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بسم الله الرحمن الرحيم

Oral Contraceptives

FINAL | Lecture 10

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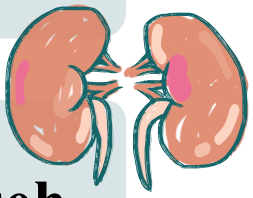
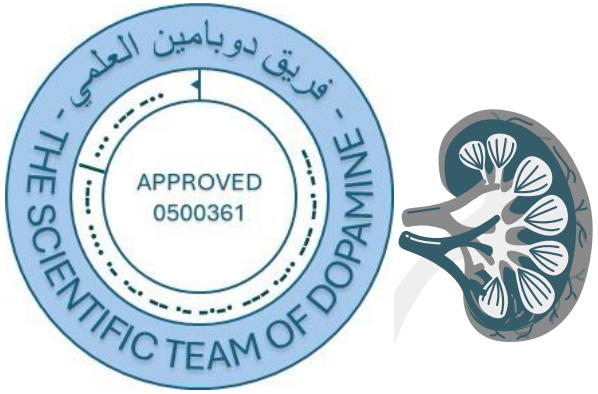
﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾





"اللَّهُمَّ إِنِّي أَسْأَلُكَ فَهْمَ النَّبِيِّينَ، وَحِفْظَ الْمُرْسَلِينَ، وَإِلْهَامَ الْمَلَائِكَةِ الْمُقَرَّبِينَ، بِرَحْمَتِكَ يَا أَرْحَمَ الرَّاحِمِينَ"

Oral Contraceptives

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There are other methods of contraception such as **mechanical devices**.
We will be focusing on **orally administered contraceptives**.

Hormonal Contraception

الله أكبر

Mainly administered orally, though could be administered sub-cutaneously.

A. Combinations of estrogens and progestins: **Combined**: the two hormones present in the same tablet

1. **Monophasic forms: constant dosage of both components during the cycle.** The same dose of both estrogen and progestin throughout the full menstrual cycle (It is then paused in the 28th day to allow for bleeding)

2. **Biphasic forms: dosage of one or both components is changed once during the cycle.** One of the doses of the two hormones changes during the cycle. **For example**: Progestin is given at a dose of 0.05 till day 12. From the 13th day onwards, the dose of progestin is increased to 0.1. This helps better **mimic** the normal physiological alterations of estrogen and progesterone throughout the menstrual cycle, with **the exception of ovulation occurring**. Ovulation is inhibited due to feedback inhibition on the hypothalamic and pituitary glands.

3. **Triphasic forms: dosage of one or both components is changed twice during the cycle.**

4. **Tetra-phasic forms**: Dosage of one or both components is changed thrice during the cycle.

Combination therapy is more common than continuous therapy

This slide was skipped by the doctor

TABLE 40–3 Some oral and implantable contraceptive agents in use.[1]

	Estrogen (mg)		Progestin (mg)	
Monophasic combination tablets				
Alesse, Aviane, Lessinea, Levlite	Ethinyl estradiol	0.02	L-Norgestrel	0.1
Levlen, Levora, Nordette, Portia	Ethinyl estradiol	0.03	L-Norgestrel	0.15
Crysella, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	0.03	Norgestrel	0.30
Yasmin	Ethinyl estradiol	0.03	Drospirenone	3.0
Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Cyclen, Sprintec	Ethinyl estradiol	0.035	Norgestimate	0.25
Necon 1/35, Norinyl 1+, Nortrel 1/35, Ortho-Novum 1/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ovcon-35	Ethinyl estradiol	0.035	Norethindrone	0.4
Demulen 1/50, Zovia 1/50E	Ethinyl estradiol	0.05	Ethynodiol diacetate	1.0
Ovcon 50	Ethinyl estradiol	0.05	Norethindrone	1.0
Ovral-28	Ethinyl estradiol	0.05	D,L-Norgestrel	0.5
Norinyl 1/50, Ortho-Novum 1/50	Mestranol	0.05	Norethindrone	1.0
Biphasic combination tablets				
Ortho-Novum 10/11, Necon 10/11				
Days 1–10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Triphasic combination tablets				
Enpresse, Triphasil, Tri-Levlen, Trivora				
Days 1–6	Ethinyl estradiol	0.03	L-Norgestrel	0.05
Days 7–11	Ethinyl estradiol	0.04	L-Norgestrel	0.075
Days 12–21	Ethinyl estradiol	0.03	L-Norgestrel	0.125
Ortho-Novum 7/7/7, Necon 7/7/7				
Days 1–7	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 8–14	Ethinyl estradiol	0.035	Norethindrone	0.75
Days 15–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Tri-Cyclen				
Days 1–7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8–14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15–21	Ethinyl estradiol	0.035	Norgestimate	0.25
Daily progestin tablets				
Nora-BE, Nor-QD, Ortho Micronor, Jolivette, Camila, Errin	...		Norethindrone	0.35
Ovrette	...		D,L-Norgestrel	0.075
Implantable progestin preparation				
Implanon	...		Etonogestrel (one tube of 68 mg)	

