GONADAL HORMONES, CONTRACEPTIVES & ANTAGONISTS

Comprehensive High-Yield Comprehensive Review Summary

1. Endogenous & Synthetic Estrogens

Physiological Overview

- **Endogenous Estrogens:** The main natural estrogens are **estradiol** (the primary secretory product of the ovary), **estrone**, and **estriol**. Estrone and estriol are primarily synthesized in the liver from estradiol or converted from peripheral tissues using androstenedione and other androgens.

- **Pharmacokinetics & Bioavailability:** Natural estrogens exhibit **extremely low oral bioavailability** due to **substantial intestinal and hepatic first-pass metabolism**, rendering them **clinically useless when swallowed directly.**

- **Transport:** In systemic circulation, **estradiol binds with high affinity to Sex Hormone-Binding Globulin (SHBG)** and with a significantly lower affinity to albumin.

- **Metabolism & The Antibiotic Interaction: Estrogens** are cleared via **glucuronidation in the liver** and **excreted into the bile**. **Intestinal microbial flora normally hydrolyze these glucuronide conjugates, liberating the original free estrogen to be reabsorbed back into circulation via the enterohepatic cycle**.

> ⚠ **Critical Interaction Pearl:** ***Concurrent administration of broad-spectrum antibiotics*** *obliterates the protective natural gut flora. This halts the essential hydrolysis of conjugated estrogen, accelerates its direct fecal excretion, drops plasma concentrations below the therapeutic threshold, and* ***can cause catastrophic oral contraceptive failure****.*

Synthetic Estrogens

To **bypass the hepatic first-pass effect** and **ensure high oral efficacy**, key structural modifications have been developed:

1. Steroidal Agents: **Ethinyl estradiol** and **mestranol** (orally effective steroidal compounds widely used in clinical formulations).
2. Nonsteroidal Agents: All **plant-derived estrogenic substances (phytoestrogens)** and structural compounds that **lack a steroid backbone** but **exhibit potent estrogenic activity**.

Therapeutic Uses

1. **Primary Hypogonadism:** Usually **initiated at 11–13 years of age** to **stimulate the development of secondary sexual characteristics**, **induce menses, optimize skeletal growth development, prevent early severe osteoporosis, and improve the clinical psychological well-being of the patient**. (Note: Estrogen replacement cannot restore fertility if there is underlying primary ovarian failure).

2. **Postmenopausal Hormone Replacement Therapy (HRT): Endogenous estrogen naturally protects the skeletal and cardiovascular systems (Increases TAGs, Phospholipids, HDL and Decreases LDL)** which explains why premenopausal women have significantly lower rates of coronary care unit (CCU) admissions for myocardial infarction than age-matched men. However, **routine postmenopausal HRT failed clinical trials** because it **did not show cardiovascular benefit** and **instead substantially increased risks for breast and endometrial cancers**.

*HRT is now used for **Premature menopause** (e.g., due to early surgical ovariectomy) remains a **valid long-term indication to reduce cardiovascular health risks.***

3. **Osteoporosis Management:** Used as a **secondary (not first-line) preventative agent**. It must always be **coupled with direct calcium** and **vitamin D supplementation** to establish normal bone turnover parameters.

2. Progestins (Progesterone & Analogs)

Classification & Properties

- **Natural Progesterone:** Rapidly absorbed but **undergoes extensive hepatic first-pass metabolism**, yielding a plasma half-life of approximately 5 minutes → **Can't be given orally**. It is **excreted in the urine**, because it is cleared via the renal route without significant enterohepatic recycling, **broad-spectrum antibiotics do not compromise its systemic plasma levels.**

- **Progesterone Derivatives:** Modified natural or semi-synthetic agents including **Hydroxyprogesterone** caproate, **Medroxyprogesterone acetate**, and **Megestrol acetate.**

- **Synthetic Progestins (19-Nortestosterone Derivatives): Modified testosterone formulations** including **Norethindrone**, **L-norgestrel, Norethindrone acetate, Desogestrel**, **Lynestrenol**, and **Ethynodiol diacetate**.

