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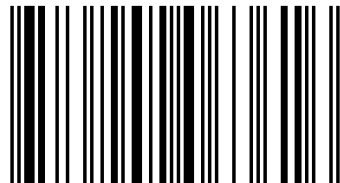
This book discussed on Estrogen hormone that are important for sexual are reproductive development, mainly in the women they are also referred to as female sex hormone. Also we discussed on it's importance, types and disturbance of estrogen levels. In this book you will find the symptoms of low estrogen, role of estrogen in fat metabolism, relationship between estrogen and cardiovascular diseases, cancer, infections and methods used to measure estrogen.



Mosab Nouraldein Mohammed Hamad; Head of Parasitology and Medical Entomology Department , Faculty of Health Sciences, Medical Laboratory Department; Member in International Society of Infectious Diseases; Member in African Society of Laboratory Medicine Editor in many academic journals.

# Estrogen a Wonderful Hormone

Mosab Nouraldein Mohammed Hamad  
Fania Abdallah Elbadri



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**Mosab Nouraldein Mohammed Hamad  
Fania Abdallah Elbadri**

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# **Estrogen a Wonderful Hormone**

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## **ESTROGEN A WONDERFUL HORMONE**

Mosab Nouraldein Mohammed Hamad

**Head of Parasitology and Medical Entomology Department, Medical Laboratory Sciences  
Department, Faculty of Health Sciences, Elsheikh Abdallah Elbadri University, Sudan**

Dr: Fania Abdallah Elbadri

**Dean of the Faculty of Health Sciences, Elsheikh Abdallah Elbadri University, Sudan**

**Corresponding author: Mosab Nouraldein (email: [musab.noor13@gmail.com](mailto:musab.noor13@gmail.com))**

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## **Dedication**

**To the founder of the university:**

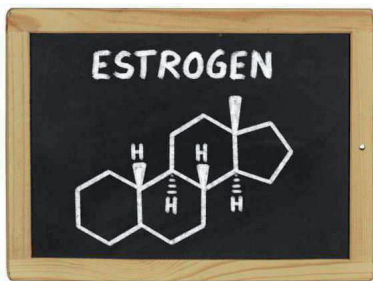
**Professor: Alsheikh Abdallah Elbadri**

## **Acknowledgement**

Many thanks to the administration of Alsheikh Abdallah Elbadri for their great effort exerted by them to promote the education systems and techniques in the university in order to graduate qualified personnel to the globe.

## Introduction

Estrogens are hormones that are important for sexual and reproductive development, mainly in women. They are also referred to as female sex hormones. The term "estrogen" refers to all of the chemically similar hormones in this group, which are estrone, estradiol (primary in women of reproductive age) and estriol.



In women, estrogen is produced mainly in the ovaries. Ovaries are grape-sized glands located by the uterus and are part of the endocrine system.

Estrogen is also produced by fat cells and the adrenal gland. At the onset of puberty, estrogen plays a role in the development of so-called female secondary sex characteristics, such as breasts, wider hips, pubic hair and armpit hair.

Estrogen also helps regulate the menstrual cycle, controlling the growth of the uterine lining during the first part of the cycle. If the woman's egg is not fertilized, estrogen levels decrease sharply and menstruation begins. If the egg is fertilized, estrogen works with progesterone, another hormone, to stop ovulation during pregnancy.

During pregnancy, the placenta produces estrogen, specifically the hormone estriol. Estrogen controls lactation and other changes in the breasts, including at adolescence and during pregnancy.

Estrogen is instrumental in bone formation, working with vitamin D, calcium and other hormones to effectively break down and rebuild bones according to the body's natural processes. As estrogen levels start to decline in middle age, the process of rebuilding bones slows, with postmenopausal women eventually breaking down more bone than they produce. This is why postmenopausal women are four times more likely to suffer from osteoporosis than men, according to the Cleveland Clinic.

Estrogen also plays a role in blood clotting, maintaining the strength and thickness of the vaginal wall and the urethral lining, vaginal lubrication and a host of other bodily functions.

It even affects skin, hair, mucous membranes and the pelvic muscles, according to Johns Hopkins Medicine. For example, estrogen can make the skin darker. Some researchers hope to use this information to create safe fake tanning lotions by activating the skin darkening reaction in estrogen, without triggering other changes in the body due to the hormone.

"If you expose melanocytes to estrogen, they respond by making more melanin, but they don't have the classic estrogen receptor," Dr. Todd Ridky, senior author of a 2016 study on estrogen and skin color and an assistant professor of dermatology at the University of Pennsylvania.

The hormone also affects the brain, and studies also show that chronically low estrogen levels are linked with a reduced mood, according to the National Library of Medicine.

Men produce estrogen as well, but at lower levels than women. Estrogen in males is secreted by the adrenal glands and by the testes. In men, estrogen is thought to affect sperm count. Overweight men are more commonly affected by low sperm count due to estrogen because there is more adipose tissue in the obese, which can set off the creation of excess estrogen, according to a 2010 paper published in the Asian Journal of Andrology. <sup>(1)</sup>

Estrogen is an important part of the female menstrual cycle and its secretion depends on two other menstrual hormones, luteinizing hormone and follicle stimulating hormone. When estrogen levels are low (at the beginning of the menstrual cycle), follicle stimulating hormone increases. This stimulates the ovaries into the development of a follicle, which will ultimately produce an egg. The follicle produces luteinizing hormone. The combination of these two hormones allows estrogen to be secreted. One function of estrogen, in terms of menstruation, is the thickening of the lining of the uterus. This helps prepare the uterus to support a fertilized egg if the woman becomes pregnant. If fertilization does not occur, estrogen levels fall, causing the uterine lining to slough off, resulting in menstruation. <sup>(2)</sup>

## **Functions of estrogen**

Estrogens are present in significant amounts in both men and women. They are present in significantly higher amounts in women after menarche (onset of menstrual periods at puberty) until menopause (cessation of menstrual periods after completion of reproductive age).

