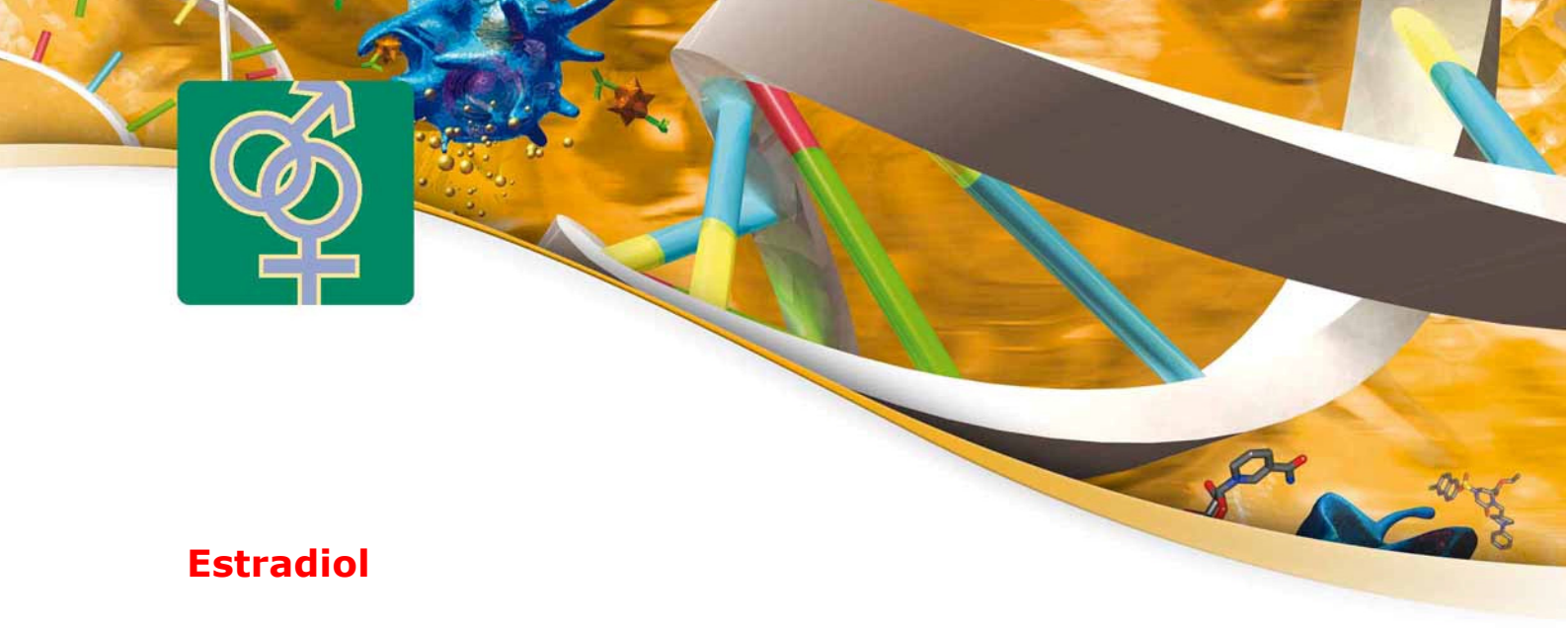
Reproductive

Estradiol

Analyte Information



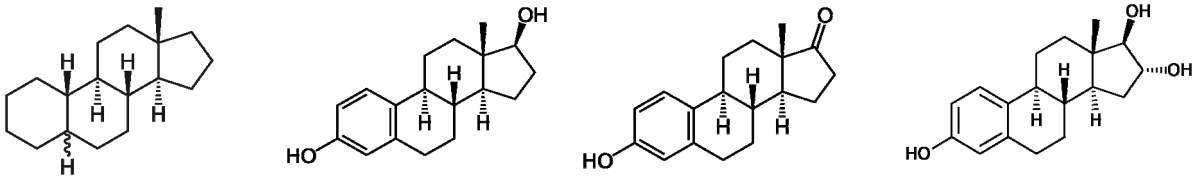
Estradiol

Introduction

Estradiol (E2 or 17β-estradiol) is the major estrogen in humans. Although it is often called the "female" hormone, it is also present in males. It is the aromatized C_{18}-steroid with a 3-hydroxyl group and a 17-hydroxyl group. Its chemical name of which is (17β)-estra-1,3,5(10)-triene-3,17-diol, its summary formula is $C_{18}H_{24}O_2$ and its molecular weight is 272.38 Da.

Like the other natural estrogens estrone (E1) and estriol (E3), estradiol is a derivative of the hydrocarbon estrane with an aromatic ring and an 18-carbon molecule (see fig.1).

Fig.1: Structural formulas of estrane and its derivatives estrone, estradiol and estriol.



Estrane Estradiol Estrone Estriol

There are also several other names for this compound, e.g.including: oestradiol, 3,17β-dihydroxy-1,3,5(10)-estratriene or and dihydrofolliculin.

Biosynthesis

Estradiol, like other sex steroids, is synthetized from cholesterol that has been converted into androstenedione.

