SEX STEROIDS

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LEARNING OBJECTIVES:

This section covers the mechanism of action and therapeutic uses of sex steroids. At the end of this lecture you should be able to:

- Summarize the biosynthesis and mechanism of actions of androgens, estrogens, and progestins.
- Identify the different therapeutic uses of sex steroid-based drugs (including HRT and birth control) and their mechanism of action.
- Interpret the parallel and contrasting uses of these drugs in men vs. women; contrast the use of these drugs in cancer versus non-cancer indications.
- Identify the basic structural features and the general pharmacological differences (including mechanisms of action, side effects, etc.) between estrogenic, progestinic, and androgenic drugs.
- Describe the different treatment options for endocrine-related disorders of sex steroids.
- In a given postmenopausal patient, identify risk factors for the use of HRT, list the types of drugs available and identify when they should be used.
- Interpret the phase relationships between different OCP preparations and why they exist.
- Recognize the use of non-pharmacological options for contraception.

I. INTRODUCTION

A. The sex steroids are the effector arm of the hypothalamic-pituitary-gonadal axis (see lecture on “Hypothalamic Pituitary Axes”).

B. Sex steroids are some of the most widely used drugs pharmaceutically, particularly in birth control.
   1. This is an oddity in pharmacology and medicine, in that the drug is given to healthy normal individuals.
   2. Because the drug is used on a healthy person, it has to be under more stringent control to avoid potential side effects.
   3. Since very large numbers of healthy people receive oral contraceptives, the risk-to-benefit ratio must be higher than for drugs given to sick patients. For example, in a sick patient dying of cancer, the benefits of the meds outweigh the risks and the concern regarding adverse side effects is diminished.

C. Pharmacological Intervention.
   1. Three ways to intervene in steroid hormone action.
      a. Use of agonists or antagonists of the hypothalamic (GnRH) or pituitary (gonadotropins), which stimulate or inhibit steroid synthesis, and reproductive competence.
      b. Use of enzyme inhibitors that block steroid hormone synthesis.
      c. Use of nuclear receptor agonists or antagonists.

II. STEROID HORMONE ACTION

A. Sex steroids mediate their actions through specific nuclear receptors.

B. Steroids circulate bound to carrier proteins. Conditions that change the level of these serum binding proteins can have major effects on steroid actions.

C. Steroids are metabolized by the liver. Altered liver enzyme function affects the half-life of the steroid. This is the basis for some important drug-drug interactions discussed below under oral contraceptives.

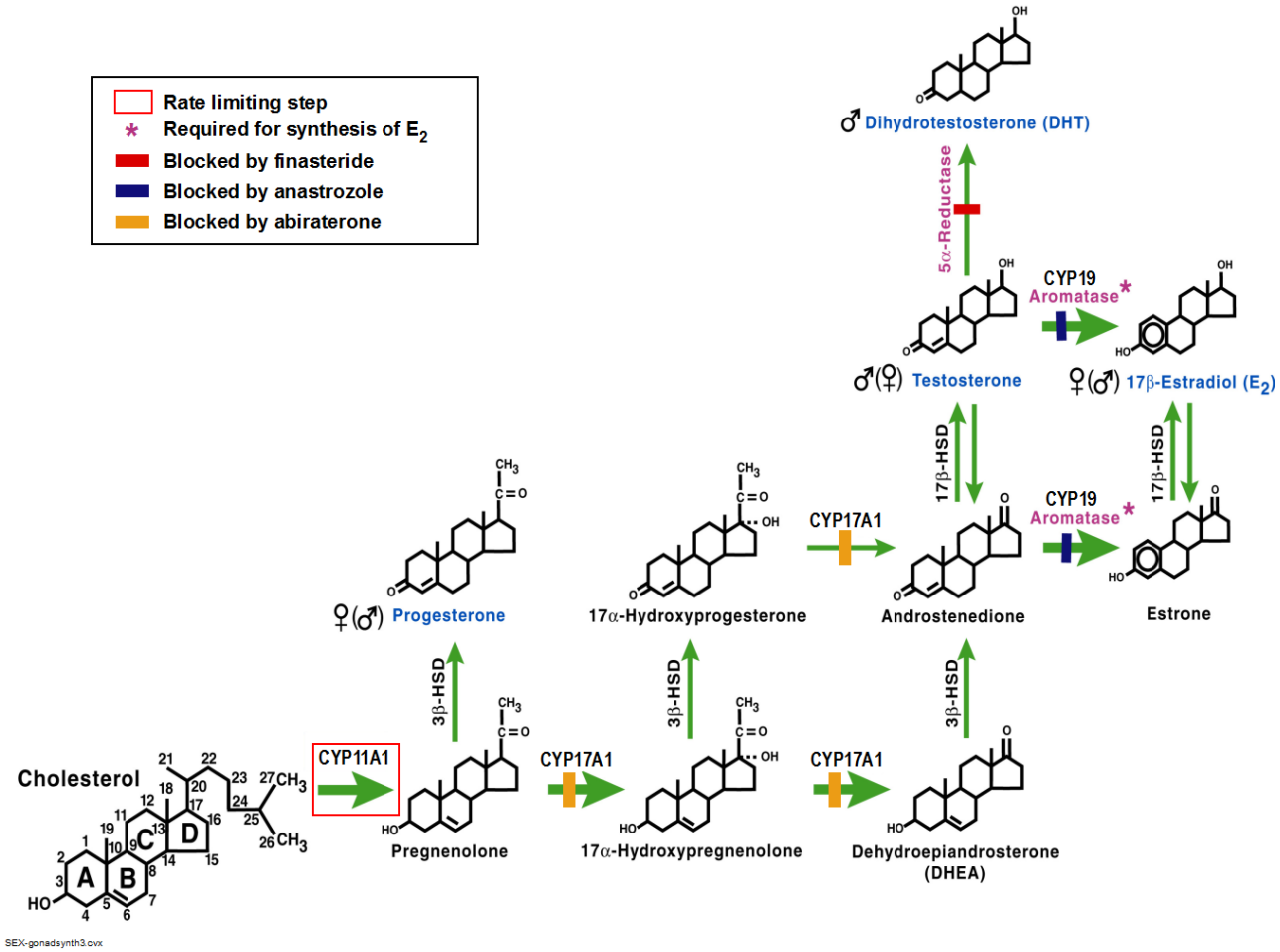


Figure 1: Gonadal steroid hormone synthesis.

III. BIOSYNTHESIS OF SEX STEROID HORMONES

A. During reproductive years, sex steroids predominantly are produced in the gonads (testes and ovaries). Therefore, if the gonads stop functioning, sex steroid levels diminish.

1. The rate-limiting step in steroid biosynthesis is the transport of cholesterol into the mitochondria. The first enzymatic step is then catalyzed by the P450 side-chain cleavageenzyme (**CYP11A1**, also called $P450_{scc}$). Both the mitochondrial transporter and CYP11A1 are regulated by gonadotropins (e.g., LH) in gonads and by ACTH in the adrenals.
2. CYP11A1 catalyzes the removal of the 5-carbon side-chain from cholesterol, resulting in synthesis of pregnenolone, which is the precursor to all steroid hormones.
3. Through a series of further enzymatic steps catalyzed by 3β-HSD and **CYP17A1** (a P450 with 17α-hydroxylase and lyase/desmolase activity), pregnenolone is converted into the major physiological sex steroids progesterone, testosterone, and estradiol.

4. In humans, the pathway through DHEA is preferred (larger arrow in Figure 1). Synthesis of testosterone in both males and females is regulated by LH.
5. The most potent androgen is **dihydrotestosterone** (**DHT**), which is made from testosterone via **steroid 5α-reductases**. Both hormones bind to the androgen receptor, but DHT has higher affinity (more on this later).
    a. The steroid 5α-reductase enzyme occurs in two subtypes, which are differentially expressed in various target tissues.
        i. **Type I 5α-reductase (SRD5A1)**: found primarily in liver and non-genital skin (e.g., scalp).
        ii. **Type II 5α-reductase (SRD5A2)**: found primarily in liver and the urogenital tract. Defects in Type II steroid 5α-reductase cause a form of male to female disorder of sexual development in which there is a failure to virilize the male external genitalia in utero.
6. Androgens (androstenedione and testosterone, but not DHT) are also the precursors for estrogens.
    a. The most important reaction for the production of estrogen is catalyzed by **aromatase (CYP19)**.
        i. Aromatase attacks the A ring (which in testosterone has a desaturated double bond at the 4 position and a ketone at the 3 position) and aromatizes it to make **17β-estradiol (E_2)** - the major circulating estrogen in females.
        ii. Aromatase expression in granulosa cells is induced by FSH; without FSH, androgens cannot be converted into estrogens in females.
7. Note the similarities and differences in steroid biosynthesis in gonads versus adrenals. For example, 17beta-HSD and CYP19 are lacking in adrenals, which is why the adrenal gland cannot make T or E_2. However, CYP11A1 and CYP17A1 are present in both gonads and adrenals and thus are required for both sex steroid and glucocorticoid production. LH/FSH governs steroid synthesis in gonads, ACTH in adrenals.

IV. ANDROGENS

A. Major sites of production.
    1. Testes.
        a. Leydig cells make testosterone (and some DHT) under regulation by LH.
    2. Ovaries.
        a. Androgens are the precursor to E_2 and are made by theca cells under stimulus of LH.
        b. Both FSH and LH are needed to synthesize and convert testosterone into E_2 in the ovaries.
        c. Estrogens are formed from testosterone but not from DHT.
B. Testosterone vs. DHT.
    1. DHT binds to the androgen receptor with 10 times higher affinity than testosterone and it is therefore more effective in activating transcription of target genes.

2. Testosterone can replace most, but not all of the functions of DHT; the latter is crucial for normal male development of external genitalia and prostate (Figure 2).