The primary function of estrogens is development of female secondary sexual characteristics. These includes breasts, endometrium, regulation of the menstrual cycle etc. In males estrogen helps in maturation of the sperm and maintenance of a healthy libido.

Physical functions:

Estrogen is responsible for development of the female body and the secondary sexual characters. It helps decelerate height increase in females during puberty, accelerates burning of body fat and reduces muscle bulk.

It also stimulates growth of the inner lining of the uterus (endometrium) during the menstrual cycle, increases uterine growth, improves lubrication of the vagina, and thickens the vaginal wall while increasing blood vessels to the skin.

Effects on various biochemical parameters:

Estrogens reduce bone resorption and increase bone formation.

They help in protein synthesis, increase hepatic production of binding proteins, coagulation proteins (factors II, VII, IX, X, plasminogen). Estrogens increase platelet adhesiveness and reduce antithrombin III.

Estrogens increase good cholesterol (HDL) and also increase triglycerides. They decrease LDL and promote fat deposition.

On fluids and electrolytes estrogens cause salt (sodium) and water retention. In the gastrointestinal tract they reduce bowel motility and increase cholesterol in bile. They also improve lung functions.

Effects on hormones:

Estrogens increase cortisol and Sex hormone binding globulin. Estrogens increase melanin and pheomelanin and reduce eumelanin.

Estrogens and cancer:

Estrogens help in the growth and maintenance of hormone-sensitive breast cancers.

Estrogen and libido:

Sexual desire is dependent on androgen levels rather than estrogen levels.

Estrogen and development of the fetus:

Estrogen helps in causing physical differentiation of the fetus to either males or females as per their genetic code. While androgens like testosterone lead to masculinizing the fetus, estrogen feminizes the fetus. Prenatal androgens act on behavior and other tissues, with the possible exception of effects on bone via androgen receptors.

Estrogen and mental health:

Estrogen is considered to play a significant role in women's mental health. Sudden decrease in blood levels of estrogen and periods of sustained estrogen low levels correlate with significant mood lowering.

After childbirth, nearing menopause and after menopause low levels of estrogen can predispose to depression.

Estrogen and skin:

For many years it has been recognized that estrogens are important in the maintenance of human skin. They improve collagen content and quality, increase skin thickness and improve blood supply to the skin. Estrogens act via estrogen receptors on human skin.

The number of estrogen receptors varies in different parts of the body. Highest receptor levels are seen on the facial skin and skin over thigh or breast.

Estrogen and heart disease:

Estrogen deficiency increases the risk of heart disease. Lack of estrogen is an impetus to atherosclerosis.

Estrogen in men:

Males also possess estrogen receptors and estrogen to some extent and levels in the male blood are higher than post-menopausal women. Estradiol has been found to be responsible for initiating spermatogenesis or formation and maturation of sperms in men. It helps in bone strength, sexual maturation and cholesterol metabolism. <sup>(3)</sup>

## **Types of estrogen:**

There are three major estrogens that are produced in women, which are estrone (E1), estradiol (E2), and estriol (E3). For women who are in their reproductive years, estradiol is the most active type of estrogen and has the highest levels. The predominant hormones change during pregnancy when estriol levels are higher and during menopause when estrone is the only estrogen that continues to be produced.

### **Estrone (E1):**

Estrone is found in increased amounts in postmenopausal women. Because of that and its connection to an increased risk of cancer it is not included as part of estrogen replacement therapy. Taking estradiol orally can lead to increased levels of estrone as it is metabolized by the liver. Increased levels of estrone in the body are avoided by the use of non-oral methods of estradiol delivery like creams and gels.

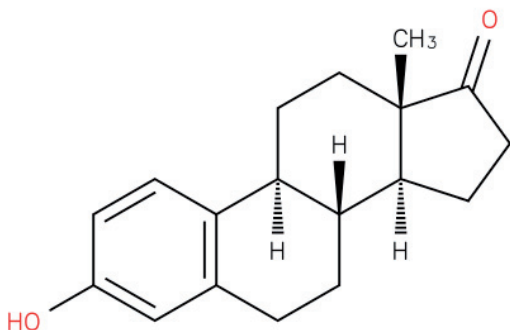
### **Estradiol (E2):**

The most commonly prescribed type of estrogen for HRT is estradiol. It is the most potent type of estrogen and the one that is predominant in women during their reproductive years. Replacing estradiol mimics the release of this essential female hormone from the ovaries. Estradiol has the potential to reduce multiple symptoms of menopause including hot flashes, night sweats, and vaginal symptoms. It has also been shown to reduce the risk of osteoporosis and coronary artery disease.

### **Estriol (E3):**

Estriol is sometimes considered a “weaker” estrogen but can be an effective part of HRT, especially when applied locally to treat vaginal symptoms of menopause. Although estriol has been used in Europe for over 60 years, it has failed to gain widespread use in the United States mostly due to the fact that it cannot be patented. <sup>(4)</sup>

## Estrone (E1):



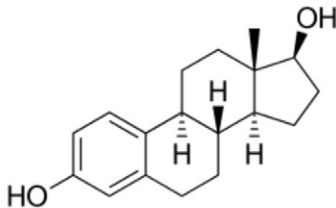
Estrone (E1), also spelled oestrone, is a steroid, a weak estrogen, and a minor female sex hormone. It is one of three major endogenous estrogens, the others being estradiol and estriol. Estrone, as well as the other estrogens, are synthesized from cholesterol and secreted mainly from the gonads, though they can also be formed from adrenal androgens in adipose tissue. Relative to estradiol, both estrone and estriol have far weaker activity as estrogens.<sup>(4)</sup>

Estrone, one of the major mammalian estrogens, is an aromatized C18 steroid with a 3-hydroxyl group and a 17-ketone. It is produced *in vivo* from androstenedione or from testosterone via estradiol. It is produced primarily in the ovaries, placenta, and in peripheral tissues (especially adipose tissue) through conversion of androstenedione. Estrone may be further metabolized to 16- $\alpha$ -hydroxyestrone, which may be reduced to estriol by estradiol dehydrogenase.

