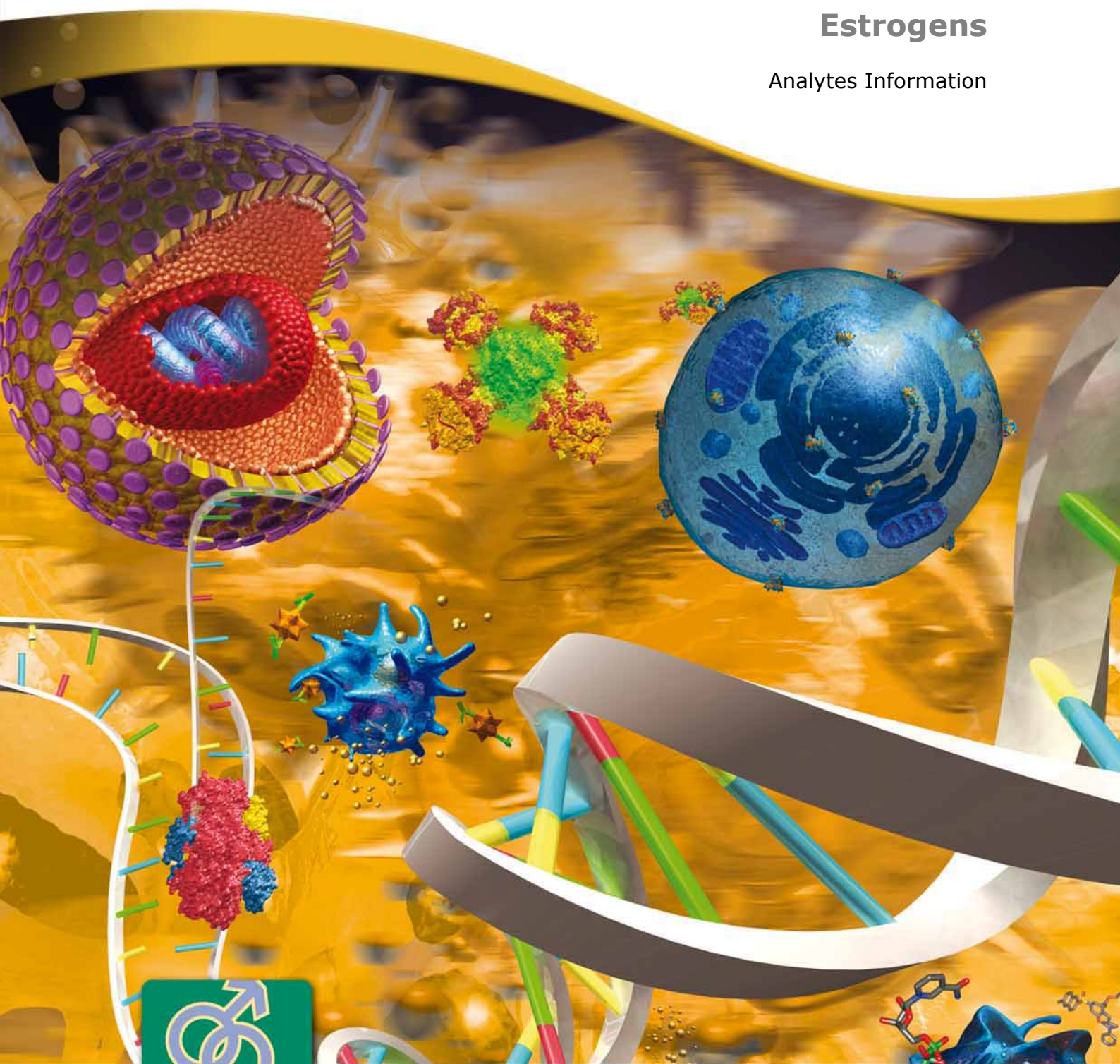




# Reproductive

## Estrogens

Analytes Information





## Estrogens

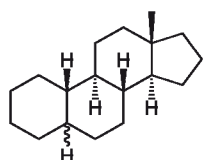
### Introduction

Estrogens (otherwise oestrogens or œstrogens) are the group of steroid compounds, named for their importance in the estrous cycle (cyclical changes induced by reproductive hormones in most mammalian females; in human called menstrual cycle). All estrogens are the derivatives of the hydrocarbon estrane with aromatic ring and 18-carbone molecule.

