

**Review Article***Copyright © All rights are reserved by Sinisa Franjic*

# Estrogens Act on Many Systems in the Body

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Estrogens are a group of steroidal chemical compounds that got their name because of their importance in mammalian estrus (menstrual cycle in women). Estrogens are female sex hormones. They are used as a contraceptive and replacement therapy in menopausal women. The largest amount of estrogen is produced in the developing ovarian follicle, corpus luteum and placenta. Follicle stimulating hormone and luteinizing hormone stimulate estrogen production in the ovaries. A certain amount of estrogen is also produced by the liver, adrenal glands and breast. These so-called secondary sources of estrogen are very important in menopausal women.

**Keywords:** Menstrual Physiology, FSH, Ovary, Uterine Changes, Osteoporosis, Female Sex Hormones, Steroidal, Estrogen, Estrone (E1), Estradiol (E2), Estriol (E3)

**Introduction**

Estrogen is a steroid hormone produced typically within the ovaries, breasts, and adipose tissue and in smaller portions within the skin, liver, brain, and intestines [1]. Estrogen has big outcomes within the female reproductive system. The 3 most important estrogen derivatives are Estrone (E1), Estradiol (E2), and Estriol (E3). Estrone is the primary form of estrogen after menopause, estradiol is the primary form of estrogen previous to menopause, and estriol is a byproduct of estrogen metabolism this is additionally produced with the aid of using the placenta all through being pregnant. Estrogen is synthesized from Low-Density Lipoprotein (LDL) cholesterol in reactions that require transportation of cholesterol throughout the cell membrane through a transport mechanism this is inspired with the aid of using LH (Luteinizing Hormone), ACTH (Adrenocorticotropic Hormone), cyclic Adenosine Monophosphate (AMP), and calcium. Cholesterol is transformed to pregnenolone and subsequently to progesterone, androgens, estrogens, and corticosteroids.

**Brain**

The brain regulates metabolism, growth, reproduction, emotions and different physiological and social features via now no longer most effective the nervous system through neurotransmitters however additionally the endocrine system [2]. Hormones (the chemical messengers launched from endocrine glands) can have an impact on behaviour, for example, sexual inclinations, life-style and parenting style. The brain has receptors for a variety of hormones, consisting of metabolic hormones (along with insulin and leptin), thyroid hormones, steroid hormones and others which are produced in reaction to stress, the circadian rhythm and emotional states. In reaction to incoming alerts, neurones within the mind set off the pituitary gland to secrete elements into the blood that increase or decrease hormone manufacturing with the aid of using the target endocrine gland. The neurones within the hypothalamus produces gonadotropin-releasing hormone which stimulates the pituitary gland to launch Follicle Stimulating Hormone (FSH) and

Luteinizing Hormone (LH) into the bloodstream. These act at the ovary to set off follicular development, production of oestrogen, ovulation, luteinization, and production of progesterone.

In males, they promote spermatogenesis and launch of testosterone. A comments loop transmits alerts lower back to the brain to hold hormone stages as required. Through such comments loops the mind acts as a manage centre for a variety of human behavioural responses to environmental and social challenges. These responses include eating, drinking, learning, coping with stress and formation of social bonds. Thus, for example, oestradiol affects intercourse motivation and behaviour, vasopressin impacts reminiscence and learning, testosterone mediates aggression and oxytocin controls social bonding. Maternal care-giving is inspired with the aid of using now no longer most effective social situations however additionally oxytocin and dopamine. Just as hormones should have an effect on behaviour, so should behaviour have an effect on hormone stages. For example, the anticipation of sexual intercourse has been proven to boom testosterone stages in women. Breastfeeding induces a surge of oxytocin. More common associate hugs bring about better oxytocin levels which in turn are related to decrease blood pressure and heart rate in premenopausal women.

## FSH

The characteristic of the ovaries and hormone secretion is regulated with the aid of using the hypothalamo-pituitary-ovarian axis [3]. The primary factor influencing the transition from regular menstruation to the perimenopause seems to be the quantity of ovarian follicles. While at birth there are about 700,000 follicles in a woman's ovaries, the numbers lessen markedly within the decade earlier than the menopause and, on the time of the last menstrual period, few follicles remain. Follicle Stimulating Hormone (FSH) concentrations regularly increase and serum inhibin concentrations reduce within the years main as much as the perimenopause. These at the moment are regarded as beneficial indices of the quantity and/or exceptional of follicles closing within the ovary. During the reproductive years oestradiol is the primary form of oestrogen produced however after the menopause oestrogen production does now no longer stop due to the fact some other oestrogen, oestrone, is produced.