Estrone, a synthetically prepared or naturally occurring steroidal estrogen obtained from pregnant equine urine, is the primary circulating estrogen after menopause. Estrone is naturally derived from the peripheral conversion of androstenedione by an aromatase enzyme found in adipose tissues and is converted to estradiol in peripheral tissues. The estrogenic potency of estrone is one third that of estradiol. Estropipate is piperazine-stabilized estrone sulfate. Estrone, and estropipate are used to treat abnormalities related to gonadotropin hormone dysfunction, vasomotor symptoms, atrophic vaginitis, and vulvar atrophy associated with menopause, and for the prevention of osteoporosis due to estrogen deficiency.

Estrogens enter the cells of responsive tissues (e.g. female organs, breasts, hypothalamus, and pituitary) where they interact with estrogen receptors. Hormone-bound estrogen receptors dimerize, translocate to the nucleus of cells and bind to estrogen response elements (ERE) of genes. Binding to ERE alters the transcription rate of affected genes. Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) release from the anterior pituitary. <sup>(5)</sup>

**Estradiol (E2):**



Estradiol (E2), also spelled oestradiol, is a steroid, an estrogen, and the primary female sex hormone. It is named for and is important in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is essential for the development and maintenance of female reproductive tissues such as the breasts, uterus, and vagina during puberty, adulthood, and pregnancy, but it also has important effects in many other tissues, including bone, fat, skin, liver, and the brain. While estrogen levels in men are lower compared to those in women, estrogens have essential functions in men, as well. It is found in most vertebrates and crustaceans, insects, fish, and other animal species.

Estradiol is produced especially within the follicles of the female ovaries, but also in other endocrine (i.e., hormone-producing) and nonendocrine tissues (e.g., including fat, liver, adrenal, breast, and neural tissues). Estradiol is biosynthesized from cholesterol through a series of chemical intermediates. One principal pathway involves the generation of androstenedione, which is converted into estrone by aromatase and then by 17 $\beta$ -hydroxysteroid dehydrogenase into estradiol. Alternatively, androstenedione can be converted into testosterone, an androgen and the primary male sex hormone, which in turn can be aromatized into estradiol.

**Biological function:**

**Sexual development:**

The development of secondary sex characteristics in women is driven by estrogens, to be specific, estradiol. These changes are initiated at the time of puberty, most are enhanced during the reproductive years, and become less pronounced with declining estradiol support after

menopause. Thus, estradiol produces breast development, and is responsible for changes in the body shape, affecting bones, joints, and fat deposition.

In females, estradiol induces breast development, widening of the hips, a feminine fat distribution (with fat deposited particularly in the breasts, hips, thighs, and buttocks), and maturation of the vagina and vulva, whereas it mediates the pubertal growth spurt (indirectly via increased growth hormone secretion) and epiphyseal closure (thereby limiting final height) in both sexes.

### **Reproduction:**

#### **Female reproductive system:**

In the female, estradiol acts as a growth hormone for tissue of the reproductive organs, supporting the lining of the vagina, the cervical glands, the endometrium, and the lining of the fallopian tubes. It enhances growth of the myometrium. Estradiol appears necessary to maintain oocytes in the ovary. During the menstrual cycle, estradiol produced by the growing follicles triggers, via a positive feedback system, the hypothalamic-pituitary events that lead to the luteinizing hormone surge, inducing ovulation. In the luteal phase, estradiol, in conjunction with progesterone, prepares the endometrium for implantation. During pregnancy, estradiol increases due to placental production. The effect of estradiol, together with estrone and estriol, in pregnancy is less clear. They may promote uterine blood flow, myometrial growth, stimulate breast growth and at term, promote cervical softening and expression of myometrial oxytocin receptors.

In baboons, blocking of estrogen production leads to pregnancy loss, suggesting estradiol has a role in the maintenance of pregnancy. Research is investigating the role of estrogens in the process of initiation of labor. Actions of estradiol are required before the exposure of progesterone in the luteal phase.

#### **Male reproductive system:**

The effect of estradiol (and estrogens in general) upon male reproduction is complex. Estradiol is produced by action of aromatase mainly in the Leydig cells of the mammalian testis, but also by some germ cells and the Sertoli cells of immature mammals. It functions (in vitro) to prevent apoptosis of male sperm cells. While some studies in the early 1990s claimed a connection between globally declining sperm counts and estrogen exposure in the environment, later studies found no such connection, nor evidence of a general decline in sperm counts. Suppression of estradiol production in a subpopulation of subfertile men may improve the semen analysis.

Males with certain sex chromosome genetic conditions, such as Klinefelter's syndrome, will have a higher level of estradiol.

## **Skeletal system**

Estradiol has a profound effect on bone. Individuals without it (or other estrogens) will become tall and eunuchoid, as epiphyseal closure is delayed or may not take place. Bone structure is affected also, resulting in early osteopenia and osteoporosis. Also, women past menopause experience an accelerated loss of bone mass due to a relative estrogen deficiency.

## **Skin health**

The estrogen receptor, as well as the progesterone receptor, have been detected in the skin, including in keratinocytes and fibroblasts.

At menopause and thereafter, decreased levels of female sex hormones result in atrophy, thinning, and increased wrinkling of the skin and a reduction in skin elasticity, firmness, and strength.

These skin changes constitute an acceleration in skin aging and are the result of decreased collagen content, irregularities in the morphology of epidermal skin cells, decreased ground substance between skin fibers, and reduced capillaries and blood flow.

The skin also becomes drier during menopause, which is due to reduced skin hydration and surface lipids (sebum production). Along with chronological aging and photo aging, estrogen deficiency in menopause is one of the three main factors that predominantly influences skin aging.

## **Nervous system**

Estrogens can be produced in the brain from steroid precursors. As antioxidants, they have been found to have neuroprotective function.

