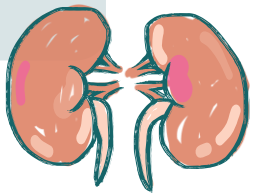
بسم الله الرحمن الرحيم

Gonadal Hormones & Inhibitors

FINAL | Lecture 8

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

Written by: Ammar Abusheikha



The Gonadal Hormones & Inhibitors

Yacoub M. Irshaid, MD, PhD

Concept : Oral contraceptive

Study this lecture with the oral contraceptive (OCP) lecture (10) as they are very related.

Here are some basics you'll need for this lecture:
2 types:

Combined pill – estrogen and progesterone
Progesterone only pill (only when estrogen is contraindicated)

They have a low consistent dose that work by supressing the anterior pituitary release of gonadotropins (FSH and LH)

- FSH decrease prevents follicular growth and estrogen secretion.
- LH decrease prevents androgen production and ovulation.

They are given to: prevent pregnancy (no ovulation), PCOS (more later), dysmenorrhea, androgenic acne, endometriosis, etc.

Estrogens

We will talk today about female gonadal hormones specifically.

- 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 the endogenous hormones. They can't be given orally as they have low oral bioavailability (metabolized in the intestine and the liver - first pass effect).

Estrogens

Synthetic estrogens:

1. Steroidal: Ethinyl estradiol, mestranol.
2. Nonsteroidal: all drugs that have estrogenic activity (all plant derived estrogenic substances are non-steroidal)

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

Estrogens

Pharmacokinetics:

- Estradiol in the circulation binds to sex hormone-binding globulin (SHBG, an α_2- globulin) and albumin with lower affinity. Major binding is to SHBG.
- Estrogens hydroxylated derivatives and conjugated metabolites are excreted in bile, so metabolism of estrogen is by glucuronidation.

Pharmacokinetics:

- Excreted glucuronides are reabsorbed after hydrolysis (to original compound) within the gut by microbial flora
- This means that broad spectrum antibiotic use will kill the natural gut flora, prevent hydrolysis, increase excretion, and decrease plasma concentration.
- So relatively broad-spectrum antibiotics fail estrogen-containing oral contraceptives.

Pharmacokinetics:

- Although Estrogens are excreted in small amounts in breast milk. At high doses, one tablet of estrogen can suppress lactation totally, for mothers who don't want to breast feed their newborns (either because a medical contraindication or personal choices).

Doctor:
Women should breast feed their infants for at least 6 months, and preferably for at least 1 year.

Estrogens

Therapeutic uses:

1. Primary hypogonadism: Replacement therapy for estrogen deficient patients is usually begun at 11-13 years of age.

   Primary hypogonadism is a disease where a female child reaches age 11-13 yrs and doesn't show any signs of puberty (secondary sex characteristics, menses). This indicates a failing ovary, and estrogen therapy although useful will not be able to restore ferality

Estrogens

Therapeutic uses:

1. Primary hypogonadism: Replacement therapy for estrogen deficient patients is usually begun at 11-13 years of age in order to:

   1) stimulate development of secondary sex characteristics and menses,

   2) to stimulate optimal growth,

   3) to prevent osteoporosis,

   4) to improve psychology of the patient.

Estrogens

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

- Estrogen has a protective effect on the skeletal and cardiovascular systems. This is reflected in the relatively low number of women under 50 admitted to coronary care units (CCUs) compared with men, who may experience (MI) in their 40s.
- After menopause, estrogen levels decline significantly, and this protective effect is reduced. As a result, chronic conditions in women increases, becoming more similar to that of age-matched men.

Estrogens

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

- This observation led researchers to investigate hormone replacement therapy (HRT) after menopause in an attempt to maintain estrogen's protective effects and treat cardiac disease.
- This therapy failed because it increased risk of endometrial and breast cancer (Estrogen sensitive (ER+) types only), and there wasn't any cardiovascular benefit.
- When necessary to administer HRT (more later), it must be given with progestins to reduce the cancer risk (endometrial cancer, breast cancer risk doesn't decrease).

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 cancer in patients receiving HRT.

Estrogens

- Therefore, routine HRT in postmenopausal women is currently not recommended.
- HRT may be beneficial in young women with premature menopause (e.g.: due to ovariectomy), where it's beneficial for cardiovascular health risk reduction.

