female sex steroids and contraceptive agents

Dr. Laila M Matalqah

UGS

Faculty of Medicine

Objectives

1. Describe the nature, mechanisms of actions and the adverse effects of female sex steroids and various female contraceptive agents.
2. Indicate the therapeutic applications of antiestrogenic agents.

Estrogens

a. Natural estrogens

(1) Natural estrogens include **17β-estradiol, estrone, and estriol.**

(2) **The most potent natural estrogen is 17β-estradiol.**

(3) **Natural estrogens are produced by the metabolism of cholesterol; testosterone is** the immediate precursor of estradiol. Conversion of testosterone to 17β-estradiol is catalyzed by the enzyme aromatase.

(4) **Estrone and estriol are produced in the liver and other peripheral tissues from** 17β-estradiol

b. Synthetic estrogens

Frequently used synthetic estrogens include the steroidal agents:

(1) **ethinyl estradiol** and **mestranol**

(2) **nonsteroidal compounds: diethylstilbestrol (DES) and dienestrol**

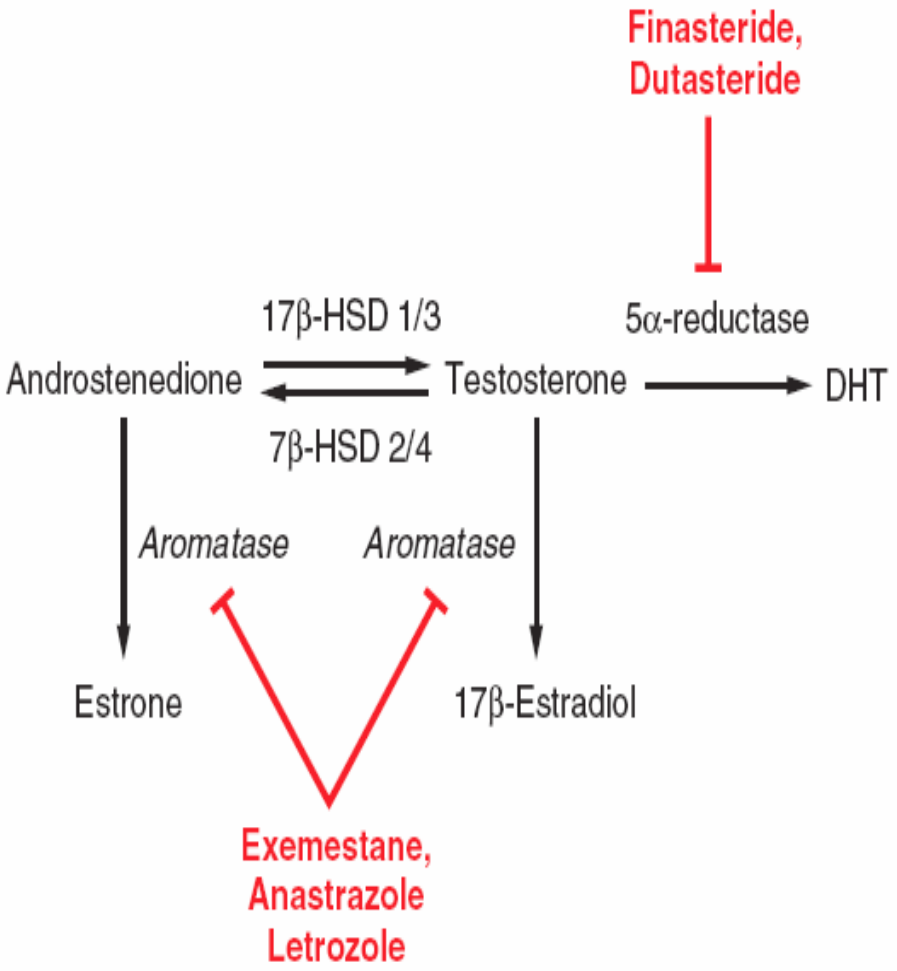
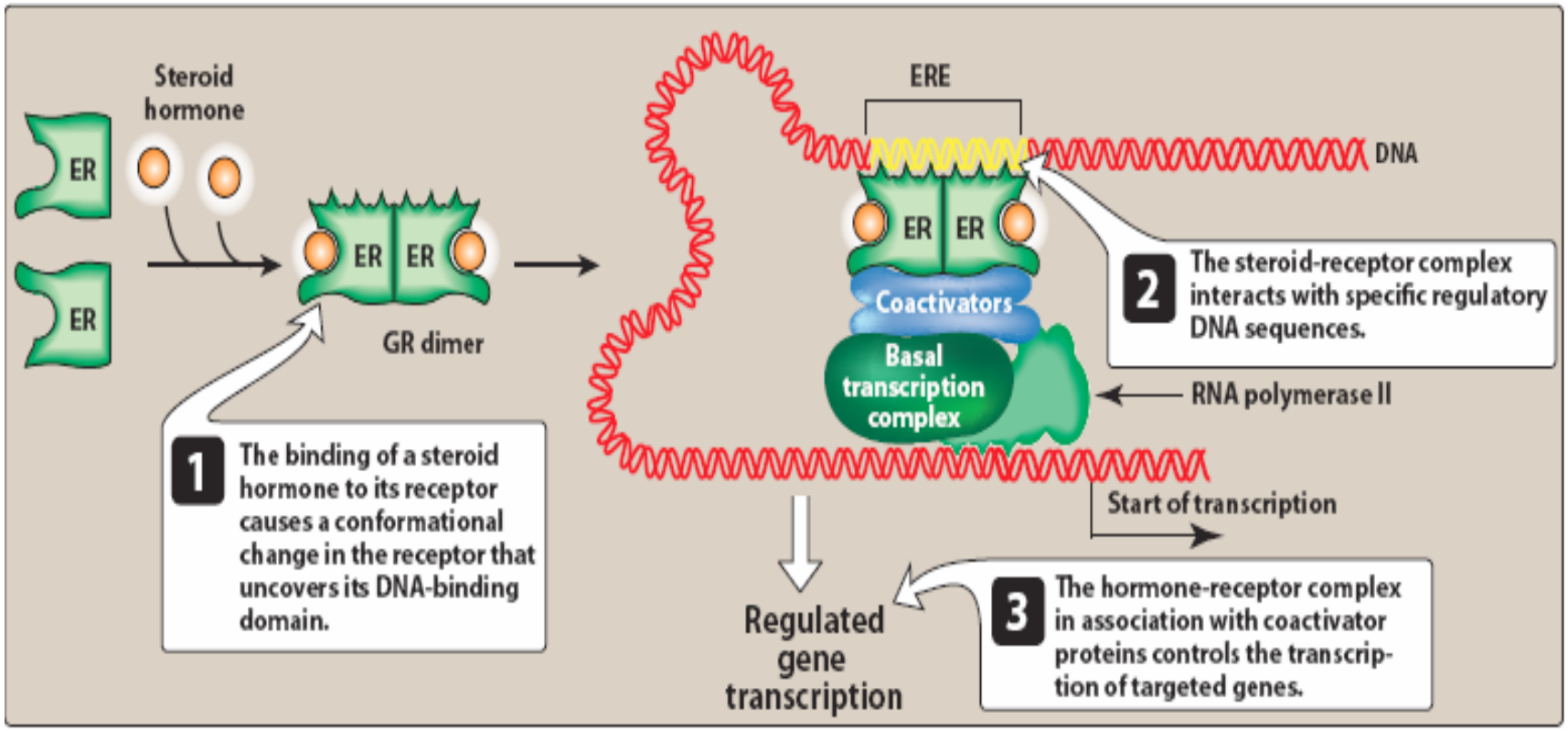