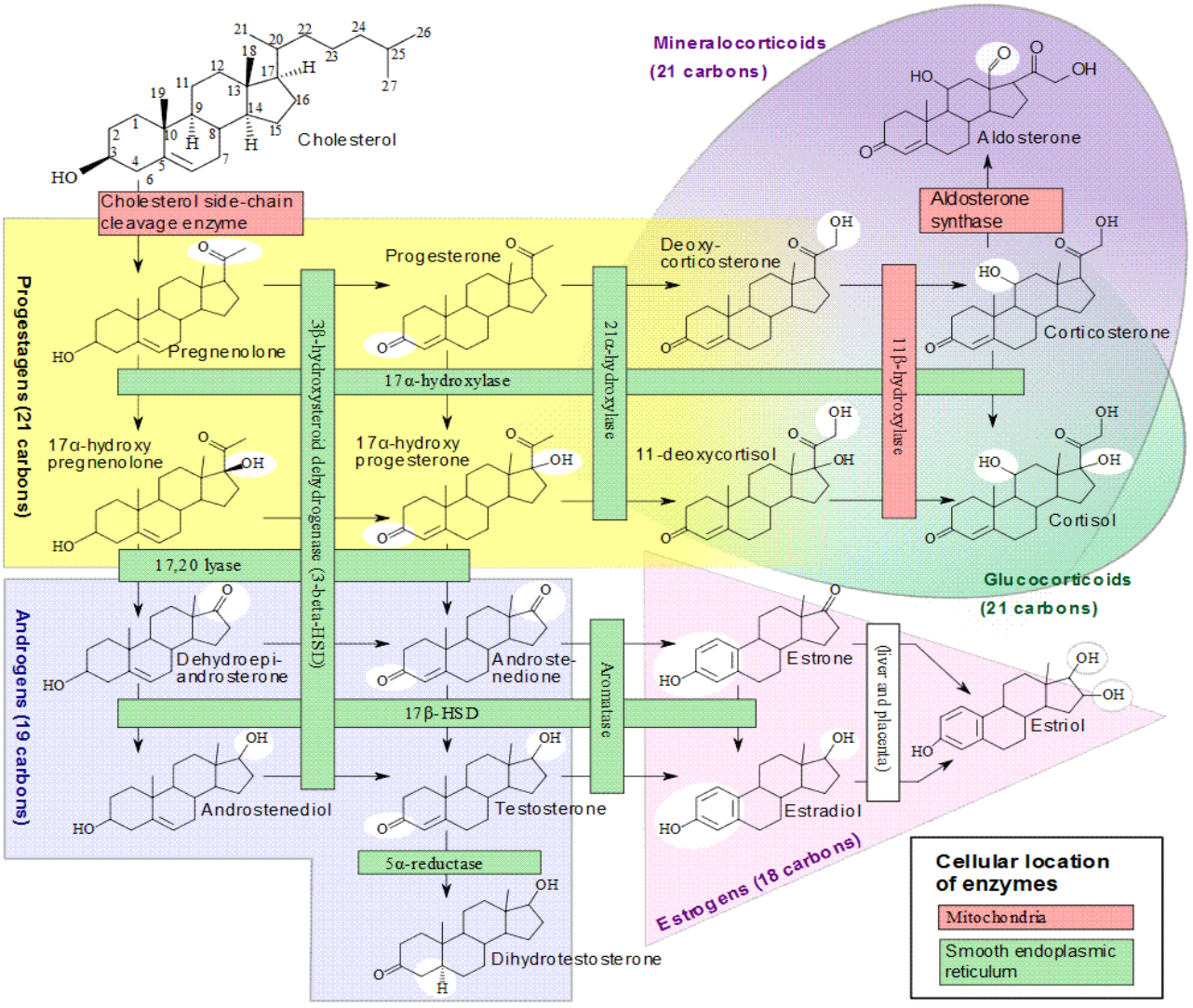
There are two mechanisms of estradiol synthesis from androstendione[10]:
- via testosterone, which then undergoes aromatization to estradiol
- via aromatization to estrone, which is then converted to estradiol.

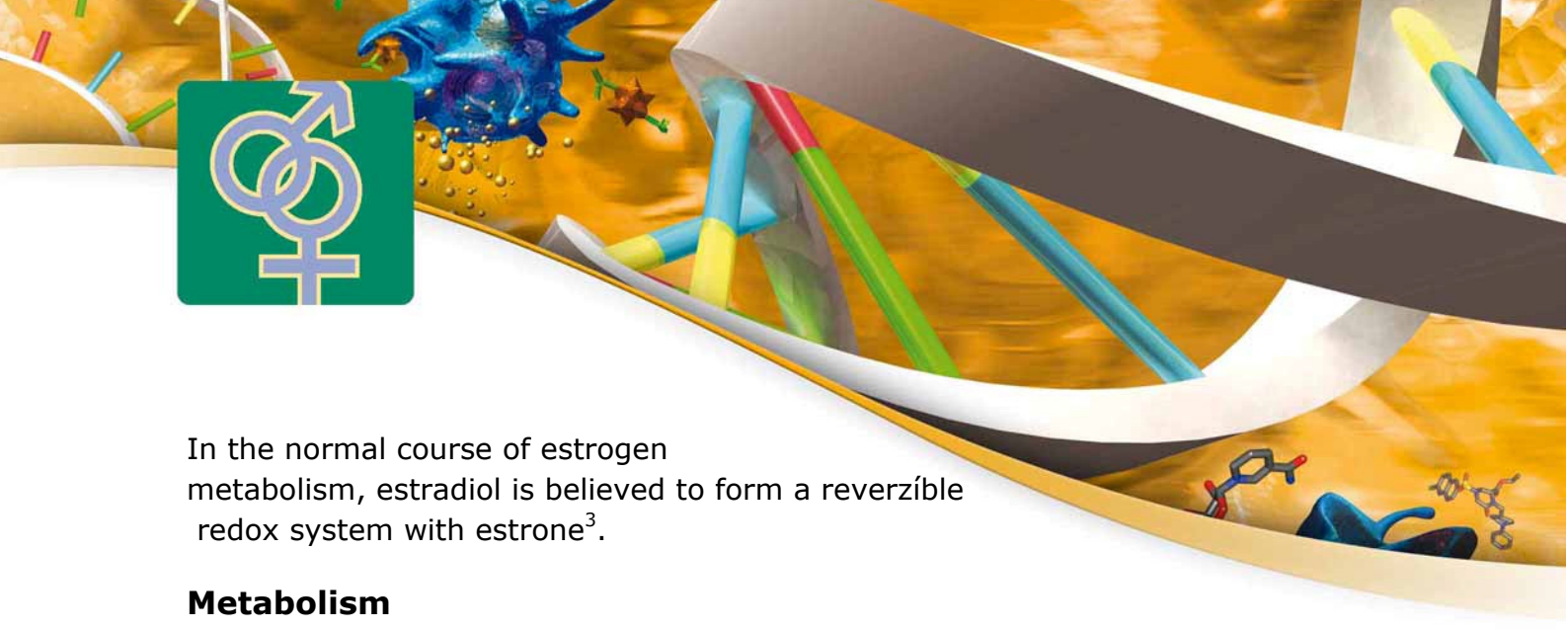
In cycling women, most estradiol is produced in the ovaries by the granulosa cells and corpus luteum. The main source of estradiol during pregnancy is the placenta.