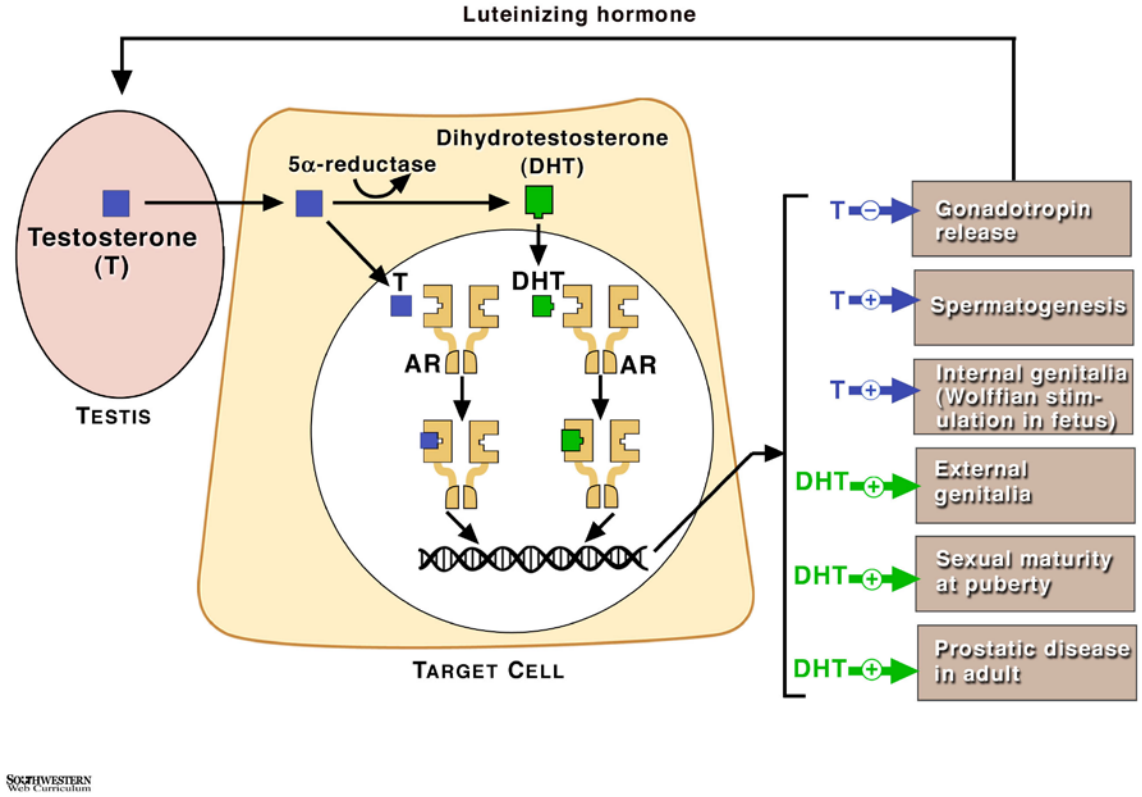


Figure 2: Actions of testosterone and DHT in males.

C. Actions of androgens. Testosterone is required for normal male development and reproductive function. Androgens have two classes of activities: **androgenic** and **anabolic**.

1. Androgenic.
   a. Testosterone is required for male sex differentiation (especially during fetal development), maintaining libido, and as the precursor to estrogen.
   b. DHT is required for virilization of male external genitalia during development and male sexual maturation at puberty (including enlargement of the penis and scrotal sack).
   c. Other androgenic changes due to increased testosterone and DHT: pubic hair growth, sexual maturation, spermatogenesis, male-pattern baldness, increased sebaceous gland secretion.
2. Anabolic.
   a. Anabolic changes: closure of epiphyses, increased muscle mass, nitrogen retention.

D. Regulation of testosterone levels in males.
1. LH regulates synthesis of testosterone by Leydig cells. Unlike female sex steroid regulation, male sex steroid regulation is not cyclical, although testosterone does show some diurnal rhythm with highest levels in the early AM.
2. Testosterone, but not DHT, feeds back and inhibits LH secretion. This may be mediated by estrogen derived from aromatase activity. Progesterone can also inhibit gonadotropin secretion, and a depot form (**MEDROXYPROGESTERONE ACETATE**, see below) is used in some states to chemically castrate convicted sex offenders.

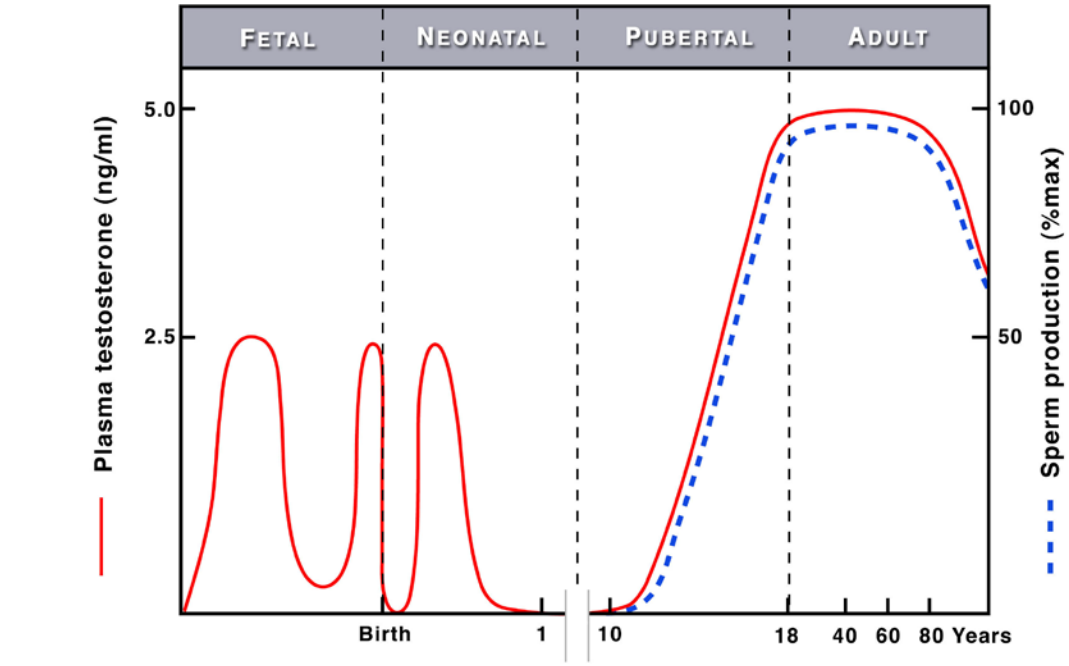


Figure 3: Regulation of testosterone levels and spermatogenesis during the human male life cycle.

3. Figure 3 shows the level of testosterone throughout a normal human male's life.
   i. In males, testosterone synthesis begins around 8 weeks after conception and stimulates male differentiation of the internal genitalia from the Wolffian ducts. DHT likewise stimulates male differentiation of the external genitalia.
   ii. Testosterone decreases just before birth and then increases briefly just after birth. This second rise in the neonate is believed to "set" the maleness traits in the brain of boys.
   iii. During puberty, testosterone levels begin to rise and reach their adult levels in the late teen years. Sperm production follows the pubertal/adult testosterone levels and persists throughout life.
   iv. After ~40 years of age, there is a 1-2% drop per year in circulating testosterone levels and sperm production.
4. Note that in normal, healthy adult males, the level of testosterone remains relatively constant and is high enough to completely saturate every androgen receptor in the body. This raises the issue of whether pharmacologic doses of androgens exert significant benefits in healthy adult males. Despite considerable effort, it has not been possible to separate the anabolic and androgenic properties of androgens, and thus side effects are unavoidable.
   i. Although the anabolic effects of androgens (increased muscle mass, strength, stamina) can sometimes occur without rigorous, sustained exercise, they generally are only seen at very high concentrations of steroid. Since the AR is saturated in normal adult males, this has suggested that some of these effects are due to hormone spillover on other metabolic system (such as inhibition of glucocorticoid catabolic effects).
   ii. In females or young boys without high testosterone, the situation is quite different and there can be dramatic anabolic and androgenic effects after androgen treatment.
   iii. Anabolic steroids have significant side-effects (see below), making the benefits of taking anabolic steroids in normal men and women questionable.

E. Androgenic Disorders.
   1. Impaired virilization can be either congenital or acquired and can result from hypothalamic/pituitary disease (hypogonadotropic hypogonadism), primary diseases of the testes (e.g., mumps orchitis) or inherited disorders of either the components of the testosterone pathway or of the androgen receptor (complete and partial androgen insensitivity).
   2. With the exception of patients with complete androgen insensitivity, who have severe AR mutations that cannot respond to even very high doses of testosterone, treatment is generally with pharmacologic doses of testosterone formulations to induce virilization and secondary sex characteristics.

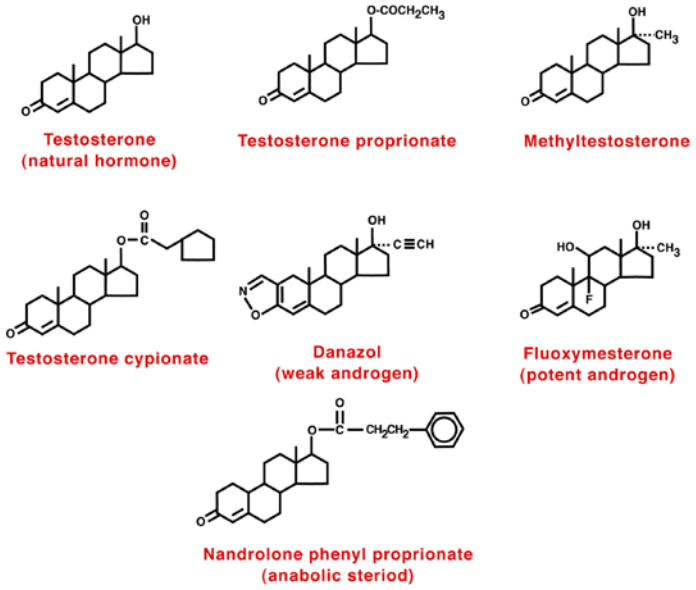


Figure 4: Androgens and anabolic steroids.

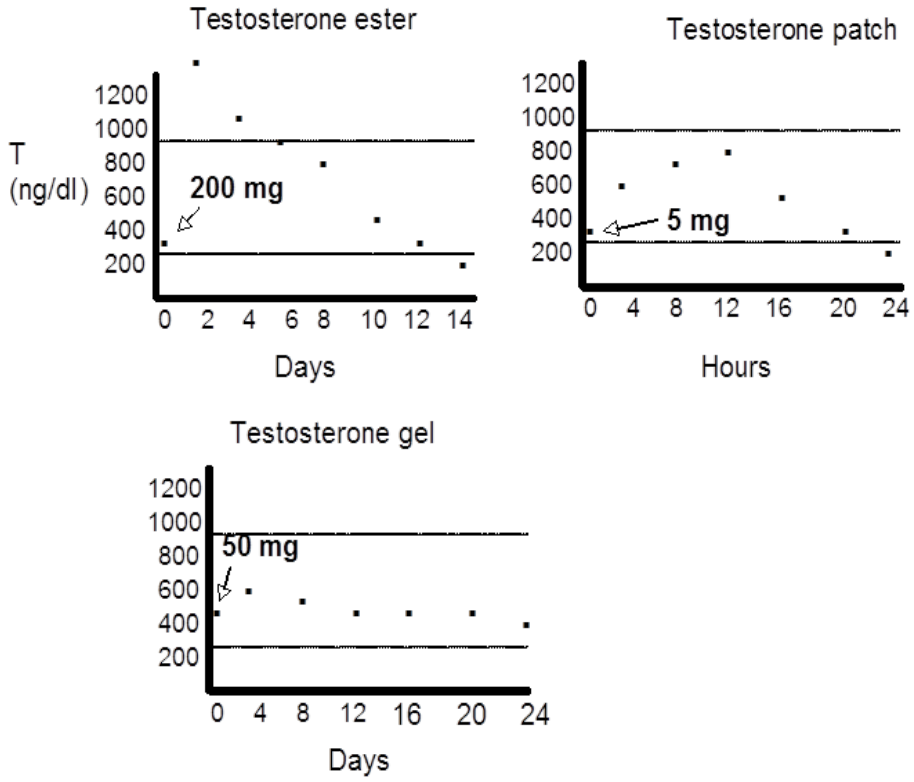


Figure 5: Plasma testosterone levels in different formulations. Horizontal lines indicate upper limits of normal.