[1]The estrogen-containing compounds are arranged in order of increasing content of estrogen. Other preparations are available. (Ethinyl estradiol and mestranol have similar potencies.)

Hormonal Contraception

B. Continuous progestin therapy without concomitant administration of estrogen, orally or by implantation under the skin.

An implant is administered **subdermally**. (An incision is made, the implant is placed, then the skin is patched up again.) Implants have a very long duration: **Months**.
In contrast, oral tablets requires daily administration,

In hajj season, some women take progestin in order to delay their periods (menstrual bleeding).
This causes the endometrial tissue to continue proliferation. The endometrial tissue is only able to shed, when exogenous progestin administration is terminated, (meaning when they stop taking the contraceptives.)

Hormonal Contraception

These are synthetic hormones

- **Estrogens:**

The most commonly used estrogen

Ethinyl estradiol, Mestranol.

- **Progestins:**

The most commonly used progestins

L-Norgestrel, Drospirenone, Norethindrone, Norgestimate, Ethynodiol diacetate.

The tables in this slide and the next are **not** for memorization, just to clarify phasic administration

The reason for phasic dosage is due to the potential adverse effects that could manifest. A prescription is required in order for the gynecologist/ obstetrics to choose a combination tailored to the patient. Then, follow up is crucial, so that the doctor could monitor the adverse effect and change the dosage based on that.

Some oral and implantable contraceptive agents

	Estrogen	mg	Progestin	mg
Monophasic Combination Tablets	Ethinyl estradiol	0.02	L-Norgestrel	0.1
From day 1-27 all throughout	Ethinyl estradiol	0.03	L-Norgestrel	0.15
	Ethinyl estradiol	0.02	Norethindrone	1
	Ethinyl estradiol	0.035	Norethindrone	1
	Mestranol	0.05	Norethindrone	1
Biphasic Combination Tablets				
Days 1–21	Ethinyl estradiol	0.02	Desogestrel	0.15
Days 22–27	Ethinyl estradiol	0.01	None	
Days 1–10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11–21	Ethinyl estradiol	0.035	Norethindrone	1
Triphasic Combination Tablets				
Days 1–6	Ethinyl estradiol	0.03	L-Norgestrel	0.05
Days 7–11	Ethinyl estradiol	0.04	L-Norgestrel	0.075
Days 12–21	Ethinyl estradiol	0.03	L-Norgestrel	0.125

You stop in the 28th day to allow bleeding then resume medication the 29th day

Each rectangle is a specific medication course/combination

Observe the increase of progestin dosage

It's important to understand the complicated nature of contraceptives and the fact they need a prescription.

Days 1–7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8–14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15–21	Ethinyl estradiol	0.035	Norgestimate	0.25
4-Phasic Combination Tablet				
Days 1–2	Estradiol valerate	3	None	
Days 3–8	Estradiol valerate	2	Dienogest	2
Days 9–25	Estradiol valerate	2	Dienogest	3
Day 26–27	Estradiol valerate	1	None	
Daily Progestin Tablets	None	-	Norethindrone	0.35
Contraceptive Transdermal Patch (Apply 1 Patch per Week)	Ethinyl estradiol	0.02/24 h Multiply the dosage here by 7, since its given once weekly	Norgestromin	0.150/24 h
Implantable Progestin Preparation	None	-	Etonogestrel	(one tube of 68 mg)

Notice how the number of "changes" to the first dose is 3 in the tetra-phasic combination.