This arises from 3 principal sources: the adrenal cortex, not directly from the body's fat cells which convert androstenedione to oestrone, and from the ovaries which maintain to supply small portions of androgens which can be transformed to oestrogens. Testosterone stages stay at about the same stage after the menopause, being produced with the aid of using the adrenal glands and with the aid of using conversion of different hormones. The average age of menopause is predicted to be 50-51 years in most western countries however tends to be in advance in a few developing countries and is related to poverty and nutrition. Current people who smoke experience their final menstruation on common years in advance than non-smokers and women who've a

hysterectomy tend to have an in advance menopause even if their ovaries are conserved. In the US Study of Women's Health Across the Nation (SWAN), ethnic variations in hormone stages have been discovered.

Some of this changed into defined with the aid of using smoking and frame mass index (BMI), however variations in FSH (highest in Hispanic and African American and lowest in Japanese women) and testosterone (highest in Hispanic and African American and lowest in Japanese women) have been obtrusive whilst confounding elements have been controlled. The Melbourne Women's Midlife Health Project in addition documented the organic and subjective adjustments skilled by women during the menopause transition. The main hormone changes were increases in FSH and reduces in oestradiol happening all through the menopause transition and early postmenopause, with most change years earlier than the final menstrual period. Oestradiol reached a solid decrease stage (under 20pmol/l) among and 5 years after the final menstrual period. Nevertheless, defining levels of menopause in clinical settings typically is predicated on age and menstrual standards in preference to measuring hormone stages.

## Ovary

The ovary, which incorporates the germ cells, is the main reproductive organ within the female [4]. It also functions as an endocrine organ, secreting estrogen and progesterone in reaction to gonadotropin and paracrine signaling. Ovaries exist as a couple of glands, about the scale of almonds, on both facet of the uterus. Within the stomach cavity, ovaries are discovered closest to the lateral wall of the pelvis, connected to the lower back part of the huge ligament of the uterus. This vicinity is referred to as the ovarian fossa and is surrounded with the aid of using the outside iliac vessels, the umbilical artery, and the ureter. The ovary accommodates numerous different layers and types of tissues. The innermost layer is the medulla, which homes the blood vessels crucial to assisting the ovary. To the out of doors of that is the ovarian cortex, that is made from follicles and stromal tissue. The outermost layer of the ovary includes a skinny layer of epithelial cells. Known because the germinal epithelium, this sediment produces hundreds of primordial follicles all through fetal growth. Underlying the germinal epithelium is a robust connective tissue layer referred to as the Tunica Albuginea (TA). Ovum manufacturing and oocyte maturation arise in the cortex of the ovary. As primordial follicles are recruited and broaden, they circulate toward the outer fringe of the ovary, in the end bursting via the floor all through ovulation.

## Menstrual Physiology

The arcuate nucleus placed within the medial basal hypothalamus secretes Gonadotropin Releasing Hormones (GnRH) in a pulsatile fashion [5]. GnRH stimulates gonadotrophs within the anterior pituitary to synthesize, store, and secrete Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). These

gonadotropins input the peripheral circulation and act at the ovary to stimulate each follicular improvement and ovarian hormone production, consisting of estrogen, progesterone, androgens, and inhibin. Inhibin blocks FSH synthesis and secretion. Development of mature follicle outcomes in a fast upward thrust in estrogen levels, performing definitely on the pituitary cogenerate a mid-cycle surge in LH launch and simultaneously stimulate the improvement of a thickened, proliferative endometrial lining. Following ovulation, LH stimulates luteinization of the follicular granulosa cell and surrounding theca cells to form the corpus luteum. The corpus luteum produces estrogen and progesterone. Progesterone adjusts the endometrium in a secretory pattern. If pregnancy does not occur, then progesterone and estrogen ceases, corpus lute regresses, and endometrial sloughing occurs. If pregnancy occurs, then Human Chorionic Gonadotropin (HCG) is secreted from syncytiotrophoblast and the corpus luteum is stored all through early pregnancy due to similarity withinside the structure of HCG in comparison to LH.

