# Estrogen

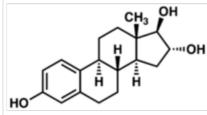
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Estrogens (AmE), oestrogens (BE), or œstrogens, are a group of compounds named for their importance in the estrous cycle of humans and other animals. They are the primary female sex hormones. Natural estrogens are steroid hormones, while some synthetic ones are non-steroidal. Their name comes from the Greek words estrus/οίστρος = sexual desire + gen/ $\gamma$ óvo = to generate.

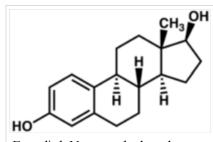
Estrogens are synthesized in all vertebrates<sup>[1]</sup> as well as some insects.<sup>[2]</sup> Their presence in both vertebrates and insects suggests that estrogenic sex hormones have an ancient evolutionary history.

Estrogens are used as part of some oral contraceptives, in estrogen replacement therapy for postmenopausal women, and in hormone replacement therapy for trans women.

Like all steroid hormones, estrogens readily diffuse across the cell membrane. Once inside the cell, they bind to and activate estrogen receptors which in turn modulate the expression of many genes.<sup>[3]</sup> Additionally, estrogens have been shown to activate a G protein-coupled receptor, GPR30.<sup>[4]</sup>



Estriol. Note two hydroxyl (-OH) groups attached to the D ring (rightmost ring).



Estradiol. Note one hydroxyl group attached to the D ring. The 'di' refers both to this hydroxyl and the one on the A ring (leftmost).

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# Steroidal 1 Types

1.1 Steroidal

■ 1.2 Nonsteroidal The three major naturally occurring estrogens in women are estrone (E1), estradiol (E2) Bansy estresis (E3).

■ 3 Function

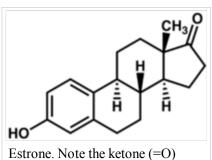
Estrone is produced dirln getrel repeal some stadiol is the predominant form in nonpregnant females, and Meental is ealth primary estrogen of pregnancy. In the body these are all produced from androgens through actions of enzymes. [citation needed]

■ 4.1 Oral contraceptives

- From menarche Hormone pausa comentate vastrogen is estradiol. In postmenopausal women the primary estrogen sastcancer
- The enzymetarorinatase converts testosterone to estradiol. Aromatase also converts androstenedione to estrone. • 4.5 Miscellaneous
- Estrone is weaker than estradiol.
  - 5 Cosmetics

Premarin a continuously prescribed estrogenic drug, contains the steroidal estrogens equilin and equilenin. There are oestradioliskin pateless auch estate the original brand, introduced in the late 1980s) that offer a completely asserable ternative. (A skin patch rather than pill also has the advantage of direct transmission into the blood steeker without going through the liver.) [citation needed]

■ 10 External links

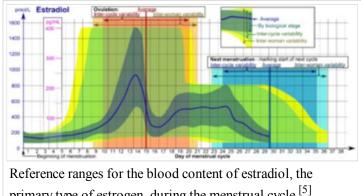


group attached to the D ring.

#### **Nonsteroidal**

A range of synthetic and natural substances have been identified that also possess estrogenic activity.<sup>[6]</sup>

- Synthetic substances of this kind are known as xenoestrogens.
- Plant products with estrogenic activity are called phytoestrogens.
- Those produced by fungi are known as mycoestrogens.



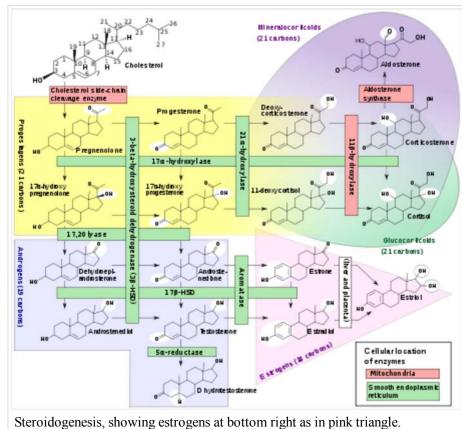
primary type of estrogen, during the menstrual cycle.<sup>[5]</sup>

Unlike estrogens produced by mammals, these substances are not necessarily steroids.

