GENITOURINARY SYSTEM

SUBJECT : Pharmacology

LEC NO. : "4"

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Genitourinary System Module

Pharmacology

Female Sex Hormones

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Menstrual cycle: Highlights

The cycle is divided into

follicular or proliferative phase, the developing ovarian *follicle* produces most of the gonadal hormones, which stimulate cellular *proliferation* of the endometrium.

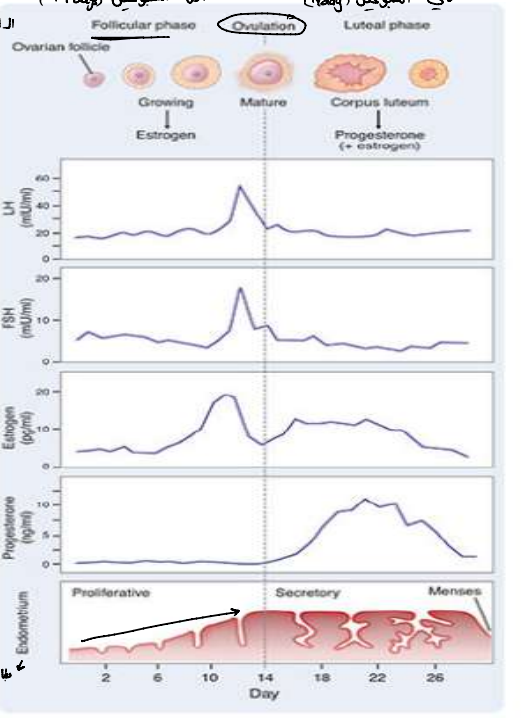
the luteal or secretory phase, the corpus luteum produces progesterone, and the endometrium becomes *secretory* rather than proliferative.

Ovulation occurs at the midportion (about day 14) of each cycle.

At the start of the menstrual cycle: low production of estrogen results in release of FSH and LH from pituitary gland, this stimulate maturation of four to six follicles, each containing an ovum. After 5 or 6 days the dominant follicle develop more rapidly, and releases estrogen in increasing rates. Initial partial suppression of FSH and LH results in other follicles to be atretic, only one follicle matures. Increased estrogen stimulate endometrium proliferation.

Dominant follicle release estrogen, mid cycle surge of FH and LH causes the follicle to rupture and release the ovum into fallopian tube (ovulation).

Corpus luteum (life span of around 14 days) secrets both estrogen and progesterone. Causing the endometrium to switch to a secretory phase. (increase protein synthesis and blood supply). if pregnancy does not occur, the corpus luteum begins to degenerate and ceases hormone production. The endometrium, is shed (menstruation). FSH and LH increase again, new cycle starts.



* هلا في بداية الـ cycle بتكون نسبة الـ estrogen و الـ progesterone قليلة هاد الذي ليؤدي إلى تحفيز الـ Anterior pituitary gland انها تفرز لي gonadal hormone اللي هما LH و FSH

* بعدين الـ Follicular stimulating hormone يؤدي إلى تحفيز الـ follicle الموجودين بالـ ovary انو يصيرلها developed

* بعدين بيلش الـ follicle تكبر بسرعة لحد ما توصل لحد انو وحدة منهم بس اللي بتكون the dominant follicle وبيلش يصير عنا زيادة في انتاج الـ estrogen

* زيادة تصنيع الـ estrogen في البداية ليؤدي إلى نقصان الـ level الـ FSH و الـ LH و هلا تقل كمية الـ FSH و الـ LH رح يصير الـ degenerated الـ other follicles (اللي ما تحولو لـ domaine)

* بعدين الـ peak الـ estrogen بكون اعلى اشي قبل evaluation (قبل منتصف الـ cycle) بعد فترة من وصول الـ estrogen الـ peak رح يصير عندي زيادة بالـ FSH و الـ LH تدفع الـ dominant follicle انها تكبر اكتر ويصير بعد فترة rupture بالـ follicle وتطلع الـ Ovum من الـ Fallopian tube هيك بتكون خلصنا الـ Follicular phase

* بعد الـ follicular phase بصير عندي الـ ovulation وبعديها بيلش بالـ secretory phase

* ليش في عنا secretory phase ؟ انو لما طلعت الـ ovum من الـ follicle باقي الـ follicle ما كبيناها وتجمعت وصار اسمها corpus luteum

* بعدين بصير عندي زيادة في إفراز الـ progesterone وزيادة افرازه بتزيد سُمك بطانة الرحم endometrium وتخليها thick وتسمى مي الـ phase

لـ ١٤ يوم مازا ما صار حمل بيلش الـ corpus luteum يصيرله degenerate ويرجع الـ estrogen و الـ progesterone للبداية وبيلش cycle جديدة

