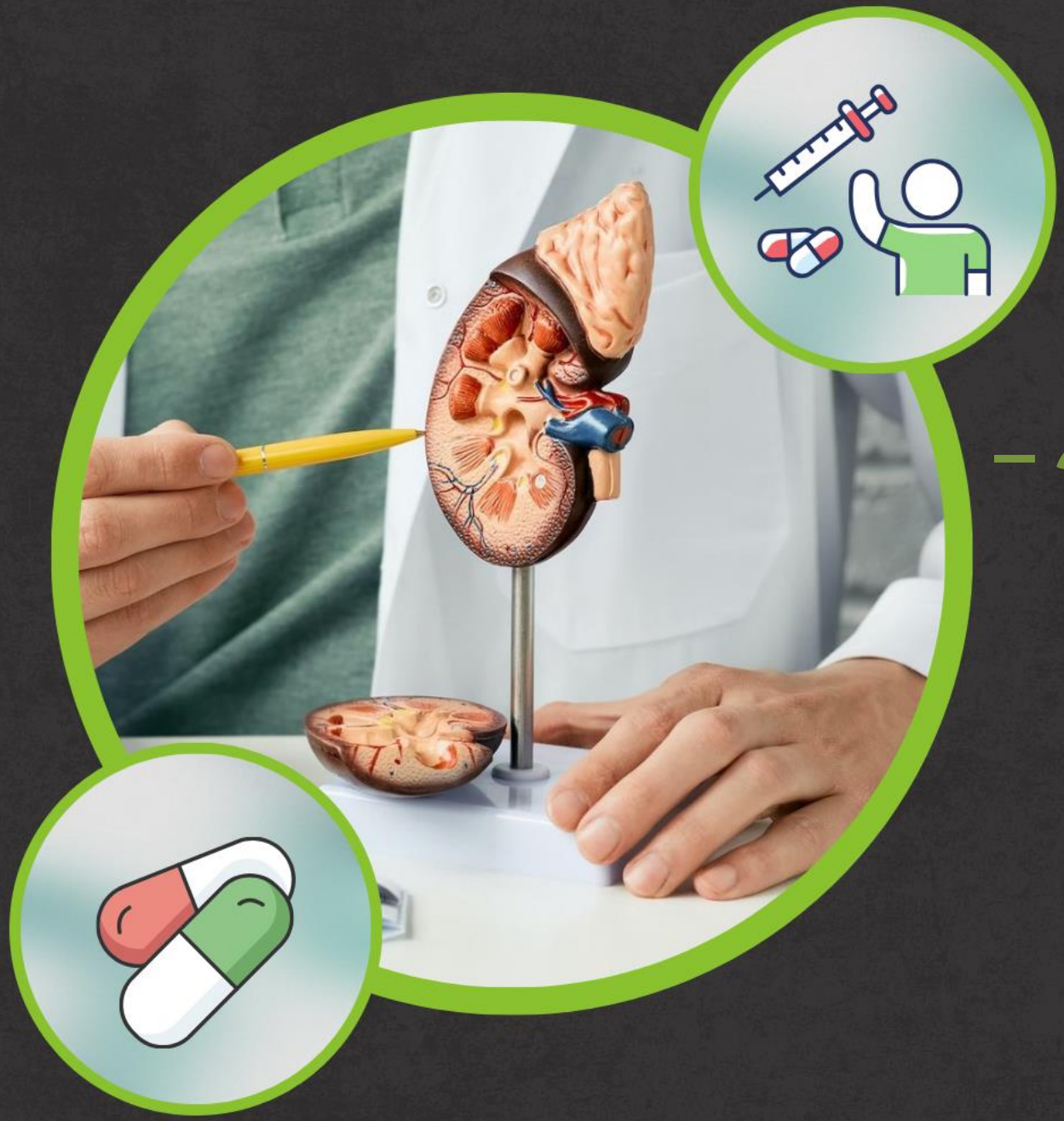

PHARMA

MODIFIED NO. 7

الكُتّاب: محمود جرادات - بشار جادالله – أحمد مطارنة

المدققين: تم التدقيق

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The Gonadal Hormones & Inhibitors