FIGURE 10.4. Enzymatic conversion of androgens to estrogens and dihydrotestosterone. 17β-HSD is hydroxysteroid dehydrogenase. There are multiple isoforms of this enzyme: types 1 and 3 catalyze reactions that make more-active steroids; types 2 and 4 make less active metabolites.

Mechanism of action

- **Estrogens bind to specific intracellular receptors.**
- **The hormone–receptor complex** interacts with specific DNA sequences and alters the transcription rates of target genes by recruiting coactivators
- They may also affect the half-life of specific **messenger RNAs.** These events lead to a change in the synthesis of **specific proteins** within a target cell.
- **There are two estrogen receptors, ER-α and ER-β,** that differ in their tissue distribution; while both receptors have about the same affinity for 17β-estradiol, they have differential affinities for other ligands and affect target genes in a differential manner

Mechanism of action



Metabolism

a. **17β-Estradiol is extensively (98%) bound to sex steroid-binding globulin (SSBG) and serum albumin.**
b. **Estrone sulfate** is effective orally, but natural estrogens are subject to a large first-pass effect.
c. Synthetic estrogens may be administered **orally, topically, transdermally, or by injection.**
d. **All estrogens are extensively metabolized in the liver and are conjugated with either** glucuronic acid or sulfate, hydroxylated or O-methylated.
e. Most metabolites are excreted in the urine, with approximately 10% undergoing **enterohepatic circulation and eventual elimination in the feces**

Actions

a. Growth and development

(1) **Estrogens are required for the development and maturation of female internal** and external genitalia, growth of the breasts, linear bone growth at puberty, and closure of the epiphyses.

