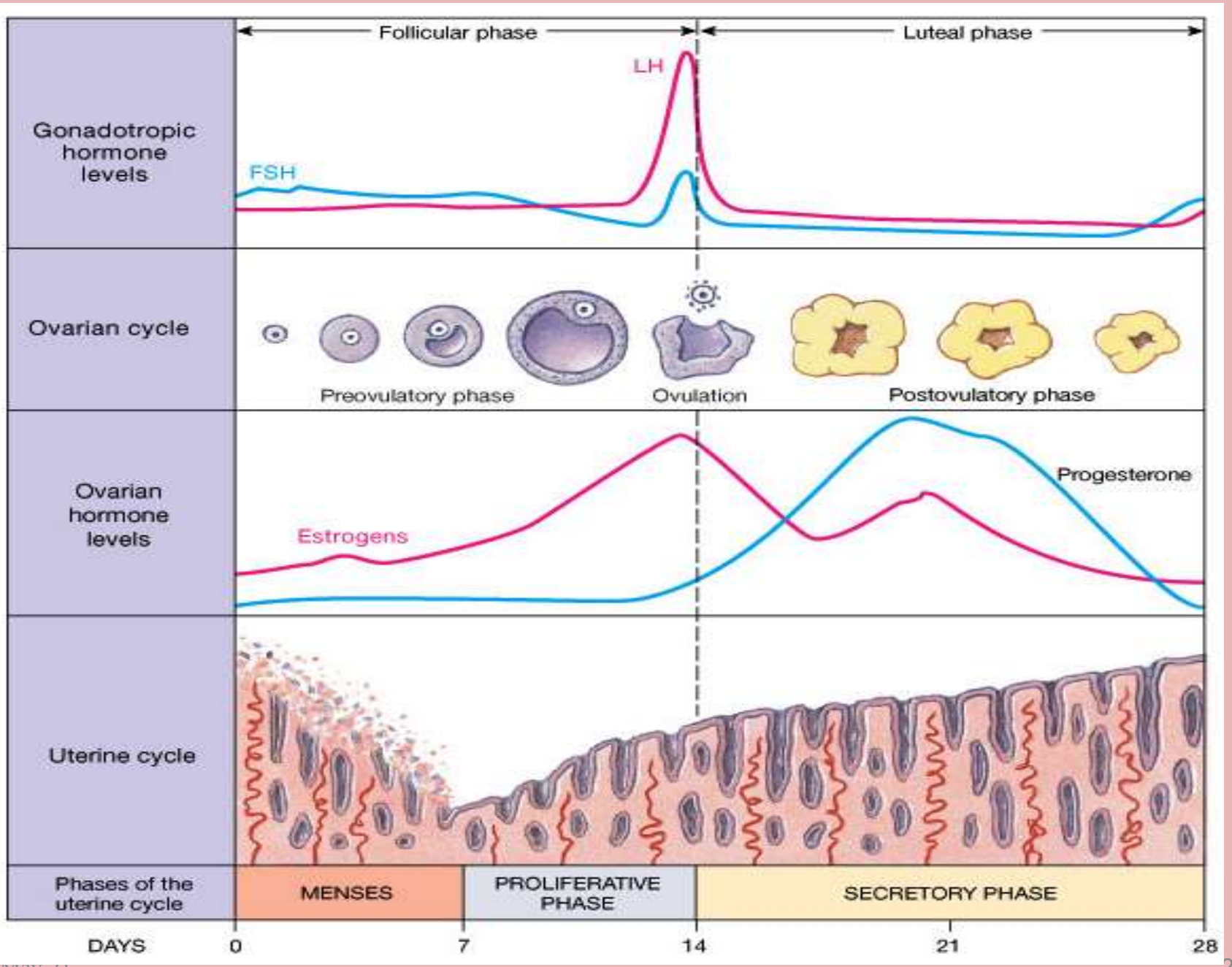
Estrogens and Progestins


Follicular phase
Luteal phase
Gonadotropic hormone levels
LH
FSH
Ovarian cycle
Preovulatory phase
Ovulation
Postovulatory phase
Ovarian hormone levels
Progesterone
Estrogens
Uterine cycle
Phases of the uterine cycle
MENSES
PROLIFERATIVE PHASE
SECRETORY PHASE
DAYS
0
7
14
21
28