The positive and negative feedback loops of the menstrual cycle involve ovarian estradiol as the link to the hypothalamic-pituitary system to regulate gonadotropins.

Estrogen is considered to play a significant role in women's mental health, with links suggested between the hormone level, mood and well-being. Sudden drops or fluctuations in, or long periods of sustained low levels of estrogen may be correlated with significant mood-lowering. Clinical recovery from depression postpartum, perimenopause, and postmenopause was shown to be effective after levels of estrogen were stabilized and/or restored.

Recently, the volumes of sexually dimorphic brain structures in transgender women were found to change and approximate typical female brain structures when exposed to estrogen concomitantly with androgen deprivation over a period of months, suggesting that estrogen and/or androgens have a significant part to play in sex differentiation of the brain, both prenatally and later in life.

There is also evidence the programming of adult male sexual behavior in many vertebrates is largely dependent on estradiol produced during prenatal life and early infancy. It is not yet known whether this process plays a significant role in human sexual behavior, although evidence from other mammals tends to indicate a connection.

Estradiol has been found to increase the secretion of oxytocin and to increase the expression of its receptor, the oxytocin receptor, in the brain. In women, a single dose of estradiol has been found to be sufficient to increase circulating oxytocin concentrations.

### **Gynecological cancers:**

Estradiol has been tied to the development and progression of cancers such as breast cancer, ovarian cancer and endometrial cancer. Estradiol affects target tissues mainly by interacting with two nuclear receptors called estrogen receptor  $\alpha$  (ER $\alpha$ ) and estrogen receptor  $\beta$  (ER $\beta$ ).

One of the functions of these estrogen receptors is the modulation of gene expression. Once estradiol binds to the ERs, the receptor complexes then bind to specific DNA sequences, possibly causing damage to the DNA and an increase in cell division and DNA replication. Eukaryotic cells respond to damaged DNA by stimulating or impairing G1, S, or G2 phases of the cell cycle to initiate DNA repair. As a result, cellular transformation and cancer cell proliferation occurs.

### **Other functions:**

Estradiol has complex effects on the liver. It affects the production of multiple proteins, including lipoproteins, binding proteins, and proteins responsible for blood clotting. In high amounts, estradiol can lead to cholestasis, for instance cholestasis of pregnancy.

Certain gynecological conditions are dependent on estrogen, such as endometriosis, leiomyomata uteri, and uterine bleeding.

Estrogen affects certain blood vessels. Improvement in arterial blood flow has been demonstrated in coronary arteries.

### **Biological activity:**

Estradiol acts primarily as an agonist of the estrogen receptor (ER), a nuclear steroid hormone receptor. There are two subtypes of the ER, ER $\alpha$  and ER $\beta$ , and estradiol potently binds to and activates both of these receptors. The result of ER activation is a modulation of gene transcription and expression in ER-expressing cells, which is the predominant mechanism by which estradiol mediates its biological effects in the body. Estradiol also acts as an agonist of membrane estrogen receptors (mERs), such as GPER (GPR30), a recently discovered non-nuclear receptor for estradiol, via which it can mediate a variety of rapid, non-genomic effects. Unlike the case of the ER, GPER appears to be selective for estradiol, and shows very low affinities for other endogenous estrogens, such as estrone and estril. Additional mERs besides GPER include ER-X, ERx, and Gq-mER.

ER $\alpha$ /ER $\beta$  are in inactive state trapped in multimolecular chaperone complexes organized around the heat shock protein 90 (HSP90), containing p23 protein, and immunophilin, and located in majority in cytoplasm and partially in nucleus. In the E2 classical pathway or estrogen classical pathway, estradiol enters the cytoplasm, where it interacts with ERs. Once bound E2, ERs dissociate from the molecular chaperone complexes and become competent to dimerize, migrate to nucleus, and to bind to specific DNA sequences (estrogen response element, ERE), allowing for gene transcription which can take place over hours and days.

Estradiol is reported to be approximately 12 times as potent as estrone and 80 times as potent as estriol in its estrogenic activity. As such, estradiol is the main estrogen in the body, although the roles of estrone and estriol as estrogens are said to not be negligible.

### **Biochemistry:**

#### **Biosynthesis:**

Estradiol, like other steroids, is derived from cholesterol. After side chain cleavage and using the  $\Delta^5$  or the  $\Delta^4$ - pathway,  $\Delta^4$ -androstenedione is the key intermediary. A portion of the  $\Delta^4$ -androstenedione is converted to testosterone, which in turn undergoes conversion to estradiol by aromatase. In an alternative pathway,  $\Delta^4$ -androstenedione is aromatized to estrone, which is subsequently converted to estradiol.

During the reproductive years, most estradiol in women is produced by the granulosa cells of the ovaries by the aromatization of  $\Delta^4$ -androstenedione (produced in the theca folliculi cells) to estrone, followed by conversion of estrone to estradiol by  $17\beta$ -hydroxysteroid dehydrogenase. Smaller amounts of estradiol are also produced by the adrenal cortex, and, in men, by the testes.

Estradiol is not produced in the gonads only, in particular, fat cells produce active precursors to estradiol, and will continue to do so even after menopause. Estradiol is also produced in the brain and in arterial walls.

The biosynthesis of estradiol-like compounds has been observed in leguminous plants, such as *Phaseolus vulgaris* and soybeans.

Where they are termed phytoestrogens. Thus, consumption may have oestrogenic effects. In light of this, consumption can be counterproductive to patients undergoing treatment for breast cancer, which usually includes depriving the cancer cells of estrogens.

#### **Distribution:**

In plasma, estradiol is largely bound to SHBG, and also to albumin. Only a fraction of 2.21% ( $\pm$  0.04%) is free and biologically active, the percentage remaining constant throughout the menstrual cycle.