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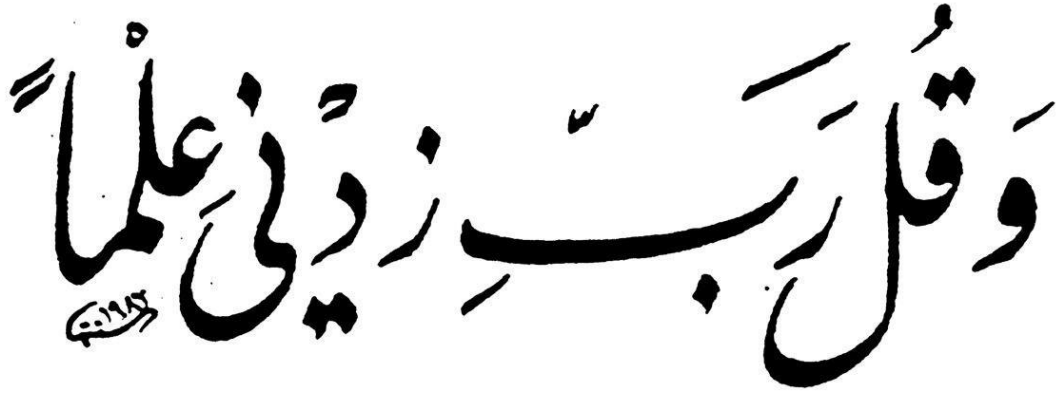

Color code

- Slides
- Doctor
- Additional info
- Important

Estrogens

- **The major estrogens produced by women are estradiol, estrone and estriol.**
- **Estradiol is the major secretary product of the ovary.**
- **Most estrone and estriol are formed in the liver from estradiol, or in peripheral tissues from androstenedione and other androgens, these are not useful to be given to the patient because they undergo to rapid first pass and they have short half life so they will be destroyed .**

Estrogens

Synthetic estrogens:

1. **Steroidal: Ethinyl estradiol, mestranol.**
2. **Nonsteroidal: drugs that have estrogenic activity**

- **These compounds, in contrast to natural estrogens, are orally effective.**

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Estrogens

Pharmacokinetics:

- **Estradiol in the circulation binds to sex hormone-binding globulin (SHBG, an α_2 -globulin) and albumin with lower affinity.**
- **Estrogens hydroxylated derivatives and conjugated metabolites are excreted in bile , and reabsorbed after hydrolysis within the gut.**
- **Estrogens are excreted in small amounts in breast milk.**
- Biliary excretion is used for large molecular weight compounds because it is an active process, while renal excretion deals with smaller molecules and often occurs through passive mechanisms.

The kidney uses both passive and active mechanisms for drug excretion, whereas biliary excretion is primarily active.

In the lumen of the GI tract, the normal flora hydrolyzes conjugated drug metabolites (e.g., glucuronides), allowing them to be reabsorbed. This reabsorption can prolong the drug's duration of action.

Drugs that eradicate the normal flora can lead to oral contraceptive failure due to:

Reduced hydrolysis of excreted conjugates, resulting in decreased reabsorption and lower circulating levels of the active drug.

Induction of hepatic enzymes, which increases the metabolism of the contraceptive drug (a drug-drug interaction).

- Induction: is the stimulation of the synthesis of the enzyme at the gene level

Estrogens

Therapeutic uses:

1. **Primary hypogonadism: Replacement therapy for estrogen deficient patients is usually begun at 11-13 years of age in order to stimulate development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis, and to improve psychology of the patient.**

Estrogens

2. **Postmenopausal hormonal therapy (hormonal replacement therapy [HRT]).**

- **It has a beneficial effect on circulating lipids and lipoproteins.**
- **No cardiovascular benefit from estrogen plus progestin replacement in perimenopausal or postmenopausal women.**
- **There have been an increased risk of breast and endometrial cancer in patients receiving HRT.**

- Postmenopausal symptoms: flushing, tachycardia, ischemic heart disease, hypertension and psychological symptoms.so if they take replacement therapy some of these symptoms disappear.

- The clinical studies don’t recommend the usage of HRT because of there adverse reactions.
- Estrogen is protective against cardiovascular disease.