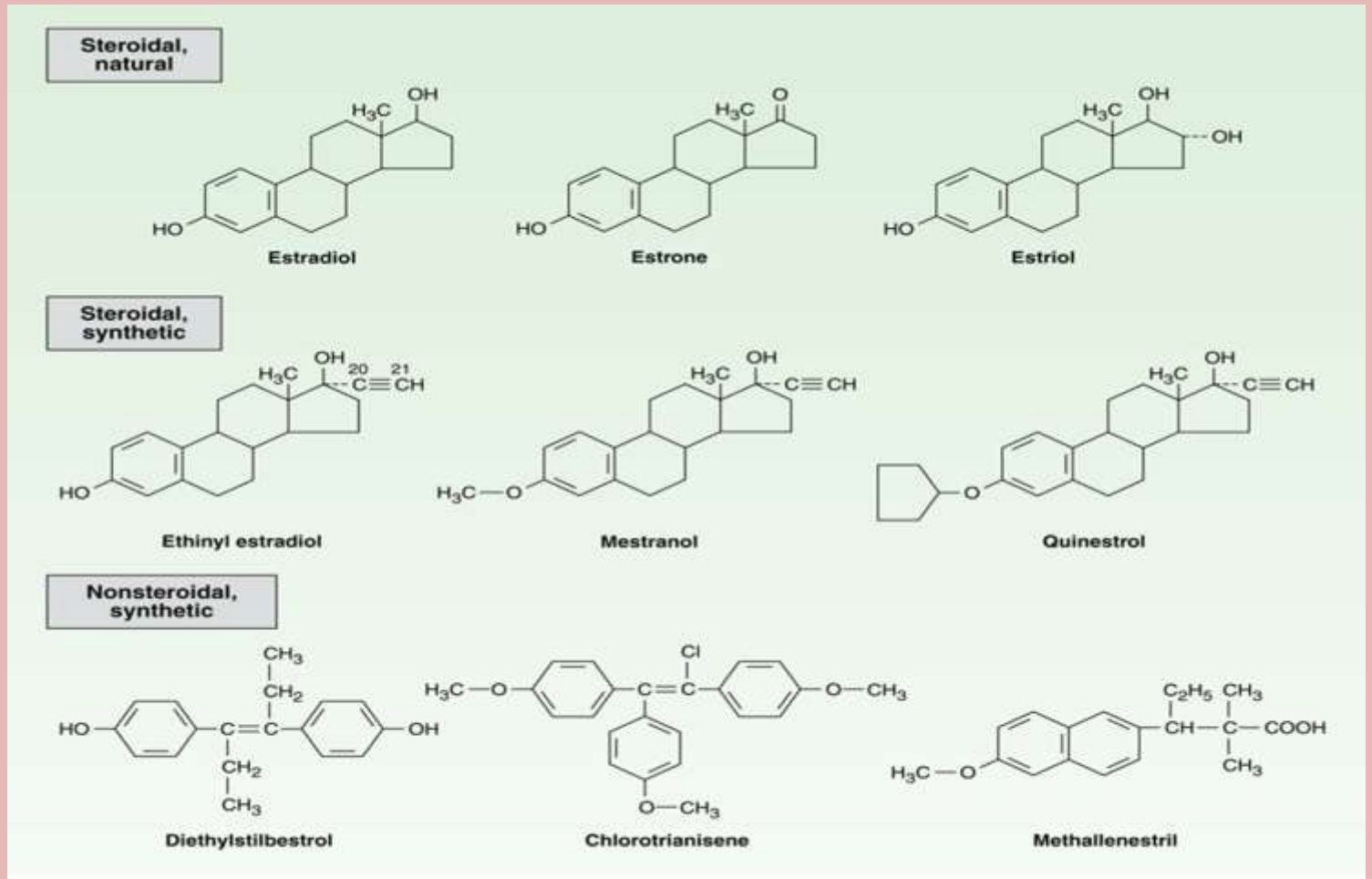
Estrogens

- **Natural Estrogens:**
- Estrogen or oestrogen is the primary female sex hormone and is responsible for development and regulation of the female reproductive system and secondary sex characteristics.