F. Clinical uses of androgens.

1. Chemistry.

a. **TESTOSTERONE** is relatively ineffective when given orally or intravenously because it is rapidly degraded by first-pass hepatic metabolism. To circumvent this problem, the most frequently used formulations of testosterone are patch (***Androderm®, Testoderm®***), gel (***Testim®, Androgel®***), or buccal (***Striant®***) formulations that provide relatively constant plasma testosterone levels via transdermal or transbuccal absorption throughout the day (see Figure 5).

b. 17α-alkyl derivatives. This chemical modification improves the activity, half-life, and bioavailability of the parent testosterone. 17α-alkylated androgens are orally available (a distinct advantage) but have severe liver toxicity and other side effects [e.g., **METHYLTESTOSTERONE (*Testred®*)**]. An advantage with one 17α-alkylated congeners is that it has reduced estrogenic activity because it is a poor substrates for aromatase (e.g., **FLUOXYMESTRONE**).

c. **TESTOSTERONE ESTERS** [e.g., enanthate (***Delatestryl®***), cypionate (***Depo-testosterone®***)] are administered in an oil vehicle by deep IM injection. They are more slowly absorbed and provide more sustained testosterone levels (up to 2 weeks). Typically, the levels reach supraphysiologic levels shortly after injection and then decline to subnormal levels immediately before the next injection (see Figure 5). They are the least expensive form of testosterone replacement but may have increased incidence of side effects, perhaps due to the transient supraphysiologic testosterone levels.

2. Indications for androgen agonists. In approved clinical use, androgens are largely restricted to use in men.
    a. Hormone replacement therapy for primary hypogonadism (testicular failure), secondary hypogonadism (hypothalamic/pituitary dysfunction), delayed puberty, and in aging men.
        i. Androgens induce secondary sexual maturation when the deficiency occurs before puberty and restore sexual function and libido in post-pubertal hypogonadism; they do not cure infertility, which also requires gonadotropins for spermatogenesis (hCG to induce high local testosterone concentrations and FSH to stimulate support function of Sertoli cells).

    b. Anabolic effects in catabolic states.

        i. Androgens promote muscle growth and nitrogen retention in hypogonadal males and in wasting diseases such as AIDS.
    c. Athletic performance enhancement.
        i. The risks of androgen therapy in normal adults far outweigh the benefits and there is little direct evidence to support any significant positive long-term benefits. Except for overt hypogonadism, the positive effects of androgens on nitrogen balance are short-lived.
        ii. Anabolic steroids are banned in most competitive sports. Because of widespread abuse, there are several sensitive assays that routinely screen for these drugs and their metabolites. Testosterone is the most difficult anabolic steroid to detect, but its metabolite ratio in urine can be detected.
        iii. Derivates of **NANDROLONE** have been reported to be among the best anabolic steroids and they are also among the most abused.
        iv. **Androstenedione** ("Andro") was available OTC and has been promoted and sold OTC for its body building attributes. In 2004 the FDA banned the sale of Andro.
        v. **Dehydroepiandrosterone** (DHEA) is another popular OTC nutritional supplement. Proponents have extolled its youth-promoting properties, including increased memory, energy, libido and preserving lean body mass. As with Andro, the benefits and risks of DHEA are not known and caution should be exercised in advising patients to take this drug.
    d. Aging males. As noted above, testosterone levels in males over age 40 decline by ~1%/year, such that overtly low levels are present by age 75 in over half of men. Some have proposed that testosterone supplementation might ameliorate some of the adverse effects of aging (e.g., decreased muscle mass, increased adiposity, decreased bone mass). The long-term risks (see below) and benefits of such therapy are completely unknown.
    e. OB/GYN: Danazol is used to treat E_2-dependent diseases such as endometriosis and fibrocystic breast disease (why? - because it feeds back and suppresses E_2 synthesis).
    f. Although women normally make androgens, which play physiological roles in libido, androgen therapy with a transdermal patch was not approved by the FDA for use in women.

3. Side effects of androgens.
    a. A major side effect, especially with 17α-alkylated derivatives, is hepatotoxicity. Jaundice is the primary clinical sign and occurs within 2-5 months of use. Bile accumulation in biliary capillaries and cholestasis are the cause. Other liver problems (e.g., hepatic tumors) also have occurred.
    b. Edema. Water retention likely accounts for most of the weight gain in short-term androgen treatment.
    c. Virilization in females and prepubertal males. These are mediated by the AR and are a predictable outcome in these patients.
    d. Feminizing effects, particularly gynecomastia in men. These are due to the conversion of androgens to estrogen by aromatase. The effects are severe in children and men with liver disease (because they can't metabolize the androgen and so it is shunted to estrogens). Some androgens (e.g., **FLUOXYMESTRONE**) are poor aromatase substrates and ∴ have less feminizing side effects.
    e. Polycythemia. Especially in men with chronic obstructive pulmonary disease, testosterone replacement is associated with increases in red blood cell count, sometimes to the extent that potentially dangerous polycythemia can result. This adverse effect occurs most frequently with the depot injections of testosterone esters.
    f. Prostate effects. As discussed below, prostate growth is androgen dependent and many prostate cancers respond to androgen deprivation therapy. Thus, there is considerable concern that androgen therapy, particularly in older men, may increase the incidence or severity of conditions such as benign prostatic hypertrophy or even prostate cancer. This is controversial, but the PSA should be checked before initiating androgen replacement therapy and periodically thereafter.
    g. Other effects. A number of other effects due to high levels of synthetic androgens (particularly anabolic steroids) include aggression, deranged lipid metabolism (e.g., increased LDL-cholesterol, decreased HDL-cholesterol), decreased sperm output, hair growth or loss, and acne.
4. Contraindications. These largely derive from the adverse effects of androgens and include prostate cancer, obstructive prostate enlargement, and polycythemia (baseline hematocrit > 52).
5. Monitoring response to therapy.
    a. With injected testosterone esters, the plasma testosterone level is generally checked just before the next dose (trough, see Figure 5). The goal is a level at the lower limits of the normal range.
    b. With transdermal testosterone preparations, a level can be checked at any time, with a goal of a testosterone level in the mid-normal range.
    c. Prostate-specific antigen and the hematocrit should be checked at baseline and periodically during therapy.
6. Clinical uses of anti-androgen drugs. There are three classes: androgen receptor antagonists, H-P axis inhibitors and androgen synthesis enzyme inhibitors.
    a. Androgen receptor antagonists
        i. Cyproterone acetate (note it is a C21 steroid, see Figure 6). It binds to the androgen receptor with high affinity and competitively inhibits all androgen activity. Because it also has progesterone receptor agonist activity, it feeds back and inhibits LH and FSH, enhancing its overall anti-androgen action.

Cyproterone acetate is being considered for use in hirsutism and has orphan drug status in the U.S. The major limiting factor for FDA approval is hepatotoxicity.

ii. The first pure AR antagonist to be marketed was **FLUTAMIDE** (***Eulixin***®). Newer AR antagonists in clinical use are **BICALUTAMIDE** (***Casodex®***) and nilutamide (***Nilandron®***). **BICALUTAMIDE** has less hepatotoxicity than flutamide and can be administered once daily; it therefore is more widely used clinically. Common side-effects include loss of feedback inhibition of the H-P axis causing loss of sexual activity and hot flashes. For this reason, the AR antagonists must be given with an H-P axis inhibitor (see below).

iii. **Selective Androgen Receptor Degraders (SARDs)**. These compounds are designed to cause degradation of AR protein based on the observation that most AR antagonists fail because the receptor becomes resistant to the antagonist, but the receptor continues to be required as a transcription factor that is required for prostate cancer cells to survive and proliferate. SARDs are effective in 3 ways: they inhibit androgen binding to AR, they prevent AR from entering the nucleus, and they inhibit AR binding to DNA. The first of these to be approved is **ENZALUTAMIDE (*Xtandi*®)**, a non-steroidal antagonist that is used to treat castration-resistant prostate cancer.

b. Hypothalamic-pituitary inhibitors.

i. Long-lived GnRH agonists (e.g., **LEUPROLIDE**) eventually cause receptor desensitization, which inhibits pituitary LH/FSH release and thereby blocks testosterone synthesis. They generally are used in combination with AR antagonists to treat advanced prostate cancer. Prostate cancer is a steroid-dependent cancer whose growth is dependent on stimulation by androgens, and therefore it is very responsive to anti-androgen therapy. The combination of AR antagonists (to inhibit the AR) and **LEUPROLIDE** (to inhibit the compensatory increase in testosterone synthesis that normally follows loss of feedback inhibition) is used to treat metastatic prostate cancer (so called "total androgen blockade"). The problem is that these cancers often become steroid-independent after several months and the patients relapse.

ii. **DEGARELIX** is a new generation GnRH receptor antagonist that also inhibits gonadotropin release. Unlike **LEUPROLIDE** that initially causes a transient but marked increase in LH/FSH release, **DEGARELIX** provides complete and immediate suppression of GnRH receptor activity.

c. Androgen biosynthesis inhibitors.

i. 5α-reductase inhibitors.

(a) **FINASTERIDE** is a 5α-reductase inhibitor that prevents the conversion of testosterone to DHT in peripheral tissues. **FINASTERIDE** is relatively selective for the Type II 5α-reductase enzyme (found in the urogenital tract), but also inhibits the Type I enzyme (found in the scalp).

(b) In 1 mg tablets **FINASTERIDE** is marketed as ***Propecia®*** for male-pattern baldness. Recall that the hair follicle is very sensitive to androgen (especially DHT), which is the reason for male-pattern baldness. **FINASTERIDE** works only moderately well because it is not very active against the type I enzyme.

(c) In 5 mg tablets **FINASTERIDE** is marketed as ***Proscar®*** and is used to treat men with enlarged prostates (benign prostate hyperplasia, BPH). However, the drug only reduces prostate size by 20%, which is often not significant enough to be of benefit unless prostate volumes are >40 ml. The reason **FINASTERIDE** is not more effective may be because blocking 5α-reductase increases testosterone levels 10-fold, which may offset the benefits of reducing DHT. Alternatively, inhibiting the 5α-reductase enzyme may prevent not only the synthesis of DHT, but also of another metabolite that is a ligand for estrogen receptor β (ERβ), which is expressed in the prostate. ERβ normally represses the expression of androgen receptor, and keeps prostate growth in check. Absence of the putative ERβ ligand would allow AR to increase and stimulate prostate growth. Because of the limitation of **FINASTERIDE**, **adrenergic α-blockers** (e.g., which promote relaxation of bladder and urethra; see lectures on adrenergic agents) are currently thought to be as good or better drugs for relief of symptoms of BPH. Combination therapy is also used.

(d) **FINASTERIDE** is contraindicated in women who are pregnant or may become pregnant. (W*hy? What is the risk?*) Women should also exercise caution in having unprotected sex with a man who is using **FINASTERIDE** and avoid handling the medication with bare hands. **FINASTERIDE** is readily absorbed through the skin and is carried in semen. Although a pregnant woman would need to take in 3 liters of semen in order to have enough of the drug to cause birth defects, doctors are still advised to counsel women to avoid having unprotected sex with treated men, particularly men that are known for their high capacitation.

(e) **DUTASTERIDE** is a dual-specificity 5α-reductase inhibitor that inhibits both type I and II enzymes. It is used to treat BPH (***Avodart®***) and hair loss (*Avolve*®), with similar contraindications in women.