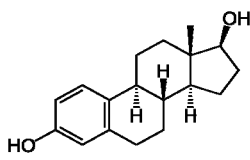
They function primarily as the female sex hormones, but play important role in male fertility as well. Their production is much higher in women.

Although more than 30 different forms of estrogens are known, three of them are the most important ones: estrone (E1), estradiol (E2) and estriol (E3). Estradiol (17 $\beta$ -estradiol, E2) is the predominate form in nonpregnant females, estrone (E1) is dominant during menopause, and estriol (E3) is the primary estrogen of pregnancy. The overview of estrogens is given in Fig.1:

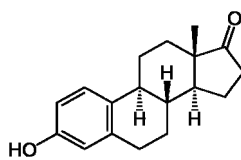
**Fig.1: The formulas of estrone, estradiol, estriol and some other estrogens**



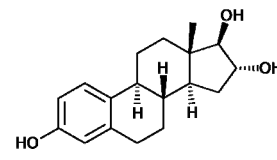
Estrane



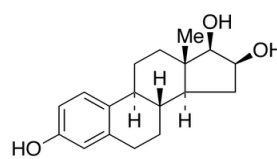
Estradiol



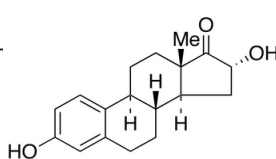
Estrone



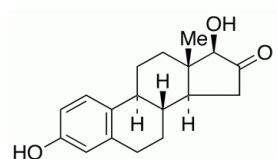
Estriol



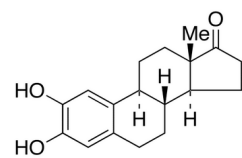
16-Epiestriol



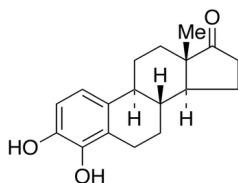
16 $\alpha$ -Hydroxyestrone



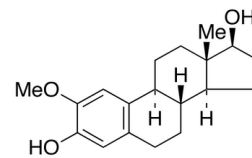
16-Oxoestradiol-17 $\beta$



2-Hydroxyestrone



4-Hydroxyestrone



2-Methoxyestradiol





## Estrogen biosynthesis

Estrogen biosynthesis and regulation depends on the reproductive status of the organism.

In **fertile, nonpregnant women**, estrogens are produced mainly in the ovaries (ovarian follicles as well as corpus luteum). Some estrogens are also produced, in smaller amounts, by other tissues such as the liver, adrenal glands, breasts, and adipose tissue.

These secondary sources of estrogens become important after **menopause**, when the ovarian synthesis decreases.

Main source of estrogen production during **pregnancy** is placenta.

In **men**, small amounts of estrogens are produced by the adrenal glands and testicles.

