**MENOPAUSE/CONTRACEPTION/DUB SECTIONS:**

**“BASIC SCIENCE” LEARNING OBJECTIVES**

- Describe the structure and function of the female reproductive system
- Describe how peptide hormones of the hypothalamus and pituitary regulate reproductive system structure and function
- Describe how steroid hormones regulate reproductive system differentiation, structure and function
- Describe the production of steroid hormones in the ovarian substructures and how steroid hormone production is regulated by hypothalamic and pituitary peptide hormones. Note the key biosynthetic steps and precursors, and how genetics, disease and drugs may influence biosynthetic processes.
- Characterize variations in hypothalamic and pituitary hormone levels and steroid hormone levels during maturation, puberty, pregnancy, the climacteric phase and menopause.
- Generally describe how genetic defects or reproductive tissue pathologies may influence contribute to menstrual disorders/menopause
- Describe the biochemical events involved in estrogen receptor stimulation and expression of estrogenic activity. Describe the different estrogen receptor subtypes and their tissue localization.
- Generally describe the modulatory roles of the estrogenic hormones in skin and skeletal tissue, cardiovascular pathology, CNS function, the gut and other estrogen-dependent tissues (breast)
- Describe the causes, clinical presentation, laboratory assessment of various reproductive tract disorders.
- Describe the consequences of estrogen deficiency on the organ systems of the body
- Describe the relationship between reproductive tract disorders and common comorbid conditions that develop
- Describe the various structural sub-classes of estrogenic hormone drugs and how structure influences pharmacologic activity, key pharmacokinetic properties and adverse reaction profiles. Describe the rationale for differences in properties based on structure.
- Describe the different formulations for the various structural sub-classes of steroid hormone drugs. Describe the rationale for different formulations.
- Compare the available therapeutic modalities for estrogen replacement therapy (ERT), hormone replacement therapy (HRT) and other steroid hormone therapies (see cases related materials)
OVERVIEW OF REPRODUCTIVE PHYSIOLOGY AND PATHOPHYSIOLOGY AND THE STEROID HORMONES

I. INTRODUCTION: REVIEW OF PHYSIOLOGY AND PATHOPHYSIOLOGY

A. Embryonic Sexual Differentiation: *Physiology and Pathophysiology Coursework*
   - Gonadal sex and testes versus ovary development
   - Induced phenotypes
   - Puberty and the gonadotropin-releasing hormones
   - Estrogen-Dependent Tissues

B. Brief review of physiology: *Physiology and Pathophysiology Coursework*
   - Ovaries and Follicle structure: the role of granulosa cells, thecal cells
   - Uterus and endometrial lining: Menstrual bleeding
   - Uterine tubules AND Vagina

C. Review of the Menstrual Cycle:
   - Regulation by hypothalamus, pituitary, ovary and uterus with liver (SBG) and adrenals and thyroid gland
   - Hypothalamus: GnRH
   - Pituitary: Gonadotrophs (FSH and LH)
   - Ovarian Responses: See Estrogen Biosynthesis Chapter
   - Maturation of the Oocytes: Ovulation and Atresia
   - Synthesis and Secretion of Steroid Hormones: Phases
     - Thecal Cells: Androgen production (LH-modulation)
     - Granulosa Cells: Estrogen production from Androgens (FSH)
       Progesterone production: FSH -> LH receptors
   - Ovulation
   - Luteal Phase: Formation of the Corpus Luteum (Follicle)
     - Estrogen and Progesterone production: Endometrial maturation
   - LH production declines (Progesterone feedback)
   - Peak estradiol (E2: 200-400 pg/mL) and estrone (E1: 170-200 pg/mL) during the late follicular phase, then decrease to 40-60 pg/mL (estradiol) and 40-60 pg/mL (estrone) to early follicular phase. In menopause average E2 and E1 concentrations are 5-20 pg/mL and 30-70 pg/mL, respectively. The change in E2/E1 profile is derived from peripheral (adipose) formation of E1 from androstenedione:
     Pre-menopause: E2/E1 > 1
     Menopause: E2/E1 < 1
   - End of Menstrual Cycle: Absence of fertilization and Implantation
   - Fertilization and Implantation: Placenta and hCG Production (P production)
   - HCG: Independent of E and P levels
The following diagram illustrates the hormonal inter-relationships in the control of the female reproductive system (GF = Graafian follicle, CL = corpus luteum, LH = luteinising hormone, FSH = follicle stimulating hormone and GnRH (LHRH) = gonadotrophin-releasing hormone).
D. Pregnancy:
E. Lactation:
F. Menopause

1. Natural History and Diminished Reproductive Function
   - Climacteric Phase: LH/FSH Levels, E, P and A levels and follicle and tissue development: *FSH as a diagnostic marker*
   - Change in steroid biosynthesis and level profiles (peripheral tissues)
   - Vasomotor symptoms: hot flashes, sweating and chills;
   - Psychologic/Mental status
   - Delayed systemic changes: Osteoporosis, CV, Skin, etc.

G. Reproductive Tract Disorders: *Tissue-based classification*

1. Disorders of Sexual Differentiation:
   - Turner’s Syndrome:
   - Gonadal Dysgenesis:
   - Pseudohermaphroditism

2. Disorders of hypothalamic and Pituitary Function
3. Disorders of the Ovary
4. Disorders of the Uterus and Uterine Tubes and Vagina
5. Disorders of Pregnancy
6. Disorders of the Breast

H. Menstrual Disorders:

1. Amenorrhea
   - Etiology: Normal versus pathologic (structural/functional disorders above)
   - Pathology and Pathogenesis:
   - Uterine Disorders: Curettage
   - Ovarian Failure:
   - Genetic Based: Turner’s Syndrome and mosaicism
   - Premature Ovarian Failure: Causes
   - Chronic Anovulation:
   - Hormonal Feedback Disorders: Polycystic ovary syndrome
   - Pituitary and Hypothalamic Disorders: Trauma, Sheehan’s Syndrome
   - Others: Anorexia nervosa, Stress, Hypothyroidism, hyperprolactinemia:
   - Clinical Manifestations: (KBL Notes/Cases)