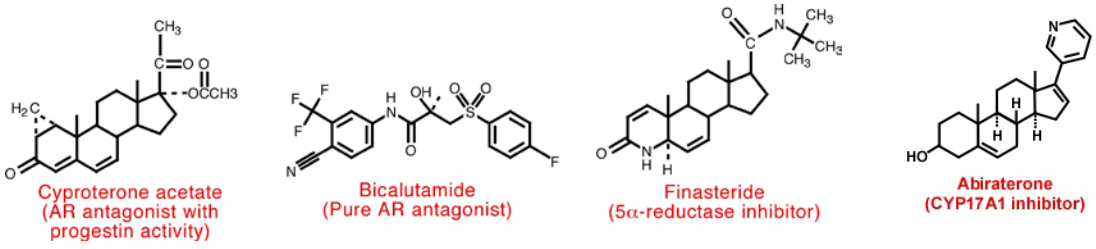


Figure 6: Anti-androgenic drugs.

ii. CYP17A1 inhibitor. **ABIRATERONE (*Zytiga*®)** is a 17 α-hydroxylase/C17,20 lyase (CYP17A1) inhibitor that is used to treat advanced stage, metastatic castrate-resistant prostate cancer (CRPC). CRPC has been a challenge to treat in part because the cancer may still be responsive to androgens from non-gonadal sources. The efficacy of **ABIRATERONE** comes from its ability to block both gonadal (testes) and non-gonadal (adrenal and prostate tumor) conversion of pregnenolone into 17-hydroxyprogesterone, DHEA and Andro, which are precursors to testosterone (see Fig. 1). **ABIRATERONE** must be given with a glucocorticoid, such as **PREDNISONE** (*why?*), and must be kept away from women who are pregnant (or want to become pregnant) and children (*why?*).

V. ESTROGENS

A. Major sites of production.
   1. Ovaries.
      a. Made from testosterone precursor by aromatase under the direct control of FSH.
   2. Also made in testes, adipose tissue (especially in obese individuals), placenta, and fetal adrenal cortex.

B. Chemistry
   1. The most potent natural estrogen is 17β-estradiol (E_2), followed by estrone and estriol (see Figure 7).

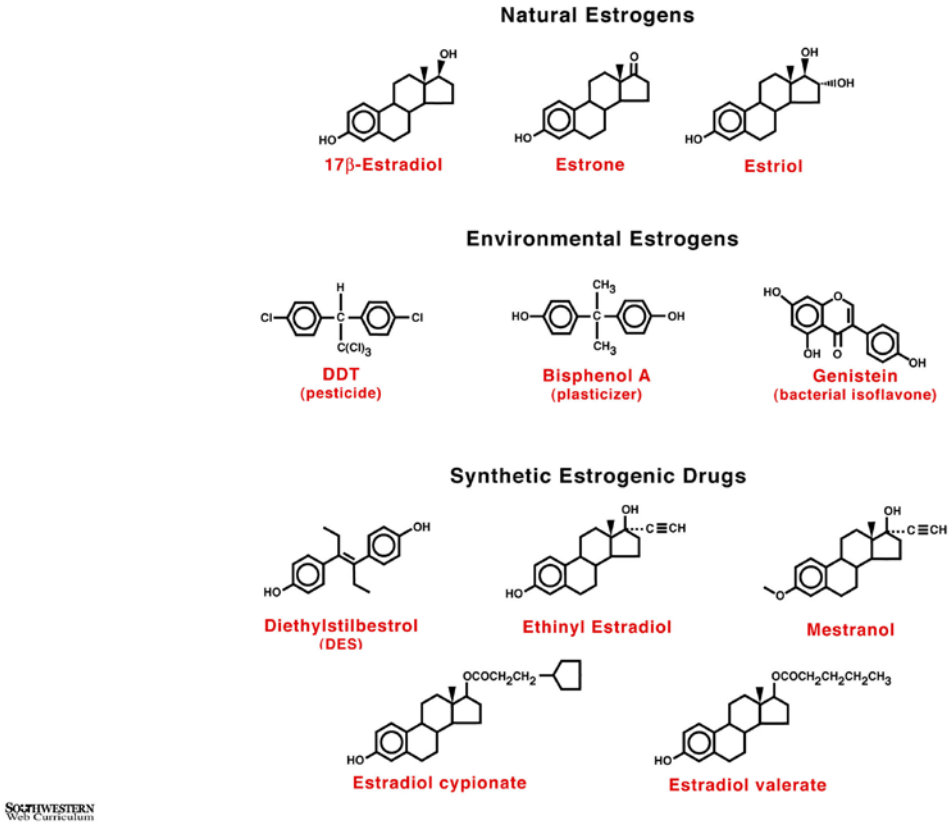


Figure 7: Natural and synthetic estrogens.

   2. In addition to the natural estrogens and the estrogenic drugs that have been designed by the pharmaceutical industry, there are a number of non-steroidal compounds that exist naturally or are pollutants in the environment and have estrogen-like activity.
      a. These are called environmental estrogens. Examples:
         i. DDT, the infamous pesticide.
         ii. Bisphenol A, a plasticizer. Phenol red is a derivative that is used in tissue culture as a pH indicator dye. It also has estrogenic activity.
         iii. Genistein, a bacterial isoflavone.
            a. Although these compounds are relatively weak estrogens, they can accumulate in adipose tissue in wildlife. This has raised the concern that low birth rates may be attributed to their effects in male and female animals (including the two-legged variety).

C. Actions of estrogens. Estrogen has both reproductive and non-reproductive effects in many tissues.
    1. Estrogen is a growth-promoting hormone. Its primary roles in reproduction are promotion of endometrium growth early in the cycle, and induction of the synthesis of progesterone receptors late in the cycle (review lecture notes from "Anterior Pituitary Drugs").
    2. E_2 is required for development of secondary sex characteristics in females, including pubertal changes in growth and development of vagina, uterus, fallopian tubes, breasts; fat redistribution, and hair distribution.
    3. Estrogens feed back and regulate LH/FSH secretion as discussed previously.
    4. A number of weak androgenic and anabolic effects are due to estrogens: positive nitrogen balance, closure of epiphyses in long bones.
    5. Metabolic effects. These are the effects that are most commonly associated with HRT in postmenopausal women.
        a. Bone: ↑bone mass, ↓bone resorption, ↑vitamin D hormone and calcium retention. Prevents osteoporosis and decreases fracture incidence.
        b. Cardiovascular effects: ↑HDL, ↓LDL, cholesterol metabolism and excretion in bile. Proposed to prevent cardiovascular disease.
        c. CNS: ↑cognition, ↓ hot flashes.
            i. Epidemiological data suggest that estrogens improve cognition and may help prevent Alzheimer's disease (randomized trials would suggest otherwise).
        d. Serum proteins: ↑ steroid and thyroid serum binding proteins.

D. Mechanism of action.
    1. Estrogens primarily regulate transcription through their binding to nuclear receptors.
    2. There are two known receptors, ERα and ERβ (encoded by distinct genes). Novel drugs are being developed that can distinguish between the two receptors, possibly improving the therapeutic profile of estrogens.

E. Estrogenic disorders.
    1. Estrogen deficiency. The consequences of estrogen deficiency vary depending on age of onset. In congenital conditions, patients generally present with failure to undergo puberty and primary amenorrhea. After puberty, the effects are less striking and may include amenorrhea and symptoms normally associated with menopause (e.g., hot flashes, vasomotor instability, mood disorders). Finally, all women who live long enough will undergo menopause, a decrease in ovarian function associated with marked decreases in estrogen levels.
    2. Cancer. A number of cancers (specifically breast, uterine, cervical cancers) are estrogen responsive and therefore candidates for anti-estrogen therapy.

F. Therapeutic uses.
    1. By far the most widely prescribed use of estrogen agonists is in combination oral contraceptives (OCPs) and hormone replacement therapy (HRT). The pharmacological considerations for these two applications differ considerably. HRT and OCPs are addressed in greater detail in Sections VIII and IX.
    2. Postmenopausal symptoms and complications.
        a. Osteoporosis.
        b. Vasomotor symptoms (e.g., hot flashes, night sweats, paresthesia).
        c. Mood swings, difficulty sleeping.
        d. Prevention of cardiovascular disease (note that effects on CV system are controversial and estrogens are no longer used to treat CVD, but may be beneficial in preventing it – see below).

e. Vaginal dryness and atrophy.

3. Failure of ovarian development.
    a. Turner's syndrome or ovarian dysgenesis.
    b. Hypopituitarism (hypogonadotropic hypogonadism).
4. Prostate cancer in men (*Why?*) and breast cancer in women (for palliation only).
5. Acne.
6. Dysmenorrhea.

G. Estrogen agonists (see Figure 7).
1. A significant advance in women's health was the development of orally effective, synthetic estrogens. The first of these was diethylstilbestrol (DES), a potent non-steroidal agonist that was initially used to treat some women early on in pregnancy to prevent spontaneous abortions. Later it was discovered to be toxic to the fetus and now it is absolutely contraindicated during pregnancy.
    a. DES is still rarely used as palliative treatment for inoperable prostate and breast cancers. Interestingly, it is labeled as a known carcinogen.
2. The major synthetic estrogen agonists used today are:
    a. E_2 derivatives esterified at the C-17 position (e.g., **ESTRADIOL-VALERATE** and **-CYPIONATE**). These esters are common in IM formulations, because they act as depot drugs that are slowly metabolized to release E_2 over several weeks (similar to testosterone esters described above).
    b. C-17 alkylated estrogens. The two most commonly used are **ETHINYL ESTRADIOL** and **MESTRANOL** (see Figure 7). Because of their slower metabolism they are 10-20X more potent then E_2 when taken orally. These two agonists are the most common constituents as the estrogenic component of oral contraceptives.
    c. ***Conjugated estrogens*** (mostly sulfated) that are found naturally occurring in pregnant mares (e.g., ***Premarin***) are less potent than E_2 and the other synthetic estrogens. They are most commonly used in post-menopausal HRT.
3. Estrogens can be given orally, IM, or by transdermal patch.
4. Side effects.
    a. Major: cancer, thromboembolism. Note that the possibility of developing endometrial or breast cancer has been a major concern, although the data are controversial. New formulations of oral contraceptives with lower dose estrogen and novel estrogen receptor agonists (called SERMs, see below) for HRT have lessened concerns.
    b. Minor: nausea, fluid retention, headache, breast tenderness, hypercalcemia, hypertension, altered glucose tolerance, cholesterol gallstone disease.