(الدكتورة حكت نرجع لـ physiology بهاد الموضوع وانو هاد بس overview)

Estrogen

- The major estrogens produced by women are estradiol, estrone, and estriol.
- **Estradiol** is the major secretory product of the ovary and most potent estrogen. Principal estrogen in premenopausal women. A minute amount of estradiol is synthesized in the testes.
- Most **estrone** and **estriol** are formed in the liver from estradiol or in peripheral tissues from androgens precursors.
- **Estrone** is the primary circulating estrogen after menopause, and estriol, is present in significant amounts during pregnancy, because it is synthesized by the placenta.
- First-pass metabolism in the gastrointestinal tract rapidly breaks down estradiol tablets before entering the systemic circulation. The bioavailability of oral estrogens is said to be 2-10% due to significant first-pass effects.

Synthetic Estrogens

- A variety of chemical alterations have been applied to the natural estrogens to increase their oral effectiveness.
- The esterification of estradiol improves the administration (such as with **estradiol valerate**) or to sustain release from intramuscular depot injections (including **estradiol cypionate**) via higher lipophilicity. After absorption, the esters are cleaved, which leads to the release of estradiol.

* بتخزن بال lipid

- **Ethinylestradiol (EE)** is a synthetic form of estradiol commonly used as the estrogenic component of most combination oral contraceptive pills. Ethinyl estradiol is different from estradiol due to its higher bioavailability and increased resistance to metabolism, rendering it more suitable for oral administration.

↑ more stable يعني *

- A variety of nonsteroidal compounds with estrogenic activity have been synthesized and used clinically. These include dienestrol, diethylstilbestrol, and chlorotrianisene.

Estrogen uses

* الـ major uses كلاو هو الـ Contraceptive Pill

1. **Primary Hypogonadism**

➢ Hypogonadism in females describes the inadequate function of the ovaries, with impaired production of germ cells and sex hormones (estrogen and progesterone).

➢ Treatment of primary hypogonadism is usually begun at 11–13 years of age in order to stimulate the development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis, and to avoid the psychological consequences of delayed puberty and estrogen deficiency.

start treatment at Puberty

* ليش بنعطيه ؟ (1) (2) (3)

➢ Treatment attempts to mimic the physiology of puberty. It is initiated with small doses of estrogen is slowly increased to adult doses and then maintained until the age of menopause (approximately 51 years of age**). A progestin is added after the first uterine bleeding**. When growth is completed, chronic therapy consists mainly of the administration of adult doses of both estrogens and progestins.

* بنبلش بـ doses صغيرة وبعدين بزيدها

Period

* عشان نتفادى أي اعراض عن زيادة الـ estrogen اول ما بيجي الـ Period الـ female بنعطيها progesterone

Estrogen uses

1. **Postmenopausal Hormonal Therapy**

➢ Menapause signs:

- Symptoms that follow closely upon the cessation of normal ovarian function include:

estrogen deficiency نتيجة الـ

loss of menstrual periods, vasomotor symptoms (hot flashes), sleep disturbances, and genital atrophy.

① ② Cardiac sclerosis دحدة من العوامل اللي تؤدي إلى

- Longer-lasting changes : acceleration of bone loss, lipid changes (rise in plasma cholesterol and LDL), which may contribute to the③acceleration of atherosclerotic cardiovascular disease noted in postmenopausal women.

Postmenopausal Hormonal Therapy

- The primary indication is relief of menopausal symptoms, such as hot flashes, vaginal atrophy and dryness, insomnia and urinary urgency
- If the main indication for therapy is **hot flashes and sleep disturbances**, therapy with the lowest dose of estrogen required for symptomatic relief is recommended. Treatment may be required for only a limited period of time and the possible increased risk for breast cancer is avoided.
- In case of premature menopause (before the age of 40) or early menopause (before the age of 45), it's particularly important to begin therapy as soon as possible for maximum protection against osteoporosis
- Patients with **mild atrophic vaginitis** can be treated with **topical preparations**. The vaginal route of application is also useful in the treatment of urinary tract symptoms in these patients
- The administration of an opposed estrogen is associated with an increased risk of endometrial carcinoma. However, progesterone antagonize the beneficial effect of esterogen on lipid.
- For women with an **intact uterus**, a progestogen is included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with estrogen alone. Women who have undergone a **hysterectomy** may use estrogen alone.

Estrogen uses

1. Suppression of ovulation

- Estrogens combined with progestins can be used to suppress ovulation in patients with intractable dysmenorrhea (moderate to severe pain caused by menstrual periods).
- or treatment of hirsutism (growth of excessive male-pattern hair in women after puberty) and amenorrhea (absence of menstruation) due to excessive secretion of androgens by the ovary.