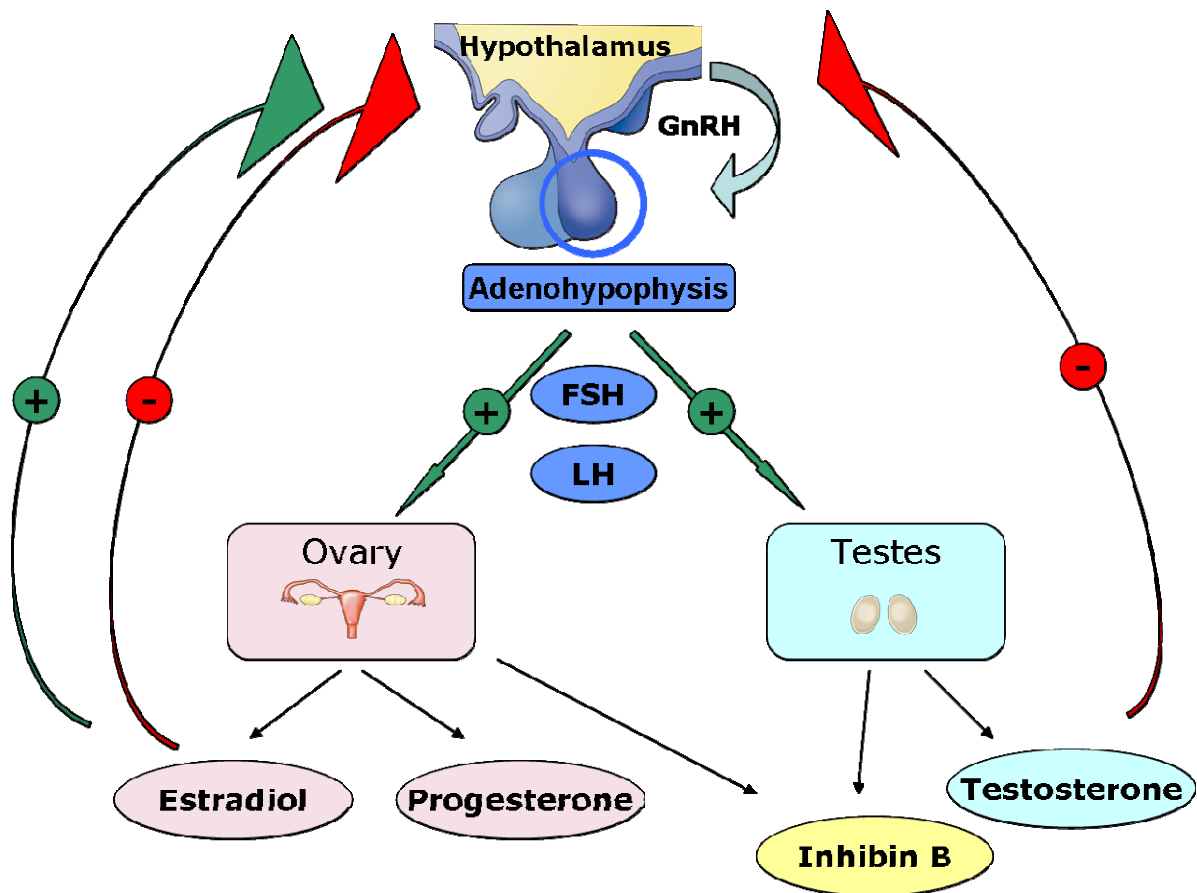
## Regulation of estrogen synthesis by hypothalamic-pituitary-gonadal axis

Estrogen synthesis and secretion is stimulated and controlled mainly by hypothalamic-pituitary-gonadal axis (HPG axis) in nonpregnant women and, in certain extent, also in men. This axis involves the mutual effects of the hypothalamus, pituitary glands and gonads. Hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion. GnRH is then transferred to pituitary gland where it induces secretion of LH and FSH. In response to LH and FSH, gonads produce steroid hormones. Thus, ovaries produce estrogens, progesterone, and androgens in women, and testes produce androgens and estrogens in men. Steroid hormones down-regulate gonadotropin secretion by negative feedback mechanism, either by direct action on pituitary gland or via inhibition of hypothalamic production of GnRH.

Besides that, estrogens may influence anterior pituitary by mechanism of positive feedback loop under certain conditions in women. Thus, significantly increased follicular synthesis of estrogens before ovulation exert positive feedback on the hypothalamus and pituitary glands<sup>19,20</sup>, resulting in a surge (sharp rise) in GnRH, and starts the ovulation.



**Fig.2: The regulatory feedback loop of the hypothalamic-pituitary-gonadal axis<sup>18</sup>**



### **Biosynthesis**

In **ovulating women**, synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of moderate androgenic activity. This compound passes the basal membrane into the surrounding granulosa cells, where it is converted to estrone or estradiol, either immediately or via testosterone. The conversion of testosterone to estradiol, and of androstenedione to estrone, is catalyzed by the enzyme aromatase.



Ovaries form large amount of estradiol and small amount of estrone. Estrogens may be also produced by peripheral tissue conversion, from androstenedione of adrenal origin.

In normal course of estrogen metabolism, estradiol is believed to form reversible redox system with estrone<sup>15</sup>. Estradiol is predominant, most of estrone originates from conversion of estradiol and from the peripheral aromatisation of androstenedione.

During **pregnancy**, the biosynthesis of estrogens differs quantitatively compared to nonpregnant women. The major estrogen source is placenta, not ovaries, like in nonpregnant women<sup>6</sup>. Compared to microgram quantities secreted daily by nonpregnant women, the amount of estrogens secreted during pregnancy increases to milligram amounts and the level increases steadily until the childbirth.