#### **Metabolism:**

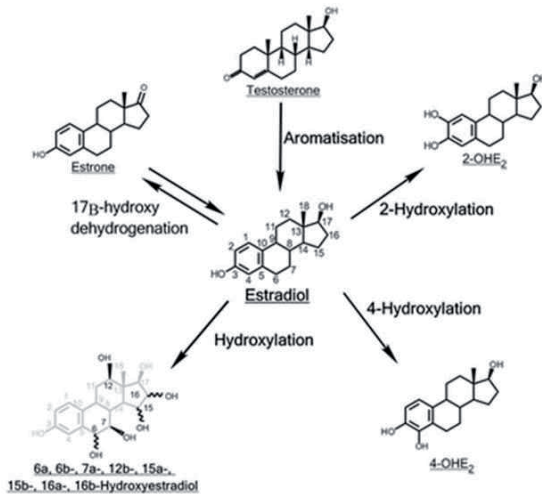
Inactivation of estradiol includes conversion to less-active estrogens, such as estrone and estriol. Estriol is the major urinary metabolite.

Estradiol is conjugated in the liver to form estrogen conjugates like estradiol sulfate, estradiol glucuronide and, as such, excreted via the kidneys. Some of the water-soluble conjugates are

excreted via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

Estradiol is also metabolized via hydroxylation into catechol estrogens. In the liver, it is non-specifically metabolized by CYP1A2, CYP3A4, and CYP2C9 via 2-hydroxylation into 2-hydroxyestradiol, and by CYP2C9, CYP2C19, and CYP2C8 via 17 $\beta$ -hydroxy dehydrogenation into estrone, with various other cytochrome P450 (CYP) enzymes and metabolic transformations also being involved.

Estradiol is additionally esterified into lipoidal estradiol forms like estradiol palmitate and estradiol stearate to a certain extent; these esters are stored in adipose tissue and may act as a very long-lasting reservoir of estradiol.



### Levels:

Levels of estradiol in premenopausal women are highly variable throughout the menstrual cycle and reference ranges widely vary from source to source.

Estradiol levels are minimal and according to most laboratories range from 20 to 80 pg/mL during the early to mid-follicular phase (or the first week of the menstrual cycle, also known as menses). Levels of estradiol gradually increase during this time and through the mid to late follicular phase (or the second week of the menstrual cycle) until the pre-ovulatory phase. At the time of pre-ovulation (a period of about 24 to 48 hours), estradiol levels briefly surge and reach their highest concentrations of any other time during the menstrual cycle.

Circulating levels are typically between 130 and 200 pg/mL at this time, but in some women may be as high as 300 to 400 pg/mL, and the upper limit of the reference range of some laboratories are even greater (for instance, 750 pg/mL).

Following ovulation (or mid-cycle) and during the latter half of the menstrual cycle or the luteal phase, estradiol levels plateau and fluctuate between around 100 and 150 pg/mL during the early and mid-luteal phase, and at the time of the late luteal phase, or a few days before menstruation, reach a low of around 40 pg/mL. The mean integrated levels of estradiol during a full menstrual cycle have variously been reported by different sources as 80, 120, and 150 pg/mL.

Although contradictory reports exist, one study found mean integrated estradiol levels of 150 pg/mL in younger women whereas mean integrated levels ranged from 50 to 120 pg/mL in older women.

During the reproductive years of the human female, levels of estradiol are somewhat higher than that of estrone, except during the early follicular phase of the menstrual cycle; thus, estradiol may be considered the predominant estrogen during human female reproductive years in terms of absolute serum levels and estrogenic activity.

During pregnancy, estriol becomes the predominant circulating estrogen, and this is the only time at which estetrol occurs in the body, while during menopause, estrone predominates (both based on serum levels).

The estradiol produced by male humans, from testosterone, is present at serum levels roughly comparable to those of postmenopausal women (14-55 versus <35 pg/mL, respectively). It has also been reported that if concentrations of estradiol in a 70-year-old man are compared to those of a 70-year-old woman, levels are approximately 2- to 4-fold higher in the man.

### **Estriol (E3)**

Estriol (E3), also spelled oestriol, is a steroid, a weak estrogen, and a minor female sex hormone. It is one of three major endogenous estrogens, the others being estradiol and estrone. Levels of estriol in women who are not pregnant are almost undetectable.

However, during pregnancy, estriol is synthesized in very high quantities by the placenta and is the most produced estrogen in the body by far, although circulating levels of estriol are similar to those of other estrogens due to a relatively high rate of metabolism and excretion. Relative to estradiol, both estriol and estrone have far weaker activity as estrogens. Although it is less

commonly used than other estrogens, estriol is available for medical use throughout the world in a variety of formulations, including for oral and vaginal administration.

Estriol is an estrogen, specifically an agonist of the estrogen receptors ER $\alpha$  and ER $\beta$ . It is a far less potent estrogen than is estradiol, and as such is a relatively weak estrogen. According to one in vitro study, the relative binding affinity (RBA) of estriol for the human ER $\alpha$  and ER $\beta$  was 11.3% and 17.6% of that estradiol, respectively, and the relative Trans -activational capacity of estrone at the ER $\alpha$  and ER $\beta$  was 10.6% and 16.6% of that of estradiol, respectively. According to another in vitro study however, the RBA of estriol for the ER $\alpha$  and ER $\beta$  were 14% and 21% of those of estradiol, respectively, suggesting that unlike estradiol and estrone, estriol may have preferential affinity for ER $\beta$ .

Although estriol is an efficacious agonist of the ERs, it is reported to have mixed agonist–antagonist (partial agonist) activity at the ER; on its own, it is weakly estrogenic, but in the presence estradiol, it is antiestrogenic. Relative to estradiol, the estrogenic potency of estriol and estrone have been reported to be 80- and 12-fold lower than that of estradiol, respectively.

It is notable that unlike estriol, estrone can be metabolized into estradiol, and most of its potency in vivo is in fact actually due to conversion into estradiol.

In addition to acting as an agonist of the nuclear ERs, estriol also acts as an antagonist of the GPER at high concentrations, a membrane estrogen receptor where, conversely, estradiol acts as an agonist. Estradiol increases breast cancer cell growth via activation of the GPER (in addition to the ER), and estriol has been found to inhibit estradiol-induced proliferation of triple-negative breast cancer cells through blockade of the GPER.