2. Dysmenorrhea (Pain)
3. Menorrhagia (heavy menses)
4. Metrorrhagia (longer duration)

I. Infertility:
J. Preeclampsia-Eclampsia:
II. STEROID HORMONE OVERVIEW: SEE CHAPTER

A. General Structure and Nomenclature
B. Stereoisomerism: Role in ER binding
C. Overview of Steroid Hormone Biosynthesis
D. Overview of Steroid Hormone Receptor Actions
E. Overview of Steroid Hormone Structural Alterations

III. ESTROGENIC HORMONES AND ESTROGENIC DRUGS

A. Introduction:

The sex hormones, those endocrine substances involved in reproduction, the menstrual cycle and in giving women and men their characteristic physical differences, are all steroid in nature. While estrogens and progesterone are usually termed female sex hormones and testosterone is called a male sex hormone, it is important to note that all these steroids are biosynthesized in both males and females.

B. Estrogen Biosynthesis: See Figure on Next Page

- Cholesterol (C): Storage and biosynthesis in response to gonadotrophs
- Biosynthetic Sites and Enzymes: Many, including aromatase, are CYP 450s
  - Thecal cells: Cholesterol ->Androgens (testosterone)
  - Granulosa Cells Androgens (testosterone) -> Estrogens (Estradiol)
  - Corpus Luteum: Progesterone and Estrogens
  
  Androstenedione -> Testosterone ->Estradiol (reproductive)
  Androstenedione -> Estrone (peripheral tissues)

- Aromatase: Both Androstenedione and Testosterone are substrates (An>T):
- Variation with physiologic state: i.e. In pregnancy placenta main organ of E production
- Other sites: Testes, adrenal cortex, hypothalamus and pituitary, adipose tissues (major site of estrogen production in post-menopausal women)
- The major endogenous estrogens include 17ß-estradiol, estrone and estriol. 17ß-Estradiol is present in highest levels and is most active as an estrogen; estrone is about one-third as active as estradiol and estriol is about one-sixteenth as active. (Estradiol > Estrone > Estriol).
Biosynthesis of the Estrogens

Testosterone/Androstenedione

\[
\text{CH}_3 \quad \text{CH}_3 \quad \text{OR} \quad \text{OR} \quad \text{HO} \quad \text{HO} \quad \text{HO} \quad \text{HO} \quad \text{O} \quad \text{Enz} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{HO} \\
\text{CH}_3 \quad \\
\]

Aromatase \text{NADPH} \text{O}_2

\[
\]

H\text{2O}

Aromatase \text{NADPH} \text{O}_2

Estradiol (R=OH and H) or Estrone (R = O)
C. Receptor Actions:

1. Steroid Receptors and Actions: Estrogens versus other Steroid Hormones

   - Transport to site: Steroid Binding Proteins
   - Diffusion across the cell membrane
   - Stereospecific binding (17β-) to receptors in nucleus: A, E and Ps in nucleus, Gs in cytosol
   - Conformation change in receptor allowing for dimer formation
   - Dimeric complexes interact with Hormone responsive elements (HREs) of DNA
   - Stimulation of Transcription -> mRNA (response time)
   - mRNA -> Protein synthesis in ER P receptors, etc.
   - Compare receptors and HREs for various steroids (Gs, As, Es and Ps)

2. Estrogen Receptors:

   - Estrogen receptor affinity does not necessarily correlate with biologic potency (see Table)
   - Subtypes ER-beta and ER-alpha:
     - DNA binding domains (97% homologous) and Ligand binding domains (40% heterogeneity).

3. Differences in estrogenic activity of different estrogen products:

   - Different affinities for ERs and different activities at ER-ligand complexes: compound may be an agonist at one receptor site and antagonist at another
   - Pharmacokinetic differences: rate, nature of metabolism
   - ER receptor variability (alpha vs beta) and function in different tissues

   See Table: Estrogen Receptor Subtypes and Physiologic Actions at end of section

C. Pharmacology of estrogens:

   - Promote development of secondary sex characteristics: growth of hair, softening of skin, growth of breasts, accretion of fat in thighs, hips and buttocks.
   - Stimulate growth and development of female reproductive tract: endometrium, myometrium and vaginal and urethral epithelium
   - Enhance vascular flow in the genital tract
   - Increase cervical gland secretions
   - Induce expression of progesterone and LH receptors
D. Long-term benefits of estrogen therapy:
- Prevent coronary atherosclerosis in women before menopause: Lipid effects
- Improved cognitive function” dementia
- Maintenance of skeletal integrity
- Prevention of tooth loss
- Protect against macular degeneration: Skin and collagen
- Protect from colon cancer

E. Estrogen Metabolism and Clearance:
- The three estrogens are interconvertible by estradiol dehydrogenase and related enzymes. 17β-Estradiol is rapidly metabolized by oxidation to estrone and thereby partially inactivated (see activity data above). Substitution of alkynyl groups at the 17-position of 17β-estradiol yield estrogenic drugs which are not subject to this oxidative pathway (see drugs below). Estrone is converted by reduction to 17β-estradiol and by oxidation to estriol, the major estrogen in human urine.

- Clearance: As sulfate and glucuronides in liver (kidneys and intestines play a smaller role). Hepatic metabolism by conjugation involving D-ring alcohol O-glucuronidation and A-ring 3-O-sulfonate predominate. These conjugates are devoid of activity, but are recycled and may be reabsorbed and converted back to the parent estrogens by hydrolysis. More than 50% of administered estrogens are
excreted in bile and recycled as these conjugated metabolites. Because estrogens are reabsorbed by the intestine, orally administered estrogens have a high ratio of hepatic to peripheral effects. The remaining fraction of steroid metabolites are eliminated renally.