We only relay on daily administration when combination therapy is contradicted.

These options help with compliance since oral tablets require daily administration.

Implants have a duration that spans months

Combination Oral Contraceptives

- **Mechanism of Action:**
  - **Inhibition of ovulation by inhibiting pituitary function.**

    These structural changes occur as a result of inhibiting ovulation
  - **Changes in cervical mucus, endometrium, and motility and secretions of uterine tubes decrease the likelihood of conception and implantation.**

    The reason Implantation does not occur is because the enviroment in the uterus is unprepared.

Combination Oral Contraceptives

Pharmacologic effects:

1. **Ovary:** Atrophy occurs due to **reduced use/function**

- **Depression of ovarian function with chronic use, and the ovaries get smaller. This is reversible in most cases.** Not in all cases though!

2. **Uterus:**

- **Hypertrophy of the cervix and polyp formation with chronic use.** Polyps could bleed as well.

Combination Oral Contraceptives

- **Cervical mucus becomes thick and less copious.** Rare
- **Effects on endometrium are related to hormonal content.**

3. **Breast:**

- **Enlargement.**
- **Suppression of lactation.** This is inconsequential/insignificant since breast feeding does not occur anyway.
- **Small amounts cross to breast milk.**

Combination Oral Contraceptives

4. **CNS:**

- **Low changes in mood, affect and behavior.** Some women experience depression
- **Estrogens may be useful for premenstrual tension syndrome, postpartum depression and climacteric depression.** **Postpartum: After** childbirth and **climacteric:** during menopause

  Please see next slide for more details.
- **Progestins have central thermogenic action.**

As discussed in physiology, body temperature increases during the **latter half of the menstrual cycle (the luteal phase)** due to **elevated progesterone levels**. Specifically, the **LH surge triggers ovulation, leading to the expulsion of the ovum from the follicle, and the formation of the corpus luteum. The corpus luteum subsequently increases progesterone.**

Contraceptives and Depression

Hormonal contraceptives contain **synthetic hormones** that **alter** the **normal fluctuations of estrogen and progesterone**. This alteration to physiological estrogen could cause **depression** or **exacerbate pre-existing depressive symptoms,** thus leading to the progression to major depression.
These effects are more commonly associated with **major depressive disorder**, not **reactive** depression.

What's the difference between **major** and **reactive** depression?

- Major depression is caused by alterations/deficiencies in **biogenic amines** (such as **serotonin** and **catecholamines**) within the CNS. Similar to how diabetic patients have **insulin deficiencies**.
- Major depression is not delusion nor "craziness" and should not be stigmatized.

Combination Oral Contraceptives

5. **Endocrine function:**

Na+ and water retention cause hypertension, edema and swelling. Not necessary heart failure since the **demographic** that take contraceptives are **young adult women**.

- **Estrogens increase plasma corticosteroid-binding globulin.**
- **Increase plasma renin activity and aldosterone secretion.**
- **Increase thyroxine-binding globulin**
- **Estrogens increase plasma levels of SHBG → decrease plasma levels of free androgens.**

SHBG- sex hormone binding globulin

Increasing the concentration of **plasma binding proteins** increases the **bound fraction** of hormones while **reducing their free fractions**. This could **reduce their effects on the body.**
We can summarize that hormonal contraceptives influence the activities of androgens, renin, thyroid hormones and corticosteroids

Combination Oral Contraceptives

6. **Blood:** A **previously healthy woman with no known medical conditions** may present to the hospital with **severe thromboembolism**.

- **Serious thromboembolism.**
- **Estrogens increase clotting factors VII, VIII, IX, and X and decrease antithrombin III.** Antithrombin 3 is the physiological anti-coagulant
- **Increase serum iron and total iron binding capacity.** Advantage.

Some patients develop folic acid deficiency anemia.