- The major estrogens produced by women are17-β- **estradiol, estrone** and **estriol**
- **Estrogens are produced in the ovary, liver, and the placenta**
- Estriol is synthesized by the placenta and is excreted at high levels in the urine of pregnant women.
- The ovary is the major site of estrogen and progestin biosynthesis in nonpregnant premenopausal women.
- In pregnant women, the fetoplacental unit is the major source of estrogens and progestins

Estrogens

- **Synthetic Estrogens:**
- A variety of chemical alterations have been applied to the natural estrogens. The most important effect of these alterations has been to increase their oral effectiveness.
- In addition to the steroidal estrogens, a variety of nonsteroidal compounds with estrogenic activity have been synthesized and used clinically like diethylstilbestrol.



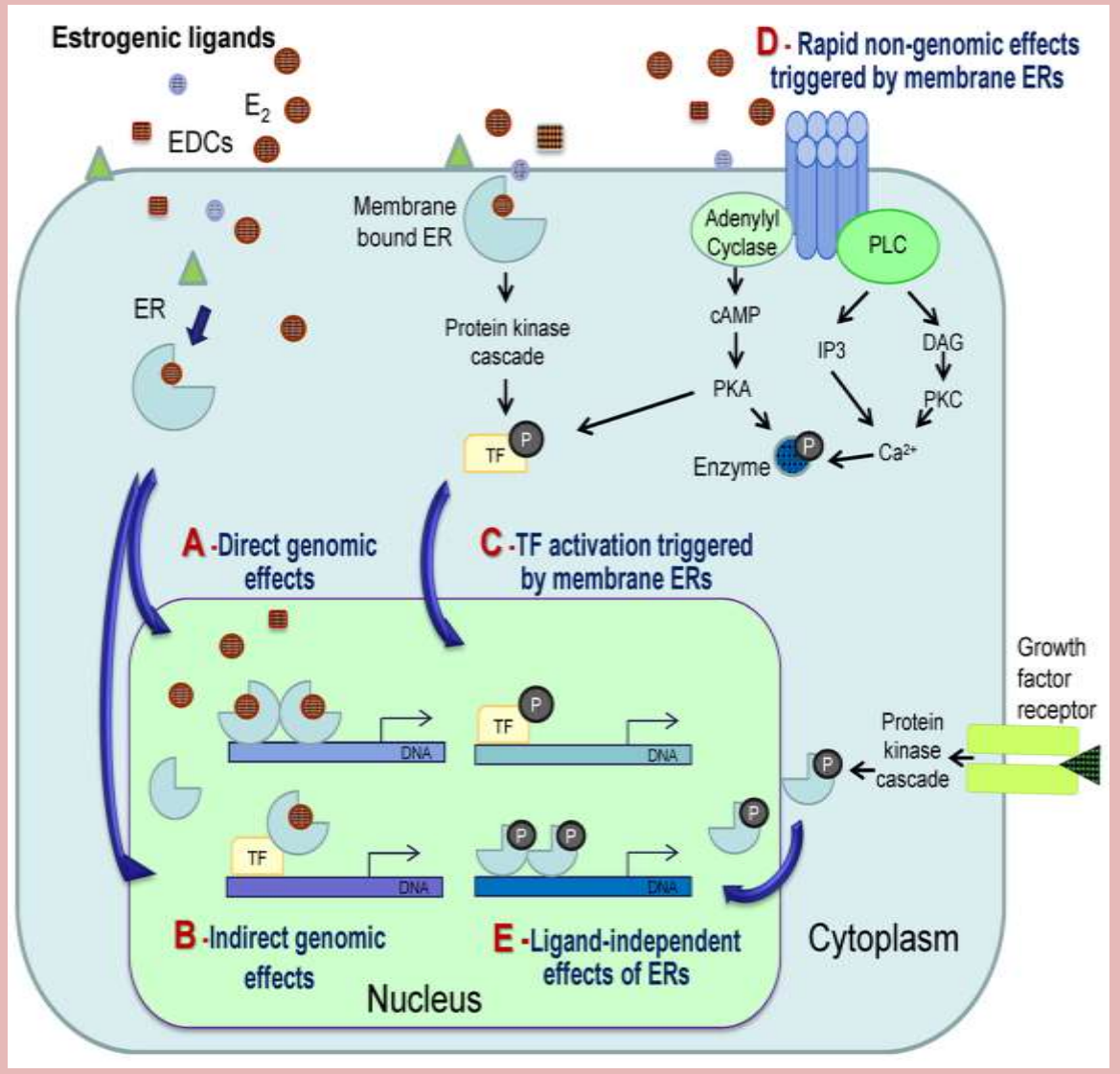
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Estrogens