- Also 2- and 4-oxidation of estrone and estradiol in some tissues (particularly the CNS) to give catechols which are conjugated by methylation (at 2- or 3-OH) and these eliminated as conjugates. Some catechol estrogens (3-hydroxy estrone, but not 2-OH estrone; 2-OH estradiol has both estrogenic and catecholaminergic activity) have estrogenic activity and interact with CNS (pituitary and hypothalamus) E receptors. Also may interact with CNS NE, DA and 5-HT pathways and thereby modulate behavior (cognition, Alzheimer’s)

F. Therapeutic Estrogen Products

1. Natural Estrogens and Derivatives

The so-called "natural estrogens" used therapeutically can be further subdivided into two classes: the human estrogens and derivatives and the equine estrogens and derivatives. The major human estrogens and derivatives include 17ß-estradiol, estrone and estriol and the derivative, ethinyl estradiol. These are all produced by semi-synthesis. Most estrogens are sufficiently lipophilic to be absorbed rapidly through skin, mucous membranes and gut (see Product Formulations Below). 17ß-Estradiol and estrone are available for oral administration and as IM, vaginal, topical and implant formulations; Estradiol and the 17α-ethinyl derivative are orally active. The 17α-ethinyl group of ethinyl estradiol blocks oxidative metabolism at this position and extends efficacy and enhances lipid solubility (estrogenic potency equals estradiol).
The major equine estrogens in use today include estrone, equilin, equilenin and derivatives. These were originally obtained from horse urine. At least 10 other active estrogenic products contained in the mixture, and there may be as many as 200 total steroids. Others include 17α-dihydroequilin sulfate, 17β-dihydro-equilin sulfate and 17a-estradiol sulfate: Equilin and Equilinin: secreted in urine of mares as water soluble sodium sulfate conjugates. Note that equilin and equilenin differ from estrone only in the degree of unsaturation in the B-ring at positions 6, 7, 8, and 9. Two major components are estrone and equilin as sodium sulfates.

**Estrogen Lipophilic Ester Prodrugs**

Estrogens of increased lipophilicity are prepared by esterification of the 3 and/or 17-hydroxyl groups (estradiol-3-benzoate, 3,17-dipropionate, 17-valerate and 17-cyclopentylproprionate) or by formation of 3-alkyl ethers of the A-ring hydroxy (mestranol and quinestrol). It is important to note that these derivatives are prodrugs and require hydrolysis (esters) and oxidative O-dealkylation (ethers) to yield the parent steroids. Absorption of the intact ethers or esters prevents first pass conjugative reactions. Mestranol, the 3-methyl ether of ethinyl estradiol is a common estrogen in oral forms. Quinestrol, a 3-cyclopentyl ether is the most potent estrogen and long-acting. This derivative is stored in body fat and slowly released.
It is theoretically possible to form ionic, hydrophilic salts of the estrogens via ionization-neutralization of the acidic C3-phenolic-OH. However, since this function is very weakly acidic requiring the use of relatively strong alkali for neutralization, the resulting salts would form highly alkaline aqueous solutions thereby limiting their therapeutic utility. Hence, therapeutically useful ionic, hydrophilic salts of estrogens are formed by initially esterifying (reversible derivatization) the C3-phenolic-OH with a strong acid (such as sulfonic acid) generating a strongly acidic derivative followed by subsequent neutralization with a base such as sodium or piperazine. It is interesting to note that human and equine steroids are normally metabolized (in part) by sulfate conjugation!
2. **Natural products:**

- Mexican yam: Steroid precursors, sodium salts of estrone and equilin
- Plants (soybeans, dates, pomegranates): Contain phytoestrogens: analogs of human and horse estrogens

3. **Non-Steroidal Estrogens:**

- Structure-activity studies with the estrogen steroids have revealed that appropriately substituted diarylethene derivative possess potent estrogenic activity,

- The nonsteroidal estrogens such as DES can be viewed as a form of estradiol with rings B and C open and an aromatic ring D. The trans-(Z)-DES isomer is approximately 10-times more potent than cis-DES,

- The estrogenic activity of compounds like DES was initially explained on the basis of the similarity in intramolecular distances between 3-OH and 17-OH groups in DES and 17β-estradiol. However, the experimentally determined OH → OH distance in DES is 12.1 Å and 10.9 Å in estradiol. However, in an aqueous system (e.g. *in vivo*) estradiol has two H₂O molecules hydrogen bound to the 17-OH. If one of the two water molecules is included in the distance measurement, there is a perfect with the two OH groups of DES (see figure below). This suggests an important role for water in the interaction of estradiol with its receptor.
G. Variable Activities of Estrogenic Products

1. Inhibition of Gonadotropin Secretion:
   Equilin sulfate > CEE = Piperazine estrone sulfate = micronized estradiol

2. Uterine Growth:
   17B-estradiol and 17b-dihydroequilin > estrone sulfate

3. Vasomotor and Urogenital:
   Estrone sulfate = equilin sulfate = 17B-dihydequilin = CEE = transdermal estradiol

4. Beneficial effect on lipid profiles:
   Equilin sulfate > Estrone sulfate = CEE > estradiol products

5. Osteoporosis:
   CEE = estradiol = estriol; (dosage form independent) > equilin sulfate

6. Cognitive Function: All estrogens

7. Nerve Cell growth: Equilin > estradiol, estrone and estriol
IV. PROGESTERONE AND THE PROGESTINS

A. Introduction: Physiologic Actions and Potential Therapeutic Applications

- **Progestins** are compounds that have biologic actions similar to progesterone. They include two structural classes of steroids, the **Progesterones** (pregnanes) and **testosterones/19-Nortestosterones** (androstanes).

  The progesterone derivative megestrol acetate is used in treatment of advanced breast and endometrial cancer. The 19-nortestosterone derivatives are so-called "third generation" progestin with minimal androgenic activity.

- Progesterone is secreted from corpus luteum during second half of menstrual cycle causing development of a secretory endometrium. Concentrations greatly increased during pregnancy to suppress uterine contractions.

- Progestins exert their physiologic effects through activation of gene transcription, similar to other steroid hormones, following binding to progesterone receptors in the cell nucleus and cytoplasm. Ligand-receptor complex activates gene transcription.