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Estrogens

- **Therefore, routine HRT in postmenopausal women is currently not recommended.**
- **HRT may be beneficial in young women with premature menopause.**

Estrogens

- **For prevention of osteoporosis, estrogen can be used with the addition of calcium supplements and vitamin D.**
- **This may be associated with an increased risk of endometrial carcinoma, which can be prevented by the addition of progestin (**Causes complete sloughing of the endometrium and prevents progression to endometrial cancer).

Estrogens

3. Other uses:

Estrogens combined with progestins can be used to:

A. suppress ovulation in patients with intractable dysmenorrhea (difficult or painful menses).

B. suppress ovarian function in treatment of hirsuitism and amenorrhea due to excessive secretion of androgens by the ovary.

In polycystic ovary disease androgens are secreted by the ovaries, they are not coming from external sources. Although the amount of androgen produced is not very high, female tissues are particularly sensitive to it. This sensitivity is evident, for example, in the development of acne. There is an increase in androgen production, not in excessive amounts, but enough to have an effect due to the heightened sensitivity of certain tissues, like the sebaceous glands. Even a small amount of androgen can have noticeable effects in females. .

If you suppress ovarian function, you reduce the production of both androgens and estrogens. This suppression can help improve symptoms such as hirsutism or amenorrhea.

In treating women with polycystic ovary disease, we often prescribe metformin, which improves insulin sensitivity and can help restore ovulatory cycles. In some cases, estrogen can also be given to help regulate menstrual cycles and reduce androgen effects.

Estrogens

Adverse effects:

1. **Uterine bleeding,** due to endometrial thickening and irregular sloughing. The bleeding may become continuous or unpredictable.
2. **Breast cancer**
3. **Endometrial carcinoma**
4. **Infertility, ectopic pregnancy and premature delivery,** linked to dysovulation.
5. **Breast tenderness,** due to increased growth of breast tissue, which can become painful.
6. **Hyperpigmentation** (in specific areas of skin)

Estrogens

7. **Migraine headache**
8. **Cholestasis and gallbladder disease** (even cholelithiasis)
9. **Hypertension** (related to sodium & water retention)

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يَوۡمَ يَقُومُ ٱلۡحِسَابُ ﴿٤١﴾

Estrogens

Contraindications:

1. **Estrogen-dependent neoplasms: endometrium and breast.**
2. **Avoid in patients with undiagnosed vaginal bleeding, liver disease and history of thromboembolic disorders.** (due to estrogen increasing some clotting factors)
3. **Avoid in heavy smokers.**

Progestins

- **Natural progestins: Progesterone, can't be given orally, so we use derivatives.**

- **Progesterone derivatives (chemically modified): Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate**

Progestins

- **Synthetic progestins:**

A. 17-ethinyl testosterone derivatives:

Dimethisterone

B. 19-nortestosterone derivatives:

Desogestrel, Norethynodrel, Norethindrone, L-norgestrel.

Note: Both A and B classes are derived from androgens.

Progestins

Pharmacokinetics:

- **Progesterone is rapidly absorbed after administration.**
- **Undergoes extensive first pass metabolism and excreted in urine as pregnanediol glucuronide.**
- **t½ in plasma is approximately 5 minutes** ,meaning that after 5 minutes, half of the drug is eliminated; after 10 minutes, only a quarter remains; by 20 minutes, the drug is essentially cleared from circulation, because of this fast drop in concentration, natural progesterone is not effective and not given orally.
- **Most of synthetic agents are also metabolized extensively to inactive products that are excreted mainly in urine,** but they still manage to attain therapeutic concentrations.

TABLE 40–2 Properties of some progestational agents.

	Route	Duration of Action	Activities[1]				
			Estrogenic	*Androgenic*	*Antiestrogenic*	*Antiandrogenic*	*Anabolic*
Progesterone and derivatives							
Progesterone	IM	1 day	–	–	+	–	–
Hydroxyprogesterone caproate	IM	8–14 days	sl	sl	–	–	–
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks	–	+	+	–	–
Megestrol acetate	PO	1–3 days	–	+	–	+	–
17-Ethinyl testosterone derivatives							
Dimethisterone	PO	1–3 days	–	–	sl	–	–
19-Nortestosterone derivatives							
Desogestrel	PO	1–3 days	–	–	–	–	–
Norethynodrel[2]	PO	1–3 days	+	–	–	–	–
Lynestrenol[3]	PO	1–3 days	+	+	–	–	+
Norethindrone[2]	PO	1–3 days	sl	+	+	–	+
Norethindrone acetate[2]	PO	1–3 days	sl	+	+	–	+
Ethynodiol diacetate[2]	PO	1–3 days	sl	+	+	–	–
L-Norgestrel[2]	PO	1–3 days	–	+	+	–	+

[1] **Interpretation:** + = active; – = inactive; sl = slightly active. Activities have been reported in various species using various end points and may not apply to humans.