- **Pharmacokinetics**
- Estrogens are metabolized by the liver and other tissues and metabolites are excreted in the bile.
- Estrogens are also excreted in small amounts in the breast milk of nursing mothers.
- Because significant amounts of estrogens and their active metabolites are excreted in the bile and reabsorbed from the intestine, the resulting enterohepatic circulation ensures that orally administered estrogens will have a high ratio of hepatic to peripheral effects.
- The hepatic effects are thought to be responsible for some undesirable actions such as synthesis of increased clotting factors and plasma renin substrate which has in inducing hypertension.
- The hepatic effects of estrogen can be minimized by routes that avoid first-pass liver exposure, ie, vaginal, transdermal, or by injection.

Estrogens

- **Molecular Mechanism :**
- There are two forms of the estrogen receptor,
- ER-α and ER-β,
- Receptor binding by estrogens and progestins can activate a classic pathway of steroid hormone gene transcription.
- Estrogen enter the cell and bind to their receptor.
- The estrogen receptors are found predominantly in the nucleus.
- The receptor-hormone complex binds to a specific sequence of nucleotides called **estrogen response elements (EREs)** in the promoters of various genes and regulate their transcription.



Estrogens

- **Female Maturation:**
- Estrogens are required for the normal sexual maturation and growth of the female.
- They stimulate the development of the vagina, uterus, and uterine tubes as well as the secondary sex characteristics.
- They stimulate stromal development and ductal growth in the breast and are responsible for the accelerated growth of the long bones that occur at puberty.
- They contribute to the growth of axillary and pubic hair and alter the distribution of body fat to produce typical female body contours.
- Larger quantities also stimulate development of pigmentation in the skin, most prominent in the region of the nipples and in the genital region.
- **Endometrial Effects:**
- Estrogen plays an important role in the development of the endometrial lining, as well as the uterine muscle..
- estrogen production is properly coordinated with the production of progesterone during the normal human menstrual cycle, leading to the regular periodic bleeding and shedding of the endometrial lining .

Estrogens

- **Metabolic and Cardiovascular Effects:**
- Maintenance of the normal structure and function of the skin and blood vessels in women.
- Decrease the rate of resorption of bone.
- Increase the circulating levels of thyroxine, testosterone, iron, copper, and other substances.
- Increase levels of high-density lipoproteins (HDL), reduce low-density lipoproteins (LDL), and total plasma cholesterol levels. Plasma triglyceride levels are also increased.

Estrogens

- **Effects on Blood Coagulation:**
- Estrogens enhance the coagulability of blood.
- decrease platelet adhesiveness.
- **Other Effects:**
- Stimulate central components of the stress system, including the activity of the sympathetic system, and promote a sense of well-being when given to women who are estrogen-deficient.
- Facilitate the loss of intravascular fluid into the extracellular space, producing edema.