- The know the main physiologic effects the progestins and how they affect their clinical use
  - stimulate lipoprotein lipase
  - increase basal insulin levels and insulin response to glucose
  - promote glycogen storage in liver
  - promote ketogenesis
  - increase body temperature
  - proliferation of mammary gland acini

- Progesterone's principal target organs are the uterus, breast and brain. The major therapeutic uses of the progestins include:
  - hormone replacement therapy (HRT) and hormonal contraception (most frequent use!!)
  - ovarian suppression
  - metastatic endometrial, renal and breast carcinomas

- Many synthetic progestins (discussed in the sections that follow) are orally active with longer duration of action. Some may have estrogenic and androgenic activity. The new "third generation" progestins have lower androgenic activity (*e.g.*, **norgestimate**)

- Primary adverse effects of progestin products are an increased blood pressure and lower HDLs
B. Biosynthesis and catabolism of Progesterone (see steroid biosynthesis figure presented in the "Overview" section)

- Endogenous progesterone is produced in the ovaries by the corpus luteum from cholesterol (2 steps) upon LH stimulation. Its production is subject to feedback inhibition at the pituitary and hypothalamus similar to estrogens.

- Exogenous progesterone shows relatively good oral absorption but poor oral bioavailability because of extensive first-pass hepatic extraction and metabolism ($t_{1/2} = 5$ min); progesterone can be injected IM in oil. The major pathways of metabolic inactivation include reductions at C-3, C4-5 and C-20. The major excretory product of progesterone metabolism forms from a combination of these pathways and is 5β-pregnane-3α, 20-diol and its conjugates:

\[
\text{Metabolism of Progesterone}
\]

C. Therapeutic Progestins

1. Progesterone Derivatives:

- Hydrophobic esters of the 17β-hydroxy of progesterone yields active compounds with a longer duration of action related in part to protection of C-20 ketone from reduction:

- 6α-CH$_3$ or Cl derivatives: protects the unsaturated keto function in ring A as well as the C-20 carbonyl from catabolism producing active compounds with long duration of action:
2. Testosterones and 19-Norandrostanes:

- Testosterone analogues with progestational activity include ethisterone and Dimethisterone. Both of these compounds retain the 19-methyl group present in testosterone.

- 19-Nortestosterone derivatives include those analogues which lack the 19-methyl and retain progestational activity

- Highly potent progestin-like activity widely used in oral contraceptive products. Other structural modifications such as 17-ethinylation and 17β-OH esterification produces therapeutically useful progestins. Substituents at C-17 block metabolic oxidation (and inactivation)
Testosterones and 19-Norandrostanes

D. Progestin Structure, Receptor Binding and Potency

The structural requirements for progesterone receptor binding include the 4-en-3-one moiety of Ring A and a conformation that differs significantly from that of testosterone and the glucocorticoids. Although the testosterone and 19-nortestosterones may produce androgenic side effects, their primary activity is progestational. The primary trends summarized in the table below include:

- 17α-ester substitution enhances oral activity and progestational activity.
- 6-Methyl substitution further enhances oral and progestational activity
- 17α-Ethinylation in the testosterone and 19-nortestosterone series enhances oral activity, but generally reduces progestational activity. This substitution also reduces androgenic and anabolic activity of these compounds compared to progesterone
### Progestin Relative Oral Activity SC activity

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<th>SC activity</th>
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**E. PROGESTERONE ANTAGONIST**

Mifepristone (RU 486) is proposed to be a selective progesterone receptor antagonist.
V. THERAPEUTIC PROFILES OF ESTROGENS AND PROGESTINS

A. Introduction

This section is intended as an overview of some of the primary therapeutic applications of estrogen and progestin drugs and a study guide. More detailed discussions are provided in the Dipiro text.

B. Hormonal Contraception

• Two major types of preparations available are combined: estrogen and progestin and with progestin alone if needing to avoid estrogenic side effects. Depot and implantable progestins are also available for estrogen-free, long-term contraception.

• Estrogen and progestin inhibit circulating levels of FSH and LH, respectively. Estrogen inhibits ovulation and progestin induces physiologic withdrawal bleeding. Makes cervical mucous thicker, an important effect in contraception, as the thick mucous inhibits movement of sperm and can even be spermicidal. Combination agents inhibit coordinated tubal and uterine contractions. These actions play a major role in contraceptive effectiveness of continuous progestin treatment even when ovulation is not inhibited.

• understand the physiologic and pharmacologic differences between the combination agents and the progestins alone

• understand the importance of the current use of low-dose estrogen as compared to earlier oral contraceptive preparations:

  The adverse effects of estrogen are dose-related. They were a bigger deal in the past, because estrogen doses used to be much higher. Today’s doses are much lower, and the adverse effects are not as pronounced.

• recognize that there are many preparations available

• which component generally varies in the sequential preparations?

• The adverse effects
  - mild
    i. frequent and generally transient
    ii. often eliminated by using different formulation

  - moderate (similar to early pregnancy effects primarily due to estrogen)
    i. may require discontinuation
    ii. include breakthrough bleeding, nausea, headache, weight gain, acne, skin pigmentation (associated with combination pills formulated with progestin with androgenic activity), hirsutism, resilient vaginal infections, and amenorrhea following discontinuation
- severe
  i. incidence has markedly decreased as the dose of estrogen in oral contraceptives has been reduced (Risk greatest in women over 35 who smoke)
  ii. vascular disorders venous thromboembolism, myocardial infarction, cerebrovascular disease (stroke), hypertension, depression