This is either due to **altered metabolism** or **decreased absorption** of **folic acid**.
This explains the necessity of follow-up with a CBC and peripheral blood film. Blood films are important for studying the morphology/size of RBCs
Remember: Folic acid deficiency causes **megaloblastic anemia, thus we expect larger RBCs.**

Combination Oral Contraceptives

7. **Liver:**

- **Estrogens reduce serum haptoglobins.**
- **Cholestasis and cholelithiasis** Gall bladder disease and gall bladder stones.

8. **Lipid metabolism:**

The importance of Hatoglobin:

- **Haptoglobin is an acute phase protein capable of binding haemoglobin, thus preventing iron loss and renal damage. Haptoglobin also acts as an antioxidant**

Combination Oral Contraceptives

8. **Lipid metabolism:**

- **Estrogens increase triglycerides, phospholipids, and HDL; while size of LDL particles is decreased.** This is **pathology in normal LDL structure**
- **This effect may be modified by progestins**

  Meaning, dyslipidemia **may or may not develop clinically**. If dyslipidemia occurs, the physician may adjust the hormonal regimen to increase the dose of progestin.

- **Progestins <u>with androgenic properties</u> and synthetic progestins diminish the beneficial effects of estrogens on lipoprotein metabolism, and <u>lower HDL.</u>**

  Specifically progestins with androgenic properties lower HDL
  (note: Not all progestins **have** androgenic properties.)

Combination Oral Contraceptives

Dyslipidemia/hyperlipidemia is the cause behind this

- **The mechanism of increased cardiovascular disease in combined hormonal contraceptoion (CHC) users may be due to thromboembolic and thrombotic changes, rather than atherosclerosis.**

In post-menopausal women, atherosclerosis is the culprit being CVD.
This is not commonly seen in young women taking contraceptives.
What causes the **CVD** in that scenario, is a **thrombosis** that affects the **arterioles** in the **cardiovascular system.**

- **Women with controlled dyslipidemia can use low-dose CHCs, with periodic fasting lipid profiles.**
- **Women with uncontrolled and additional risk factors should not take CHCs.** *Please see next slide.*

More on dyslipidemia

Some women, before taking contraceptives have **dyslipidemia** due to **hereditary causes**. If their dyslipidemia is **uncontrolled** its **contraindicated** to take combined hormonal contraceptives (CHCs). However, women with **controlled dyslipidemia** , are allowed low dose CHCs as long as they have frequent **fasting lipid profile assessments**.
A fasting lipid profile assessment requires **12 hours** of fasting, in contrast to fasting blood sugar assessments that require from **8-10 hours**.

Why is dyslipidemia controlled in some patients and controlled in others?
Statins (lipid-lowering drugs) are less effective in individuals who lack functional LDL receptors in the liver. LDL receptors are responsible for the **endocytosis and clearance** of LDL particles into hepatocytes. Statins act via **inhibiting hepatic cholesterol synthesis, which normally leads to the up regulation of LDL receptors and thus increased LDL clearance from the circulation**. However, if LDL receptors are **absent or defective**, statins are less effective. This explains why some patients have difficulty controlling their dyslipidemia despite taking medications

Combination Oral Contraceptives

9. **Carbohydrate metabolism:**

- **Reduced rate of absorption of carbohydrate from GIT.**
- **Progesterone increases basal insulin levels and the rise in insulin induced by carbohydrate ingestion (carbohydrate-containing meal) – *Note:* *focused on progesterone itself.***

- **Potent progestins may produce a reversible progressive decrease in carbohydrate tolerance over years which may eventually contribute to the development of diabetes mellitus.**
  - ***Note:*** *refers to the synthetic progesterone class used in oral contraceptives.*

Combination Oral Contraceptives

- **Therefore, nonsmoking women younger than 35 years with diabetes but no associated vascular disease can safely use CHCs.**
- **Diabetic women with vascular disease (nephropathy, retinopathy, neuropathy, or other vascular disease, cardiopathy) or diabetes of more than 20 years duration should not use CHCs.**

- ✓ Smoking is avoided because it reduces metabolism and increases the risk of cardiovascular diseases, especially atherosclerosis.
- ✓ However, this is not completely accurate because the contraceptives do not contain natural progesterone. Instead, they contain potent progestins, which are synthetic progesterone derivatives that produce a strong effect even at low dose.
- ✓ These statements may appear contradictory. Diabetes mellitus is associated with the development of atherosclerosis even before obvious symptoms of cardiovascular disease appear.