Clinical Uses of Estrogens

- **Primary Hypogonadism:**
- Estrogens have been used extensively for replacement therapy in estrogen-deficient patients. The estrogen deficiency may be due to primary failure of development of the ovaries, premature menopause, or menopause.
- Treatment of primary hypogonadism is usually begun at 11–13 years of age in order to stimulate the development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis and to avoid the psychological consequences of delayed puberty and estrogen deficiency.
- Treatment attempts to mimic the physiology of puberty. It is initiated with small doses of estrogen on days 1–21 each month and is slowly increased to adult doses and then maintained until the age of menopause (approximately 51 years of age).
- A progestin is added after the first uterine bleeding.

Clinical Uses of Estrogens

- **<u>Postmenopausal Hormonal Therapy:</u>**
- Immediate signs and symptoms:
  - Loss of menstrual periods, sleep disturbances, and genital atrophy.
- Longer-lasting changes:
  - Acceleration of bone loss, which in susceptible women may lead to vertebral, hip, and wrist fractures; and lipid changes, which may contribute to the acceleration of atherosclerotic cardiovascular disease noted in postmenopausal women.

Vaginal atrophy, also called atrophic vaginitis, is thinning, drying and inflammation of the vaginal walls

Clinical Uses of Estrogens

- **Postmenopausal Hormonal Therapy:**
- Estrogen replacement therapy has a beneficial effect on circulating lipids and lipoproteins, and this was earlier thought to be accompanied by a reduction in myocardial infarction by about 50% and of fatal strokes by as much as 40%. These findings, however, have been disputed by the results of a large study from the Women's Health Initiative (WHI) project showing no cardiovascular benefit from estrogen plus progestin replacement therapy in perimenopausal or older postmenopausal patients.
- In fact, there may be a small increase in cardiovascular problems as well as breast cancer in women who received the replacement therapy.
- A protective effect against colon cancer was observed.
- Women with premature menopause should definitely receive hormone therapy.
- In some studies, a protective effect of estrogen replacement therapy against Alzheimer's disease was observed.

Adverse Effects of Estrogens

- **Uterine Bleeding**
- Estrogen therapy is a major cause of postmenopausal uterine bleeding.
- Unfortunately, vaginal bleeding at this time of life may also be due to carcinoma of the endometrium.
- To avoid confusion, patients should be treated with the smallest amount of estrogen possible. It should be given cyclically so that bleeding, if it occurs, will be more likely to occur during the withdrawal period.

Adverse Effects of Estrogens

- **Cancer:**
- The relation of estrogen therapy to cancer continues to be the subject of active investigation.
- Breast cancer: a small increase in the incidence of this tumor may occur with prolonged therapy.
- Endometrial carcinoma: The risk seems to vary with the dose and duration of treatment.
- Adenocarcinoma of the vagina in young women whose mothers were treated with large doses of diethylstilbestrol early in pregnancy. Also, the risks for infertility, ectopic pregnancy, and premature delivery are increased.