- This table shows the routes of administration, duration of action, and most importantly, the hormonal activities (estrogenic, androgenic, antiestrogenic, antiandrogenic, anabolic) of various progestins.
- Not all progestins are the same.
- Progestins with estrogenic activity: Norethynodrel, Lynestrenol
- Progestins with androgenic activity (7): Medroxyprogesterone acetate, Megestrol acetate, Lynestrenol, Norethindrone, Norethindrone acetate, Ethynodiol diacetate, L-norgestrel
- Progestins with antiestrogenic activity (6): Progesterone, Medroxyprogesterone acetate, Norethindrone, Norethindrone acetate, Ethynodiol diacetate, L-norgestrel
- Progestin with antiandrogenic activity (1): Megestrol acetate
- Progestins with anabolic properties (4): Lynestrenol, Norethindrone, Norethindrone acetate, L-norgestrel
- This variation is critical when prescribing: giving a female a progestin with androgenic or anabolic effects may lead to unwanted side effects.
- Doctors should be aware of these properties before choosing a progestin, especially for purposes like oral contraceptives. This isn't something to leave to chance or pharmacy suggestions — it requires a personalized, evidence-based prescription.
- These differences in hormonal activity also explain why different progestins can have different side effects — like acne, weight changes, mood swings — depending on whether they have androgenic, estrogenic, or other hormonal actions.

- **If you don't understand the hormone properties, you won't succeed in treating the patient properly.**

Progestins

- **Progestins without androgenic activity include Progesterone, dimethisterone, desogestrel, norgestimate, gestodene, norethynodrel.**

Which of the following progestins does NOT have androgenic activity?
A. Norethindrone
B. L-norgestrel
C. Desogestrel
D. Megestrol acetate
→ Answer: C. Desogestrel

This is the type of the exam questions about this lecture: "A drug with/out Androgenic/estrogenic...etc effect is:"

Progestins

The doctor read all the slide

Therapeutic uses:

1. **Hormonal replacement therapy.** (not recommended)
2. **Hormonal contraception.** (in combination with estrogen)
3. **To produce long-term ovarian suppression → prolonged anovulation and amenorrhea. This therapy has been employed in the treatment of dysmenorrhea, endometriosis and bleeding disorders when estrogens are contraindicated.**

Progestins

The doctor read all the slide

Adverse effects:

1. Elevation of blood pressure.
2. Reduce plasma HDL levels (androgenic progestins).
3. Enhance effects of estrogen on breast cancer risk in postmenopausal women.

Estrogen and Progesterone Inhibitors and Antagonists

Why would we give estrogen antagonists?

- To treat **estrogen-sensitive tumors.**

Tamoxifen and Related Drugs

The doctor read all the slide

- Is a competitive partial agonist / antagonist at estrogen receptors.
- The first selective estrogen receptor modulator (SERM) discovered.
- It is extensively used in the palliative treatment of breast cancer in postmenopausal women.
- It is a nonsteroidal agent that is given orally.

Tamoxifen and Related Drugs

- **Prevents -osteoporosis- loss of lumbar spine bone density, changes in plasma lipid levels and risk for atherosclerosis after menopause.** (The drug works here as partial antagonist)
- **This treatment may increase risk of endometrial cancer.** (The drug works here as partial agonist)

The reason "lumbar spine" is specifically mentioned is because that's where clinical studies most consistently observed bone density preservation with tamoxifen use.