(2) **Estrogens are required in the uterus for growth of myometrium and for growth** and development of the endometrial lining. Continuous exposure can lead to **endometrial hyperplasia and bleeding.**

(3) **Menstrual cycle. Estrogens are required for ovarian follicular development and** Regulation of the menstrual cycle

Actions

Systemic metabolism

(1) Estrogens increase plasma triglycerides, and tend to **decrease serum cholesterol** by decreasing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL) concentrations.

(2) Estrogens decrease total serum proteins but increase levels of transferrin, steroid and thyroid-binding globulins (TBG), plasminogen, fibrinogen, and coagulation factors II, VII, VIII, IX, and X. Antithrombin III, protein C, and protein S levels are decreased. Overall, estrogens increase the coagulability of blood.

(3) Estrogens decrease bone resorption, with little effect on bone formation.

Therapeutic uses

a. Hypogonadism. usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women (11 to 13 years of age) with primary hypogonadism.

b. Menstrual abnormalities

c. Oral contraception

e. Androgen-dependent prostatic tumors are effectively treated by diethylstilbestrol (DES).

Therapeutic uses

f. Menopausal therapy

(1) **Menopausal hormone therapy (MHT) can be achieved with oral, parenteral,** topical (intravaginal), or transdermal estrogens,

(2) Postmenopausal estrogen therapy improves hot flashes, sweating, and atrophic vaginitis

(3) Postmenopausal estrogen therapy slows the rate of bone loss

(4) Estrogens are usually administered in a cyclical manner to avoid long periods of continuous exposure.

(5) Concomitant use of estrogen therapy with a progestin reduces the incidence of endometrial carcinoma.

(6) Transdermal delivery of 17β-estradiol using a skin patch is effective and longlasting in treating menopausal symptoms.

Adverse effects and contraindications

a. Estrogens are associated with nausea, headaches, cholestasis, hypertension, and gallbladder disease.

b. Estrogens present an increased risk (5–15 times) of endometrial cancer that is dose and duration dependent. Risk is reduced by periodic withdrawal of estrogen therapy and replacement by progestin treatment, or concomitant treatment with both drugs.

c. **DES is associated with adenocarcinoma of the vagina;**

d. **Estrogens are contraindicated in the presence of estrogen-responsive carcinoma, liver disease, or thromboembolic disease.**

f. Recent large clinical trials indicate that some regimens of MHT are associated with **increased risk of myocardial infarction, stroke, breast cancer, and dementia.**

Whether this risk is solely attributable to the estrogenic component and whether or not all estrogenic preparations at all doses share these liabilities are unresolved

Antiestrogens

- **Antiestrogens interfere with the binding of estrogen with its specific receptor, and they may** also alter the conformation of the estrogen receptor such that it fails to activate target genes.

1. Clomiphene and fulvestrant

- **Clomiphene and fulvestrant are nonsteroidal agents.**
- **Clomiphene and fulvestrant bind competitively to the estrogen receptor**
- **Clomiphene has partial agonist activity in some tissues including the ovary and endometrium; fulvestrant appears to be an antagonist is all tissues**.
- **These agents eventually reduce the number of functional receptors available for** endogenous estrogens and **diminish estrogen action both along the hypothalamic-pituitary axis and in peripheral tissues.**

Clomiphene

- **Clomiphene is used to treat infertility in cases of anovulation in women with an intact** hypothalamic-pituitary axis and sufficient production of estrogen.
- For Induction of ovulation: Administered orally: clomiphene citrate, 50 mg/day for five days. Ovulation should occur 5 to 10 days after final dose
- **Fulvestrant is used to treat women with progressive breast cancer after tamoxifen**

Side effects: These agents may cause ovarian enlargement, hot flashes, nausea, and vomiting

2. Danazol

a. Danazol is a testosterone derivative with antiandrogen and antiestrogenic activities.

b. MOA:

1. **Danazol inhibits several of the enzymes involved in steroidogenesis, but does not inhibit aromatase;**
2. **may also bind to estrogen and androgen receptors;**
3. **inhibits gonadotropin release in both men and women.**

c. Danazol is used to treat endometriosis and fibrocystic disease of the breast.

d. Side effects: This agent may cause edema, masculinization (deepening of the voice and decreased breast size) in some women, headache, and **hepatocellular disease.**

e. Danazol is contraindicated in pregnant women or in patients with hepatic disease.