H. Estrogen antagonists and selective estrogen receptor modulators (Figure 8).

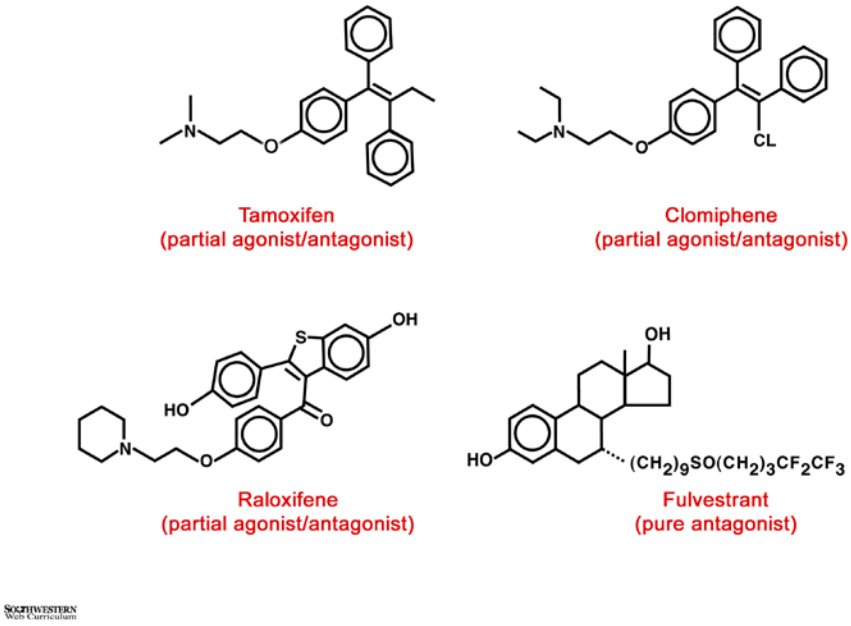


Figure 8: Estrogen antagonists and SERMs.

1. Ligands that bind to estrogen receptors (ERs) can have actions that range from full agonists (e.g., estrogen) to partial agonists/antagonists (e.g., **TAMOXIFEN** and **RALOXIFENE**) to full antagonists (e.g., **FULVESTRANT**).
2. The antagonistic properties of **TAMOXIFEN** and **CLOMIPHENE** make them attractive as drugs to treat breast cancer and female infertility, respectively. Interestingly, **CLOMIPHENE** in animals inhibited the gonadotropic function of the pituitary and was a potent contraceptive. In women with a functional HP axis and normal estrogen, clomiphene stimulates ovulation. Mechanistically, **CLOMIPHENE** may antagonize (i.e., derepress) E_2 feedback on the H-P axis, thereby stimulating gonadotropin release. **TAMOXIFEN** on the other hand has a mix of both estrogenic and anti-estrogenic properties and the drug's activity depends on the tissue in which it is tested (see below).
   a. **CLOMIPHENE** is used in both women and men for infertility. It is used in conjunction with **GONADOTROPINS** to simulate ovulation in women with normal estrogen and HP function, but who fail to ovulate. In men, it stimulates gonadotropin release and spermatogenesis.
   b. **TAMOXIFEN** stabilizes the ER protein and is used as both a chemotherapeutic and chemopreventive drug for breast cancer. This drug is one of the most important breast cancer drugs and is a first-line therapy of ER-positive tumors (aromatase inhibitors may be gaining ground in post-menopausal women). Note that the problem is the development of resistance of the cancer to the drug.
      i. **TAMOXIFEN** functions as an ER agonist in bone and endometrium, but functions as an antagonist in breast.

c. **FULVESTRANT** (ICI-182,780) is approved for treatment of ER-positive breast cancer in post-menopausal women (*why only in these women?*) that is unresponsive to **TAMOXIFEN**. It has no estrogenic activity and exhibits no spillover on other receptors. It effectively destabilizes ER protein, causing proteolysis of the receptor, and has strong anti-tumor activity in breast cancer.

3. **Selective Estrogen Receptor Modulators** or **SERMs** are ER ligands that have both estrogenic and anti-estrogenic properties (see Table 1). The discovery of such "partial agonist/antagonists" has led to the pharmacologic design of novel SERMs that simultaneously have the beneficial effects of an agonist and antagonist, without the side effects.

	Estrogen Receptor Activity in:					**Primary Indication**
SERM	**Bone**	**Cardio-vascular**	**Breast**	**Uterus**	**Brain/CNS**	
The "Ideal" SERM	Agonist	Agonist	Antagonist	Antagonist	Agonist	–
17β-ESTRADIOL	Agonist	Agonist	Agonist	Agonist	Agonist	OCP
TAMOXIFEN (*Nolvadex®*)*	Agonist	Agonist	Antagonist	Agonist	No reported beneficial activity*	Breast cancer
RALOXIFENE (*Evista®*)	Agonist	Agonist	Antagonist	Antagonist	No reported beneficial activity	Osteoporosis
BAZEDOXI-FENE**	Agonist	Agonist	Antagonist	Antagonist	None reported	Osteoporosis
FULVESTRANT (*Faslodex®*)	Antagonist	Antagonist	Antagonist	Antagonist	Antagonist	Breast cancer

Table 1: Properties of SERMs as HRT drugs. **Adverse effects are underlined. *Tamoxifen has been reported to increase hot flashes, suggesting that it may function as a CNS antagonist. **Bazedoxifene is approved in the U.S. as a combination therapy with low dose estrogens.**

a. The first SERM was **TAMOXIFEN**. The advantage of **TAXOXIFEN** is that it functions as an antagonist in breast, and as an agonist in bone and the cardiovascular system. The disadvantage is that it stimulates growth of the reproductive tissues, including endometrium, vagina, and uterus and can also increase thromboembolism. It does not prevent hot flashes, but may induce them.

b. **RALOXIFENE** is a second generation FDA-approved SERM that has many of the right properties one would want in a postmenopausal HRT drug. Thus far, the drug is used to prevent osteoporosis in postmenopausal women (note that it also does not prevent hot flashes). It is not used to treat invasive breast cancer, but is being used preventively (see below). A third generation SERM, called **BAZEDOXIFENE**, has many of the same properties and is used in combination with conjugated estrogens to prevent postmenopausal osteoporosis and hot flashes (see section on HRT below).
c. The most recent use of **TAMOXIFEN** and **RALOXIFENE** is in *preventing* invasive breast cancer from occurring in postmenopausal women who are known to be at high risk for the disease. These patients usually have non-invasive ductal or lobular carcinoma in situ (DCIS or LCIS) and other associated risk factors.

I. Aromatase inhibitors (e.g., **ANASTROZOLE, letrozole, and exemestane**). Aromatase inhibitors block the final reaction in estrogen synthesis. They are used to treat locally advanced or metastatic breast cancer in postmenopausal women (why only these women?), particularly in those patients whose disease initially responded to **TAMOXIFEN** therapy.
1. Aromatase inhibitors rarely work in ER-negative cancers or in patients who are <u>not</u> initially responsive to **TAMOXIFEN**. No additional benefit has been observed in patients treated with both **ANASTROZOLE** and **TAMOXIFEN**.
2. The major use of aromatase inhibitors is to prevent E_2 synthesis from adrenal androgens in postmenopausal women. Because they also inhibit ovarian estrogen synthesis and create an immediate rapid loss of E_2 that results in a menopausal-like state, they are contraindicated in pre-menopausal women.
3. Major side effects include asthenia, arthralgias, myalgias, and pain (resulting from a "flare reaction" at the site of tumor and caused by the tumor's abrupt loss of estrogen – common in bone metastasis).

VI. PROGESTINS

A. Major sites of production. Progesterone is the only naturally occurring progestin.
1. Ovaries (mainly the corpus luteum during 2nd half of the menstrual cycle).
2. Testes.
3. Adrenals.
4. Placenta.
5. Note that progesterone is under the same feedback regulation circuit as androgens and estrogens.

B. Actions of progestins.
1. Reproductive tract. In general, progesterone opposes the proliferative effects of estrogen in the reproductive tract.
a. Development of secretory endometrium.
b. The main determinant of the onset of menstruation is the decline in progesterone at the end of the cycle if fertilization does not occur.
c. Alters cervical secretions from nonviscous to viscous.
2. Mammary gland.
a. Induces proliferation of mammary gland acini.
3. CNS effects.
a. Alters body temperature (increased) from mid-cycle to menstruation.
b. Depressant and hypnotic actions may account for drowsiness.

4. Metabolic effects.
   a. ↑ insulin.
   b. ↑ fat deposition.
   c. May ↓ HDL.
   d. May ↓ sodium retention.
5. Neuroendocrine effects.
   a. As previously discussed, progesterone decreases the frequency of the hypothalamic pulse generator and increases the amplitude of LH pulses.

C. Mechanisms of action.
1. Progesterone acts via a nuclear receptor that exists in two isoforms (made by alternative splicing from the same gene), called PR-A and PR-B.
2. As noted, progesterone opposes the action of estrogens and this may be due to the ability of progestins to decrease estrogen receptors and increase estrogen turnover.

D. Chemistry. Progesterone itself is rarely used as a drug due to its rapid hepatic clearance, and ability to be converted into other steroids. Four major classes of synthetic progestins are currently available (Figure 9). Unlike estrogen, which has a 3 hydroxyl and aromatic A ring, progestins have a 3-one and a Δ4 unsaturated double bond. The main chemistry surrounds C-21 and C-19-nor compounds.
1. Pregnanes. C-21 compounds more closely resemble the natural hormone progesterone. The C-20, C-21 chemistry is the key difference between progesterone and androgens. They have no androgenic activity.
   a. **MEDROXYPROGESTERONE ACETATE** and **HYDROXYPROGESTERONE CAPROATE** are examples.
2. Estranes. Lack C-21 (making them more testosterone-like) and C-19 methyl groups. 19-nor compounds are more potent, but have androgenic side effects (e.g., **NORETHINDRONE**). Used primarily in combination oral contraception pills. Androgenic activity may enhance libido.
3. Gonanes. Also lack C-21 and C-19 methyl, but have C-13 ethyl groups. These compounds are more potent, but have less androgenic side effects than estranes.
   a. **NORGESTREL** is a racemic mixture of the inactive d and active l (called **LEVONORGESTREL**) isomers.

4. Spironolactone derivative. **DROSPIRENONE** is the first of its class and is used in combination OC (see below). It is the only progestin that is not based on the chemistry of testosterone (which limits its androgenic effects). Because of its derivation from spironolactone (an anti-mineralocorticoid), it also may lower blood pressure, elevate potassium levels and cause diuresis-induced weight loss. It is also unique in being contra-indicated in individuals with adrenal insufficiency.