Adverse effects:

- **Most common: Hot flushes and nausea in 25% of patients.**

Tamoxifen and Related Drugs

The doctor read all the slide

- **Toremifene** is structurally similar with similar properties, indications and toxicities.
- **Raloxifene** is similar at some but not all estrogen receptors.
- It has similar effects on lipid and bone, **but does not stimulate endometrium or breast**. (doesn't cause cancer)
- It is indicated for **prevention of postmenopausal osteoporosis**. (not first-line nor second or third)

Mifepristone

- **19-norsteroid.**
- **Strong progesterone receptor blocker**
- **Has luteolytic properties when given in mid-luteal period → contraceptive effect.**
- **It is an emergency post-coital contraceptive.**
- **Acts also as an antagonist at glucocorticoid receptors.**

- Although this drug has valid emergency uses, it is **not permitted for abortion use in Jordan** except in very limited cases — such as when continuing the pregnancy poses a danger to the mother's life, and with approval from trusted, authorized physicians.

Mifepristone

- **May be useful in treatment of endometriosis, Cushing's syndrome, breast cancer, and neoplasms that contain glucocorticoid or progesterone receptors such as meningiomas.** (But no need for it, we already have treatment for those)

  Adverse effects: prolonged bleeding, abdominal or pelvic pain, nausea and vomiting.

Danazol

- **It is a 17α-ethinyltestosterone derivative.**
- **Has weak progestational, androgenic and glucocorticoid activities.**
- **It suppresses ovarian function by inhibiting the mid-cycle surge of LH and FSH, but does not have significant effect on basal FSH and LH in normal women.**

- Suppresses Ovulation and gonadal function

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Danazol

Therpeutic uses:

- **Endometriosis: It inhibits gonadal function.**

  - Endometriosis is a chronic medical condition where tissue similar to the lining of the uterus (endometrium) grows outside the uterus. This tissue is ectopic, can be found on the abdomen, peritoneum cavity, surfaces of viscera, causing bleeding and pain, particularly bleeding in the peritoneum is very painful and to suppress that we suppress ovarian function

- **Fibrocystic disease of the breast**
- **Adverse effects:**
- **Weight gain,** resulted from **edema** (sodium and water retention)
- **Decreased breast size** (antiestrogen effect)
- **Acne and oily skin** (androgenic effect)
- **Increased hair growth** (over growth in places with little hair)

Danazol

- **Deepening of voice**
- **Hot flushes,**
- **Changes in libido**
- **Contraindicated in pregnancy and breast feeding as it may produce urogenital abnormalities in the offspring.**
- breast feeding may be toxic to the male and particularly the female fetus

Aromatase Inhibitors

Anastrozole, Fadrozole.

- **May be useful in women whose breast cancer has become resistant to tamoxifen.**
- **May be employed as adjuncts to androgen antagonists in the treatment of precocious puberty, and primary treatment in the excessive aromatase syndrome.**

Fulvestrant

- **Is a pure estrogen receptor antagonist.**
- **May be useful in breast cancer patients who have become resistant to tamoxifen.**

- Not the drug of choice !
- the drug of choice are **Aromatase Inhibitors**

Antiandrogens

- Work against prostate

A. Androgen Receptor blockers:

1. Flutamide:

- Is a substituted anilide
- Potent antiandrogen. (small doses needed)
- Used for treatment of prostatic carcinoma. (prostatic carcinoma always androgen dependent)
- Rapidly metabolized.
- Causes mild gynecomastia probably by increasing testicular estrogen production
- May useful in the management of excess androgen effect in women. But not the drug of the first choice!

- Spironolactone, Aldosterone antagonist also make gynecomastia
- gynecomastia add a site for breast cancer; it's an enlargement and growth producing secretion that are not milk since its need prolactin to be produced

﴿رَبَّنَا وَلَا تُحَمِّلْنَا مَا لَا طَاقَةَ لَنَا بِهِ ۖ﴾

Antiandrogens

2. Bicalutamide and Nilutamide:

- **Potent and orally active antiandrogens.**
- **Used in patients with <u>metastatic carcinoma of the prostate.</u>**

Antiandrogens

B. 5α-reductase inhibitors:

Reductase because reduction is needed for synthesis of androgen

There are subtypes of 5α-reductase inhibitors

Finasteride:

- **Is an orally active steroid-like drug.**
- **Decreases dihydrotestosterone levels** (the active part of testosterone)
- **t1/2 ~ 8 hours**
- **50% metabolized**
- **Moderately effective in reducing prostate size in men with <u>benign prostatic hyperplasia.</u>**

Antiandrogens

Dutasteride:

- **It is a similar orally active steroid derivative with a slow onset of action and a much longer half-life than finasteride.**
- **It is mainly approved for use in for benign prostatic hyperplasia.**

Antiandrogens

(GnRH) & its Analogs

Leuprolide, Goserelin

- **Can also be used in <u>prostate cancer.</u>**

- GnRH physiologically (normally) are secreted in a pulsatile fashion (released then stopped release, then released again) to release the gonadotropin LH & FSH, to stimulate the ovaries and the cycle in female, and spermatogenesis in male and testosterone secretion

- If they are secreted continuously their effect will be reversed and cause depression, normally the pulsatile fashion prevent this.