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Combination Oral Contraceptives

10. Cardiovascular system:

- **Increase blood pressure, heart rate and slightly increase cardiac output.**

11. Effects on the skin:

- **Increase skin pigmentation especially in women with dark complexions.**
- **Androgen-like progestins increase formation of sebum and may produce acne.**

Combination Oral Contraceptives

- **The sequential agents and estrogens alone *often* decrease sebum production.**
- **Many patients may show suppression of sebum production, acne and hair growth because of suppression of ovarian androgens.**

Combination Oral Contraceptives

Therapeutic uses:

1. **Oral contraception:**

- **Failure rate of pregnancy ~ 0.5-1 per 100 women-years.**

Next slide

- **Contraception failure has been observed in women missing one or more doses, those taking phenytoin or those taking antibiotics.**

2. **Endometriosis.**

- ✓ The term "**women-years**" does not refer only to the number of women. It is calculated by multiplying the number of women by the duration of contraceptive use in years. Some women may use hormonal contraceptives for one year, others for five years, several months, or even 20 years.
- ✓ For example, one woman using contraception for one year equals one woman-year, while one woman using contraception for six months equals 0.5 woman-year.

- ➢ **In endometriosis, ectopic endometrial tissue is present within the abdominal cavity. These tissues undergo cyclical hormonal changes similar to normal endometrial tissue,** which can lead to **abdominal pain.**
- ➢ **Hormonal contraceptives help relieve symptoms by suppressing these cyclical changes and reducing endometrial shedding and sloughing.**

Combination Oral Contraceptives

- **Contraception failure has been observed in women missing one or more doses, those taking phenytoin** (also occur with drugs such as carbamazepine and rifampin; drug-induced metabolism of contraceptive hormones) **or those taking antibiotics.**

  - **Phenytoin** induces *hepatic enzymes*, which increase the metabolism and elimination of contraceptive hormones, leading to **reduced contraceptive efficacy.**

  - **Antibiotics** may also **decrease the effectiveness of oral contraceptives** by eliminating intestinal flora. Normally, intestinal bacteria hydrolyze glucuronide-conjugated metabolites excreted in the bile, allowing reabsorption of **estrogen** through enterohepatic circulation. This process helps maintain a certain plasma level of *estrogen*.

  - When intestinal flora are reduced by antibiotics, hydrolysis of the glucuronide conjugates does not occur. As a result, the glucuronide metabolites are excreted in the feces instead of being reabsorbed, leading to reduced estrogen levels and possible contraceptive failure.

Combination Oral Contraceptives

Adverse effects:

A. **Mild:** ✓ may be managed by changing the dose or modifying the contraceptive preparation.

1. **Nausea, mastalgia** (breast tenderness) **, breakthrough bleeding and edema (related to estrogen content of the pill).** may be improved by reducing the estrogen dose.

2. **Increased sedimentation rate (ESR) due to increased fibrinogen.** which can contribute to an increased tendency for coagulation.

Combination Oral Contraceptives

3. Changes in serum proteins should be taken into account when evaluating endocrine functions.

- For example, in conditions involving binding proteins such as thyroid-binding proteins, an increase in binding protein results in an increase in total hormone concentration, while the free (biologically active) hormone level remains unchanged and is the most clinically relevant.

- Therefore, **total hormone** levels may appear elevated due to increased binding proteins, but **free hormone** levels reflect the true physiological activity.

Combination Oral Contraceptives

4. **Headache is often mild and transient, but migraine is made worse.**

5. **Failure of withdrawal bleeding (change prep).**

Combination Oral Contraceptives

B. Moderate: (may require discontinuance of oral contraception).

1. **Breakthrough bleeding is common (25% of patients) with the use of progestational agents alone** which means that sloughing may still occur even with progesterone alone.
2. **Weight gain with combination agents containing androgen-like progestins.** Weight gain is also related to fluid retention caused by progesterone, in addition to the androgenic properties of certain progestins, which can increase body weight.
3. **Increased skin pigmentation exacerbated by vitamin B12 and folic acid deficiency. It is slowly reversible.**