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<th>Progestin (mg)</th>
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</tr>
<tr>
<td>Days 8–14</td>
<td>Ethinyl estradiol 0.035</td>
<td>Norgestimate 0.215</td>
</tr>
<tr>
<td>Days 15–21</td>
<td>Ethinyl estradiol 0.035</td>
<td>Norgestimate 0.25</td>
</tr>
<tr>
<td>Daily progestin tablets</td>
<td>Ethinyl estradiol 0.035</td>
<td>Norethindrone 0.35</td>
</tr>
<tr>
<td>Micronor</td>
<td>Ethinyl estradiol 0.035</td>
<td>Norethindrone 0.35</td>
</tr>
<tr>
<td>Nor-QD</td>
<td>Ethinyl estradiol 0.035</td>
<td>△-Norgestrel 0.075</td>
</tr>
<tr>
<td>Ovrette</td>
<td>Ethinyl estradiol 0.035</td>
<td>△-Norgestrel (6 tubes of 36 mg each)</td>
</tr>
<tr>
<td>Implantable progestin preparation Norplant System</td>
<td>Ethinyl estradiol 0.035</td>
<td>△-Norgestrel (6 tubes of 36 mg each)</td>
</tr>
</tbody>
</table>
• Progestin treatment alone has a high incidence of abnormal bleeding

• Depo-Provera achieves long-term contraception but has risk of permanent infertility understand the controversy regarding oral contraceptives and cancer
  - appear to decrease the incidence of endometrial and ovarian carcinomas
  - concern regarding breast cancer but risk is decreased when preparations contain less than 50 µg of estrogen

• Know the contraindications for oral contraceptives
  Some antibiotics can destroy normal GI flora ----> interfere with enterohepatic recycling of estrogen ----> reduce estrogen levels. This is why oral contraceptives can fail when taken with some antibiotics.

• Know the advantages and disadvantages of contraception with progestins alone:
  - Combined Oral Contraceptives: The main reason progestins are added to oral contraceptives is to ensure prompt withdrawal bleeding.
  - Progestins used alone are not as effective (96.5-97%) as combined oral contraceptives (99%).
  - There is no menstruation at all when using progestins alone.

• Post-coital contraception
  - Schedule for post-coital contraception. ‘Morning after’ occurs with short-term administration of high doses of estrogens alone or in combination with progestins. Treatment is begun 72 hours of coitus and is 99% effective. Mifepristone is also an effective single dose postcoital contraceptive.
  - Mechanism unclear, but it may disturb the environment in the uterus, making it unfavorable for implantation.

C. Post-Menopausal Therapy

• Equine and natural estrogen derivatives are used for post-menopausal therapy (See Table below)

• Some beneficial effects:
  • Antagonizes the effect of PTH on bone ----> prevent bone loss after menopause.
  • Estrogen does not appreciably add bone mass, but it can prevent bone loss.
  • Increases plasma levels of HDL, and decreases LDL, thus it is effective in preventing heart disease.
  • Even in low doses, it prevents hot flashes associated with Menopause.
Formulations of Estrogenic HRT Products:

<table>
<thead>
<tr>
<th>ESTROGEN ONLY PRODUCTS</th>
<th>Brand Name:</th>
<th>Dosage Forms Available:</th>
<th>Strength:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONJUGATED ESTROGENS:</strong> Conjugated Equine Estrogens (CEE)</td>
<td>Premarin</td>
<td>Oral Tablets</td>
<td>CEE 0.3 mg CEE 0.625 mg CEE 0.9 mg CEE 1.25 mg CEE 2.5 mg</td>
</tr>
<tr>
<td>Conjugated Estrogens Vaginal Cream</td>
<td>Premarin Vaginal Cream In nonliquefying base</td>
<td>Vaginal Cream</td>
<td>CEE- each gram contains 0.625 mg CEE</td>
</tr>
<tr>
<td>Conjugated Estrogens Injection</td>
<td>Premarin</td>
<td>IM or IV Injection</td>
<td>25 mg / 5 ml</td>
</tr>
<tr>
<td>Synthetic Conjugated Estrogens A</td>
<td>Cenestin</td>
<td>Oral Tablets</td>
<td>SCE 0.625 mg SCE 0.9 mg</td>
</tr>
<tr>
<td><strong>ESTRONE:</strong> Esterified Estrogens with 75 to 85% Estrone Sulfate and 6 to 15% sodium equilin sulfate, in such proportion that these 2 components is &gt;90% of the total esterified estrogens content.</td>
<td>Estratab Menest</td>
<td>Oral Tablets</td>
<td>EE 0.3 mg EE 0.625 mg EE 1.25 mg EE 2.5 mg</td>
</tr>
<tr>
<td>Estrone Aqueous Suspension</td>
<td>Kestrone</td>
<td>IM Injection</td>
<td>5 mg / ml</td>
</tr>
<tr>
<td>Estrone Vaginal Cream</td>
<td></td>
<td>Vaginal Cream</td>
<td></td>
</tr>
<tr>
<td><strong>STERADIOL:</strong> Micronized Estradiol Tablets</td>
<td>Estrace Generic estradiol</td>
<td>Oral Tablets</td>
<td>Estradiol 0.5 mg Estradiol 1 mg Estradiol 2 mg</td>
</tr>
<tr>
<td>Estradiol Cypionate in Oil</td>
<td>DepGynogen Depogen Depo-Estradiol Cypionate</td>
<td>IM Injectable</td>
<td>5 mg / ml</td>
</tr>
<tr>
<td>Estradiol Valerate in Oil</td>
<td>Delestrogen Gynogen LA Valergen 20 and 40 Estra-L 40</td>
<td>IM Injectable</td>
<td>10 mg / ml 20 mg / ml 40 mg / ml</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>Estinyl</td>
<td>Oral Tablet</td>
<td>0.02 mg 0.05 mg 0.5 mg</td>
</tr>
<tr>
<td>Estradiol Patch</td>
<td>FemPatch Vivelle / Vivelle Dot Alora Climara Estraderm Esclim</td>
<td>Transdermal Patch</td>
<td>FemPatch 0.025 (7 day patch) Vivelle 0.0375, 0.05, or 0.075, or 0.1 mg QD (apply 2x per week) Alora 0.05, 0.075, or 0.1 mg QD (apply 2x per week) Climara 0.05, 0.075, or 0.1 mg QD (7 day patch) Estraderm 0.05, 0.075, or 0.1 mg QD (apply 2x per week)</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------------------------</td>
<td>------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Estradiol SQ</td>
<td>Subcutaneous Pellets</td>
<td>Micronized Estradiol Vaginal Cream Estrace Vaginal Cream</td>
<td>Vaginal Cream 0.1 mg estradiol per gram of vaginal cream, in nonliquefying base</td>
</tr>
<tr>
<td>Estradiol Vaginal Ring</td>
<td>Estring Vaginal Ring</td>
<td>Estradiol Hemihydrate Vagifem Vaginal Tablet (white, film-coated vaginal tablet with single-use applicator)</td>
<td>25 ug</td>
</tr>
<tr>
<td>Estradiol Vaginal Ring</td>
<td>Estring Vaginal Ring</td>
<td>Estradiol Hemihydrate Vagifem Vaginal Tablet (white, film-coated vaginal tablet with single-use applicator)</td>
<td>25 ug</td>
</tr>
<tr>
<td>ESTROPIPATE:</td>
<td>OrthoEst Ogen Estropipate Generic</td>
<td>Oral Tablets</td>
<td>0.625 mg sodium estrone sulfate, equivalent to 0.75 mg Estropipate</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.25 mg sodium estrone sulfate, equivalent to 1.50 mg Estropipate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5 mg sodium estrone sulfate, equivalent to 3.0 mg Estropipate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 mg sodium estrone sulfate, equivalent to 6.0 mg Estropipate</td>
</tr>
<tr>
<td>Estropipate Vaginal Cream</td>
<td>Ogen Vaginal Cream</td>
<td>Vaginal Cream</td>
<td>1.5 mg Estropipate per gram of cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With calibrated applicator</td>
<td></td>
</tr>
<tr>
<td>OTHERS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinestrol</td>
<td></td>
<td>Oral Tablets</td>
<td></td>
</tr>
<tr>
<td>Chlorotrianisene</td>
<td></td>
<td>Oral Tablets</td>
<td></td>
</tr>
<tr>
<td>Dienestrol Vaginal Cream</td>
<td>Ortho Dienestrol Vaginal Cream</td>
<td>Vaginal Cream</td>
<td>0.001% dienestrol, in 78 grams</td>
</tr>
</tbody>
</table>
### ESTROGEN AND PROGESTIN PRODUCTS

