Natural steroidal estrogens [17-β- estradiol, estrone and estriol]
➢ **the primary female sex hormone.** responsible for development and regulation of the female reproductive system and secondary sex characteristics. produced in the ovary, liver, and the placenta. ➢ The **ovary** is the major site of estrogen and progestin biosynthesis in <u>nonpregnant premenopausal women</u>. ➢ Estriol is synthesized by the placenta and is excreted at high levels in the urine of pregnant women. <u>In pregnant women</u>, the **fetoplacental** unit is the major source of estrogens and progestins.
Synthetic steroidal estrogens
➢ drugs that are completely synthesized and drugs that are a synthesized by chemically alterating and modifying the natural estrogens. ➔ <u>*increase their oral effectiveness and increase the duration of action*</u>.
Synthetic non-steroidal estrogen compounds with estrogenic activity like diethylstilbestrol

- Pharmacokinetics: **metabolized in the liver** and other tissues. metabolites are **excreted** in small amounts in the breast milk of nursing mothers and **in the bile ➔ enterohepatic circulation** ensures that orally administered estrogens will have a <u>high ratio of hepatic to peripheral effects</u> ➔ These hepatic effects responsible for <u>undesirable actions</u> [synthesis of increased clotting factors and plasma renin → hypertension.] // hepatic effects can be minimized by routes that *avoid first-pass liver exposure* [vaginal, transdermal, or injection]

- MOA: Estrogens enter the cell and bind to their receptors <u>in the nucleus</u> → the receptor-hormone complex binds to a specific sequence of nucleotides <u>[estrogen response elements (EREs)]</u> in the promoters of various genes → regulate their transcription. // estrogen receptors are ER-α and ER-β.

- functions in the body:

  1- **Female** sexual **maturation** and growth including the secondary sex characteristics + stromal development and ductal growth in the **breast** + accelerated growth of the long **bones** that occur at puberty + **pigmentation** of the nipples and in the genital region.
  2- development of the **endometrial** lining and the uterine muscle. Estrogen production properly coordinated with the production of progesterone → regular periodic bleeding and shedding of the endometrial lining.
  3- normal structure and function of the **skin and blood vessels** + Decrease the rate of resorption of bone. + Increase thyroxine, testosterone, iron, copper, triglyceride, HDL + reduce LDL and total plasma cholesterol levels.
  4- enhance the **coagulability of blood** + decrease platelet adhesiveness
  5- Stimulate central components of the **stress** system including the activity of the sympathetic system + 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:

  1- **Primary Hypogonadism:** begun at 11–13 years of age → stimulate the development of secondary sex characteristics and menses + optimal growth. Prevent osteoporosis and the psychological consequences of delayed puberty and estrogen deficiency. // small doses on days 1–21 each month → slowly increased to adult doses → maintained until the age of menopause. progestin is added after the first uterine bleeding. [mimic the physiology of puberty]
  2- **Postmenopausal hormonal therapy**: <u>*Immediate signs of menopause*</u>: Loss of menstrual periods, sleep disturbances, and vaginal atrophy. <u>*Longer-lasting changes due to menopause*</u>: Acceleration of bone loss [vertebral, hip, and wrist fractures], Lipid changes [acceleration of atherosclerotic cardiovascular disease]
  Estrogen replacement therapy has **a beneficial effect on circulating lipids and lipoproteins** [however has no cardiovascular benefit in perimenopausal or older postmenopausal patients, may be a small **increase** in cardiovascular problems and breast cancer] + **a protective effect against colon cancer and Alzheimer's disease was observed.**

3- **Women with premature menopause should definitely receive hormone therapy**

- Adverse Effects:

1- Uterine Bleeding: postmenopausal → 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.
2- Breast cancer [a small increase in the incidence occurs with prolonged therapy], **Endometrial carcinoma** [The risk varies 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 + the risks for **infertility**, **ectopic pregnancy**, and **premature delivery** are increased.
3- Nausea and breast tenderness [minimized by using the smallest effective dose of estrogen].
4- Hyperpigmentation.
5- increase in frequency of **migraine headaches, cholestasis, gallbladder disease, and hypertension**.

- Contraindications: Estrogens should not be used in patients with **estrogen-dependent neoplasms** [**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**. + They should be avoided in **heavy smokers** [due to increased risk of developing cancer].

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.

- Pharmacokinetics: rapidly absorbed following administration by any route. half-life in the plasma is approximately 5 minutes. small amounts are stored temporarily in body fat. completely **metabolized in** one passage through **the liver** (first pass metabolism) ➔ ineffective when the usual formulation is administered orally, and synthetic drugs are preferred over the natural progesterone.
In the liver, progesterone → pregnanediol excreted into the urine → pregnanediol glucuronide [index of progesterone secretion].

- Clinical Uses:

hormone replacement therapy and hormonal contraception
alone in large doses parenterally ➔ prolonged **anovulation** and **amenorrhea** result. [*treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated, and for contraception*].
Prolonged time will be required for ovulatory function to return after cessation of therapy ➔ 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. [delay premature labor in animals with encouraging results].

- Contraindications, Cautions & Adverse Effects:

increase blood pressure. reduce plasma HDL. increase breast cancer risk.