> **Clinical Implication in PCOS:**
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> **The Core Imbalance: Insulin Resistance + Chronically Increased LH ⟶ Excessive ovarian androgen (especially** testosterone**) production.**
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> **Clinical Consequences**
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> - **Hyperandrogenism:** Causes **hirsutism**, **acne** and **decreases HDL cholesterol**, which increases atherogenic risk.
> - **Chronic Anovulation: (Due to the abcense of the LH Surge) ⟶ Decreased Progesterone ⟶ Amenorrhea**
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> 📌 **Endocrine Spectrum Note:** *Many **synthetic progestins are not perfectly selective**; they can display **cross-reactivity with other steroid receptors**,* especially the 19-nortestosterone derivatives, **exaggerating the androgenic effects of PCOS patients**. Therefore, **anti-androgenic progestins are preferred in these patients** to suppress ovarian androgen production while minimizing androgenic side effects.

Summary of Estrogen vs. Progestin Adverse Effects

Hormone Class	Primary Adverse Effects & Pathophysiological Mechanisms
Estrogens	**Uterine Bleeding**: Stimulates un-stabilized endometrial growth, leading to irregular sloughing, spotting, or breakthrough bleeding. (Should be **avoided in patients with undiagnosed vaginal bleeding**)
	Oncologic: Substantially **increases the risk of Prolactinoma and endometrial carcinoma. (Avoided in patients with endometrial or breast neoplasms)**
	Thromboembolism: Induces a **highly hypercoagulable state** by **increasing hepatic synthesis of clotting factors** and **Fibrinogen** and directly **decreasing antithrombin III** (Net result: **Increased ESR**). **(Avoided in patients with thromboembolic disorders)**
	Biliary/Liver: Causes **cholestasis, gallbladder disease, cholelithiasis**, and **hypertension secondary to increased (RAAS) activation** Increased incidence of **hepatic adenomas, Decreased Haptoglobins** and **Increased hepatic carrier protein production (Predictable increase in total hormone levels). (Avoided in patients with liver diseases)**
	Hyperpigmentation
Progestins	**Androgenic Effects**: **Androgenic progestins** directly **reduce plasma HDL levels**, creating an **atherogenic profile, Acne and Hirsutism**.
	Fluid Retention: Causes **sodium (Na+) and water retention,** predisposing patients to systemic **blood pressure elevations** and **weight gain**.
	Depression
	Ureteral Dilation
	Carbohydrate Intolerance: By **reducing Carbohydrates absorption** and **altering insulin secretion and peripheral sensitivity** (**Contraindicated in patients with DM**)
	Bleeding Abnormalities: Including **Amenorrhea**, **Breakthrough bleeding** (Spotting), or **failure of withdrawal bleeding**
	Oncologic Interaction: When administered with estrogen in postmenopausal HRT, **progestins further exacerbate the baseline risk of breast cancer**, though they **successfully reduce the risk of endometrial cancer.**

3. Pharmacology of Hormonal Contraception

Mechanisms of Action

Combined Oral Contraceptives (COCs) leverage **low, consistent doses of synthetic hormones** to achieve **multi-tiered contraceptive efficacy** through the following pathways:

1. Ovulation Suppression (Primary): Suppresses the anterior pituitary's release of gonadotropins (FSH and LH) via negative feedback. The decrease in FSH prevents follicular growth and natural estrogen secretion, while the suppression of the mid-cycle LH surge completely halts ovulation.

2. Cervical Mucus Alteration: Progestins cause **cervical mucus to become thick, highly viscous, and sparse,** creating an **effective physical barrier that blocks sperm penetration**.

3. Endometrial Dyssynchrony: Alters the endometrial lining and **reduces the motility and normal secretions of the uterine tubes**, creating a hostile local environment that severely decreases the likelihood of conception and blastocyst implantation.

Formulations & Regimens

- **Monophasic Combinations:** Delivers a **constant, unvarying dosage of both components throughout the full 21–27 day treatment cycle** before **pausing on day 28 to allow for withdrawal bleeding.**

- **Phasic Combinations: The dosage of one or both components changes once (biphasic), twice (triphasic), or thrice (tetraphasic) during the cycle**. This phasic scheduling **alters hormone ratios to better mimic physiological shifts**, minimize cumulative steroid exposure, and reduce instances of breakthrough bleeding.
- **Progestin-Only Therapy ('Mini-Pill'):** Formulated exclusively **for patients where estrogen is strictly contraindicated** (e.g., active heavy smokers over 35, history of thromboembolic disorders, or active liver disease).