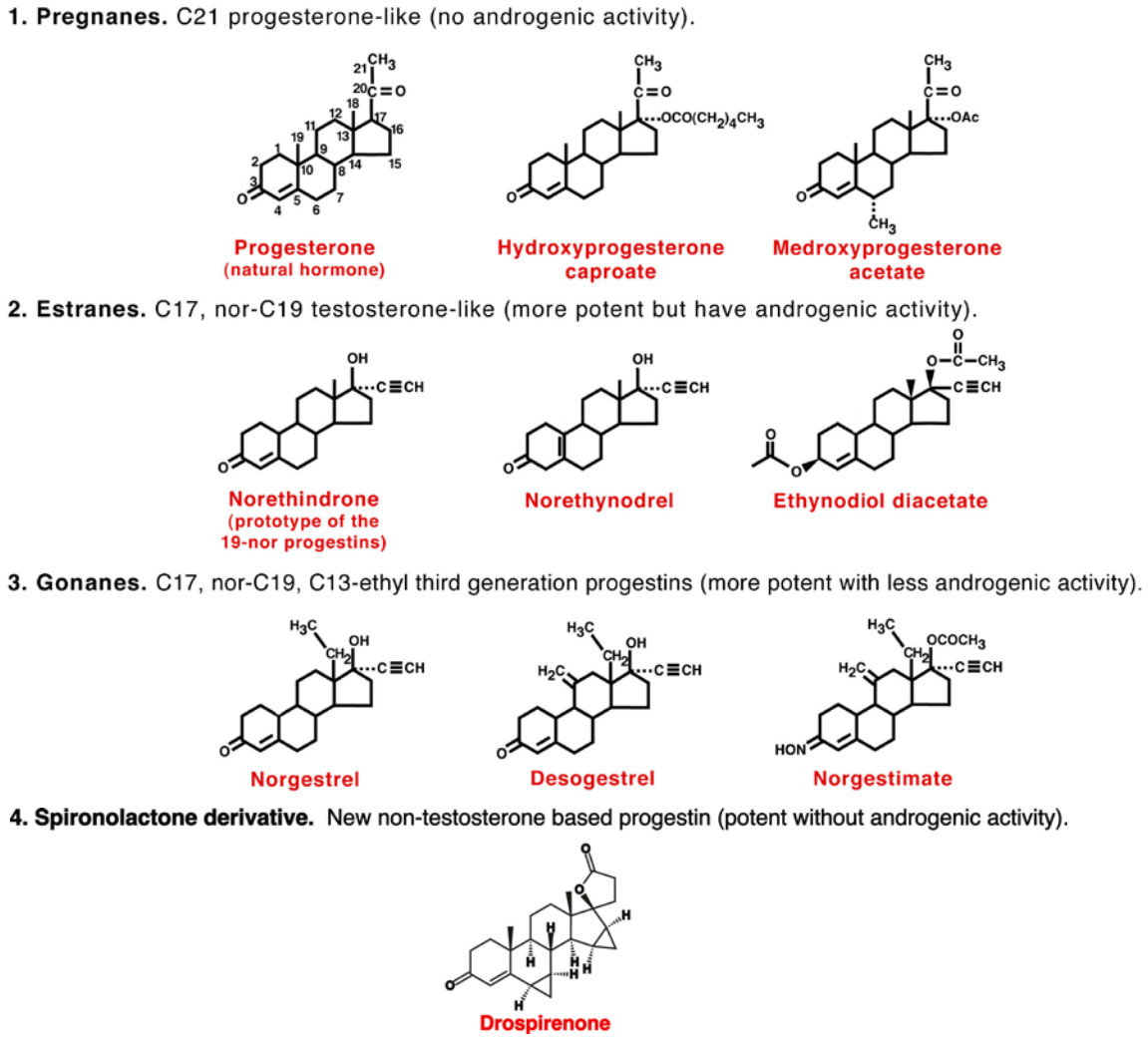


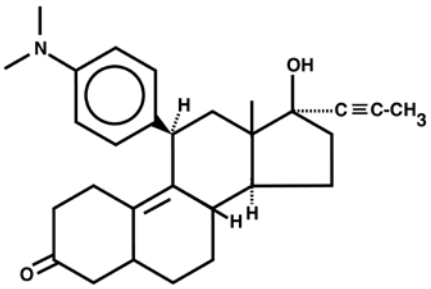
Figure 9: Progestin drugs.

E. Therapeutic uses.
   1. The two most common uses are in combination with estrogen for oral contraception (OCPs) and postmenopausal HRT. These are discussed further in Sections VII and VIII.
   2. Progestins are also used to treat various menstrual cycle disorders:
      a. Dysmenorrhea (painful), amenorrhea (lack of) and menorrhagia (heavy).
      b. Endometriosis.
      c. Dysfunctional uterine bleeding.
   3. Prevention of preterm birth (**HYDROXYPROGESTERONE CAPROATE**).
   4. Cancer.
      a. Palliative therapy for endometrial carcinoma.
      b. Renal and breast cancer.
      c. Prostate cancer (esp. **MEDROXYPROGESTERONE ACETATE**).

5. Female contraception (discussed in detail below).
6. Male contraception. As previously mentioned, **MEDROXYPROGESTERONE ACETATE** (***Depo-Provera®***) is also used to chemically castrate male sex offenders in some states (*why is this drug used?*).

F. Side Effects. Progestins have significant hormone spillover effects. In particular, they have both androgenic and estrogenic activities and even glucocorticoid-like activities at high concentrations.
1. Breast tenderness (breast cancer in postmenopausal women has been suggested).
2. Androgenic effects: masculinization of female fetus, increased or decreased libido, increased appetite, acne.
3. With continued long-term use alone they can actually cause amenorrhea.
4. Decreased bone mass, particularly with depot formulations. Because of this, the FDA required that a "Black box" warning be added to labeling for ***Depo-Provera*** warning that the drug should not be used for more than 2 years unless other birth control methods were inadequate for that patient.
5. Fatigue.
6. Headaches, depression, and sleeplessness.
7. Deep vein thrombosis (the literature is controversial on this finding), uterine bleeding and tumors (particularly with **LEVONORGESTREL**). Because of this there has been a push to take it off the market.

G. Anti-progestins. There is only one that is available therapeutically:
1. **MIFEPRISTONE**, also called **RU486**. It is marketed under the trade name ***Mifeprex®***. This is an abortive therapeutic and the FDA has issued special guidelines on its use. One reason women might choose the method is to avoid other invasive techniques. When used as approved, it has been determined to be safe and effective to terminate a pregnancy.



Mifepristone
(RU486)

Figure 10: Mifepristone, the FDA-approved anti-progestin for abortions.

2. **MIFEPRISTONE** is a PR antagonist that works by blocking progesterone's action to prepare the lining of the uterus for implantation and disrupting the pregnancy maintenance function of progesterone. Therefore, it is an abortive agent that causes detachment of the blastocyst. The regimen for use requires administering a prostaglandin E_1 analog (**MISOPROSTOL**) to expel the fetus. **MIFEPRISTONE** is also a GR antagonist that is used rarely in patients with adrenocortical carcinoma to suppress excess glucocorticoid effects.

a. The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of **MIFEPRISTONE.** For example, the drug must be administered by or under the supervision of a healthcare provider who meets certain qualifications (e.g., must be able to accurately detect the age of pregnancy, determine whether it is an ectopic or tubal pregnancy, and provide any necessary surgical intervention if required). The drug can only be dispensed in medical practice institutions by certified providers, patients must be provided with a copy of the Mifeprex Medication Guide and they must sign a special agreement form. The following treatment regimen is approved to terminate a pregnancy up to 70 days or less since the first day of a woman's last menstrual period):
   i. Day one: 200 mg of **MIFEPRISTONE**, PO.
   ii. After 24-48 hours receiving **MIFEPRISTONE**: 800 mcg of **MISOPROSTOL** (***Cytotec®***), taken buccally (in the cheek pouch) at a location appropriate for the patient.
   iii. Approximately 7-14 days after taking **MIFEPRISTONE** a follow up visit to the healthcare provider is required.
b. Nearly all women experience side-effects:
   i. Cramping and vaginal bleeding are expected. Nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness are common (some of which may reflect the prostaglandin component).
   ii. Surgery may be required to stop heavy bleeding.
   iii. A potentially serious side effect is septic shock due to infection with *Clostridium sordelli*. Although a cause-and-effect relationship has not been established, all patients should be warned about the risk and told to see a physician if they experience fever, severe abdominal pain, prolonged heavy bleeding, or syncope.
c. Contraindicated in ectopic pregnancy, greater than 70 days since the first day of the last period, IUD-using patients, persons with bleeding problems, and persons with adrenal problems or taking corticosteroids (*why?*).
d. RU486 by itself is also efficacious as a stand-alone morning after pill.

VII. HRT

Hormone replacement therapy in the U.S. is a major and controversial medical issue (see below). The two most common reasons for HRT are following surgical removal of the ovaries in conjunction with hysterectomy and for menopausal/post-menopausal (PM) problems.

A. Hysterectomy: over 500,000 women annually receive a hysterectomy in the U.S. (there is a 50% chance a woman will have one in her lifetime).
B. Both menopause and a total hysterectomy (including removal of ovaries) can result in similar medical problems:
   1. ↑ CNS problems (e.g., depression, hot flashes, etc).
   2. ↓ Bone mass (prevention of osteoporosis and fractures is major concern).
   3. ↓ Cardiovascular health (numerous animal and human studies have shown that estrogen has protective cardiovascular effects).
   4. ↓ Sexual function and libido.
   5. ↑Urinary incontinence.
C. An important consideration in HRT is to reduce the side effects of unopposed estrogen (such as endometrial cancer) by also including a progestin. Progestin should be included in HRT in women with a uterus to protect the endometrium from the proliferative action of estrogen.
D. In general, HRT uses much lower doses of estrogen than oral contraception.

E. One popular drug for HRT combinations is ***Premarin®***, which supplies the estrogenic component. ***Premarin*** is derived from **pre**gnant **mar**e's ur**in**e and contains a variety of natural, relatively weak conjugated estrogens. It is effective for treating hot flashes.

F. Other estrogenic agents that are no longer as popular include the esterified estrogens (estradiol-valerate and –cypionate) sometimes used in combo with methyltestosterone (why? – anabolic effects and libido). Data from the Women's Health Initiative (see below) suggest that this specific combination may be associated with a significantly increased risk of breast cancer.

G. The most popular progestin component in HRT combo-therapy is the C-21 derivative **MEDROXYPROGESTERONE ACETATE** (MPA). This is in contrast to oral contraceptives, which use the more potent 19-nor progestins. Premarin plus MPA is marketed as ***Prempro®***.

H. The development of SERMs (discussed above) like **BAZEDOXIFENE** provide a new therapeutic alternative to conventional HRT for the prevention of osteoporosis. **BAZEDOXIFENE** by itself does not relieve all of the symptoms of menopause, including CNS effects. For this reason it is used in combination with conjugated estrogens in a formulation (***Duavee®***) to prevent osteoporosis and treat hot flashes in PM women. Because it inhibits estrogenic effects on endometrium, a progestin is not needed and thus far has been approved only for use in women with a uterus.

I. Regimens for PM women aimed at osteoporosis prevention should include an adequate intake of vitamin D and calcium. Note that estrogen is no longer considered first-line therapy for osteoporosis by itself. In addition to SERMs like **RALOXIFENE**, other drugs such as **bisphosphonates** are now used.

J. **Risks:** In 2002 data were released that initiated dramatic changes for HRT in PM women. The Women's Health Initiative (WHI) Study Group found a slight increased risk of breast cancer, deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in PM women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen [0.625 mg] combined with MPA) [2.5 mg], relative to placebo. However, significant benefits included less bone fractures, less CNS/mood swings, less complaints about vaginal drying, decreased colon cancer, less diabetes, and an overall decrease in mortality. The subsequent WHI Memory Study (WHIMS) further found an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment. Nevertheless, the study prompted a substantial decrease in HRT usage because of this.

   It is now accepted that the WHI study was poorly designed and controversial on scientific grounds, since many women in the study were well past menopause (in their mid-60s and without premenopausal levels of estrogen for over 10 years) and already at risk for several of the diseases they ended up getting. Estrogen is believed to have protective effects that prevent cardiovascular problems but cannot reverse disease that has already started. Therefore, it is no longer used to treat CVD, but may be beneficial in prevention of CVD, especially if given early in menopause. As a positive, the WHI led to a discussion on how to treat this important issue of women's health.