In men, estradiol is produced by the testes.

In addition to being produced by the gonads in both sexes, estradiol is also produced in the adrenal cortex. Another source is the conversion of testosterone or other precursor hormones. This conversion takes place in many tissues, particularly in adipose tissue, and does not decease after menopause. Finally, estradiol is produced in the brain and arterial walls.

Fig.2: Steroidogenesis





In the normal course of estrogen metabolism, estradiol is believed to form a reverzíble redox system with estrone[3].

Metabolism

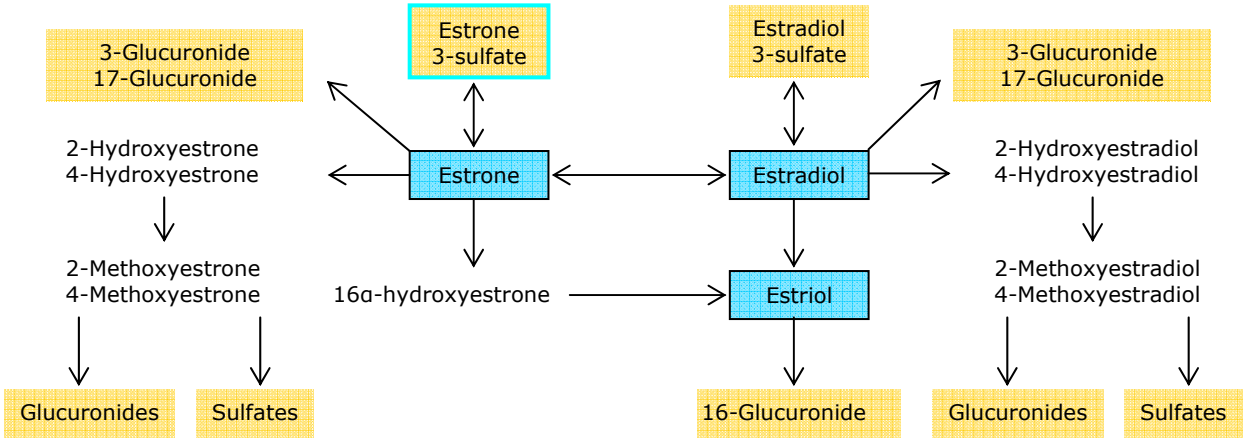
Deactivation includes conversion to the less-active estrogen estrone, which is then further metabolized to estrone-3 sulphate, estrone-17 glucuronide, or processed via either the 2-, 4- or 16α-hydroxylation pathways to form 2-hydroxyestrone, 4-hydroxyestrone or 16α-hydroxyestrone. Direct estradiol conversion to 2-hydroxyestradiol, 4-hydroxyestradiol and 16-hydroxyestradiol is also possible. These hydroxyderivates are further processed and finally excreted in urine in the form of glucuronides.

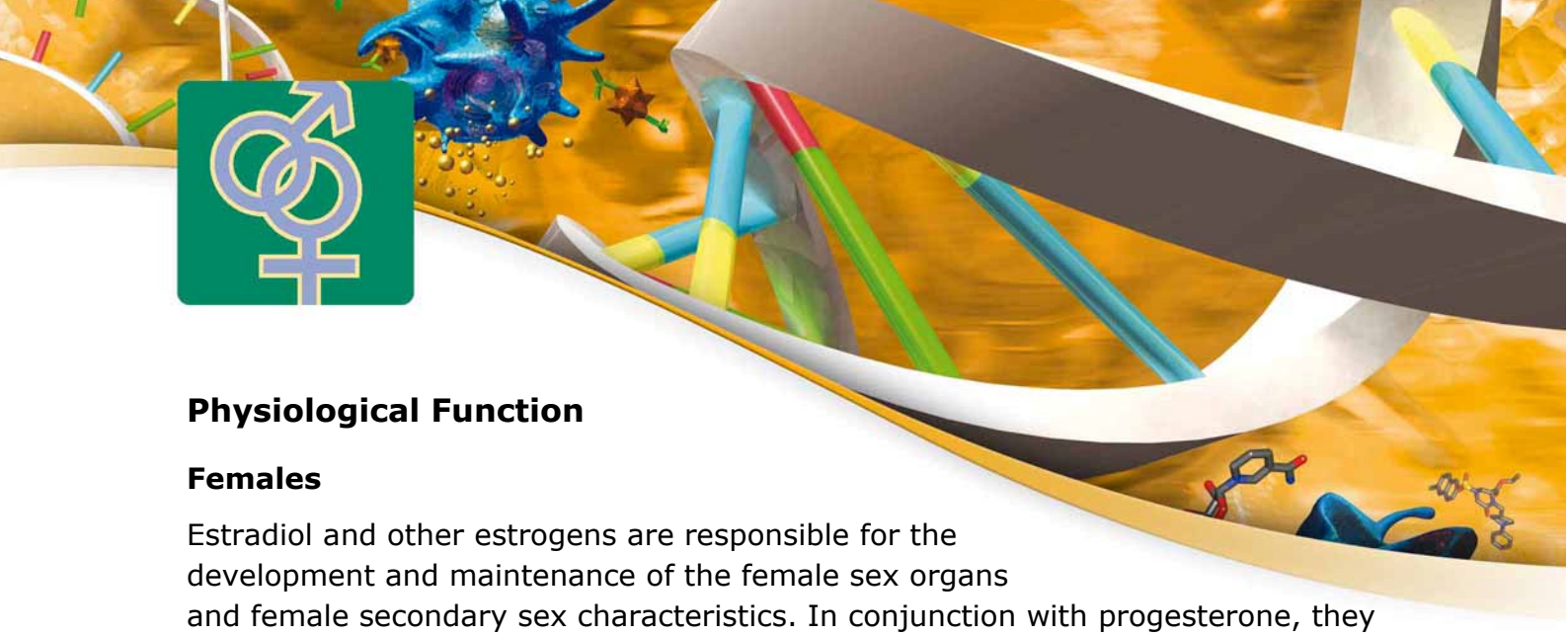
16α-hydroxyestrone may be also be metabolized to estriol via another pathway.