HRT is now treated like a **symptom-targeted therapy**, not a lifelong preventive hormone replacement for aging.

Estrogens

- For prevention of osteoporosis (not 1st line)
  - Estrogen can be used with the addition of calcium supplements. This isn't unique as any attempt to treat or prevent osteoporosis requires calcium and vit. D supplementation to reach normal levels.
- This may be associated with an increased risk of endometrial carcinoma, which can be prevented by the addition of progestin. Progestins have a stabilizing (anti-proliferative) effect on the endometrium.

Estrogens

3. Other uses:

   Estrogens combined with progestins (like combined oral contraceptives) can be used to:

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

Estrogens

3. Other uses:

   Estrogens combined with progestins can be used to:

B. suppress ovarian function in treatment of hirsutism (male-pattern hair growth in women) and amenorrhea due to excessive secretion of androgens by the ovary. Acne is also caused by androgens in both men and women, where women have highly androgen-sensitive sebaceous gland.

Under LH stimulation, the ovary (theca interna) produces androgens, and if produced at a rate too high like in Polycystic Ovarian Syndrome (PCOS), androgens cause hirsutism, acne etc.

Androgens can be in adipose tissue to produce estrogens which inhibit pituitary release of gonadotropins (FSH) causing anovulation (amenorrhea). More on PCOS in PBL lec 2.

If exogenous estrogen and progestins are administered (i.e.: oral contraceptives) they can inhibit pituitary release of gonadotropins (LH), decreasing androgen production and improving symptoms.

Another method of treatment for PCOS is administering Metformin, the blood glucose lowering drug. This is because PCOS is an endocrine-metabolic disease with insulin resistance strongly involved in its pathogenesis.

Estrogens

Adverse effects:

1. Uterine bleeding: because they stimulate the endometrium to grow, but they don't always stabilize it properly, so it undergoes irregular sloughing and (non-menstrual) bleeding such as spotting or breakthrough bleeding.
2. Breast cancer
3. Endometrial carcinoma

Estrogens

Adverse effects:

4. Infertility (anovulation), ectopic pregnancy and premature delivery (do your own research for last 2)
5. Breast tenderness
6. Hyperpigmentation (near body folds - do your own research)
7. Migraine headache
8. Cholestasis and gallbladder disease
9. Hypertension (increase blood volume due to increased RAAS)

Will be explained more in the Oral contraceptives lecture

Estrogens

Adverse effects:

10. For patients taking estrogen pills (to prevent pregnancy, regulate cycles, or treat irregular bleeding), pregnancy may occur and cause menstruation to stop. The patients may not realize they are pregnant and think its just the OCP suppressing menstruation or that the period is late, so they may keep taking estrogen pills (oral contraceptives), which is toxic to the fetus (debatable) and causes delayed recognition of pregnancy and lack of prenatal care.

Estrogens

Contraindications:

1. Estrogen-dependent neoplasms: endometrium and breast.
2. Avoid in patients with undiagnosed vaginal bleeding (vaginal bleeding is a side effect of the drug, so administering estrogen before diagnosis of the current bleeding reason will become harder), liver disease (where the drug is metabolized) and history of thromboembolic disorders (next slide).

Estrogens

Contraindications:

2. Avoid in patients with undiagnosed vaginal bleeding, liver disease, and history of thromboembolic disorders, estrogens (in pharmacological doses) cause a hypercoagulable state by inducing clotting factor synthesis (more in the OCP lecture).

Estrogens

Contraindications:

3. Avoid in heavy smokers as they produce monocyclic aromatic hydrocarbons that induce drug hepatic metabolism enzymes. The main reason is the synergistic increase in risk of cardiovascular disorders due to smoking-induced atherosclerosis, and estrogen-induced hypercoagulability.

Progestins

- Natural progestins:

  Progesterone

- Progesterone derivatives: Semi-synthetic / modified natural

  Hydroxyprogesterone caproate

  Medroxyprogesterone acetate

  Megestrol acetate

Progestins

- Synthetic progestins: testosterone derivatives

A. 17-ethinyl testosterone derivatives: Dimethisterone

B. 19-nortestosterone derivatives:

Desogestrel , Norethynodrel , Norethindrone, L-norgestrel.