Selective Estrogen Receptor Modulators (SERMs)

1. **SERMs are ligands for the estrogen receptor that have agonist activity in one tissue but** may have **antagonist** activity or no activity in another tissue.
2. The response of a tissue is determined by the conformation that the ligand confers upon the estrogen receptor, and the set of coactivators that are expressed in that tissue
3. Currently, there are three SERMs approved for use in the United States: **Tamoxifen, Raloxifene, and Toremifene;** many others are in clinical trial

SERMs

1. **Tamoxifen is an estrogen antagonist in the breast and in the brain but is an agonist in the uterus and in bone**.
   - It is used in the **treatment of advanced, hormone receptor-positive breast cancer and for primary prevention of breast cancer in women at high risk** of the disease.
   - Tamoxifen increases the risk of endometrial cancer.
2. **Raloxifene is an agonist in bone but has no effect on the uterus or breast and is an** estrogen antagonist in the brain.
   - **It is used for the treatment and prevention of osteoporosis and for uterine fibroids.**
   - **Raloxifene has been shown to reduce the risk of estrogen** receptor-positive invasive breast cancer by 66%–76%.

c. Toremifene an estrogen antagonist in the breast is used to treat metastatic breast cancer

SERMs

- **Common adverse effects of SERMs are edema, hot flashes, nausea, vomiting, vaginal** bleeding, and vaginal discharge
- There is an increase in thromboembolic events with raloxifene but not with tamoxifen

Aromatase Inhibitors

- **Aromatase is the enzyme that catalyzes the final step in the production of estrogens from** androgenic precursors within the ovary or in peripheral tissues.
- **Aromatase inhibitors are a new class of oral estrogen synthesis inhibitors.**

1. **Exemestane** is a steroidal, irreversible aromatase inhibitor. **It is approved for use in the treatment of breast cancer.**
2. **Testolactone i**s another irreversible aromatase inhibitor , **use in the treatment of breast cancer.**

- Major adverse effects include hot flashes, fatigue, and CNS effects such as insomnia, depression, and anxiety.

Aromatase Inhibitors

b. Anastrazole and letrozole are nonsteroidal competitive inhibitors of aromatase.

- **These** drugs are used as first- or second-line agents in the treatment of **breast cancer.**
- Adverse effects include hot flashes, vaginal bleeding, insomnia, bone pain, and GI disturbances