The major product of placenta is estriol, the estrogen that is produced in significant amount only during pregnancy. Placenta produces pregnenolone and progesterone from circulating cholesterol. Pregnenolone is converted into weak androgen dehydroepiandrosterone (DHEA) in the fetal adrenal gland and subsequently sulfonated to dehydroepiandrosterone sulfate (DHEA-S). DHEA-S is converted to 16-OH DHEA-S in the fetal liver. Finally, 16-OH DHEA-S is converted to estriol in the placenta.

Estradiol and estrone are produced in a similar way, i.e. in placenta from DHEA of fetal origin.

In **postmenopausal women**, peripheral conversion of adrenal androstenedione is the major source of estrogen production. Thus, estrone becomes predominant estrogen, whilst estradiol values significantly fall comparing to premenopausal values.

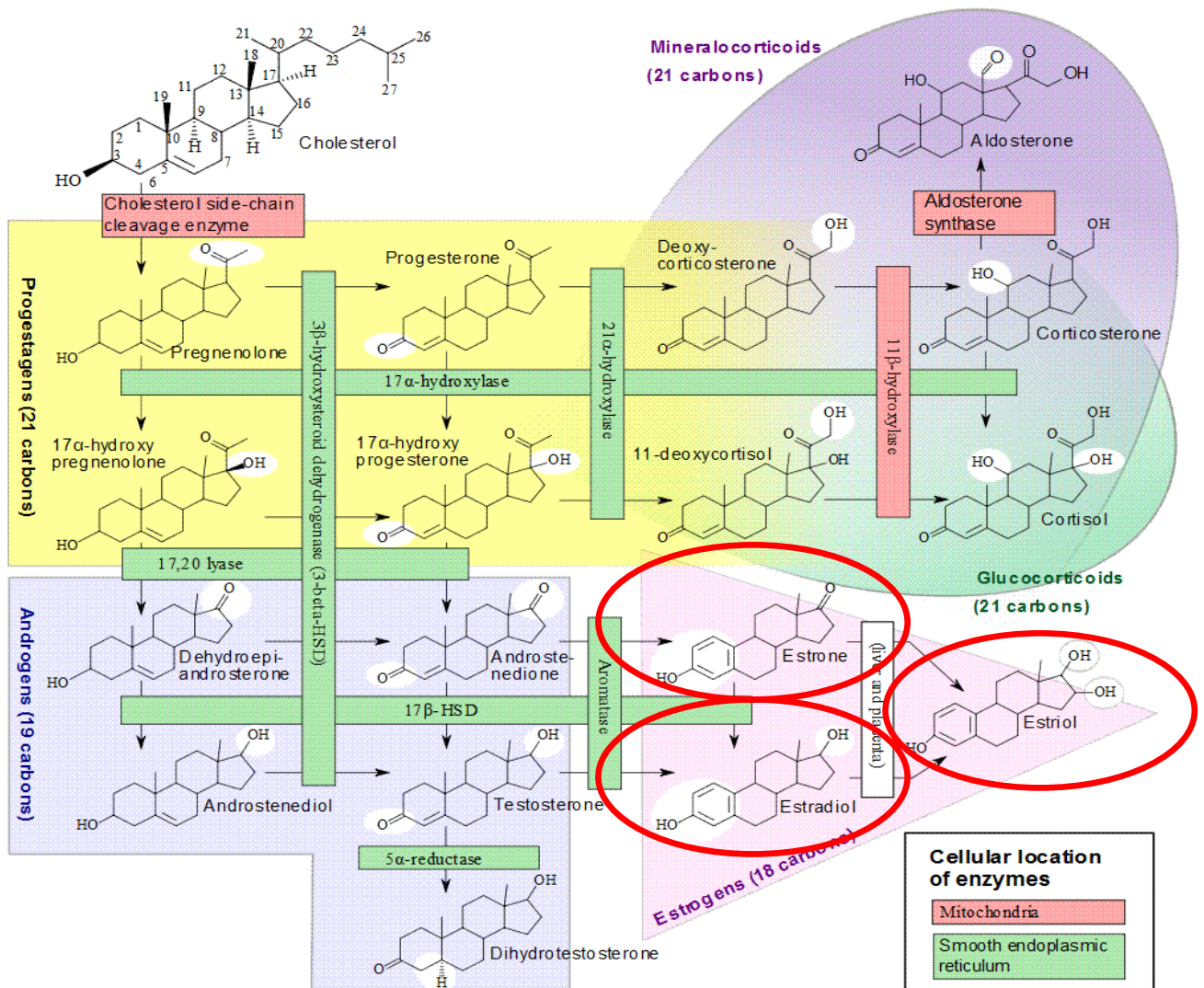
Peripheral conversion is the main source of circulating estrogens also in prepubertal **children** and in **men**. Adipose tissue and the brain are the most important sites of production in men. They are also produced in adrenals, liver, mammary glands, hair and in testes. As the estrogen production is dependent on enzyme aromatase, which is most prevalent in adipose tissue, increased estrogen synthesis may be connected with obesity.