K. In 2012 a newer study that considered the timing of women taking HRT was completed. It concluded low-dose estrogen was safe and effective at treating hot-flashes and other symptoms (without increased CVD risks) when used in women who had recently entered menopause.

Bottom Line: Conventional HRT gives clear benefits for relieving menopause symptoms (hot flashes, vaginal dryness, osteoporosis, colon cancer, and perhaps CVD). That said, the current accepted practice is that estrogen plus progestin therapy should not be used for treating cardiovascular disease or dementia. Current guidelines recommend HRT be reserved for severe cases, be started early in menopause, be administered short-term and at the lowest dose possible, and take into consideration other individual risk factors. Doctors should have a frank discussion with their patients about the risks before beginning or continuing treatment. However, stopping HRT, especially abruptly, may lead to significant adverse effects, including dramatic loss of bone, and a resumption of other undesirable PM effects (particularly on the CNS). This has led to continued use of HRT in spite of some of the risks. It is important to keep up with the literature.

VIII. HORMONAL CONTRACEPTION

These are among the most frequently prescribed drugs in the U.S.

A. Important pharmacological points:
   1. Oral contraceptive pills (OCPs), both combination and progestin-only, are among the most effective drugs available.
   2. The number of combination and dosing options available allow doctors to tailor prescriptions to almost any individual's need.
   3. In addition to contraception, there are a number of important positive health benefits of OCPs (decreased risk of iron deficiency anemia, decreased risk of ovarian and endometrial cancer, decreased incidence of fibrocystic breast changes and fibroadenoma, treatment of acne).
   4. As stressed above, birth control medications generally are given to healthy individuals, and the consideration of potential side effects is important.

B. There are several types of hormonal contraceptives. OCPs are discussed here and examples listed in Section X.G.1. The depot/slow release contraceptives and non-pharmacologic contraceptives are briefly mentioned here, but make sure you go over them in Section X.G.2.
   1. Progestin-only contraceptives (because of the bad effects of unopposed estrogen in women with a uterus, estrogen-only contraceptives are not used).
      a. Slightly less efficacious than combination OCPs (96-97%).
      b. Progestin-only mini-pill formulations are indicated for nursing mothers and those at risk for breast cancer. Major adverse effect is breakthrough bleeding.
      c. Three general types:
         i. Mini-pill, taken daily – includes low dose **NORETHINDRONE** or **NORGESTREL**.
         ii. Depot IM injection, every 3 months, **MEDROXYPROGESTERONE ACETATE** (***Depo-Provera***). Note black box warning.
         iii. Implants
            (a) IUD implants, every 5 years, **LEVONORGESTREL** (***Mirena***).
            (b) Rod implants, every 3 years, etonogestrel (***Implanon®***).

   2. Combination OCPs. These are by far the most popular.
      a. Theoretical efficacy: ≥ 99%, actual efficacy=95%.
      b. Considerations: The ratio of estrogen to progestin is important. The goal for most women is to mimic the natural cycle.

i. The progestin component counteracts the negative side effects of estrogen (in fact, it actually lessens the chance of endometrial and/or ovarian cancers by ~40-60%; and provides no apparent increased risk for breast cancer). The estrogenic component stabilizes the endometrium and suppresses FSH so that no follicle selection or emergence/development occurs.
ii. In contrast to early OCP formulations, the estrogenic component is now relatively low. Usually, patients start with the lowest dose of estrogen and if breakthrough bleeding or spotting occurs, the dose is increased. Heavier patients or those taking certain other medications may need larger doses than those in the lower dose formulation to ensure contraception.
iii. The estrogenic component also counteracts the androgenic effects of progestin-only formulations and significantly reduces the risk of cardiovascular disease.
iv. Combination OCP formulations reduce the severity of acne. In 1997 **NORGESTIMATE/ETHINYL ESTRADIOL** (***Ortho Tri-Cyclen***) was the first OCP approved for treating acne in women >14 years old.

c. Types: There are 3 basic formulations: monophasic, biphasic, and triphasic (see tables in Section I.B.7.b). The strategy of the multiphasic (sequential) preparations is to provide a changing estrogen/progesterone ratio that mimics a woman's natural cycle as closely as possible, and to use as low a dose of the E and P components as possible. These formulations are designed to permit some menstrual bleeding to occur, which is a comfort to some women psychologically and is an indicator that they are not pregnant. Multiphasics have also been a clever marketing tool that has permitted development of "designer" pills that cater to almost any women's need.
i. Combination OCPs are generally provided in 21-day packs. Medications are taken for 21 days, followed by 7 days of no medication.
ii. Monophasics are 21 days of the same dose and ratio of estrogen/progestin.
iii. Biphasics are usually 10 days of the first dose and ratio, followed by 11 days of the second dose and ratio.
iv. Triphasics have three different, sequential dosing regimens that range from 5 to 10 days each.

3. In looking at the biphasic and triphasic OCP formulations, note that the estrogen/progesterone ratio is higher earlier in the cycle and lower later in the cycle. The change is due to increasing the dose of progestin relative to a rather constant amount of estrogen. A main advantage of bi- and tri-phasic preparations is that the total amount of progestin administration is reduced overall.
4. Other hormonal contraceptive options include ***Ortho Evra*** (three 1-week transdermal patches of estrogen/progestin), ***Lunelle*** (monthly injectable of estrogen/progestin), ***NuvaRing*** (3-week vaginal ring that releases estrogen/progestin). See Section I.B.7 for full details on each.

C. Mechanism of action:
1. Combination OCPs act by preventing ovulation. This occurs through multiple mechanisms, including: diminishing the frequency of the GnRH pulse in the hypothalamus (estrogen and progestin); decreasing the response to GnRH in the pituitary (estrogen and progestin). Combination OCPs also decrease the transit of sperm and the egg in the fallopian tube (estrogen and progestin); increase viscous mucus in the cervix to prevent sperm penetration (progestin); and reduce the receptiveness of the endometrium to implantation (progestin).

2. Progestin-only contraceptives are 60-80% effective in blocking ovulation. Their effectiveness also derives from their ability to decrease sperm penetration in the cervix and thicken cervical mucus, which impairs implantation in the endometrium.

D. Postcoital or emergency contraception. (In contrast to the use of RU486 described above, this is not believed to be abortive therapy).
   1. Mifepristone (RU486) may also be efficacious when used in this way (which is quite different than when used as an abortive), but it is not FDA approved.
   2. High-dose OCPs are the current treatment option and are FDA-approved (Plan B has been approved for over-the-counter dispensing in women 18 years of age or older). The multi-pill regimen must start with the first pill given within 72h of intercourse. Effectiveness is greater if taken within 12h or intercourse. The high concentration of progestin prevents ovulation and may affect transport of sperm and ova. Examples:
      a. PLAN-B: two <u>one</u>-pill doses of 0.75mg **LEVONORGESTREL** given 12h apart.
      b. PREVEN: two <u>two</u>-pill doses of 0.25mg **LEVONORGESTREL** + 0.05mg **ETHINYL ESTRADIOL** given 12h apart.

   Major side effect is severe vomiting, which may necessitate re-administration of meds.

E. Side effects.
   1. Major effects.
      a. Thromboembolism. Drospirenone containing OCPs in particular have higher blood clotting risk.
      b. Break-through bleeding between periods. Corrected by increasing dose.
      c. Hypertension.
      d. Headaches and Depression.
      e. Gallbladder disease.
      f. Insulin resistance.
      g. Breast cancer (although this is now controversial and some recent studies suggest there is no risk).
      h. Decreased bone marrow density (esp. for long-lasting injectables like depot MPA)
   2. Minor effects.
      a. Weight gain and bloating.
      b. Mood changes and sleep disturbances.
      c. Headache.
      d. Nausea.
   3. Risk factors.
      a. Smoking is a major contraindication for even low-dose OCP use because it greatly increases the risk of cardiovascular disease.
      b. Other absolute contraindications are: cancer (particularly of breast and reproductive tract), thromboembolic disease, pregnancy, myocardial infarction, cerebral vascular disease, coronary artery disease, congenital hyperlipidemia, impaired liver function.
      c. Hormonal contraception may be rendered less effective by concurrent administration of drugs that induce hepatic enzymes and thereby decrease the estrogen level. This includes many OTC “health” supplements (e.g., St. John’s Wort) and prescription medicines (e.g., the antibiotic rifampin). If these drugs must be used, the “low-dose” formulation may be particularly susceptible to a loss of contraceptive efficacy and other forms of contraception may be preferred.
      d. Hypertension.

e. Obesity.
f. Age over 40 years.

IX. NON-HORMONAL CONTRACEPTION.

A. Includes copper IUD, and non-pharmacological (e.g., barrier devices). See lecture on contraception for details.
   1. Note that there can be significant side effects from IUDs, including perforation, infection, copper allergies or reactions, bleeding, pain and cramping, ectopic pregnancy, and septic abortion.

X. A SUMMARY OF DRUGS DISCUSSED IN THIS LECTURE

This list gives drug names in bold and all caps. Some common names and/or trade names (bolded and italicized) are also given as examples in parentheses. Following the name is the mechanism of action; primary indication; and route of administration (e.g., PO, IM, etc).

A. Androgenic drugs:

a. **ABIRATERONE (*Zytiga*®):** 17α-hydroxylase/C17,20 lyase (CYP17A1) inhibitor; decreases androgen production; used in combination with **PREDNISONE** to treat castration-resistant prostate cancer; PO (pregnant women should avoid contact).
b. **BICALUTAMIDE (*Casodex®*)**: Non-steroidal androgen antagonist; used in conjunction with **LEUPROLIDE** for metastatic prostate cancer; PO.
c. **DEGARELIX (*Firmagon*®):** GnRH receptor antagonist; suppresses FSH/LH release; used to treat advanced prostate cancer; SC injection.
d. **DANAZOL (*Danocrine®*):** Weak synthetic androgen; suppresses FSH/LH release, used to treat endometriosis, fibrocystic breast disease; PO.
e. **DUTASTERIDE (*Avodart®*):** Steroid 5α-reductase (Type I and Type II) inhibitor; BPH; PO.
f. **ENZALUTAMIDE (*Xtandi*®):** Non-steroidal androgen receptor antagonist; treats castration-resistant prostate cancer; PO.
g. **FINASTERIDE (*Proscar®, Propecia®*):** Steroid 5α-reductase (Type II) inhibitor (synthetic azasteroid); used for treatment of enlarged prostate, BPH, and androgenic alopecia; PO (pregnant women should avoid contact with drugs because of danger to male fetus).
h. **FLUOXYMESTRONE (*Halotestin®*):** Potent synthetic androgen; HRT for hypogonadism in males, E_2-dependent breast cancer and post-partum breast engorgement in females; PO.
i. **METHYLTESTOSTERONE (*Testred®*):** Synthetic androgen; HRT for hypogonadism in males, E_2-dependent breast cancer in females; PO.
j. **NANDROLONE derivatives (*Androlone®, Deca-/Durabolin®, etc.*)**: synthetic androgen; catabolic states, anemia of renal disease; this class of anabolic steroids is often abused by athletes; IM.
k. **TESTOSTERONE and its ester derivatives** (***Androderm®, Androgel®, Testoderm®, Striant®, etc.***): HRT for hypogonadism and delayed puberty in males; transdermal patch, gel, buccal capsule, IM injection.