Estrogen side effects

1. Uterine Bleeding:

Estrogen therapy is a major cause of postmenopausal uterine bleeding. To avoid confusion with carcinomas, patients should be treated with the smallest amount of estrogen possible. It should be given cyclically so that bleeding, if it occurs, will be more likely to occur during the withdrawal period.

لو انو نعطي المريضة الدوا
لفترة بعدين نوقف الدوا
بعدين نرجع نعطيها اياه مرة
ثانيه

(علة اجت المريضة تشكي من
الـbleeding بس وقفت الدوا صار
عادي اما لو اجت تشكي من
bleeding وهي تستخدمو فيلد
(carcinoma على
or serious disease

2. Estrogen increases the risk of both arterial and venous thrombosis
3. Cancer: breast cancer and endometrial carcinoma
4. breast tenderness (mild)
5. Hyperpigmentation. (mild)
6. increase in frequency of migraine headaches
7. Cholestasis: flow of bile from the liver is slowed or blocked
8. hypertension.

يعني عنا تجمع بال bile duct
ويؤدي اي تجمع الـbile لل liver

selective estrogen receptor modulator (SERM): Tamoxifen

agonist ↔ antagonist → both receptor

- Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor, was the first selective estrogen receptor modulator (SERM) to be introduced. The mechanism of its mixed agonist/antagonist is still not completely understood.
- Tamoxifen is indicated for the treatment of breast cancer in a variety of settings
- patients with estrogen receptor-positive tumors are more likely to benefit from tamoxifen
- in the breast tissue, it competes with estrogen for binding sites and causes antiestrogenic and antitumor effects. In bone, it stimulates estrogen receptors instead of blocking them, exerting an estrogenic agonist effect, and may prevent osteoporosis in postmenopausal women. It also acts as an estrogen agonist in the hypothalamus of premenopausal women, which increases gonadotropin levels and can induce ovulation

Tamoxifen- Uses

- Treatment of breast cancer in both females and males.
- Adjuvant treatment of breast cancer after patients have completed their primary treatment with surgery and radiation.
- Treatment of female patients with ductal carcinoma in situ (non-invasive breast cancer) after surgery and radiation to reduce the risk of invasive breast cancer.
- Chemoprevention of breast cancer in high-risk women

Tamoxifen-side effects

- Associated with increased incidence of uterine or endometrial cancers. In patients who were already diagnosed with breast cancer, however, the benefits outweigh the risks.
- Hot flashes, irregular periods, and vaginal discharge, nausea and vomiting.
- Increase risk of pulmonary embolism, and stroke.
- For patients taking tamoxifen for breast cancer risk reduction, it should be avoided if the patient has a history of deep vein thrombosis (DVT) or pulmonary embolism (PE). In patients that have been diagnosed with breast cancer, the benefits outweigh the risks, but it should still be used with caution in patients with a history of thromboembolic events.

SERM: Raloxifene

- Partial estrogen agonist-antagonist at some but not all target tissues.
- It has estrogenic effects on lipids and bone but appears not to stimulate the endometrium or breast.
- **Uses**: prevention of postmenopausal osteoporosis and prophylaxis of breast cancer in women with risk factors.
- **Side effects**: hot flashes, leg cramps, and increases the risk of deep-vein thrombosis and pulmonary embolism.

Progesterone

➢ Progesterone is the most important progestin in humans. It is synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy.

➢ **Effects:**

- Favors fat deposition
- Increases basal insulin levels and the insulin response to glucose.
- Compete with aldosterone for the at renal tubule, causing a decrease in Na+ reabsorption.
- Increases body temperature in humans.
- Prepares the uterus for implantation of the fertilized ovum.
- Inhibit uterine contraction that would expel the fetus.
- -ve feed back effect on luteinizing hormone so, block ovulation.
- Thick cervical secretion so, block sperm penetration.

بمعنى صعب يصل fertilization

Progesterone uses

- Primary use in HRT and contraception
- Amenorrhea (abscense of periodes), either primary or secondary
- Assisted reproductive technology treatment to enhance embryo implantation and decrease the risk of miscarriage.
- Endometrial hyperplasia

الزراعة خارج الرحم مثل الأطفال الأنابيب

Anti progesterone: MIFEPRISTONE

- Mifepristone works by being an antagonist of glucocorticoid and progesterone receptors
- Mifepristone has two main FDA-approved indications.:

1. pregnancy termination combined with misoprostol through ten weeks gestation
2. management and treatment of hyperglycemia in patients exhibiting signs of Cushing syndrome.

Side effects: anaphylactic reactions, toxic epidermal necrolysis, peripheral edema, hypertension, hypoglycemia, vaginal bleeding, uterine contractions, nausea, abdominal pain, fever, vomiting.