Major metabolite of estradiol and estrone is estrone sulfate. Although this compound is not biologically active, it may be transformed back to estrone and estradiol, serving thus as a slowly metabolized estrogen reservoir. Formation of estrone sulfate occurs in various tissues in the body, but primarily in the liver.

**Fig.3: Steroidogenesis**





### **Estrogen transport in blood**

More than 97% of estradiol circulating in blood is bound to plasma proteins. It is bound specifically with high affinity to SHBG and nonspecifically to albumin<sup>12</sup>. In women, estradiol circulates bound from 40 to 60% to SHBG and from 40 to 60% to albumin. SHBG has higher affinity to testosterone than to estradiol, therefore estradiol circulates from 20 to 30% bound to SHBG and from 70 to 80% bound to albumin in men<sup>12</sup>. Only 2 to 3% of total estradiol circulates in the free form.

Estrogens increase SHBG concentrations and therefore they are higher in women than in men. They are also increased during the pregnancy, oral contraceptive use, hyperthyroidism and application of some antiepileptic drugs. SHBG concentration may decrease in hypothyroidism, obesity or androgen excess.

In contrast, estrone, estrone sulfate and estriol circulate bound mainly to albumin, not to SHBG.

### **Metabolism**

As in the case of other steroids, the liver is the primary site for the inactivation of estrogens. The main biochemical reactions occurring there are hydroxylation, oxidation, reduction and methylation. Conjugation with glucuronic acid or sulfuric acid increases water solubility and thus allows them to be eliminated rapidly through the kidney into urine.

Some of the water soluble conjugates are excreted also via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

### **Physiological function**

Estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age, when they are one of crucial agents maintaining menstrual cycle and enabling fertilization and pregnancy.

In spite of lower circulating concentrations, their importance is indisputable in men, too.





### **Estrogens in women**

Estrogens are necessary for the normal female physical maturation. Together with other hormones, estrogens participate in processes of ovulation and implantation of the fertilized ovum, and also stimulate the development and maintain the growth of accessory organs.

In the absence of androgens, estrogens stimulate the intrauterine development of the vagina, uterus, and fallopian tubes from the embryonic Müllerian system. They also stimulate the stromal development and ductal growth of the breasts at puberty, are responsible for the accelerated pubertal skeletal growth phase and for closure of the epiphyses of the long bones. For more details see Tab.1.

Estrogens promote the development of female secondary sexual characteristics. They contribute to the growth of axillary and pubic hair. They also alter the distribution of body fat to produce the typical female body contours, including the accumulation of body fat around the hips and breasts. Estrogens have a number of other important extragenital metabolic effects (see Tab.1). For example, estrogens decrease the rate of bone resorption by antagonizing the effects of parathyroid hormone on bone. Thus, osteoporosis becomes a common problem in estrogen deficient postmenopausal women. Estrogens also affect mood; estrogen withdrawal, fluctuating estrogens, and periods of sustained estrogens low levels may cause mood lowering.

Estrogens play a very important role in the development of the fetus during pregnancy. Organs like the lungs, kidneys, liver, adrenal glands and some other would never be triggered into maturation without estrogens. Estrogens are crucial for the growth and proper operation of placenta. High estrogen (and progesterone) levels lead to the suppression of the hypothalamic axis and subsequently of the menstrual cycle.