The primary metabolic site for estradiol inactivation and modification to conjugates is the liver. These water-soluble metabolites are excreted by the kidneys as urine.

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

Fig.3: Metabolism of estradiol and other estrogens





Physiological Function

Females

Estradiol and other estrogens are responsible for the development and maintenance of the female sex organs and female secondary sex characteristics. In conjunction with progesterone, they also participate in the regulation of the menstrual cycle and breast and uterine growth.

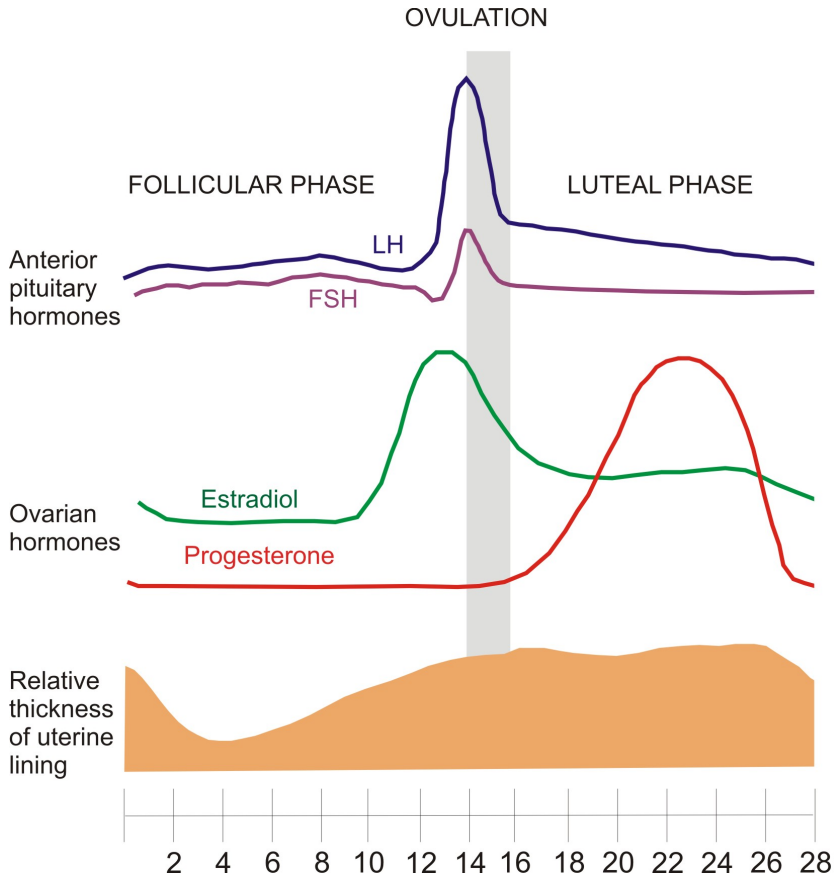
Estradiol plays a critical role not only in reproductive and sexual functioning, but also within various other organs.

It is necessary for normal female physical maturation. In the absence of androgens, estradiol and other estrogens stimulate the development of the vagina, uterus, and fallopian tubes from the embryonic Müllerian system. They also stimulate stromal development and ductal growth of the breasts during puberty, are responsible for accelerated pubertal skeletal growth, contribute to the growth of axillary and pubic hair, and alter the distribution of body fat to produce the typical female body contours.

Estradiol is one of key elements in maintaining a regular menstrual cycle.

Its concentration is low at the beginning of the cycle, but increases gradually due to production by follicular granulosa cells under the effect of FSH. This increase leads to an inhibition of FSH synthesis via negative feedback mechanisms; however, estradiol enhances the effect of FSH on maturing follicles by causing changes in the FSH receptors of follicular cells. When one dominant follicle is selected for maturation, it accumulates a great amount of granulosa cells. At this point estradiol production increases further, reaching its peak at the end of the follicular phase (around day 12). This elevation of estradiol level triggers a surge of LH, followed by ovulation (rupture of the matured follicle and release of the egg). Estradiol concentrations fall abruptly after ovulation. Corpus luteum, which is formed from the ruptured follicle, starts to produce estradiol again and concentrations in circulation increase around day 22 of the cycle. This process is halted if fertilization does not occur, resulting in a decrease in estradiol and consequent rise in FSH in preparation for the next cycle.