### Follicular Cells

During the maturation procedure of the ovarian follicles, the CT of the stroma, that is outside the basement membrane of the primary follicle, undergoes each morphological and purposeful differentiation to form concentric layers called thecae [6]. The internal layer is the theca interna, that is loose and vascular. Its cells have receptors for Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) and bring androgens as precursors of follicular estrogen. The blood vessels of the theca do now no longer pierce the basement membrane to attain the layer of follicular cells besides in the intervening time of ovulation and subsequent luteinization. The outer theca externa is much less visible, extra fibrous and dense, with dispersed smooth muscle cells, and it's miles regularly merged into the cortical stroma. Follicular cells are multiplied in reaction to the motion of FSH and Insulin-Like Growth Factor (IGF), giving upward thrust to the SMFs. A cohort of 4-6 follicles will increase their length and circulate closer to the medulla. Gradually the vacuolated spaces (Call-Exner bodies), wealthy in hyaluronic acid and containing the follicular fluid, start to seem the various follicular or granulosa cells of which there are types: secretory and dense cells. The fluid-stuffed areas boom in extent and coalesce to form the follicular antrum. The ZP of the oocyte is surrounded with the aid of using follicular cells referred to as the cumulus oophorus.

Some of those cumulus oophorus cells form cylindrical spikes which have the arrival of a radiating crown across the zona called the corona radiata. Normally, as serum stages of FSH decrease, one of the follicles from the cohort will substantially upregulate its FSH receptors and outstrip the growth of the rest of the cohort and turn out to be the dominant follicle and the alternative follicles becomes atretic. This dominant follicle will now no longer develop to extra than 10mm (containing a 120µm oocyte) till inspired by LH. At the

time of the LH surge, this dominant follicle will change into the TMF or Graafian follicle and the abovementioned systems will attain their best improvement. The LH surge will bring about vasodilation and congestion of the blood vessels of the theca interna. Moreover, growing LH can have 3 outcomes:

- I. a sharp rise in antral progesterone (P4)
- II. the end of meiosis I with the appearance of the metaphase II oocyte
- III. the rupture of the mature follicle (ovulation) with the release of the gamete ready to be fertilized. This rupture includes a hemorrhage that fills the antrum which has expelled the follicular fluid with the ovum.

### Menstrual Bleeding

The menstrual cycle includes 3 phases: menstrual (days of bleeding), proliferative (after bleeding till ovulation), and luteal (after ovulation till bleeding or pregnancy) [7]. The first day of menstrual bleeding is Day 1 of the menstrual cycle. The bleeding outcomes from sloughing of the endometrium (the liner of the uterus) this is resulting from declining stages of the hormones estrogen and progesterone withinside the bloodstream. These declining hormone stages additionally sign the pituitary to supply Follicle Stimulating Hormone (FSH), which stimulates a follicle withinside the floor of the ovary to deliver an ovum to maturity. The follicle additionally produces estrogen, which stimulates boom of the endometrium. Estrogen additionally stimulates the manufacturing of Luteinizing Hormone (LH) with the aid of using the pituitary. As the extent of estrogen withinside the blood rises, so does the extent of LH. Prior to ovulation, the extent of LH rises rapidly (the LH surge); without a LH surge, ovulation does now no longer arise. After ovulation, the follicle collapses to turn out to be the corpus luteum, which keeps to supply estrogen however additionally produces progesterone. The excessive stage of estrogen inhibits the production of FSH. Progesterone completes the procedure of constructing up the endometrium in preparation for a fertilized ovum. About ten days after ovulation, the corpus luteum starts to degenerate. In the absence of pregnancy, stages of progesterone and estrogen fall after the corpus luteum starts to degenerate, and the end result is menstrual bleeding.

### Status

After the exclusion of pregnancy, initial labs must include fasting glucose, Thyroid-Stimulating Hormone (TSH), and prolactin stages. In the absence of significant abnormalities in those values, a progestin challenge test should be performed to assess the patient's estrogen status [8]. FSH must be measured on ladies who do now no longer revel in withdrawal bleeding inside 2 weeks. An excessive FSH value (>30IU/L) is indicative of ovarian failure, while ordinary or low values suggest both a received uterine anomaly (Asherman syndrome) or hypothalamic-pituitary failure. Ovarian failure is showed with a low serum estradiol stage (<30>2.5) in ladies with

PCOS (Polycystic Ovarian Syndrome) even if FSH and LH values are inside ordinary limits. This prognosis may be showed with the aid of using size of serum testosterone and Dehydroepiandrosterone Sulfate (DHEA-S), which must be ordinary or simply mildly improved in PCOS. An expanded testosterone/DHEA-S ratio is suggestive of an adrenal source. This finding warrants further study with determination of 17-hydroxyprogesterone. This stage is improved in late-onset congenital adrenal hyperplasia and Cushing syndrome. Cushing syndrome can be excluded with a 24-hour urinary loose cortisol and dexamethasone suppression testing.