Effects of estrogens are listed listed in Tab.1





**Table1: Metabolic effects of estrogens in women**

<b>Affected processes/tissues</b>	<b>Effect</b>
<b>Growth and development</b>	
Reproductive organs	Development of secondary sex characteristics during puberty
Skeleton	Acceleration of long bone growth Closure of epiphyses at puberty
<b>Reproductive processes</b>	
Ovulation	Promotion of ovarian follicle growth
Fertilization	Alteration of cervical secretions to favor survival and transport of sperm Promotion of sperm motility within the fallopian tubes by decreasing mucus viscosity
Implantation	Promotion of endometrial lining development in the event of pregnancy
Vagina	Proliferation of vaginal mucosa
Cervix	Increase in mucus consistency
Breasts	Stimulation of stromal development and ductal growth
<b>General metabolic effects</b>	
Bone resorption	Decrease of bone resorption rate
Muscles	Reduction of muscle mass
Metabolism	Acceleration of metabolism, decrease of fat deposition
Coagulation	Increase of circulating level of factors 2, 7, 9 and 10, plasminogen Decrease of antithrombin III Increase in platelet adhesiveness
Gastrointestinal tract	Reduction of bowel motility Increase of cholesterol in bile
Fluid balance	Salt (sodium) and water retention
Plasma proteins	Increase hepatic synthesis of SHBG, TBG and other binding globulins
Lipoproteins	Increase of high-density lipoprotein amount, connected with slight decrease of low-density lipoprotein amount
<b>Pregnancy</b>	
Fetus	Stimulation of development of vagina, uterus, and fallopian tubes Stimulation of other organ development Regulation of bone density Protection of female fetuses from the effects of androgens in the mother's system. (Androgens are substances that have a masculinising effect).
Supportive function	Promotion of blood flow in the uterus Participation in development and regulation of placenta Maintainance, regulation and initiation of production of other hormones Maintainance of the endometrium Participation in preparation of lactation process



## Estrogens in men

Estrogen role in men was underestimated for many years. It was thought that these hormones only caused impairment of the gonadal function in men but didn't exert any positive influence.

Since then, it has become clear that estrogens regulate certain functions of the reproductive system important for the maturation of sperm<sup>8</sup>.

Also, it is believed now that estrogens possess some other beneficial effects in males. They take part in bone formation and in inhibition of their linear growth. They also affect lipid metabolism and sexual maturation, the effects that were attributed to testosterone action until today. They also seem to affect the cardiovascular system.

## Levels

As the production of estrogens is tightly connected with reproductive function, it is not surprising that the estrogen levels vary with age.

It is true especially in women. Basal levels of estrogens remain low in childhood, and start to increase progressively with the onset of puberty. Their increased production induces physical and psychical changes, including development of secondary sex characteristics, accelerated growth and the onset of menarche (i.e. first menstrual bleeding).

Between menarche and menopause, reproductive organs of women typically undergo series of repeated changes during menstrual cycle, associated with repetitive changes in estrogen concentrations. Ovaries are the major source of estrogen synthesis that time, with predominant synthesis of the most potent estrogen estradiol.

In female, this repetitive action is interrupted during pregnancy and in postpartum period. Estradiol and estrone levels start to rise in 6-8 weeks of gestation, and they are increased 100-fold during pregnancy comparing to normal values. Estriol level increases from very low concentration, reaching approximately 1000-fold higher concentration during pregnancy comparing to normal values.

After menopause (i.e. time when woman's final menstrual period finishes), ovarian production of estrogens stops. Estrogens derived from the adrenal cortex, represented mainly by estrone, continue to circulate in a woman's body, but they are insufficient to maintain the secondary sexual characteristics in the same manner as ovarian estrogens did.





## Estrogens - summary

Over 30 estrogens have been identified, but only estradiol, estrone and estriol are known to have any direct clinical importance. Information regarding estron sulfate may be useful, too, as it gives indirect information about total estrogen pool in the organism.

Main features of the mentioned steroids are shown in Tab.2.