# **Biosynthesis**

Estrogens are produced primarily by developing follicles in the ovaries, the corpus luteum, and the placenta. Luteinizing hormone (LH) stimulates the production of estrogen in the ovaries. Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts. These secondary sources of estrogens are especially important in postmenopausal women. Fat cells also produce estrogen, [7] potentially the reason why being underweight or overweight are risk factors for infertility.[8]

In females, 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 crosses the basal



membrane into the surrounding granulosa cells, where it is converted to oestrone or oestradiol, either immediately or through testosterone. The conversion of testosterone to oestradiol, and of androstenedione to oestrone, is catalyzed by the enzyme aromatase.

Oestradiol levels vary through the menstrual cycle, with levels highest just before ovulation.

## **Function**

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The actions of estrogen are mediated by the Estrogen receptor (ER), a dimeric nuclear protein that binds to DNA and controls gene expression. Like other steroid hormones, estrogen enters passively into the cell where it binds to and activates the estrogen receptor. The estrogen:ER complex binds to specific DNA sequences called a Hormone response element to activate the transcription of some 137 ER-regulated genes, of which 89 are direct target genes. <sup>[9]</sup> Since estrogen enters all cells, its action are dependent on the presence of the ER in the cell. The ER is expressed in specific tissues including the ovary, uterus and breast.

While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sexual characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm<sup>[10][11][12]</sup> and may be necessary for a healthy libido.<sup>[13][14]</sup> Furthermore, there are several other structural changes induced by estrogen in addition to other functions.

#### Structural

- promote formation of female secondary sex characteristics
- accelerate metabolism
- reduce muscle mass
- increase fat stores
- stimulate endometrial growth
- increase uterine growth
- increase vaginal lubrication
- thicken the vaginal wall
- maintenance of vessel and skin
- reduce bone resorption, increase bone formation
- morphic change (endomorphic -> mesomorphic -> ectomorphic)
- protein synthesis
  - increase hepatic production of binding proteins
- coagulation
  - increase circulating level of factors 2, 7, 9, 10, plasminogen
  - decrease antithrombin III
  - increase platelet adhesiveness
- Lipid
- increase HDL, triglyceride
- decrease LDL, fat deposition
- Fluid balance
  - salt (sodium) and water retention
  - increase cortisol, SHBG
- Gastrointestinal tract
  - reduce bowel motility
  - increase cholesterol in bile
- Melanin
  - increase pheomelanin, reduce eumelanin
- Cancer
- support hormone-sensitive breast cancers (see section below)
- Lung function
  - promotes lung function by supporting alveoli (in rodents but probably in humans). [15]

Sexual desire is dependent on androgen levels rather than estrogen levels. [16]

### Fetal development

In mice, estrogens (which are locally aromatized from androgens in the brain) play an important role in psychosexual differentiation, for example, by masculinizing territorial behavior; [17] the same is not true in humans. [18] In humans, the masculinizing effects of prenatal androgens on behavior (and other tissues, with the possible exception of effects on bone) appear to act exclusively through the androgen receptor. [19] As a result, the utility of rodent models for studying human psychosexual differentiation has been questioned. [20]

#### Mental health

Estrogen is considered to play a significant role in women's mental health. Sudden estrogen withdrawal, fluctuating estrogen, and periods of sustained estrogen low levels correlates with significant mood lowering. Clinical recovery from postpartum, perimenopause, and postmenopause depression has been shown to be effective after levels of estrogen were stabilized and/or restored. [21][22]

Low estrogen levels in male lab mice may be one cause of obsessive–compulsive disorder (OCD). When estrogen levels were raised through the increased activity of the enzyme aromatase in male lab mice, OCD rituals were dramatically decreased. Hypothalamic protein levels in the gene COMT are enhanced by increasing estrogen levels which is believed to return mice that displayed OCD rituals to normal activity. Aromatase deficiency is ultimately suspected which is involved in the synthesis of estrogen in humans and has therapeutic implications in humans having obsessive-compulsive disorder. [23]

# **Medical applications**

## Oral contraceptives

Since estrogen circulating in the blood can negatively feed-back to reduce circulating levels of FSH and LH, most oral contraceptives contain a synthetic estrogen, along with a synthetic progestin. Even in men, the major hormone involved in LH feedback is estradiol, not testosterone.