## **Biochemistry**

### **Biosynthesis:**

In women who are not pregnant estriol is produced in only very small quantities, and circulating levels are in fact barely detectable. Unlike estradiol and estrone, estriol is not synthesized in or secreted from the ovaries, and is instead derived mainly if not exclusively from 16 $\alpha$ -hydroxylation of estradiol and estrone by cytochrome P450 enzymes (e.g., CYP3A4) mainly in the liver. Estriol is cleared from the circulation rapidly in non-pregnant women, and so circulating levels are very low, but concentrations of estriol in the urine are relatively high.

Although circulating levels of estriol are very low outside of pregnancy, parous women have been found to have levels of estriol that are to some degree higher than those of nulliparous women.

### **In pregnant women:**

Estriol is produced in quantities that are notable only during pregnancy. Levels of estriol increase 1,000-fold during pregnancy, whereas levels of estradiol and estrone increase 100-fold, and estriol accounts for 90% of the estrogens in the urine of pregnant women. At term, the daily

production of estriol by the placenta is 35 to 45 mg and levels in the maternal circulation are 8 to 13 ng/dL.

The placenta produces Pregnenolone and progesterone from circulating cholesterol. Pregnenolone is taken up by the fetal adrenal glands and converted into dehydroepiandrosterone (DHEA), which is then sulfated by steroid sulfotransferase into dehydroepiandrosterone sulfate (DHEA-S).[citation needed] DHEA-S is hydroxylated by high CYP3A7 expression and activity into 16 $\alpha$ -hydroxy-DHEA-S (16 $\alpha$ -OH-DHEA-S) in the fetal liver and to a limited extent in the fetal adrenal glands. 16 $\alpha$ -OH-DHEA-S is then taken up by the placenta. Due to high expression of steroid sulfatase in the placenta, 16 $\alpha$ -OH-DHEA-S is rapidly cleaved into 16 $\alpha$ -OH-DHEA. Then, 16 $\alpha$ -OH-DHEA is converted by 3 $\beta$ -hydroxysteroid dehydrogenase type I (3 $\beta$ -HSD1) into 16 $\alpha$ -hydroxyandrostenedione (16 $\alpha$ -OH-A4) and 16 $\alpha$ -OH-A4 is converted by aromatase into 16 $\alpha$ -hydroxyestrone (16 $\alpha$ -OH-E1), which is subsequently converted into estriol by 17 $\beta$ -hydroxysteroid dehydrogenase and then secreted predominantly into the maternal circulation. Approximately 90% of precursors in estriol formation originate from the fetus.

During pregnancy, 90 to 95% of estriol in the maternal circulation is conjugated in the form of estriol glucuronide and estriol sulfate, and levels of unconjugated estriol are slightly less than those of unconjugated estradiol and similar to those of unconjugated estrone. As such, target tissues are likely to be exposed to similar amounts of free estriol, estradiol, and estrone during pregnancy.

Estrone and estradiol are also produced in the placenta during pregnancy. However, in the case of estrone and estradiol, DHEA-S is taken up by the placenta and cleaved by steroid sulfatase into dehydroepiandrosterone (DHEA), DHEA is converted by 3 $\beta$ -hydroxysteroid dehydrogenase type I into androstenedione, and androstenedione is aromatized into estrone. Then, placental 17 $\beta$ -hydroxysteroid dehydrogenase interconverts estrone and estradiol and the two hormones are secreted into the maternal circulation. DHEA-S that is taken up by the placenta is mainly produced by the fetal adrenal glands.

#### **Distribution:**

Estriol is poorly bound to sex hormone-binding globulin (SHBG), with much lower binding affinity for this protein, relative to estradiol, and hence a greater fraction available for biological activity.

#### **Metabolism and excretion:**

The main urinary metabolites of exogenous estriol administered via intravenous injection in baboons have been found to be estriol 16 $\alpha$ -glucuronide (65.8%), estriol 3-glucuronide (14.2%), estriol 3-sulfate (13.4%), and estriol 3-sulfate 16 $\alpha$ -glucuronide (5.1%). The metabolism and excretion of estriol in these animals closely resembled that which has been observed in humans.

#### **Chemistry:**

Estriol, also known as 16 $\alpha$ -hydroxyestradiol or as estra-1,3,5(10)-triene-3,16 $\alpha$ ,17 $\beta$ -triol, is a naturally occurring estrane steroid with double bonds between the C1 and C2, C3 and C4, and

C5 and C10 positions and hydroxyl groups at the C3, C16 $\alpha$ , and C17 $\beta$  positions. The name estriol and the abbreviation E3 were derived from the chemical terms estrin (estra-1, 3, 5(10)-triene) and triol (three hydroxyl groups).

**History:**

Estriol was discovered in 1930. It was isolated and purified from the urine of pregnant women by Marrian and colleagues. <sup>(7)</sup>

## Causes of low estrogen

Estrogen is the sex hormone that gives females their sexual traits such as wider hips, larger breasts, and additional body fat. Men have a small amount of estrogen, but it's considerably higher in females. When estrogen levels drop in a woman, it can cause discomfort. It helps to understand the reasons for low estrogen, recognize the common symptoms and know your treatment options.

### Types of Common Causes:

- Natural causes—the main natural cause of low estrogen is menopause. Premenopausal women can also suffer from it.
- Induced causes—these are those such as hysterectomies and radiation treatments
- Special causes—sometimes, low estrogen is the result of special conditions such as anorexia, genetic diseases, thyroid problems and inadequate body fat.<sup>(8)</sup>

Estrogen is the primary hormone produced in the ovaries. The ovaries begin their production of estrogen in response to chemical stimulation from the area of the brain known as the pituitary gland. Low levels of estrogen in young women can occur when there is an issue with the ovaries' ability to produce estrogen and whether or not the signaling pathway from the brain to the ovaries is working properly. Low estrogen levels can affect physical characteristics, behaviors and fertility potential.