- **Depot Medroxyprogesterone Acetate (DMPA):** An **intramuscular depot injection given every 3 months** that reliably **inhibits ovulation for up to 14 weeks.** However, because **ovulation can remain suppressed for up to 18 months after the final dose**, it is entirely **unsuitable for women planning a near-term pregnancy**. Furthermore, its **sustained suppression of endogenous estrogens can induce a reduction in bone mineral density and produce unfavorable plasma lipid profiles.**

4. Estrogen & Progesterone Antagonists / Modulators

Selective Estrogen Receptor Modulators (SERMs)

SERMs exhibit a unique tissue-selective pharmacodynamic profile, acting as **competitive antagonists in certain target tissues** while operating as **partial or full agonists in others** due to differential estrogen receptor subtype expression.

Tamoxifen and Toremifene:

Agonist in:

- **Bone tissue (maintaining lumbar spine density)**
- **Liver → (↓ LDL)**
- **Endometrium (increases the clinical risk of endometrial carcinoma)**

Antagonist in:

- **Full estrogen antagonist in breast tissue (Given for Breast Cancer patients)**

Use: For Breast Cancer patients

Adverse Effects: Promotes a ***central anti-estrogenic effect*** *resulting* ***in severe hot flushes and nausea in roughly 25% of all patients****.*

Raloxifene:

Agonist in:

- **Bone tissue (maintaining lumbar spine density)**
- **Liver → (↓ LDL)**

Antagonist in:

- **Breast tissue (Weaker**
- **Endometrium (decreases the clinical risk of endometrial carcinoma)**

Use: Prevention of postmenopausal Osteoporosis (Not First-Line)

Pure Estrogen Antagonists & Aromatase Inhibitors

Fulvestrant:

MOA: **Estrogen receptor antagonist**

Use: These agents are used primarly in **tamoxifen-resistant breast cancers**

Anastrozole & Fadrozole:

MOA: Directly **inhibit the aromatase enzyme**, **preventing the final peripheral conversion of androgens into estrogens.**

Use: These agents are used primarly in **tamoxifen-resistant breast cancers**, could be also used in: **precocious puberty**, and primary **excessive aromatase syndromes.**

Progesterone & Androgen Modulators

Mifepristone:

MOA: A 19-norsteroid that acts as a **Non-specific progesterone receptor blocker with luteolytic properties when administered during the mid-luteal period (Acts also on Glucocorticoid Receptors).**

Use: It is utilized as an **Emergency post-coital contraceptive**, and holds therapeutic value in managing **endometriosis**, **Cushing's syndrome**, and **progesterone (Or Glucocoticoids) -receptor-positive meningiomas**.

Danazol:

MOA: A 17a-ethinyltestosterone derivative that exhibits **weak**, non-selective progestational, **androgenic**, and glucocorticoid **activities.** It directly **suppresses ovarian function** by **inhibiting the mid-cycle surge of LH and FSH without affecting basal secretion rates**, leading to the atrophy of ectopic endometrial tissue.

Used for: Endometriosis and **Fibrocystic Breast Diseases**

Adverse Effects & Contraindications:

Androgenic properties cause weight gain, fluid retention, edema, decreased breast size, severe acne, oily skin, hirsutism, and irreversible deepening of the voice.

Contraindicated in pregnancy due to the severe **risk of inducing urogenital structural abnormalities in the developing offspring**.

5. Ovulation-Inducing Agents

Clomiphene

MOA: Acts as a **partial estrogen agonist.**

Binds to estrogen receptors in the hypothalamus and anterior pituitary, blocking the negative feedback loop of endogenous estradiol, the neuroendocrine axis perceives a state of gonadal deficiency, **responding by up-regulating the pulsatile secretion of GnRH, FSH, and LH, which directly drives follicular maturation.**

Clinical Applications / Uses: Indicated for **treating ovulatory dysfunction in women who wish to become pregnant, should be** administered repeatedly over consecutive months until successful conception occurs.

Note: Holds absolutely **no therapeutic value in cases of overt primary ovarian or pituitary failure.**

Adverse Effects: **Most commonly hot flushes**, **increases the rate of multiple pregnancies** to approximately **10%** (compared to 1% in natural unassisted cycles), and with some patients reporting visual phenomenon known as **palinopsia** (**intensification and abnormal prolongation of visual after-images**), posing serious risks when driving. increases the rate of multiple pregnancies to approximately **10%** (compared to 1% in natural unassisted cycles).

Contraindicated in: **Patients with enlarged ovaries** (Should receive low doses) and **patients with visual symptoms.**