<table>
<thead>
<tr>
<th>Hormone Replacement Therapy: Active Ingredient</th>
<th>Brand Name:</th>
<th>Dosage Forms Available:</th>
<th>Strength:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated Equine Estrogens (CEE) and Medroxyprogesterone Acetate (MPA)</td>
<td>Prempro (Continuous Combined)</td>
<td>Oral Tablets</td>
<td>Prempro: 0.625 mg / 2.5 mg 0.625 mg / 5.0 mg Premphase: CEE 0.625 mg x 14 days CEE 0.625 mg / MPA 5 mg x 14 days</td>
</tr>
<tr>
<td></td>
<td>Premphase (Cyclic Combined)</td>
<td>Oral Tablets</td>
<td></td>
</tr>
<tr>
<td>Norethindrone Acetate and Ethinyl Estradiol PO</td>
<td>FemHRT (Continuous Combined)</td>
<td>Oral Tablets</td>
<td>NA 1 mg EE 5 ug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-Beta- Estradiol and Norgestimate PO</td>
<td>Ortho-Prefest (Cyclic Combined)</td>
<td>Oral Tablets</td>
<td>Estradiol 1 mg x 3d Estradiol 1 mg and Norgestimate 0.09 mg x 3d Repeated for 30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol and Progestin Combination Patch</td>
<td>Combipatch (Continuous Combined)</td>
<td>Transdermal Patch</td>
<td>Estradiol 0.05 mg</td>
</tr>
</tbody>
</table>

### PROGESTIN PRODUCTS

<table>
<thead>
<tr>
<th>Hormone Replacement Therapy: Active Ingredient</th>
<th>Brand Name:</th>
<th>Dosage Forms Available:</th>
<th>Strength:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone Acetate (MPA) PO</td>
<td>Provera Cycrin Amen Curretаб MPA generic</td>
<td>Oral Tablets</td>
<td>MPA 2.5 mg MPA 5.0 mg MPA 10.0 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone Acetate (MPA) IM</td>
<td>Depoprovera</td>
<td>IM Injection</td>
<td></td>
</tr>
<tr>
<td>Norethindrone Acetate</td>
<td>Aygestin</td>
<td>Oral Tablet</td>
<td>5 mg</td>
</tr>
<tr>
<td>Norgesteral</td>
<td></td>
<td>Oral Tablet</td>
<td></td>
</tr>
<tr>
<td>Micronized Oral Progesterone</td>
<td>Prometrium Micronized Progesterone</td>
<td>Oral Tablet</td>
<td>100 mg Micronized progesterone</td>
</tr>
</tbody>
</table>
## ESTROGEN AND TESTOSTERONE PRODUCTS

<table>
<thead>
<tr>
<th>Hormone Replacement Therapy: Active Ingredient</th>
<th>Brand Name:</th>
<th>Dosage Forms Available:</th>
<th>Strength:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen and Androgen Combinations, Parenteral</td>
<td>Depo-Testadiol Depoatestostogen Duo-Cyp Valertest No. 1</td>
<td>2 mg estradiol cypionate and 50 mg testosterone cypionate / ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valertest = 4 mg estradiol cypionate and 90 mg testosterone enanthate / ml</td>
<td></td>
</tr>
<tr>
<td>Estrogen and Androgen Combinations, Oral</td>
<td>Estratest Estratetest HS</td>
<td>Estratest = 1.25 EE and 2.5 mg methyltestosterone Estratetest HS= 0.625 mg EE and 1.25 mg methyltestosterone</td>
<td></td>
</tr>
</tbody>
</table>

## NATURAL/HERBAL PRODUCTS

<table>
<thead>
<tr>
<th>Hormone Replacement Therapy: Active Ingredient</th>
<th>Brand Name:</th>
<th>Dosage Forms Available:</th>
<th>Strength:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytoestrogens: Soy isoflavins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phytoestrogens: Black Cohosh</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phytoestrogens: Dong Quai</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estrogens (17β-estradiol) taken orally are absorbed through the intestinal wall and a fraction of the dose is metabolized to estrone or estradiol glucuronide (“part of first pass”). The remainder of the dose then enters the portal circulation and reaches the liver in high concentrations. This is very different from what occurs naturally in the body before menopause. During the reproductive years, endogenous estrogen (estradiol) is produced by the ovaries or by adipose tissue (estrone). These sex hormones are secreted directly into the circulation and reach the target receptors in tissue before they reach the liver. Therefore, the concentration of estrogen that is presented to the liver through the portal circulation is much higher with oral ingestion of estrogen drug products than with endogenous production. The high concentrations of estrogen in the liver stimulate the production of hepatic proteins such as binding globulins, clotting factors, renin substrate, and lipoproteins.