### Excessive Exercise

A medical syndrome that commonly affects young women is the combination of occurrences known as the female athlete triad. The female athlete triad consists of disordered eating, bone loss and issues with menstruation. The excessive exercise and disordered eating that initiates the downward spiraling event results in low estrogen levels, according to a 2000 "American Family Physician" journal article. The competition to be the best, to fit into weight classifications and look a certain way leads to this athletic disease. The 2000 article notes that certain sports increase a young woman's risk of developing the triad, because of their restrictive and idealistic imagery. These sports include gymnastics, figure skating, and ballet, distance running, diving and swimming.

### Fat and Calorie Restriction

Estrogens are hormones. Cholesterol, a type of fat in the diet forms the backbone structure of all hormones in the body. Severely limiting fat in the diet, especially during the years of menarche, or onset of menses, can have devastating effects on estrogen production and the onset of a period, according to Aetna Intel health disease database. When body fat is below 22 percent or has not reached the level that will trigger the hypothalamus and pituitary to start speaking to the ovaries, the ovaries will not start, or will abruptly stop their production of estrogen. Low levels of circulating estrogen will halt the normal menstrual cycle in actively cycling women and may prevent the onset of the first menstrual bleed in younger, preteen or teenage women.

## **Genetics and Toxins**

A woman can have genetic reasons why her ovaries make insufficient levels of estrogen. A genetic condition known as Turner syndrome, which prevents the ovaries from developing normally, can lead to low levels of estrogen that will lead to a delay of menstruation. In this genetic condition, altered genes determine internal and external sexual characteristics. <sup>(9)</sup>

## **Symptoms of low estrogen**

Estrogen is a hormone. Although present in the body in small amounts, hormones have big roles in maintaining your health.

Estrogen is commonly associated with the female body. Men also produce estrogen, but women produce it in higher levels.

The hormone estrogen:

- is responsible for the sexual development of girls when they reach puberty
- controls the growth of the uterine lining during the menstrual cycle and at the beginning of a pregnancy
- causes breast changes in teenagers and women who are pregnant
- is involved in bone and cholesterol metabolism
- regulates food intake, body weight, glucose metabolism, and insulin sensitivity.

### **Symptoms of low estrogen**

Girls who haven't reached puberty and women approaching menopause are most likely to experience low estrogen. Still, women of all ages can develop low estrogen.

#### **Common symptoms of low estrogen include:**

- painful sex due to a lack of vaginal lubrication
- an increase in urinary tract infections (UTIs) due to a thinning of the urethra
- irregular or absent periods
- mood swings
- hot flashes
- breast tenderness
- headaches or accentuation of pre-existing migraines
- depression
- trouble concentrating
- fatigue

You may also find that your bones fracture or break more easily. This may be due to a decrease in bone density. Estrogen works in conjunction with calcium, vitamin D, and other minerals to keep bones strong. If your estrogen levels are low, you may experience decreased bone density.

If left untreated, low estrogen can lead to infertility in women. <sup>(10)</sup>

Signs and symptoms of low estrogen can vary from woman to woman and may depend on how low the estrogen level goes.

Some of the signs and symptoms that you may be suffering from low estrogen include sleep disturbances that can lead to extreme daytime fatigue, inability to focus on tasks, and a sense that you just "don't feel right". These sleep disturbances may result from a combination of heart palpitations, hot flashes, night sweats, and cold chills. You may notice that you are gaining weight -- particularly water weight -- while your eyes, skin and vagina are becoming dryer. You may begin to develop joint pain and headaches. You may be more prone to broken bones as the calcium is pulled out of your bones and your bones become more brittle. Your sex drive may lower as your estrogen level drops. You may begin to develop more vaginal and bladder infections. Any combination of these signs and symptoms of low estrogen can lead to severe depression.

The causes of low estrogen can be as variable as the signs and symptoms. In older women who are approaching menopause, decreasing estrogen levels are common and ultimately result in the cessation of menses. In younger women, low estrogen can result from several physical or behavioral problems including:

Decreased functioning of the ovaries;

Cysts on and in the ovaries;

Pregnancy problems that lead to miscarriage;

Childbirth and breast-feeding;

Decreased functioning of the pituitary gland;

Eating disorders and dieting resulting in low body fat;

Certain fertility drugs;

Excessive exercise resulting in low body fat. <sup>(11)</sup>

## **Estrogen and fat metabolism**

The good news is that you still have more estrogen than a man, and that can work in your favor. In a 1990 study by Tamopolsky, et.al. Of equally matched male and female athletes, females were found to derive more fuel from fat during exercise while sparing muscle glycogen, as compared to their male counterparts. Researchers concluded that higher estrogen levels in the women promoted greater recruitment of fat for fuel. So while estrogen depletion may promote fat storage, exercise at moderate to high intensity may balance things out by burning fatter. What's more, exercise builds metabolism-boosting muscle so you burn more calories throughout the day.

### **Influence of Nutrition on Estrogen and Fat Stores**

Because the menopausal brain is predisposed to fat storage, nutrition plays an important role in circumventing the process. Processed foods, chemicals and pesticides, hormone-laden animal products and plastic derivatives from packaged foods and bottled water can all promote fat storage. On the other hand, certain plant compounds called flavonoids and indoles serve to modulate estrogen production and fat storage. Onions, garlic and cruciferous vegetables like cabbage, broccoli and cauliflower are high in estrogen-inhibiting compounds. So green tea, dark chocolate, bee products, citrus fruits and omega-3 fatty acids found in flaxseed and salmon.

### **Hormone Replacement Therapy and Weight Gain**

Menopausal women who undergo hormone replacement therapy, or HRT, tend to gain less weight overall than women who do not. One explanation is that, because estrogen levels are kept elevated during HRT, the body does not feel the need to store extra fat as an estrogen reserve. The down side is that hormone replacement therapy has been linked to a higher risk of breast cancer, although only in certain populations of women. What's more, women on HRT tend to distribute more fat on their hips and thighs.