2. Estrogenic drugs:
    a. **ESTRADIOL *(e.g., estradiol-valerate, -cypionate, mestranol, ethinyl-estradiol*)** and **ESTERIFIED/CONJUGATED ESTROGEN** derivatives (***Estrace, Estraderm, Vivelle, Menest, Ortho-Est, Premarin, Kestrone, Estinyl, etc; over 20 different prescription varieties***): Natural and synthetic estrogen agonists; HRT in women, abnormal uterine bleeding, atrophic vaginitis (also used in oral contraception, see below); PO, IM, transdermal patch, cream.
3. Progestin drugs.
    a. **DROSPIRENONE**: Synthetic progestin; derivative of **SPIRONOLACTONE** (see hypertensive and adrenal drugs). It is a non-testosterone based progestin used in combination oral contraceptives (see below). PO.
    b. **HYDROXYPROGESTERONE CAPROATE (*Hylutin®*):** Synthetic progesterone; prevent preterm delivery, amenorrhea, metrorrhagia, induction of secretory endometrium; IM.
    c. **NORETHINDRONE (*Aygestin®, Micronor®*):** Synthetic potent progestin, HRT, amenorrhea (also used in contraception, see below); PO.
    d. **NORGESTREL (i.e., LEVONORGESTREL) and NORGESTIMATE (*under various trade names*):** Third generation progestins. Birth control, emergency contraception. Used in contraception, mini-pills, IUDs. See discussion under contraception below for delivery info.
    e. **MEDROXYPROGESTERONE ACETATE (*Provera®*):** Synthetic progestin; HRT, endometrial hyperplasia, prostate cancer, sex offenders (also as a progestin-only contraceptive, see below); PO, IM.
    f. **PROGESTERONE** derivatives (***Crinone, Prometrium***): Natural progesterone hormone; HRT, amenorrhea; IM, PO, vaginal gel.
4. Hormone replacement combinations.
    a. **ESTRADIOL/NORETHINDRONE (*Activella®, CombiPatch*)**: Combination estrogen and progesterone agonists; HRT in postmenopausal women or postoperative hysterectomy; PO, transdermal patch.
    b. **ESTROGEN/MEDROXYPROGESTERONE (*Prempro®*):** Combination of conjugated estrogens and synthetic progestin; HRT; PO.
    c. **ESTROGEN/BAZEDOXIFENE (*Duavee®*):** Combination of conjugated estrogens and the SERM, **BAZEDOXIFENE**; HRT in postmenopausal women; PO.
5. SERMs
    a. **TAMOXIFEN (*Nolvadex®*)**: Mixed function estrogen receptor agonist/antagonist; breast cancer, given for <u>both</u> chemotherapy and chemoprevention; PO.
    b. **RALOXIFENE (*Evista®*)**: Mixed function estrogen receptor agonist/antagonist; primary indication is osteoporosis prevention and treatment in postmenopausal women (HRT); also used preventively in PM women at risk for invasive breast cancer; PO.
    c. **BAZEDOXIFENE**: Mixed function estrogen receptor agonist/antagonist; approved in U.S. to prevent osteoporosis in postmenopausal women but only in combination with conjugated estrogens for HRT (see ***Duavee*** above); PO.
6. Estrogen/Progesterone antagonists.
    a. **CLOMIPHENE (*Clomid®*)**: Anti-estrogen; female infertility to induce ovulation, male infertility to stimulate gonadotropin release; PO.
    b. **MIFEPRISTONE (*Mifeprex®*):** Anti-progestin, i.e., abortion pill; abortifacient; PO. Must be used in combination with **MISOPROSTOL**, a prostaglandin.

c. **FULVESTRANT (*Faslodex®*):** Anti-estrogen; breast cancer; IM.
d. **ANASTROZOLE (*Arimidex®*):** Aromatase inhibitor; locally advanced or metastatic breast cancer (in postmenopausal women only); PO. Letrozole (*Femara*®) is another marketed aromatase inhibitor.

7. Contraceptives.
   a. Oral contraceptives. Below are listed some examples of more than 50 preparations that are marketed drugs. **You are not required to memorize these, but you should know what the estrogen and progestin components are (e.g., ethinylestradiol is an estrogenic component of oral contraceptives).** You should also know how the phasic preparations differ from one another and why they are used. (Note: in addition to birth control, some OCP preparations are also prescribed for acne [e.g., Ortho Tri-Cyclen] and severe menstrual cramps).
      a. Progestin-only OCPs.

Progestin	Trade Name
NORETHINDRONE (0.35 mg)	***Micronor***®
NORGESTREL (0.075 mg)	***Ovrette®***

      b. Monophasic combination OCPs. (same pill for 21 days, placebo for 7).

Estrogen	Progestin	Trade Name
ETHINYL ESTRADIOL (20μg)	**NORETHINDRONE** (1 mg)	***Loestrin 1/20***®
ETHINYL ESTRADIOL (30 μg)	**NORGESTREL** (0.3 mg)	***Lo/Ovral®***
ETHINYL ESTRADIOL (35 μg)	**ETHYNODIOL DIACETATE** (1 mg)	***Demulin 1/35®***
ETHINYL ESTRADIOL (35 μg)	**NORETHINDRONE** (1 mg)	***Genora 1/35®***
ETHINYL ESTRADIOL (50 μg)	**NORGESTREL** (0.5 mg)	***Ovral***®
MESTRANOL (50 μg)	**NORETHINDRONE** (1 mg)	***Ortho-Novum 1/50®***
ETHINYL ESTRADIOL (30μg)	**DROSPIRENONE** (3 mg)	***Yasmin®***

      c. Biphasic combination OCPs. (10 days first phase; 11 days second phase).

Estrogen	Progestin	Trade Name
ETHINYL ESTRADIOL (35 μg)	**NORETHINDRONE** (0.5/1mg)	***Ortho-Novum 10/11***

      d. Triphasic combination OCPs. (usually in three 7 day phases, or 6, 5, and 10 day phases).

Estrogen	Progestin	Trade Name
ETHINYL ESTRADIOL (35/35/35 μg)	**NORETHINDRONE** (0.5/0.75/1 mg)	***Ortho-Novum 7/7/7***
ETHINYL ESTRADIOL (35/35/35 μg)	**NORGESTIMATE** (0.18/0.215/0.25 mg)	***Ortho Tri-Cyclen***
ETHINYL ESTRADIOL (30/40/30 μg)	**LEVONOGESTREL** (0.05/0.075/0.125 mg)	***Triphasil –21***

   2. Depot/slow release contraceptives. These methods provide more choices to women and their clinicians. Ultimately, new methods should be safe and efficacious, but also easier to use, resulting in better compliance. **You don't need to memorize the exact formulation in the options listed, just the type of drugs in each and how applied.**

a. **Transdermal Patch *(Ortho Evra)***: Three patch system. Each patch delivers 150 mg norelgestromin (the active metabolite of **NORGESTIMATE**) and 20 mg **ETHINYL ESTRADIOL** every 24h. One patch is applied every week for 3 weeks, followed by one week with no patch. This was the first transdermal patch approved by the FDA for contraceptive use.
b. **Depot injection *(Lunelle®, Depo-Provera®)***. ***Lunelle*** is an injectable contraceptive that contains a long-acting depot derivative of progesterone and estrogen, 25 mg **MEDROXYPROGESTERONE ACETATE** (MPA), and 5mg **ESTRADIOL CYPIONATE**. Each injection provides a full month of protection, and the contraceptive effect is mediated primarily by MPA, which inhibits ovulation. ***Depo-Provera*** is a MPA-only contraceptive that delivers 150 mg drug after IM injection every 3 months.
c. **Vaginal ring *(NuvaRing)***. The vaginal ring is a flexible, soft, transparent ring with an outer diameter of 54 mm and a cross section of 4 mm. The vaginal ring is a new, highly effective contraceptive method recently approved by the FDA. The ring releases 120 µg etonogestrel (a **NORGESTREL** derivative), and 15 µg **ETHINYL ESTRADIOL**, per day. It is inserted and removed by the woman herself and intended to be used for one cycle consisting of 3 weeks followed by a 1-week ring-free period.
d. **Intrauterine device (IUD)**. There are two types, steroid-releasing, and copper-releasing.
    i. **Steroid-releasing *(Mirena)***. The IUD releases 20 µg/day of **LEVONORGESTREL** (a progestin) directly into the uterine cavity from a polymer cylinder mounted on a T-shaped frame and covered with a release rate-controlled membrane. Requires physician to insert and remove. It is approved for 5-year use.
    ii. **Copper-releasing *(Paragard T380)***. The IUD is a polyethylene body wound with 176mg of copper wire and a copper collar of 68.7mg of copper in each of the two T-shaped arms. The release of copper from the IUD is believed to enhance the contraceptive effectiveness, although how is not known. Hypotheses include interference with sperm transport, fertilization, and implantation. Requires physician to insert and remove. It is approved for 10-year use. Barium sulfate in the IUD renders it radio-opaque.
e. **Implant *(Implanon®)***. The newest contraceptive implant system, it is a single rod containing 68 mg of etonogestrel, with a membrane of ethylene vinyl acetate. Inhibition of ovulation is the primary mechanism of action and occurs within one day of insertion. Effective contraception lasts for three years.

3. Non-pharmacologic alternatives to contraception.
    a. A variety of barrier contraceptives exist including condoms (for men and women); diaphragms, sponges, and cervical caps (for women). Most effective when used with spermicidal agents (foams, lubricants, etc.). Most common spermicide is nonoxynol-9.

    b. Other options include tubal ligation and vasectomy (requires surgery), coitus interruptus, and the number one most effective method (guaranteed 100% effective), **abstinence**.

SAMPLE QUESTIONS. (Choose the single BEST answer)

1. A major limitation of progestin drugs that are based on the chemistry of steroids is:
    A. Adverse effects due to cross-over activity and lack of specificity.
    B. Increased renal metabolism and clearance.
    C. Increased risk hepatocellular carcinoma.
    D. Increased risk of sexually transmitted disease.
    E. Poor oral availability.

2. The efficacy of androgen receptor antagonists to treat prostate cancer often fails because:
    A. The cancer loses expression of the androgen receptor.
    B. The androgen receptor is present but no longer required to drive cancer progression.
    C. The antagonist no longer inhibits the androgen receptor in cancer cells.
    D. The antagonist fails to inhibit pituitary release of LH.
    E. The antagonist is metabolized to an agonist that stimulates cancer growth.

3. Estradiol is generally not given as an HRT drug to postmenopausal women because:
    A. It can stimulate uterine and breast growth.
    B. It fails to prevent the adverse effects of progesterone.
    C. It stimulates bone resorption.
    D. It increases the risk of polycythemia.
    E. All of the above.

4. Let's play the bonus round. Name up to 13 different methods of birth control. Can't get them all? Unscramble the letters to get the answers: COP, DUI, Opted Nicejoint, Chapt, Glavina Inrg, Grahamdip, Escapedrim, Carlvice Pac, Pensgo, Baltu Giantoil, Flamee Moodcn, Meal Mcodon, Myoctaves.

Answers
1. A
2. C
3. A