Combination Oral Contraceptives

4. **Acne with agents containing androgen-like progestins. Agents containing high estrogens improve acne.**
5. **Hirsutism may be aggravated by 19-nortestosterone derivatives.**
6. **Ureteral dilation.** Which also happens during pregnancy due to high progesterone levels, which may lead to urinary stasis or urinary tract infections.
7. **Vaginal infections are more common and more difficult to treat.** **(because they alter the secretions)**

Combination Oral Contraceptives

8. Amenorrhea occurs in some patients and persist for several years and is often associated with galactorrhea.

- This may suggest a prolactin-secreting adenoma.
- **It is not clearly known whether these tumors of the pituitary gland are a result of oral contraceptive use.**

- **This is specially true in women who had menstrual irregularities before taking oral contraceptives.**
- **These patients may have prolactinomas.**

Combination Oral Contraceptives

C. Severe (contraindications):

1. **Venous thromboembolic disease.**
2. **Myocardial infarction.**
3. **Cerebrovascular disease.**
4. **Ischemic bowel disease.**
5. **Cholestatic jaundice (progestin, 17-alkyl substituted agents), cholecystitis and cholangitis.**

Combination Oral Contraceptives

6. **Increased incidence of hepatic adenomas.**
7. **Depression (6%).**
8. **Cervical infection with the human papillomavirus may increase incidence of cervical cancer.**

Contraception with Progestins Alone

- **Suitable in patients for whom estrogen administration is undesirable.**

Injection of depot medroxyprogesterone acetate (DMPA) every 3 months, which inhibits ovulation for 14 weeks. It is deposited in the muscle, This is different from subcutaneous tablets , which provide a slow release of the drug.

- **All users experience episodes of spotting and bleeding.**
- **Amenorrhea is common** and may be prolonged.

Contraception with Progestins Alone

- **Not suitable for women planning a pregnancy because ovulation may be suppressed for 18 months after the last dose.**
- **Long-term DMPA reduces menstrual blood loss and is associated with a decreased risk of endometrial cancer.**
  - ✓ because it causes shedding of the endometrium, thereby reducing the risk of cancer.

Contraception with Progestins Alone

- **Suppression of endogenous estrogens may be associated with a reduction in bone density and changes in plasma lipids and increased risk of atherosclerosis.**
- **The progestin <u>implants</u> utilizes the subcutaneous implantation of capsules with an effect lasting up to 6 years.**

- ✓ **Estrogen** is mentioned here because the mechanism involves inhibition of FSH and LH.
- ✓ DMPA suppresses FSH and LH, which leads to reduced ovarian activity and decreased endogenous estrogen production.

Contraception with Progestins Alone

- **Associated with irregular bleeding rather than predictable menses.**
- **May be associated with intracranial hypertension and papilledema,** leading to optic nerve damage and abnormal vision.

- **Adverse effects: headache, dizziness, bloating, weight gain, and reversible reduction of glucose tolerance.**

PHARMACOLOGY

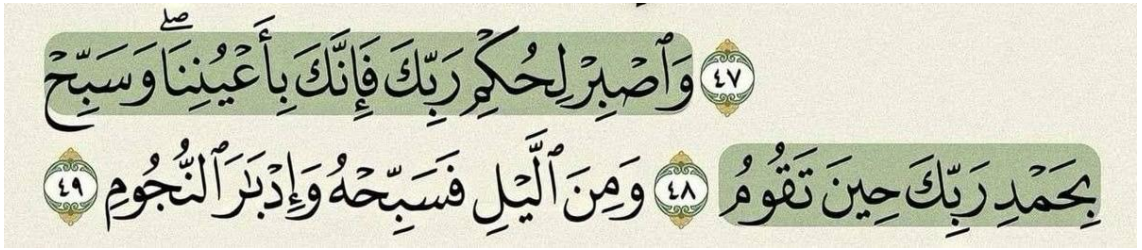
QUIZ

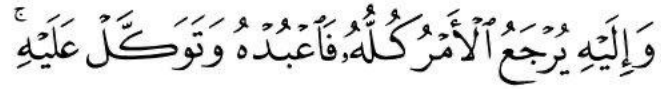
LECTURE 10

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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