Fig.4: Menstrual cycle



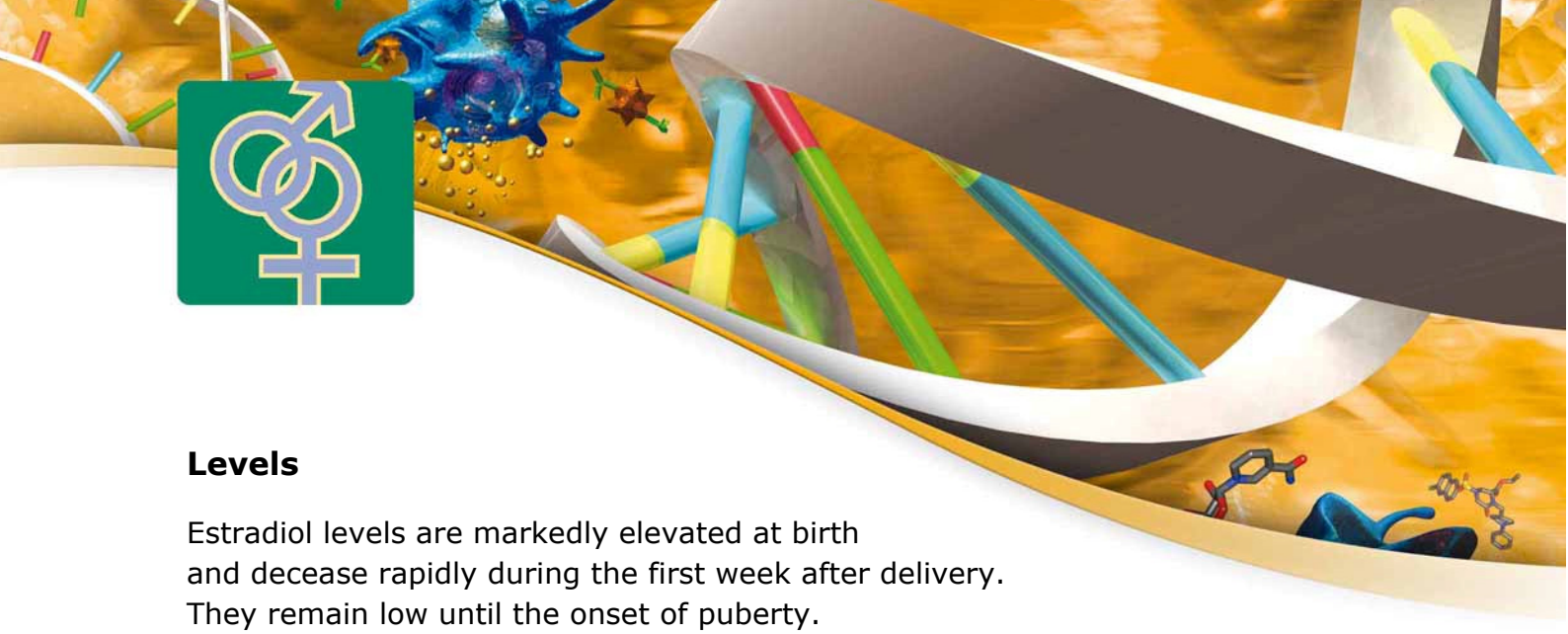
Estradiol has a significant effect on the endometrium during the menstrual cycle, especially in the preovulatory phase, when it stimulates endometrial proliferation.

Estradiol also has many important extragenital metabolic effects in adult women, such as decreasing of the rate of bone resorption, increasing high-density lipoprotein (HDL) production, and various cardioprotective effects.

A decrease in estradiol concentrations after menopause influences the health and well-being of postmenopausal women. Consequences of long-term estrogen deprivation include (among others) osteoporosis[5] and increased risk of cardiovascular disease[6].

Males

Estradiol is produced in the Sertoli cells of the testes. It seems to have complex and integral role in spermatogenesis[9], but the exact mechanism is not yet known.



Levels

Estradiol levels are markedly elevated at birth
and decease rapidly during the first week after delivery.
They remain low until the onset of puberty.

In girls, estradiol levels increase progressively throughout puberty in response to FSH and LH stimulation. Initially, increased secretion of FSH and LH occurs at night and is associated with increased estradiol levels the next morning. Later in puberty, increased secretion of LH and FSH occurs throughout the day. (Night-time increases still occur, but only during the early follicular phase.)