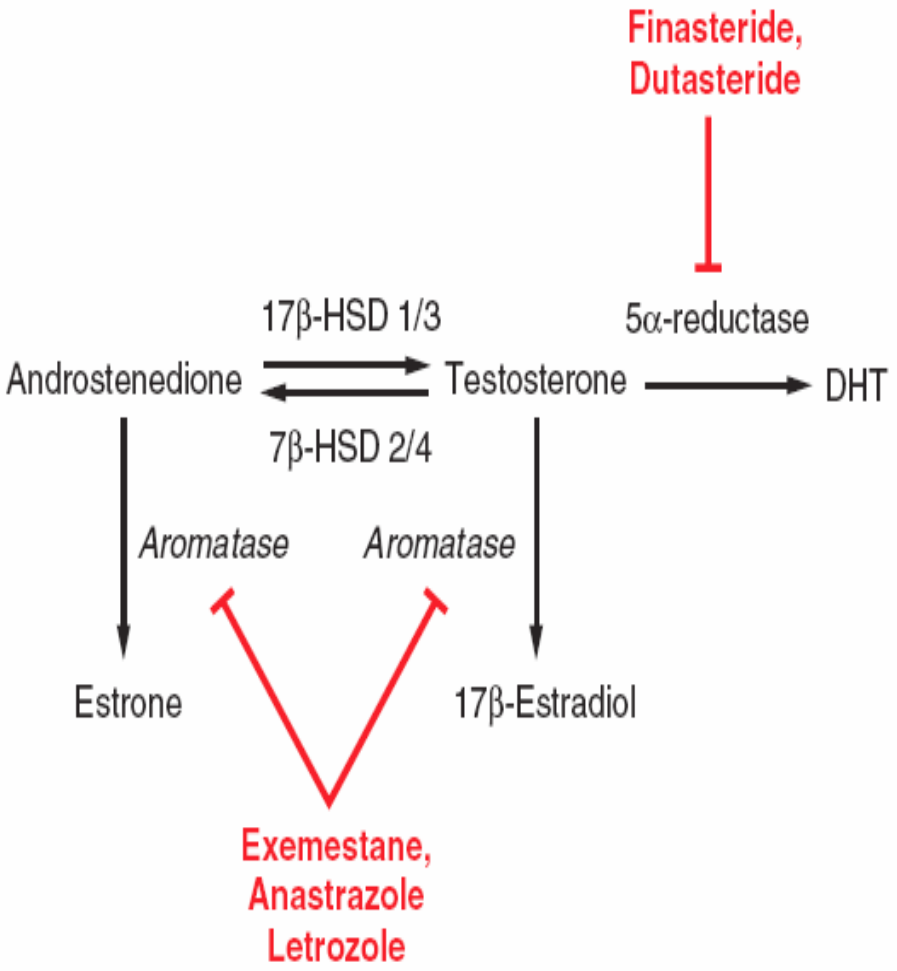


FIGURE 10.4. Enzymatic conversion of androgens to estrogens and dihydrotestosterone. 17β-HSD is hydroxysteroid dehydrogenase. There are multiple isoforms of this enzyme: types 1 and 3 catalyze reactions that make more-active steroids; types 2 and 4 make less active metabolites.

Progestins

a. The most important natural progestin is progesterone, which is synthesized by the ovaries, testes, and adrenals.

b. Synthetic progestins include the 19-nor compounds, such as norethindrone, norgestrel, and **levonorgestrel.** All of these agents are potent **oral progestins** derived from testosterone; some have androgenic activity

c. Several synthetic derivatives of progesterone have progestin activity, including:

- **megestrol (Megace),**
- **medroxy-progesterone acetate (Provera),**
- **Hydroxy-progesterone caproate**.

Actions

a. **MOA: Progestins bind to intranuclear receptors that alter the transcription of target genes.** There are two isoforms of the progesterone receptor**: PR-A and PR-B**.
b. **Progestins slow the mitotic activity of the estrogen-stimulated uterus, cause vascularization of the endometrium, and induce a more glandular appearance and function.**
c. **Progestins slightly decrease triglycerides and HDL, but they slightly increase LDL**, depending on the preparation and dose.
d. **Progestins increase basal and stimulated insulin secretion, and stimulate appetite.**

Actions

d. Progesterone is extensively bound to corticosteroid-binding globulin in the plasma and is **not administered orally** because of rapid hepatic metabolism.

e. Progestins are eliminated by hydroxylation to pregnanediol and conjugation with glucuronic acid and subsequent urinary excretion

Therapeutic uses

a. Progestins are used for contraception, alone or in combination with estrogens.

b. Progestins may be administered orally, by depot injection, as a vaginal gel, and as a slow-release intrauterine device.

c. These agents are used in the treatment of endometrial cancer and endometrial hyperplasia.

d. Progestins control abnormal uterine bleeding.

e. Progestins are used to delay menstruation for surgical or postoperative reasons.

f. megestrol is used to stimulate appetite in patients with cancer or AIDS.

Antiprogestins: Mifepristone

1. Mifepristone is a norethindrone derivative with potent antiprogestin and antiglucocorticoid activities.
2. Mifepristone acts as a competitive antagonist of progesterone and glucocorticoid receptors.
3. Mifepristone has been approved for use to induce medical abortion in the first trimester.

a. Mifepristone is combined with a parenteral or intravaginal application of a prostaglandin 48 hours after the antiprogestin to induce abortion.

b. Mifepristone causes myometrial contractions

c. This combination is approximately 99% effective.