There is many of them.

These are the drugs that we will talk about.

Progestins

Pharmacokinetics:

- Progesterone is rapidly absorbed after administration can't be given orally.
- Undergoes extensive first pass metabolism and excreted in urine as pregnanediol glucuronide.
- t½ in plasma is approximately 5 minutes
- Most of synthetic agents are metabolized extensively to inactive products that are excreted mainly in urine. Since it's excreted in urine there will be no effect of antibiotic administration on excretion and plasma levels.

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.

If you want to specialize in OB-GYN this is important for you.

Progestational agents can have 5 characteristics (side-effects other than their progesterone activity). Estrogenic, antiestrogenic, androgenic, antiandrogenic, anabolic.

<u>Not required to memorize, and you will not be asked about it.</u>

According to the patients condition the right agent with the right characteristics will be administered.
Example:
- A patient with high estrogen will be give an agent with some anti-estrogen characteristics.
- A patient with PCOS will be given a progesterone with anti androgenic effect

Progestins

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

You will not be asked about these either.

You may only be asked about the concept that progesterone (and OCPs including progesterone) can have androgenic and estrogenic properties and cause androgen and estrogen related side effects.

Progestins

Therapeutic uses:

1. Hormonal replacement therapy. Administered with estrogen for osteoporosis to protect against endometrial hyperplasia and carcinoma.
2. Hormonal contraception. (Only) when estrogens are contraindicated for any reason (cancer, etc.) we give progesterone-only oral contraceptives. Progestins are also present in the combined pill.

Progestins

Therapeutic uses:

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. Other indication for OCPs.

Progestins

Adverse effects:

1. Elevation of blood pressure. Like estrogen (because of Na^+ and water retention).
2. Reduce plasma HDL levels (androgenic progestins). This is atherogenic (causes atherosclerosis), similar to elevation of LDL.
3. Enhance effects of estrogen on breast cancer risk in postmenopausal women. Meaning increased risk of breast cancer when estrogen is given with progesterone compared to estrogen only.

Progestins

When giving HRT:

Estrogen alone: increases risk of breast cancer and endometrial cancer

Estrogen with progesterone: breast cancer risk is increased further but endometrial cancer risk is decreased

Estrogen and Progesterone Inhibitors and Antagonists

Concept Revise: Partial Agonists

A partial agonist has affinity for the receptor but produces a submaximal effect even when it fully occupies the receptor.

Its behaviour depends on the amount of full agonist present:

When the concentration of the full agonist is low:

The partial agonist binds to the receptor and activates it, producing a moderate response, so it behaves like an agonist.

When the concentration of the full agonist is high:

The partial agonist competes with the full agonist for receptor binding. Since it produces a weaker effect than the full agonist, it reduces the overall response, so it behaves like an antagonist.

So, a partial agonist can function as both:

- **agonist** (when endogenous activity is low)
- competitive **antagonist** (when endogenous activity is high).

Tamoxifen and Related Drugs

- Is a competitive partial agonist / full antagonist at estrogen receptors depending on the tissue (next slide).
- The first selective estrogen receptor modulator (SERM) discovered.
- It is extensively used in the palliative treatment of breast cancer in postmenopausal women (ER+ cancer only). Given on top of other cancer therapy
- It is a nonsteroidal agent that is given orally.

Tamoxifen is best described as a Selective Estrogen Receptor Modulator (SERM), not simply a partial agonist everywhere. Its action depends on the tissue:

Breast tissue:

Tamoxifen acts mainly as an estrogen antagonist → it blocks estrogen receptors and prevents estrogen-driven growth of breast cancer cells.

Bone tissue and Endometrium (uterus):

It acts more like a partial agonist → helps maintain bone density (prevents osteoporosis) and can stimulate the endometrium (prolonged use increases the risk of endometrial cancer).

So, tamoxifen can behave:
A full antagonist in some tissues (especially breast), and a partial agonist in others.

This tissue selectivity happens because of estrogen receptor differences:
- different tissues express different estrogen receptor subtypes (ERα vs ERβ)
- receptors interact with different co-activator and co-repressor proteins in each tissue.

Tamoxifen and Related Drugs

- Prevents loss of lumbar spine bone density, changes in plasma lipid levels and risk for atherosclerosis after menopause.
- This treatment may increase risk of endometrial cancer. In breast cancer the benefit outweighs the risk.