## Hormone replacement therapy

As more fully discussed in the article on Hormone replacement therapy, estrogen and other hormones are given to postmenopausal women in order to prevent osteoporosis as well as treat the symptoms of menopause such as hot flushes, vaginal dryness, urinary stress incontinence, chilly sensations, dizziness, fatigue, irritability, and sweating. Fractures of the spine, wrist, and hips decrease by 50-70% and spinal bone density increases by  $\sim$ 5% in those women treated with estrogen within 3 years of the onset of menopause and for 5–10 years thereafter.

Before the specific dangers of conjugated equine estrogens were well understood, standard therapy was 0.625 mg/day of conjugated equine estrogens (such as Premarin). There are, however, risks associated with conjugated equine estrogen therapy. Among the older postmenopausal women studied as part of the Women's Health Initiative (WHI), an orally administered conjugated equine estrogen supplement was found to be associated with an increased risk of dangerous blood clotting. The WHI studies used one type of estrogen supplement, a high oral dose of conjugated equine estrogens (Premarin alone and with medroxyprogesterone acetate as *PremPro*). [24]

In a study by the NIH, esterified estrogens were not proven to pose the same risks to health as conjugated equine estrogens. Hormone replacement therapy has favorable effects on serum cholesterol levels, and when initiated immediately upon menopause may reduce the incidence of cardiovascular disease, although this hypothesis has yet to be tested in randomized trials. Estrogen appears to have a protector effect on atherosclerosis: it lowers LDL and triglycerides, it raises HDL levels and has endothelial vasodilatation properties plus an anti-inflammatory component.

Research is underway to determine if risks of estrogen supplement use are the same for all methods of delivery. In particular, estrogen applied topically may have a different spectrum of side-effects than when administered orally, [25] and transdermal estrogens do not affect clotting as they are absorbed directly into the systemic circulation, avoiding first-pass metabolism in the liver. This route of administration is thus preferred in women with a history of thrombo-embolic disease.

Estrogen is also used in the therapy of vaginal atrophy, hypoestrogenism (as a result of hypogonadism, castration, or primary ovarian failure), amenorrhea, dysmenorrhea, and oligomenorrhea. Estrogens can also be used to suppress lactation after child birth.

#### **Breast cancer**

About 80% of breast cancers, once established, rely on supplies of the hormone estrogen to grow: they are known as hormone-sensitive or hormone-receptor-positive cancers. Suppression of production of estrogen in the body is a treatment for these cancers.

Recently researchers have discovered that the common table mushroom has anti-aromatase<sup>[26]</sup> properties and therefore possible anti-estrogen activity. Clinical trials have begun in the United States looking into whether the table mushroom can prevent breast cancer in people.<sup>[27]</sup> A recent study has highlighted the importance of this research. In 2009, a case-control study of the eating habits of 2,018 women, revealed that women who consumed mushrooms had an approximately 50% lower incidence of breast cancer. Women who consumed mushrooms and green tea had a 90% lower incidence of breast cancer.<sup>[28]</sup>

Hormone-receptor-positive breast cancers are treated with drugs which suppress production of estrogen in the body. <sup>[29]</sup> This technique, in the context of treatment of breast cancer, is known variously as hormonal therapy, hormone therapy, or anti-estrogen therapy (not to be confused with hormone replacement therapy). Certain foods such as soy may also suppress the proliferative effects of estrogen and are used as an alternative to hormone therapy. <sup>[30]</sup>

#### Prostate cancer

Under certain circumstances, estrogen may also be used in males for treatment of prostate cancer. [31]

#### Miscellaneous

In humans and mice, estrogen promotes wound healing. [32]

At one time, estrogen was used to induce growth attenuation in tall girls.<sup>[33]</sup> Recently, estrogen-induced growth attenuation was used as part of the controversial Ashley Treatment to keep a developmentally disabled girl from growing to adult size.<sup>[34]</sup>

Most recently, estrogen has been used in experimental research as a way to treat patients suffering from bulimia

nervosa, in addition to Cognitive Behavioral Therapy, which is the established standard for treatment in bulimia cases. The estrogen research hypothesizes that the disease may be linked to a hormonal imbalance in the brain. [35]

Estrogen has also been used in studies which indicate that it may be an effective drug for use in the treatment of traumatic liver injury. [36]

### Health risks and warning labels

Hyperestrogenemia (elevated levels of estrogen) may be a result of exogenous administration of estrogen or estrogen-like substances, or may be a result of physiologic conditions such as pregnancy. Any of these causes is linked with an increase in the risk of thrombosis.<sup>[37]</sup>