### Uterine Changes

An excess of estrogen outside the usual menstrual cycle may also result from plenty of reasons, consisting of anovulatory cycles, estrogenic drug remedy, weight problems, and polycystic ovary syndrome, and could bring about continual proliferative uterine changes [9]. With persevering with stimulation, expanded glandular hyperplasia occurs, a circumstance referred to as nonatypical endometrial hyperplasia, that is characterised with the aid of using abnormal regions of growing gland density for the duration of the uterus. These glands are regularly dilated and display a tubular ciliated shape just like the proliferative section of the menstrual cycle. Although a benign condition, long-term nonatypical endometrial hyperplasia may also broaden regions of ordinary hyperplasia (Endometrial Intraepithelial Neoplasia [EIN]), a precursor lesion to cancer. Continued presence of estrogens will bring about abnormal uterine bleeding, and a sudden lack of estrogen can result in extremely heavy menses. Benign polyps withinside the endometrium also are not unusual places. An endometrial polyp may also purpose uterine bleeding if the end will become infected or ulcerated.

### Uterine Bleeding

Normal uterine bleeding is the end result of cyclic, sequential stimulation of the endometrium with the aid of using estrogen and progesterone, and occurs after withdrawal of the hormonal effect [10]. This sample is mimicked pharmacologically with the aid of using OCs and a few HT (Hormone Therapy) regimens. Abnormal Uterine Bleeding (AUB) can end result from hormonal disturbances along with estrogen withdrawal (estrogen most effective HT, neglected pill) or unopposed estrogen with step forward bleeding (anovulatory cycles). Women on progesterone most effective medications (contraceptive pill, implant, and injections) may have peculiar bleeding styles because of progesterone withdrawal or step forward bleeding. Anovulatory cycles may be because of many etiologies consisting of PCOS (polycystic ovary syndrome), eating disorders, endocrinopathies (i.e., thyroid disease or prolactinoma), weight problems, or the suppression of ovulation from weight reduction or immoderate workout. Menstrual abnormalities in ladies with thyroid ailment arise in only under 25% of ladies with both hyperor hypothyroidism; the maximum not unusual places complaint in each groups is oligomenorrhea.

Anovulation is likewise visible on the extremes of a woman's reproductive existence. In reproductive age ladies, anovulatory bleeding and hormonal medication use are the most common causes of noncyclic bleeding. Risk elements for endometrial cancer include age (40 years), anovulatory cycles, weight problems, nulliparity, diabetes, and tamoxifen remedy. Endometrial cancer has been said in ladies more youthful than age 40 years; ladies with continual anovulation and weight problems who gift with AUB must be taken into consideration at danger. Medications along with antipsychotics, anticoagulants, SSRIs, corticosteroids, and tamoxifen were recognized to purpose AUB, as have sure natural dietary supplements (e.g., ginseng, ginkgo, soy). Renal, hepatic, adrenal, and thyroid disease and blood dyscrasias may also cause AUB. Other reasons for AUB include foreign objects, consisting of IUDs, trauma, and congenital (Müllerian) structural abnormalities. Coagulopathies, as soon as concept to be an extraordinary purpose of peculiar bleeding, were proven to be found in 13% of ladies with heavy uterine bleeding. Some reasons of AUB vary with age. The prevalence of structural lesions and endometrial cancer will increase with age. Pregnancy-associated reasons occur during the reproductive years. Anovulation can occur for the duration of the reproductive years.

### Osteoporosis

Osteoporosis, literally meaning "porous bones", is a generalized thinning and demineralization of the entire skeletal system [9]. It is the most common metabolic bone disease withinside the United States. Most instances are discovered in postmenopausal ladies, starting of their fifties, and a significant degree of osteoporosis is said to be present in approximately one-fourth of all ladies of their sixties. Osteoporosis develops every time bone resorption exceeds bone production. The prevalence is excessive in postmenopausal ladies due to the fact the lack of ovarian characteristic outcomes in estrogen deficiency. Estrogen inhibits bone resorption, and the lack of estrogen accelerates the rate, which ends up in slowly progressive thinning of the bones. Osteoporosis additionally develops in older men; however, it occurs at a much later age and is typically much less severe than in ladies. The osteoporotic bones are quite fragile and vulnerable to fracture. Fractures of vertebral our bodies are common, both from the strain of weight-bearing or after minor exertion. These fractures produce lower back pain and tenderness and are regularly characterised with the aid of using disintegrate of the anterior quantities of the vertebral our bodies (compression fractures).