Adverse effects:

- Hot flushes and nausea in 25% of patients. (anti-estrogenic effect)

Tamoxifen and Related Drugs

- 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.
- Raloxifene didn't replace tamoxifen for breast cancer because it's a weaker antagonist.
- It is indicated for prevention of postmenopausal osteoporosis. (not first-line)

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.
- Can also be used for abortion
- Acts also as an antagonist at glucocorticoid receptors.
- Not used in our region due to moral reasons.

Mifepristone

- May be useful in treatment of endometriosis, Cushing's syndrome, breast cancer, and neoplasms that contain glucocorticoid or progesterone receptors such as meningiomas.
- Adverse effects: prolonged bleeding, abdominal or pelvic pain, nausea and vomiting. Dangerous for the female too (not just the baby).
- Doctor: The drug is controversial in the USA

Danazol

- It is a 17α-ethinyltestosterone derivative.
- Has weak progestational, androgenic and glucocorticoid (immune suppression and fluid retention) activities. Not selective.
- 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.

Danazol

Therpeutic uses:

- Endometriosis: It inhibits gonadal function.
- Fibrocystic disease of the breast

- Adverse effects:
  - Weight gain (weight gain and fluid retention), edema
  - Decreased breast size. Not used for this indication
  - Acne and oily skin (androgenic)
  - Increased hair growth (androgenic)

Danazol

- Adverse effects:
  - Deepening of voice (androgenic)
  - Hot flushes (anti-estrogenic by suppressing ant. pituitary)
  - Changes in libido (androgenic) androgens increase libido in both men and women.
- Contraindicated in pregnancy and breast feeding as it may produce urogenital abnormalities in the offspring. As we said, pregnancy may occur without the patient knowing. This more to dangerous to the fetus than OCPs.

Aromatase Inhibitors

Anastrozole, Fadrozole.

- Inhibiting aromatase will decrease estrogen production
- 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.
- Specialized drug (only general knowledge question)

Fulvestrant

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

Ovulation-inducing Agents (Clomiphene)

- Clomiphene is a partial estrogen agonist.
- It is active after oral administration.

Clomiphene

Pharmacodynamics:

- Has estrogenic activity in cases of gonadal deficiency. Partial agonist.
- Inhibits the action of strong estrogens. Partial agonist (antagonist)
- It increases the secretion of gonadotropins (LH/FSH) 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 (for months) until pregnancy occurs.

- It induces ovulation (by increasing LH and FSH secretion). Gonadotrpins can also be given (next lecture)
- Normal ovulation does not usually resume, thus it is of no value in patients with ovarian or pituitary failure. If the ovaries or pituitary gland have failed, the drug has no benefit.

Clomiphene

Adverse effects:

1. Hot flushes is the most common adverse effect. Estrogenic effect
2. Intensification and prolongation of after images (Palinopsia) in some occasions. This is dangerous especially when driving
3. Occasionally: headache, constipation, allergy, hair loss.

Clomiphene

Adverse effects:

3. Ovarian stimulation and enlargement.
4. Multiple pregnancies (10% vs 1% normally). Because it causes maturation of multiple ovum.
5. Nausea, vomiting, increased nervous tension, depression, fatigue, breast soreness, weight gain (mostly sodium and water retention and some inhibition of metabolism), urinary frequency and heavy menses have been reported. They may be due to hormonal changes of ovulation rather than to the drug.

Clomiphene

Contraindications and cautions:

1. Patients with enlarged ovaries should receive small doses.
2. Caution in patients with visual symptoms, because of the after images.

We studied estrogen and progesterone analogues (semi synthetic and synthetic).

Then we studied (not in order):

- **Partial Estrogen Agonists**
  - SERM (Tamoxifen, (Toremifene), Raloxifene)
  - for Ovulation (Clomiphene)
- **Partial androgen/progesterone agonist** (Danazol)
- **Estrogen Inhibitors**
  - Aromatase inhibitors (Anastrozole, Fadrozole)
  - Estrogen Antagonists (Fulvestrant)
- **Progesterone inhibitors / antagonist** (Mifepristone)

PHARMACOLOGY QUIZ LECTURE 8

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			