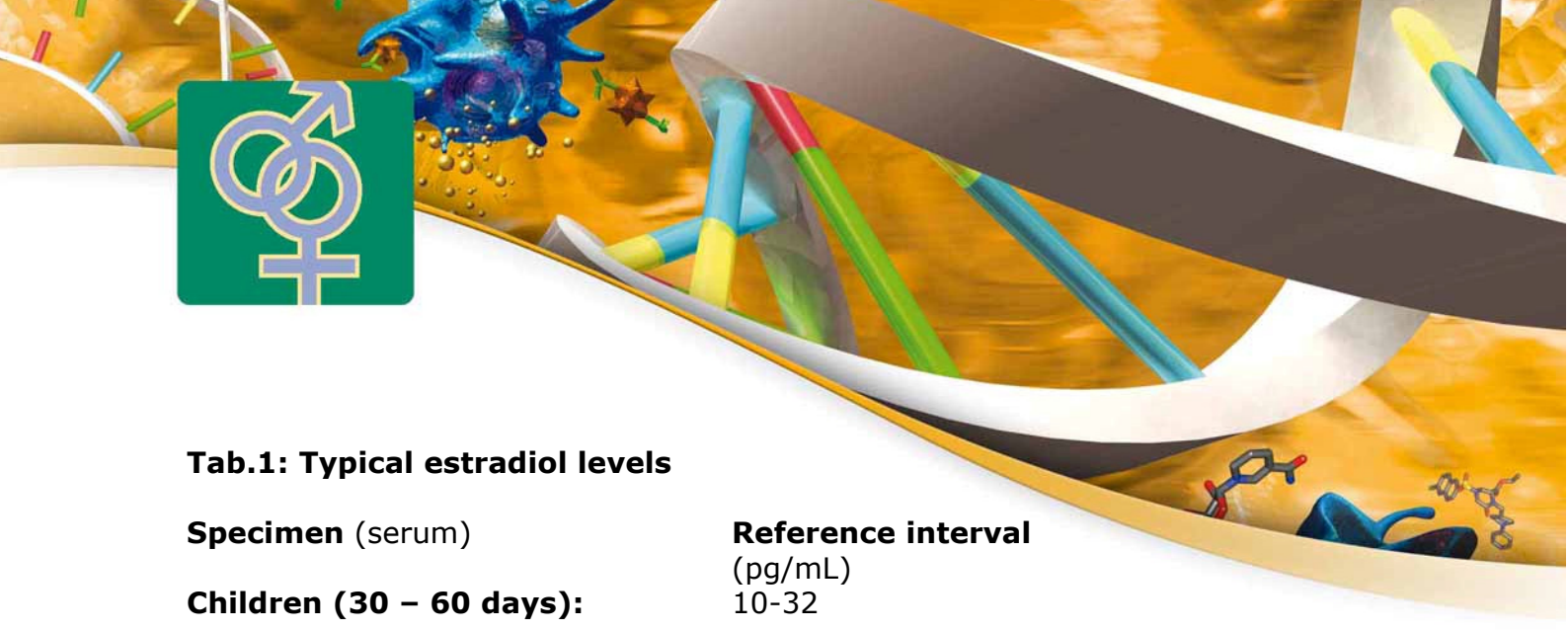
Estradiol levels in cycling women vary with menstrual cycle phase. They increase several times during pregnancy.

After menopause, estradiol levels decrease significantly due to diminished ovarian synthesis. Androstenedione conversion in peripheral tissues becomes the main source of estrogens, with estrone as the predominant estrogen in circulation.

In men, estradiol levels increase during puberty as a result of peripheral testosterone conversion and then remain relatively stable.

Approximately 20% of circulating estradiol in men is bound to SHBG (Sex Hormone Binding Globulin), and 40-60% in women. Estradiol may also be bound to albumin. Only a small fraction (about 2%) is free.

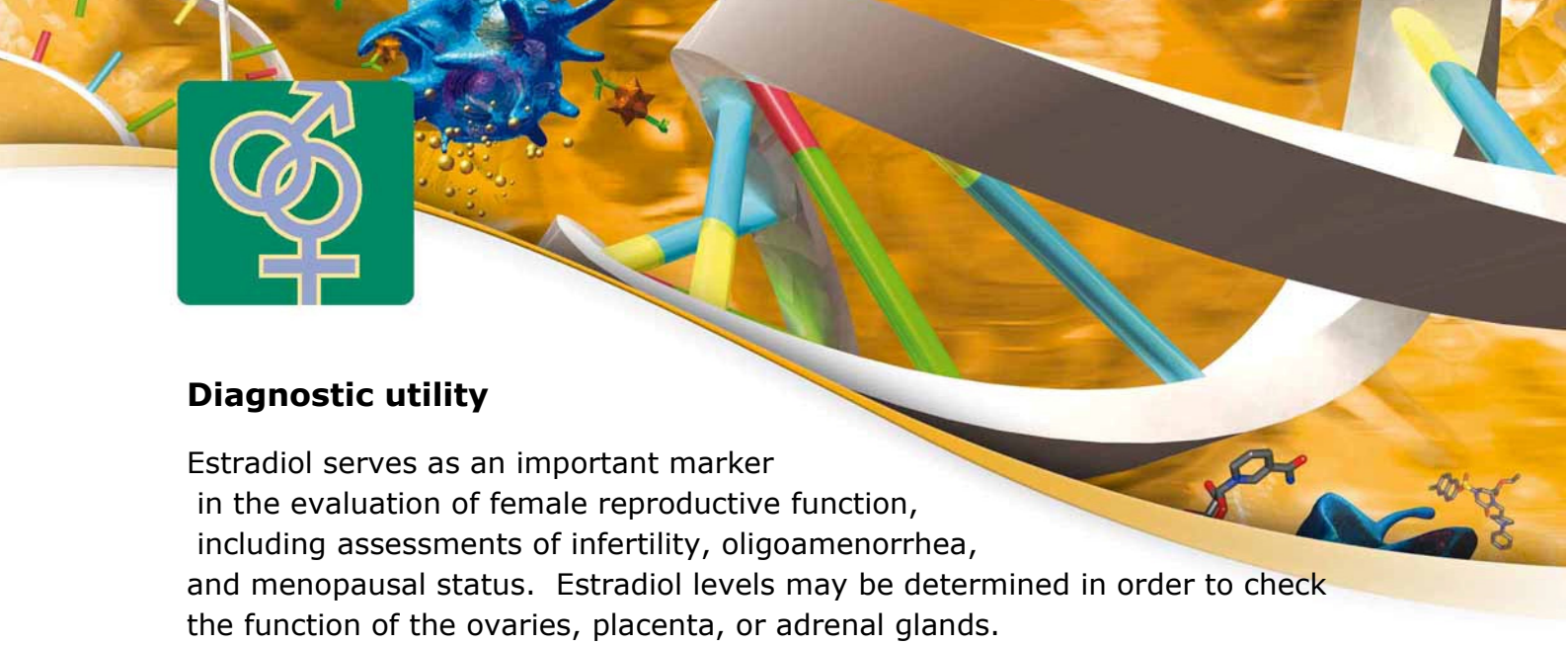
Typical estradiol levels[8] in children and adult males and females are given in table 1.
For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).