Collapse of vertebral our bodies may also compress the spinal nerve roots passing via the intervertebral foramina, inflicting pain to radiate alongside the path of the compressed nerve. Bone loss may be retarded with the aid of using regular weight-bearing exercises that assist maintain bone density, with the aid of using a high-calcium diet and calcium dietary supplements if important to guarantee a good enough calcium consumption, and with the aid of

using a good enough consumption of vitamin D, that is required to sell calcium absorption from the intestine and incorporation into bone. Estrogens are now no longer recommended to retard bone loss in postmenopausal ladies due to the long-term risks related to estrogen use. Selective Estrogen Receptor Modulators (SERM), along with raloxifene, characteristic as estrogen-like drugs taken orally and inhibit bone resorption, like estrogens, however, do now no longer have the negative outcomes of estrogen at the breast and uterus. Calcitonin, a nasal spray containing a hormone produced with the aid of using thyroid cells, inhibits the osteoclasts that breakdown bone however can be related to an expanded danger of cancer. Parathyroid hormonelike drugs utilized in day-by-day injections increase bone density with the aid of using stimulating osteoblasts, however the quantity used isn't always sufficient to stimulate osteoclasts.

Significant loss of bone density additionally may also arise in lady's athletes who interact in prolonged, intense physical activity, along with runners and gymnasts. The excessive stage of physical activity triggers the hypothalamus and pituitary gland to increase adrenal corticosteroid output as an model to the exercise-induced stress. This event, however, is also related to a fall withinside the pituitary gonadotropic hormones that stimulate ovarian characteristic. The ovaries, now no longer safely inspired with the aid of using pituitary gonadotropins, fail to supply good enough estrogen, which ends up in cessation of menses, referred to as exercise-induced amenorrhea. In addition, the estrogen-deficient athlete is at risk of the identical form of estrogen-deficiency osteoporosis that develops in postmenopausal ladies and is issue to the identical osteoporosis-associated complications. Osteoporosis associated with exercise-induced amenorrhea may be avoided with the aid of using lowering the extent of bodily hobby sufficient to reestablish ordinary menstrual cycles. Alternatively, the athlete who elects to maintain the identical stage of workout can lessen her danger of osteoporosis with the aid of using taking supplementary estrogen and progesterone hormones to update the lacking ovarian hormones and with the aid of using taking calcium dietary supplements.

## Endocrine Therapy

The objective of endocrine therapy is to block or counter the effect of estrogen [11]. Estrogen performs a vital position withinside the pathogenesis of cancer, and treatment with estrogen deprivation has confirmed to be effective. Several distinct drug instructions are used to intrude or block estrogen receptors. They encompass Selective Estrogen Receptor Modulators (SERMs), estrogen receptor downregulators, aromatase inhibitors, luteinizing hormone releasing hormone, progestin, and biologic reaction modifiers. Current recommendations for most women with ER+breast cancer is to take a hormone-like medication-known as a SERM antiestrogenic agent-day by day for as much as five years after preliminary treatment. Certain regions withinside the female

body (breasts, uterus, ovaries, skin, vagina, and brain) incorporate specialised cells referred to as hormone receptors that permit estrogen to go into the cell and stimulate it to divide. SERMs input those identical receptors and act like keys, turning off the sign for growth withinside the cell.

Although it really works well in stopping similarly unfold of cancer, it's also related to an expanded prevalence of endometrial cancer, pulmonary embolus, deep vein thrombosis, hot flashes, vaginal discharge and bleeding, stroke, and cataract formation. A relatively new SERM is the anti-osteoporosis drug raloxifene (Evista), which has proven promising outcomes. It has anti-estrogen outcomes at the breast and uterus. In a latest study regarding extra than 20,000 postmenopausal ladies at excessive danger for breast cancer, raloxifene worked in addition to tamoxifen in preventing breast cancer, however with fewer critical negative outcomes. Both drugs reduce the cancer risk in half. It changed into initially advertised entirely for the prevention and treatment of osteoporosis however is now used as adjunctive breast cancer therapy. The side effects related to those endocrine treatments include hot flashes, bone pain, fatigue, nausea, cough, dyspnea, and headache. Women with hormone-sensitive cancers can stay for lengthy intervals with none intervention other than hormonal manipulation, however quality-of-life issues need to be addressed withinside the stability among treatment and side outcomes.

## Conclusion

Estrogens act on many systems in the body, and caution is needed when treating them due to possible side effects. External administration of estrogen increases the risk of developing breast or uterine endometrial tumors. Their effect on blood vessels and clotting factors is not negligible, which can lead to myocardial infarction, deep vein thrombosis or pulmonary embolism. Estrogens, along with other hormones, are used in menopausal women to prevent osteoporosis, as well as menopausal symptoms such as hot flashes, night sweats, insomnia, palpitations, headaches, anxiety, depression, fatigue, and fatigue.

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## Conflicts of Interest

The authors declare no conflict of interest.

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