Gonadotropins: Suppression of gonadotropins serves as a marker of estrogen potency. Decreases in follicle stimulating hormone (FSH) and luteinizing hormone (LH) reflect estrogen activity. Delivery of 50 to 100 ug of estradiol, results in a 17 to 40% decrease in circulating...
FSH. However, even high doses of estradiol will not restore FSH and LH to premenopausal levels.

**Binding Globulins:** With oral therapy, cortisol-binding globulin (CBG), sex hormone-binding globulin (SHBG), and thyroid-binding globulin (TBG) are all increased. This does not happen with transdermal therapy.

**Clotting Factors:** Which clotting factors are produced? How does this affect the patient’s risk of developing a DVT? What is the risk of developing a DVT (incidence)? What are relevant risk factors?

**Renin Substrate:** Review the renin angiotensin system. How does increasing renin substrate affect blood pressure?

**Lipoproteins:** Which lipoproteins are produced? How does this affect the patient’s cardiovascular risk profile?

After the initial metabolism in the liver, estrogen is released into the bloodstream. The concentration of estrogen that is released into the circulation is much lower than the concentration of estrogen that is presented to the liver initially through the portal circulation (first pass). The concentration of estradiol that is released is similar to the levels that are present during the early follicular phase of the female cycle in menstruating women, but levels of estrone are higher than typically present at this stage of life. This is because of the estrone that is produced by the metabolism of estradiol in the intestinal wall during absorption (first-pass hepatic metabolism). Increased serum concentrations of estrone or estrone-like substances are produced by nearly all oral dosage forms of estrogen (estradiol, estradiol valerate, conjugated equine estrogens, synthetic estrogens).

Most estrogens are well absorbed through the skin and subcutaneous fat, the vagina, the nasal mucosa, and sublingually. With all of these methods of estrogen delivery, the first-pass metabolism seen with the oral estrogens is avoided, resulting in a physiologic concentration of estrogen reaching the liver. Therefore, the production of binding globulins, lipoproteins, triglycerides, renin substrate, and clotting factors are not observed with these alternative routes of administration.

The estradiol transdermal therapeutic system (TTS), releases 17-beta-estradiol continuously to the skin through a rate-limiting membrane system.

The type of patch most commonly used utilizes a reservoir system composed of four layers:

1. An occlusive backing which prevents evaporation
2. A reservoir that contains the active medication (17-beta-estradiol) dissolved in alcohol. The alcohol delivers the medication to the skin.
3. A membrane that controls the rate of medication delivery to the skin.
4. An adhesive layer that attaches the patch to the skin.
The dose of medication delivered depends on the actual size of the patch. For instance a 10 cm² patch delivers 50 ug of estradiol per day (TTS 50) and a 20 cm² patch delivers 100 ug of estradiol per day (TTS 100). Less than 10% of the medication contained in a patch is delivered, because of evaporation of the alcohol matrix. After 4 days, most of the alcohol evaporates and therefore, the medication is not delivered. This is the reason most patches are changed twice a week.

A newer design, called the matrix system has been developed to decrease the chance of skin irritation and improve patch adherence to the skin. It has one layer that contains adhesive film and the active drug. This film is covered with a transparent occlusive foil backing. This patch delivers 50 ug of estradiol per day and must be changed twice a week also.

<table>
<thead>
<tr>
<th>Patch Dosage</th>
<th>Estrone: Estradiol Serum Concentrations</th>
<th>Serum Estrone Levels</th>
<th>Serum Estradiol Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 ug</td>
<td>1:1</td>
<td>30 pg/ml</td>
<td>20 to 25 pg/ml</td>
</tr>
<tr>
<td>50 ug</td>
<td>1:1</td>
<td>40 to 45 pg/ml</td>
<td>35 to 50 pg/ml *</td>
</tr>
<tr>
<td>100 ug</td>
<td>1:1</td>
<td>60 to 70 pg/ml</td>
<td>80 to 110 pg/ml *</td>
</tr>
</tbody>
</table>

*Similar to premenopausal women during the follicular phase of the menstrual cycle.

- Estrone levels are much lower than with oral therapy.
- Patches produce more constant serum estrogen levels over a given 24-hour period than with oral therapy.
- Serum levels may decline over time the longer the patch is worn. For instance, serum levels may decrease from 50 pg/ml on day 1 to 28 pg/ml on day 3.
- Estradiol has a short half-life of less than 1 hour. This is because it can be functionally inactivated in a single metabolic step. Therefore, blood levels decline rapidly once the patch is removed.
- Estrogen does not accumulate in the body with transdermal therapy, like it does with oral therapy. Baseline values will be obtained within 3 days of discontinuing the patch. It takes up to 8 days to return to baseline values with oral therapy.

Clinical applications/Advantages of the Transdermal estrogen products:

- Transdermal estrogens lower serum triglycerides in contrast to the increase in serum triglycerides seen with oral therapy. Transdermal application is recommended for women with familial hypertriglyceridemia or increased serum triglycerides from other causes.
- Transdermal estrogen delivery is preferred for patients with a history of gallbladder disease. Nausea occurs less frequently with the transdermal delivery than with oral administration.
• Transdermal estrogen has no effect on clotting factors. Therefore, it might be beneficial to use transdermal dosage delivery systems in patients who have hypertension or risk of thrombosis.

• Transdermal estrogen has protective effects on the bone, similar to oral therapy.