4. Mifepristone is used as a contraceptive and is very effective if used within 72

5. Relatively infrequent side effects of mifepristone include bleeding, nausea, and Abdominal pain

Hormonal Contraceptives
Oral contraceptives

- **Oral contraceptives represent the primary use of estrogens and progestins.**
- **MOA:** The estrogen provides a negative feedback on the release of LH and follicle-stimulating hormone (FSH) by the pituitary gland, thus preventing ovulation.

a. Types of oral contraceptives

(1) Combination pills

(a) Combination pills contain mixtures of estrogens and a progestin. The estrogen component (20–50 µg/day) is either **ethinyl estradiol or mestranol** it is combined with a progestin (0.05–2.5 mg/day), such as **norethindrone, norgestrel, levonorgestrel, ethynodiol diacetate, or desogestrel.**

(b) Combination pills are typically taken continuously for 21 days, followed by a 7-day withdrawal (or placebo) period to induce menses.

Hormonal Contraceptives

(d) "Continuous dosage products" are available that contain ethinyl estradiol and levonorgestrel and are taken every day for 84 days followed by 7 days of inert tablets (Seasonale) or 7 days of low-dose ethinyl estradiol (Seasonique), thus producing **four** menstrual periods per year. Lybrel contains the same hormones taken continuously for 365 days to suppress menstruation completely.

(e) These pills also affect the genital tract in ways that are unfavorable for conception: thickening cervical mucus, speeding ovum transport through the fallopian tubes, and making the endometrium less favorable for implantation

Hormonal Contraceptives

2. Progestin-only preparations (“mini pills”)

(a) Progestin-only oral preparations contain <u>norethindrone.</u>

(b) These preparations are taken daily on a continuous schedule.

(c) Progestin-only preparations do not completely suppress ovulation, resulting in irregular fertile periods. They are not as effective as the combination preparations.

(d) The mechanism of contraception is unclear, but it is likely due to the formation of a relatively atrophic endometrium (which impairs implantation) and viscous cervical mucus.

(e) Breakthrough bleeding is as high as 25%.

Adverse effects of CP

(1) Cardiovascular

(a) Oral contraceptives are associated with a twofold to fourfold increase in morbidity and mortality due to myocardial infarction; this may be age dependant.

(b) The incidence of hypertension is three to six times higher among women

Taking oral contraceptives.

(c) Oral contraceptives produce a marked increase (up to 50%) in triglyceride

levels, depending on the relative doses of estrogens and progestins in the individual preparation.

(d) The risk of cardiovascular complications increases markedly in women over age 35 and in women who smoke

(2) Thromboembolic disease

(a) The risk of stroke is 2–10 times higher in individuals taking oral contraceptives.

(b) Estrogens increase levels of fibrinogen and coagulation factors II, VII, VIII, IX, and X, while decreasing concentrations of antithrombin III.

Adverse effects of CP

(3) Genitourinary tract. Oral contraceptives reduce the incidence of ovarian and endometrial cancers. They also reduce the incidence of pelvic inflammatory disease.

(4) Hepatobiliary system. Oral contraceptives increase the incidence of gallbladder disease and gallstones.

(5) Other adverse effects of oral contraceptives include weight gain, edema, breast tenderness, headache, mood alteration, breakthrough bleeding, and amenorrhea on discontinuation

c. Oral contraceptives are contraindicated:

- **Cardiovascular Disease,**
- **Thromboembolic**disease,
- Estrogen-dependent Or Estrogen-responsive Cancer, I
- Mpaired Liver Function,
- Undiagnosed Bleeding, And Migraine

Hormonal Contraceptives

2. Progestin injections

a. **Medroxyprogesterone acetate (Depo-Provera) is available as a suspension for SC or IM injections.** This preparation provides contraception for **3 months.**

3. Subcutaneous progestin implants

a. **Implanon is a synthetic progestin, etonogestrel, surrounded by a biomatrix coating.** A single rod is placed under the skin and provides effective contraception for up to 3 years. Actual effectiveness is superior to that of combination oral contraceptives. Rods must be removed after 3 years.

b. **Adverse effects are dominated by menstrual and bleeding irregularities.**

Hormonal Contraceptives

4. *Intrauterine devices (IUDs)*

a. Levonorgestrel-containing IUDs are available as a means of contraception.

b. Contraception is achieved mostly by local actions on the endometrium with hypotrophic glands and pseudodecidualization. Ovulation occurs in about 50% of menstrual cycles.

c. These devices should be implanted by a trained physician

Hormonal Contraceptives

5. Transdermal patch: An alternative to combination oral contraceptive pills is a transdermal contraceptive patch containing *ethinyl estradiol and the progestin norelgestromin.*

- *One contraceptive patch* is applied each week for 3 weeks to the abdomen, upper torso, or buttock. Week 4 is patch free, and withdrawal bleeding occurs