The estrogen-alone substudy of the WHI reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women 50 years of age or older and an increased risk of dementia in postmenopausal women 65 years of age or older using 0.625 mg of Premarin conjugated equine estrogens (CEE). The estrogen-plus-progestin substudy of the WHI reported an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and DVT in postmenopausal women 50 years of age or older and an increased risk of dementia in postmenopausal women 65 years of age or older using PremPro, which is 0.625 mg of CEE with 2.5 mg of the progestin medroxyprogesterone acetate (MPA). [38][39][40]

The labeling of estrogen-only products in the U.S. includes a boxed warning that unopposed estrogen (without progestagen) therapy increases the risk of endometrial cancer. Based on a review of data from the WHI, on January 8, 2003 the FDA changed the labeling of all estrogen and estrogen with progestin products for use by postmenopausal women to include a new boxed warning about cardiovascular and other risks.

## **Cosmetics**

Some hair shampoos on the market include estrogens and placental extracts; others contain phytoestrogens. There are case reports of young children developing breasts after exposure to these shampoos. [41] On September 9, 1993, the FDA determined that not all topically applied hormone-containing drug products for OTC human use are generally recognized as safe and effective and are misbranded. An accompanying proposed rule deals with cosmetics, concluding that any use of natural estrogens in a cosmetic product makes the product an unapproved new drug and that any cosmetic using the term "hormone" in the text of its labeling or in its ingredient statement makes an implied drug claim, subjecting such a product to regulatory action. [42]

In addition to being considered misbranded drugs, products claiming to contain placental extract may also be deemed to be misbranded cosmetics if the extract has been prepared from placentas from which the hormones and other biologically active substances have been removed and the extracted substance consists principally of protein. The FDA recommends that this substance be identified by a name other than "placental extract" and describing its composition more accurately because consumers associate the name "placental extract" with a therapeutic use of some biological activity. [42]

# **History**

In 1929 Adolf Butenandt and Edward Adelbert Doisy independently isolated and determined the structure of estrogen. [43] Thereafter, the market for hormonal drug research opened up.

The "first orally effective estrogen", Emmenin, derived from the late-pregnancy urine of Canadian women, was introduced in 1930 by Collip and Ayerst Laboratories. Estrogens are not water-soluble and cannot be given orally, but the urine was found to contain estriol glucuronide which is water soluble and becomes active in the body after hydrolization.

Scientists continued to search for new sources of estrogen because of concerns associated with the practicality of introducing the drug into the market. At the same time, a German pharmaceutical drug company, formulated a similar product as Emmenin that was introduced to German women to treat menopausal symptoms.

In 1938, British scientists obtained a patent on a newly formulated nonsteroidal estrogen, diethylstilbestrol (DES), that was cheaper and more powerful than the previously manufactured estrogens. Soon after, concerns over the side effects of DES were raised in scientific journals while the drug manufacturers came together to lobby for governmental approval of DES. It was only until 1941 when estrogen therapy was finally approved by the Food and Drug Administration (FDA) for the treatment of menopausal symptoms. [44]

### **Environmental effects**

Estrogens are among the wide range of endocrine-disrupting compounds (EDCs) because they have high estrogenic potency. When this specific EDC makes its way into the environment it may cause male reproductive dysfunction to wildlife. The estrogen excreted from farm animals makes its way into fresh water systems. During the germination period of reproduction the fish are exposed to low levels of estrogen which may cause reproductive dysfunction to male fish. [47][48]

### See also

- List of steroid abbreviations
- Diethylstilbestrol
- Atrophic vaginitis
- Endocrinology
- Equol
- Equilin

- Estradiol
- Estrogen receptor
- Progesterone
- Progestin
- Testosterone
- Endocrine disruptor

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### **External links**

- It's wise to be wary of the pill (http://www.theaustralian.news.com.au/story /0,,24891709-7583,00.html)
- MedlinePlus DrugInfo *medmaster-a682922 (http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682922.html)*
- Nussey and Whitehead: *Endocrinology, an integrated approach (http://www.ncbi.nlm.nih.gov/books /bv.fcgi?call=bv.View..ShowTOC&rid=endocrin.TOC&depth=10)*, Taylor and Francis 2001. Free online textbook.

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