**Table2: Comparison of estradiol, estrone, estrone sulfate and estriol**

	<b>Estradiol</b>	<b>Estrone</b>	<b>Estron sulfate</b>	<b>Estriol</b>
<b>Estrogenic potency</b>	Strong	Medium (1.25-5 times less potent than estradiol)	None	Weak
<b>Physiological function</b>	Main estrogen in ovulating women (see Table1)  Spermatogenesis in men	Main source of estrogenicity after menopause	Estrogen reservoir	Maintenance of pregnancy No specific function in non-pregnant women or men
<b>Transport in blood</b>	SHBG – w:~50%;m:~25% Albumin – w:~50%;m:~25% Free - 2-3%	Predominantly bound to albumin	Predominantly bound to albumin	Predominantly bound to albumin
<b>Main site of production</b>	w: <b>Ovaries</b> <b>Placenta in pregnancy</b> m: Testes Adrenal glands Peripheral conversion(adipose tissue, liver)	<b>Adipose and other tissues</b> (peripheral conversion) w: <b>Placenta in pregnancy</b> w: Ovaries	<b>Liver</b> Other tissues	w: <b>Placenta in pregnancy</b>

w – women

m: - men



## Short characteristic of estradiol, estrone, estrone sulfate and estradiol

### ESTRADIOL

Estradiol (E2) is the most effective estrogen in the peripheral circulation. It is the major estrogen produced by ovaries, further it is created in placenta, adrenals and testes. Estradiol is derived from cholesterol and its immediate precursors are androstenedione and testosterone. Over 97% of circulating estradiol is bound to serum proteins, mainly to SHBG. Catabolism in the liver leads to its transformation into estrone or estriol or into glucuronate or sulphonated conjugates, eliminated in the urine. The measurement is valuable together with gonadotropins in evaluation of menstrual and fertility problems in adult females.

#### Diagnostic information



##### Elevated estradiol levels

PCOS (polycystic ovary syndrome); estrogen producing tumors; gynecomastia; liver diseases; testicular feminization; precocious puberty; hypothyroidism



##### Decreased estradiol levels

Primary ovarian failure; Turner syndrome; hypopituitarism; hypogonadism; delayed puberty

### ESTRONE

Estrone (E1) is more potent estrogen than estriol (E3) but is less potent than estradiol (E2). Estrone is the major circulating estrogen after menopause. E2/ E1 ratios change appreciably during the menstrual cycle. Most E1 is in the form of sulphate conjugate. Estrone in non-pregnant women and in men shows significant diurnal rhythm.

#### Diagnostic information



##### Elevated estrone levels

PCOS (polycystic ovary syndrome); androgen producing tumors; estrogen producing tumors; obesity with increased tissue production of E1; liver diseases; testicular feminization ; precocious puberty; hyperthyroidism



##### Decreased estrone levels

Primary ovarian failure; Turner syndrome; hypopituitarism; hypogonadism





## **ESTRONE SULFATE**

Estrone sulfate (E1S) is a sulfated estrone derivative and it is the most abundant circulating estrogen in non-pregnant women as well as normal men. It is found in peripheral circulation, due to sulfokinases, present in peripheral tissues as well as gonad and adrenal cortex, as a major metabolite of the estradiol and estrone. It is also known to have a longer half-life in blood. Formation of estrone sulfate occurs in a variety of tissues in the body, but primarily in the liver.

### **Diagnostic information**



#### **Elevated estrone sulfate levels**

PCOS (polycystic ovary syndrome); androgen producing tumors; estrogen producing tumors; obesity with increased tissue production of E1; testicular feminization ; precocious puberty; hyperthyroidism



#### **Decreased estrone sulfate levels**

Primary ovarian failure; Turner syndrome; hypopituitarism; hypogonadism

## **ESTRIOL**

Estriol (E3) is less potent estrogen than estradiol and estrone. Its main physiological importance is in pregnancy, when its concentration increases up to 1000-fold in comparison with non-pregnant values. Estriol is produced in large amounts by the placenta, the tissue that links the fetus to the mother. It can be detected as early as the 9th week of pregnancy, and its levels increase until delivery. Estriol can be used as a marker of fetal health and wellbeing. It is also widely used as a part of screening system for chromosomal and congenital defects.

### **Diagnostic information**



#### **Elevated estriol levels**

Multiple pregnancy



#### **Decreased estriol levels**

Intrauterine growth retardation; congenital or chromosomal defects of fetus; placental sulfatase deficiency; anemia, severe liver disease.



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