Tab.1: Typical estradiol levels

Specimen (serum)	**Reference interval** (pg/mL)
Children (30 – 60 days):	10-32
Children (0.5 – 10 years):	<15
Puberty Tanner stage:	
Stage I	
male:	3 – 15
female:	5 – 10
Stage II	
male:	3 – 10
female:	5 – 115
Stage III	
male:	5 – 15
female:	5 – 180
Stage IV	
male:	3 – 40
female:	25 – 345
Stage V	
male:	15 – 45
female:	25 – 410
Adults male:	10 – 50
Adults female	
Early follicular phase:	20 – 150
Midcycle peak:	150 - 750
Luteal phase:	30 - 450
Postmenopausal:	≤20

Equation for the conversion of units: 1 pg/mLx3.67 = pmol/L



Diagnostic utility

Estradiol serves as an important marker in the evaluation of female reproductive function, including assessments of infertility, oligoamenorrhea, and menopausal status. Estradiol levels may be determined in order to check the function of the ovaries, placenta, or adrenal glands.

It is also useful for monitoring induced ovulation, as well as during preparation for in vitro fertilization (IVF).

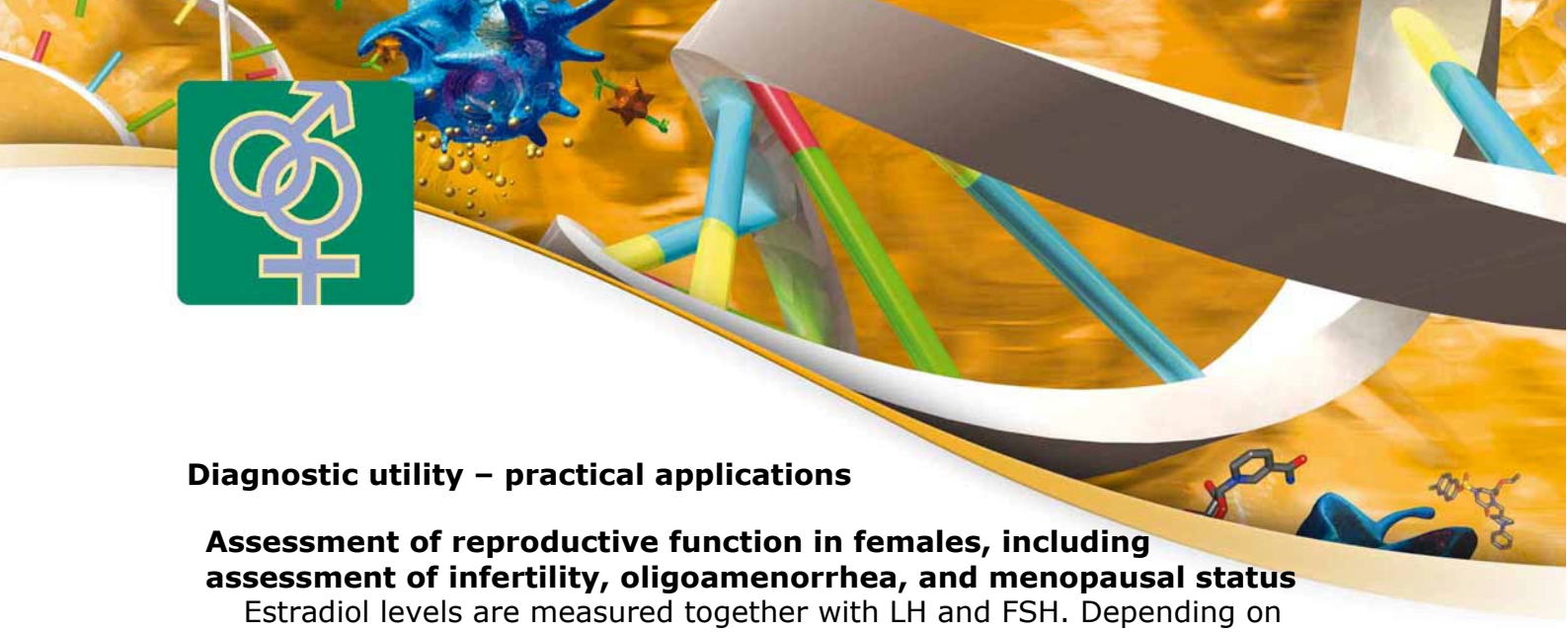
Ultrasensitive assays, simultaneous measurement of estradiol and estrone or both may be necessary in a number of other clinical situations. These include inborn sex steroid metabolism errors, pubertal disorders, estrogen deficiency in men and fracture risk assessment in menopausal women. These tests are of great value in therapeutic drug monitoring as well, either in the context of low-dose female hormone replacement therapy or in antiestrogen treatment.

Elevated estradiol levels

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

Decreased estradiol levels

- primary ovarian failure
- Turner syndrome
- hypopituitarism
- hypogonadism
- delayed puberty



Diagnostic utility – practical applications

Assessment of reproductive function in females, including assessment of infertility, oligoamenorrhea, and menopausal status

Estradiol levels are measured together with LH and FSH. Depending on particular case, other hormones may be measured as well, including prolactin, testosterone, AMH, Inhibin B, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, progesterone, and estrone.

Establishment of the time of ovulation and optimal time for conception

Serial specimens must be drawn over several days to evaluate baseline and peak estradiol levels.

Determination of the timing of ovarian stimulation initiation in IVF (in vitro fertilization)

Monitoring of female hormone replacement therapy in postmenopausal women

Estradiol levels are measured together with estrone (sulfate) in order to establish and monitor dosing.