• Transdermal estrogen is effective in the management of menopausal vasomotor symptoms, urogenital symptoms, and vaginal atrophy.

• Skin irritation is the most common complaint associated with transdermal therapy (5 to 30%). Skin reactions might include erythema, itching, discomfort, edema, vesicular rash, induration, and residual pigmentation. Regular rotation of the site decreases the risk of skin irritation. Sites of application include the buttocks or back. Never apply to the breasts. Avoid applying the patch to the waistline. If a patch comes off, reapply the same system and continue therapy. If skin irritation occurs or the patient has trouble with the patch coming off, consider using the matrix delivery system.

• The estradiol patch should only be used in patients without an intact uterus. If a patient has a uterus, an oral progestin must be added for 14 days of each month to decrease the risk of endometrial hyperplasia. An alternative is to use the CombiPatch, which has recently become available.
D. Antiestrogens and Selective Estrogen Receptor Modulators (SERMs)

1. Basic Pharmacology and Therapeutic Indications

Structural manipulation in the nonsteroidal compounds has led to the development of antiestrogens and partial agonists (selective estrogen receptor modulators: SERMs) including clomiphene, tamoxifen and raloxifene

- **Clomiphene**: Blocks estrogen receptor in hypothalamus and pituitary, disrupting normal feedback inhibition of GnRH and gonadotropin secretion. This results in increased FSH and LH production. This results in ovarian stimulation and ovulation. May induce hyperstimulation and multiple ovulation events and births. Clomiphene is orally active and is excreted from an enterohepatic pool.

- **Tamoxifen**: Has partial agonist activity (see Table below). It inhibits the binding of estrogens to their cytoplasmic receptor, thereby producing a decrease in the synthesis of cellular DNA which is normally promoted by estrogens. Due to this action, tamoxifen is of value in treated estrogen-dependent neoplasms (breast cancer in postmenopausal women). It is most often used as an adjunct to breast surgery.

- **Raloxifene**: Almost complete antiestrogen activity and is useful in the prevention of osteoporosis in postmenopausal women (treatment of postmenopausal women at risk for developing osteoporosis)
### Pharmacologic Comparison of SERMs

<table>
<thead>
<tr>
<th>SERM</th>
<th>% Estrogen Receptor Binding</th>
<th>%Agonism</th>
<th>%Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>&gt;100</td>
<td>5</td>
<td>85</td>
</tr>
</tbody>
</table>

2. Pharmacokinetics

Raloxifene is absorbed rapidly after oral administration with > 60% of an oral dose adsorbed. However, pre-systemic glucuronide conjugation is extensive and absolute bioavailability is only 2%. Bioavailability and the time to reach average maximum plasma concentration are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites. Administration with a standardized, high-fat meal increases the absorption of raloxifene (Cmax 28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. Raloxifene can be administered without regard to meals.

The apparent volume of distribution of raloxifene is 2348 L/kg and is not dose-dependent. Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins (>95%) and to albumin and a1–acid glycoprotein, but not to sex steroid binding globulin.

Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: Raloxifene-4'-glucuronide, raloxifene-6–glucuronide and raloxifene-6, 4'-diglucuronide, with < 1% existing in the unconjugated form. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Following IV administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg.hr. Following chronic oral dosing, clearance (Cl) ranges from 40 to 60 L/kg.hr. Increasing doses of
raloxifene (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma concentration time curve (AUC).

Raloxifene is primarily excreted in feces; < 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates and < 0.2% is excreted unchanged in urine. In the osteoporosis prevention trials, raloxifene and metabolite concentrations were similar for women with estimated creatinine clearances as low as 23 ml/min.

Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/ml (range, 67 to 183 ng/ml) for tamoxifen and 336 ng/ml (range, 148 to 654 ng/ml) for N-desmethyl tamoxifen. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in » 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in » 8 weeks, suggesting a half-life of » 14 days for this metabolite.

N-desalkyl tamoxifen was the major metabolite found in patients' plasma. The biological activity of N-desalkyl tamoxifen appears to be similar to tamoxifen. 4-hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma.

Tamoxifen is extensively metabolized after oral administration. Studies in women receiving 20 mg of 14C tamoxifen have shown that » 65% of the administered dose was excreted from the body over 2 weeks with fecal excretion as the primary route of elimination. The drug was excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for < 30% of the total fecal radioactivity.

Clomiphene is readily absorbed orally and is excreted principally in the feces. Excretion averaged 51% of the dose after 5 days. Drug appears in the feces 6 weeks after administration, suggesting that the remaining drug/metabolites are slowly excreted from a sequestered enterohepatic recirculation pool.
Compounds that produce estrogen-like activity in one or more desired tissues (bone or liver, as examples) together with estrogen antagonist or minimal agonist activity in breast or uterus

**Selective Estrogen Receptor Modulators**
- tamoxifen
- Clomiphene
- raloxifene

Indications for **tamoxifen**: Antineoplastic agent most often used as an adjunct to breast surgery in the treatment of breast cancer (hormone dependent breast cancer)

Clomiphene is orally active and is excreted from an enterohepatic pool. Blocks estrogen receptor in hypothalamus and pituitary, disrupting normal feedback inhibition of GnRH and gonadotropin secretion. This results in ovarian stimulation and ovulation. May induce hyperstimulation and multiple ovulation events and births.

Indications for **raloxifene**: Treatment of postmenopausal women at risk for developing osteoporosis

**E. Ovulation-inducing agents**

**Ovulation-inducing agents**
- clomiphene
- bromocriptine
- hMG (menotropins)
- GnRH

- know the primary use of ovulation-inducing agents
- understand the differences in their mechanisms of action
- know the patient populations in which they are used
OVERVIEW OF REPRODUCTIVE PHYSIOLOGY AND PATHOPHYSIOLOGY AND THE STEROID HORMONES

ENDOCRINE PHARMACOTHERAPY MODULE

SPRING, 2002

DR. JACK DeRUITER
DR. KIMBERLY BRAXTON-LLOYD
DR. CHARLES BREESE