Estrogens

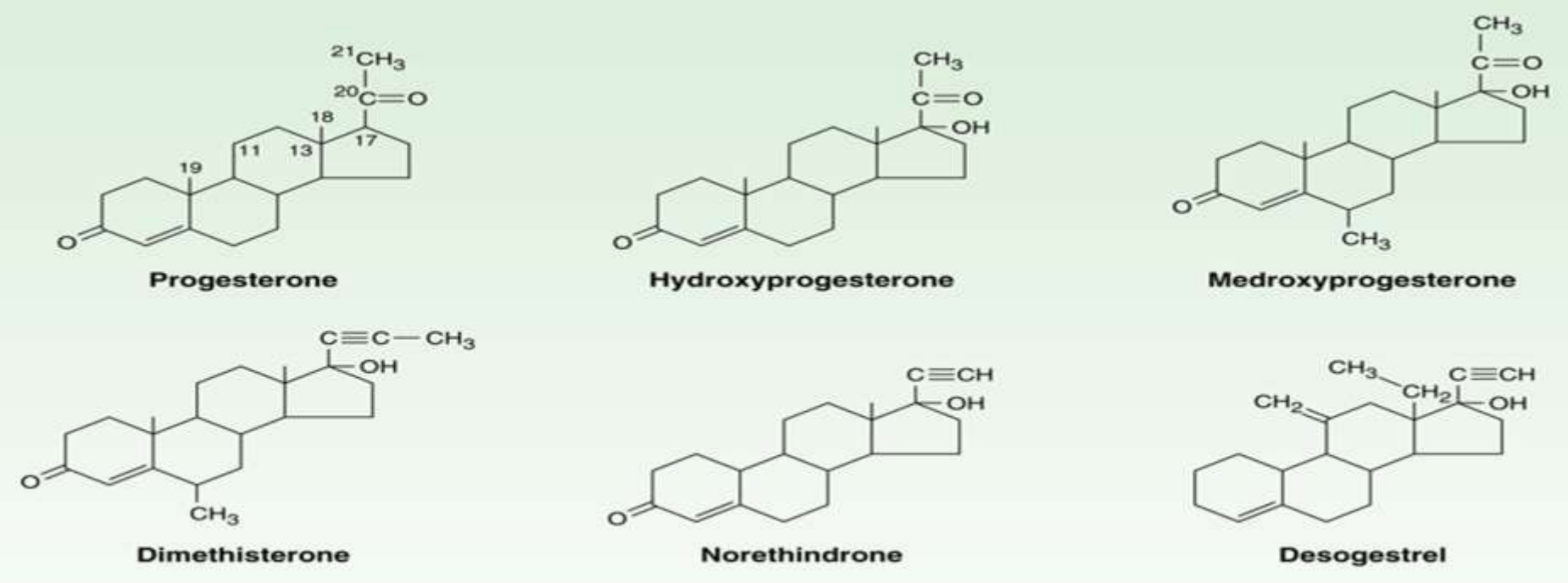
- **Other Effects**
- Nausea and breast tenderness are common and can be minimized by using the smallest effective dose of estrogen.
- Hyperpigmentation also occurs.
- Estrogen therapy is associated with an increase in frequency of migraine headaches as well as cholestasis, gallbladder disease, and hypertension.
- **Contraindications**
- Estrogens should not be used in patients with estrogen-dependent neoplasms such as carcinoma of the endometrium or in those with—or at high risk for—carcinoma of the breast. They should be avoided in patients with undiagnosed genital bleeding, liver disease, or a history of thromboembolic disorder. In addition, the use of estrogens should be avoided by heavy smokers.

Thromboembolism: Formation in a blood vessel of a clot (thrombus)

The Progestins

Natural Progestins:

- Progesterone is the most important progestin in humans.
- Serves as a precursor to the estrogens, androgens, and adrenocortical steroids.
- Synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy.
- In the ovary, progesterone is produced primarily by the corpus luteum.
- Plasma levels of progesterone are elevated and reach their peak levels in the third trimester of pregnancy.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

The Progestins

- **Pharmacokinetics:**
- Progesterone is rapidly absorbed following administration by any route.
- Its half-life in the plasma is approximately 5 minutes, and small amounts are stored temporarily in body fat.
- It is almost completely metabolized in one passage through the liver, and for that reason it is quite ineffective when the usual formulation is administered orally.
- In the liver, progesterone is metabolized to pregnanediol and is excreted into the urine as pregnanediol glucuronide.
- The amount of pregnanediol in the urine has been used as an index of progesterone secretion.

Clinical Uses of The Progestins

- The major uses are for hormone replacement therapy and hormonal contraception.
- When used alone in large doses parenterally, prolonged anovulation and amenorrhea result. This therapy has been employed in the treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated, and for contraception.
- Prolonged time will be required in some patients for ovulatory function to return after cessation of therapy. It should not be used for patients planning a pregnancy in the near future.
- Progestins do not appear to have any place in the therapy of threatened or habitual abortion. Although, progesterone will delay premature labor in animals with encouraging results.

The Progestins

- **Contraindications, Cautions, & Adverse Effects**
- Studies of progestational compounds alone and with combination oral contraceptives indicate that the progestin in these agents may increase blood pressure in some patients.
- The more androgenic progestins also reduce plasma HDL levels in women.
- Two recent studies suggest that combined progestin plus estrogen replacement therapy in postmenopausal women may increase breast cancer risk significantly compared with the risk in women taking estrogen alone.