Diagnosis of precocious puberty

GnRH stimulation test is the "golden standard" in these cases.
Estradiol is used as a supplementary indicator.

Diagnosis of delayed puberty

Estradiol levels are measured together with LH, FSH and estrone.

Diagnosis of suspected disorders of sex steroid metabolism, e.g. aromatase deficiency

Estradiol levels are measured together with other steroids.

Fracture risk assessment of postmenopausal women, and, to a lesser degree, older men

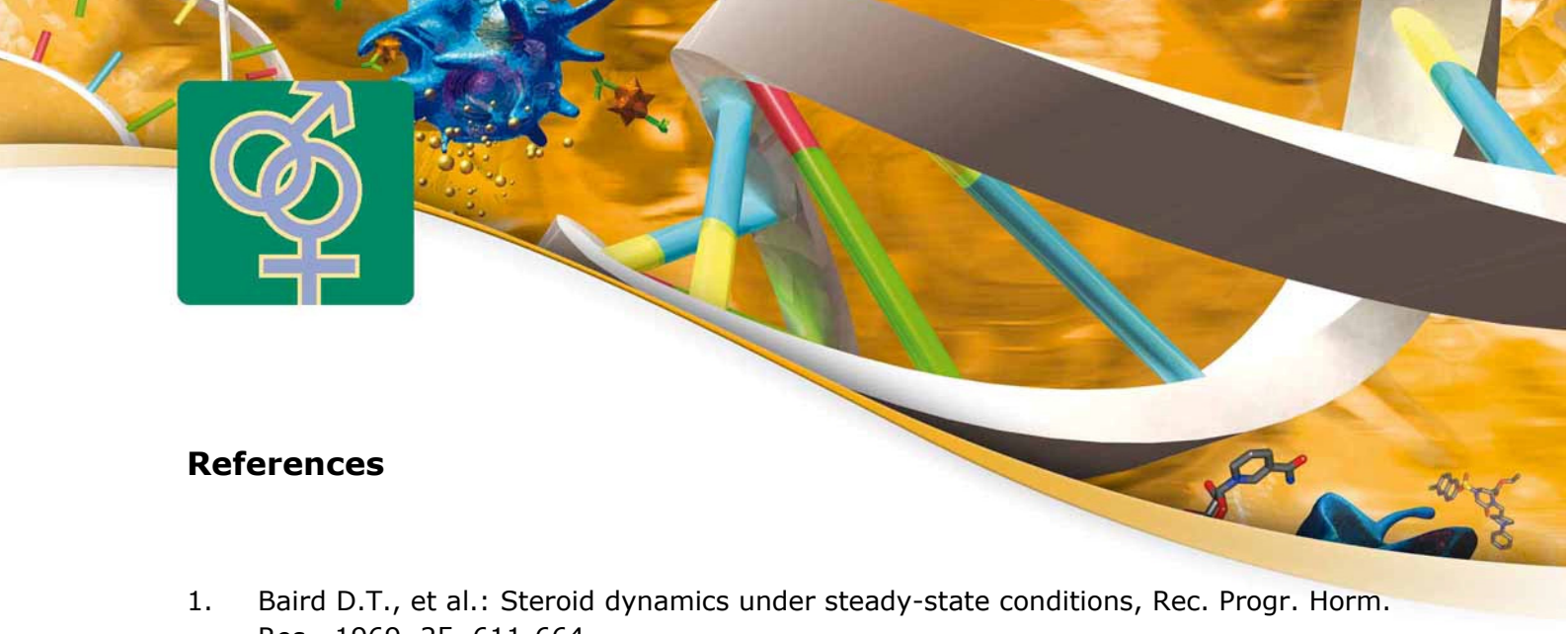
Estradiol determination acts as a supplementary test to clinical assessment, imaging studies, bone mineral density measurement and bone marker determination.

Monitoring antiestrogen therapy with aromatase inhibitor

Estradiol levels are measured together with estrone.

Diagnostics of gynecomastia and feminization in men

Estradiol levels are measured together with estrone, testosterone and adrenal androgens.



References

1. Baird D.T., et al.: Steroid dynamics under steady-state conditions, Rec. Progr. Horm. Res., 1969, 25, 611-664
2. Canez M.S., Lee K.J., Olive D.L.: Progesteron and estrogens, Infert. Reprod. Med. Clin. North Amer., 1992, 3, 59-78
3. Quest Diagnostics/Nichols Institute. The Corning Endocrine Manual, Capistrano, CA: Quest Diagnostics/Nichols Institute, 1996
4. Bourguignon, J.P., Linear growth as a function of age at onset of puberty and sex steroid dosage: therapeutic implications, Endocr. Rev.,1988, 9 (4), 467-488
5. Kleerekopper, M., Sullivan, J.M.: Osteoporosis as the model of the long-term clinical consequences of the menopause, Prog. Cardiovasc. Dis., 1995, 38, 181-188
6. Grodstein, F., Stampfer M.: The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women, Prog. Cardiovasc. Dis., 1995, 38, 199-210
7. Homburg R.: Ovulation Induction and Controlled Ovarian stimulation, Taylor & Francis, 2005, 11
8. Alan H.B. WU, PhD, DABCC, FACB: Tietz Clinical Guide To Laboratory Tests, 4th edition. W.B. Saunders Company, Philadelphia, 2006, 366-367
9. Tietz: Textbook of Clinical Chemistry, 3nd Ed., Burtis C.A., Ashwood E.R., eds. W.B. Saunders Company, 1999, 1811
10. Hess, R.A, et all: A role for estrogens in the male reproductive system, Nature, 1997, 390, 509-512
11. Oettel, M., Schillinger, E.: Estrogens and antiestrogens, Eds., Springer-Verlag: Berlin,1999, 225