous LH surge**.

(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.

If GnRH analogs are given in a way that **blocks** their effect, they can also **reduce the growth of leiomyomas**.

4. Central (pituitary or hypothalamic) precocious puberty (onset of secondary sex characteristics before 8 years in girls and 9 years in boys).

The issue is **not peripheral**—not in the ovaries or testes directly—but rather in the **pituitary and hypothalamus**

(GnRH) & Its Analogs

Adverse effects:

1. **Headache, light-headedness, nausea and flushing .**
2. **Local swelling at injections site. > Inflammation, because these are analogs .**
3. **Hypersensitivity reactions: bronchospasm , laryngeospasms and anaphylaxis.**
4. **The syndrome of menopause in women. (bc they block estrogen)**
5. **Ovarian cysts.**

(GnRH) & Its Analogs

6. **Sudden pituitary apoplexy: Abrupt hemorrhage or infarction of the pituitary gland within a pituitary adenoma (could be in the pituitary itself), leading to abrupt onset of severe headache, neck stiffness, visual disturbances (vision loss) and oculomotor palsies.**

7. **Reduced bone density and osteoporosis.**

GnRH Receptor Antagonists only (can't be agonist (partial) , they are not analogs)

Ganirelix, Cetrorelix (Synthetic decapeptides):

- **They inhibit FSH and LH secretion in a dose-dependent manner. (they don't cause stimulation)**

Therapeutic uses:

A . 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. (these are the advantages of GnRH receptor antagonist)**

- **Their use can be delayed until day 6–8 of the in vitro fertilization cycle.**

GnRH Receptor Antagonists

On the other hand: (disadvantages)

1. **Adherence to treatment regimen is more critical because effect reverses quickly after discontinuation.** إذا ما التزم المريض بأخذ الدواء ، ما بكون اله فائدة

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.**

- Generally speaking, their only advantage, is that their action is immediate

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.** **(they prevent the LH surge thus suppressing testosterone)**

- Prostate cancer requires a treatment that suppresses androgens

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. (menopause in males, somehow)**

- If the liver enzymes are 3 times more than normal , then there might be a problem with the liver function , and you have to stop the drug .

Prolactin

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 (also in women) 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.** (We can't use dopamine bc it has a short half life , so we use its agonist)
- **Adenomas that secrete excess prolactin retain sensitivity to dopamine.**

- The endogenous regulator of prolactin release >> dopamine
- Gonadotropins (and GnRH) inhibiting hormones >> estrogen and androgens
- (By the negative feedback loop inhibition)

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 hyperprolactinemic women) 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.** Psychosis due to excess dopamine
4. **Erythromelalgia (paroxysmal (attacks) throbbing and burning pain in the skin).**

Dopamine Agonists

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

دَبَبْتُ للمجدِ والساعون قد بلغوا جَهْدَ النفوس وألقَوا دونه الأُزُرا
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VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!