- So how can GnRH be antiandrogens in males and antiestrogens in females?
- By giving them continuously

Ovulation-inducing Agents
(Clomiphene)

- **Clomiphene is a partial estrogen agonist.** (also partial antagonist)
- **It is active after oral administration.**

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Clomiphene

Pharmacodynamics:

- **Has estrogenic activity in cases of gonadal deficiency.**
- **Inhibits the action of strong estrogens.**
- **It increases the secretion of gonadotropins** (LH & FSH which stimulate the ovulation) **by inhibiting estradiol's negative feedback effect on the gonadotropins.**
- **Thus, it stimulates ovulation in women with ovulatory dysfunction.**

Clomiphene

Therapeutic uses:

1. **Ovulatory dysfunction in women wishing to become pregnant. The drug should be given repeatedly** at intervals **until pregnancy occurs** stop give the drug after pregnancy.

- **Normal ovulation does not usually resume** (Clomiphene does not cure ovulatory dysfunction, so in future pregnancy you need again to stimulate the ovulation by Clomiphene)**, thus it is of no value in patients with ovarian or pituitary failure.**

- In patients with ovarian failure or pituitary failure (such as hypopituitarism, which might be caused by bleeding after delivery), here the ovulation stimulation will be of no use, resulting in no pregnancy again

Clomiphene

Adverse effects:

1. **Hot flushes is the most common adverse effect.**
2. **Intensification and prolongation of after images in some occasions.**
3. **Occasionally: headache, constipation, allergy, hair loss.**
4. **Ovarian stimulation and enlargement.**
5. **Multiple pregnancies (10%).** (more than one child in each pregnancy caused by over stimulation, instead of one ovum there will be more maybe two or there or more)

- After images is that when you look at green light for example you will continue seeing it after moving your eyes for a period of time

Clomiphene

6. **Nausea, vomiting, increased nervous tension, depression, fatigue, breast soreness, weight gain, urinary frequency and heavy menses have been reported. They may be due to hormonal changes of ovulation rather than to the drug.**

Contraindications and cautions:

1. **Patients with enlarged ovaries should receive small doses.** Or don't give any dose
2. **Caution in patients with visual symptoms.** Because of after images adverse effect

- Pregnancy cause depression due to hormones
- Oral contraceptive, over-stimulation (Clomiphene) also cause depression
- There is relation between estrogen and depression
- Weight gain caused by any hormones especially steroidal hormones (due to stimulation of aldosterone receptors), caused by water retention

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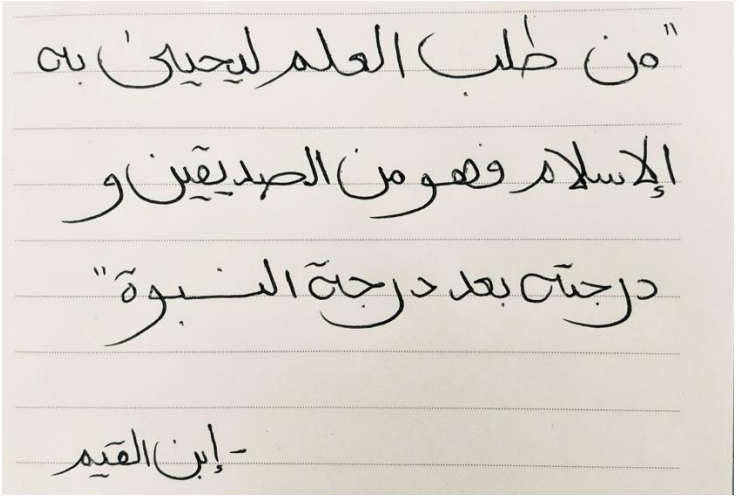
يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ
وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc



VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!