### **Natural Alternatives to HRT**

If you don't want to undergo the risks of hormone replacement therapy, the alternative is to make lifestyle changes that will minimize unwanted fatty weight and promote lean muscle. Nutritionally, this means avoiding processed foods, saturated fats and chemical-laden fruits, vegetables and animal products. A consistent diet of whole, natural organic food will help modulate weight gain, especially when accompanied by regular participation in vigorous exercise that builds muscle and burns fat. <sup>(12)</sup>

## **Estrogen and cardiovascular diseases**

Scientists are still learning about the actions of estrogen in the body. Studies have shown that estrogen affects almost every tissue or organ system, including the heart and blood vessels. Estrogen's known effects on the cardiovascular system include a mix of positive and negative:

- Increases HDL cholesterol (the good kind)
- Decreases LDL cholesterol (the bad kind)
- Promotes blood clot formation, and also causes some changes that have the opposite effect.
- Relaxes, smooth's and dilates blood vessels so blood flow increases
- Soaks up free radicals, naturally occurring particles in the blood that can damage the arteries and Estrogen probably affects the cardiovascular system in other ways that are as yet undiscovered. New research continues to give scientists and physicians more information – and raise more questions about this important and controversial hormone.

Over the years, evidence was accumulating that suggested estrogen also helped protect women against heart disease. With heart disease is the number one killer among women over age 65, this is an important issue. Women develop heart disease 10 years later than men, but by age 65, their risk is equal to that of men.

The accepted thinking was that the drop in estrogen levels associated with menopause accounted for this jump in heart disease risk in women. When estrogen levels decline, levels of LDL cholesterol (the harmful kind) increase, and levels of HDL cholesterol (the positive kind) decrease, leading to the buildup of fat and cholesterol in the arteries that contributes to heart attack and stroke. It made sense that replacing estrogen through HRT would potentially improve heart health. This thinking contributed to a huge rise in the number of women being prescribed estrogen.

### **Rethinking old ideas**

Recent studies on the long-term use of HRT are changing that way of thinking. With scientific data potentially linking HRT to higher risks of heart attack, stroke and other serious health problems, many women are reconsidering HRT.

The buzz about estrogen started in the late 1990s when a report from the Heart and Estrogen-Progestin Replacement Study (HERS) was published in the Journal of the American Medical Association (JAMA). This study of more than 2,700 women with existing coronary heart disease was designed to test whether estrogen plus progestin would prevent a second heart attack.

During the first year of HRT, women in the study had a 50 percent increase in heart attack and stroke. But, after two years of treatment, women on HRT actually had less heart disease and fewer heart attacks and strokes compared with women not taking HRT.

The study left many unanswered questions, leading researchers to take another look at these same women. They published their results in 2002. This time around, after nearly three more years of follow up, the researchers concluded that there was no lasting decrease in heart disease or heart attack/stroke risk from HRT, and HRT increased the risk of blood clots.

### **Evidence adding up**

Meanwhile, an even larger study, the Women's Health Initiative (WHI), was raising more questions about the potential risks associated with HRT. Involving more than 160,000 women, WHI is the world's largest clinical trial of health interventions for midlife women, studying the effects HRT, diet changes and calcium and vitamin D supplements on heart disease, osteoporotic fractures and breast and colorectal cancer risk.

In 2002, scientists at the National Institutes of Health (NIH) National Heart, Lung and Blood Institute halted the arm of the WHI study in which women were taking combination estrogen and progestin. Early data from this group of women showed that HRT significantly increased the risk of breast cancer, heart attack, stroke and blood clots in the legs and lungs.

Then, in 2004, the NIH stopped the estrogen-only study arm, in which women who had undergone hysterectomy were taking estrogen. Data showed that estrogen increased their risk of blood clots and stroke and did not reduce the risk of heart attack. (Estrogen's effect on breast cancer risk was unclear.)

### **A change in recommendations**

These studies were the first large-scale trials that looked for cause and effect with heart disease and HRT. HRT does offer some benefits, such as preventing osteoporosis and reducing the risk of colon cancer. But the data on heart-related risks from these studies were very compelling. As a result, the American Heart Association and the U.S. Food and Drug Administration developed new guidelines for the use of HRT:

1. HRT should not be used for prevention of heart attack or stroke.
2. Use of HRT for other problems such as preventing osteoporosis should be carefully considered and the risks weighed against the benefits. Women who have existing coronary artery disease should consider other options.
3. HRT may be used short-term to treat menopausal symptoms.
4. Long-term use is discouraged because the risk for heart attack, stroke and breast cancer increases the longer HRT is used.<sup>(13)</sup>

## **The Connection between Low Estrogen and Low Vitamin D**

Vitamin D is a fat soluble vitamin that the human body uses for bone mineralization, cell growth and immune function. Vitamin D also reduces inflammation. The compound can be found in some foods and is available as a supplement. Sunlight contains the vitamin and humans can absorb it from simple exposure to the sun. Once ingested, Vitamin D goes through various transformations before the body can use it. These processes take place in the liver and kidney. Deficiencies in vitamin D are associated with various disorders such as rickets in children and osteoporosis in older adults. Additionally, much research has looked at vitamin D and hormones, specifically estrogen.

### **Vitamin D and Hormones**

Vitamin D is studied in both human and nonhuman primates to better understand the connection between the substance and hormones. In a review published in the journal "Steroids" by researchers at the University of California in Los Angeles, scientists discuss how deficiencies in vitamin D can be related to protein binding sites at the cellular level. Through complex scientific analysis, the paper reveals that there are specific proteins determined by DNA that control the ability of the body to use and process vitamin D and estrogen. This suggests that vitamin D resistant individuals may also be at risk for low levels of estrogen.

### **Vitamin D, Estrogen and Cancer**

Prostate cancer is one of the leading causes of death among men. The disease has underlying imbalances of certain hormones such as estrogen. In 2011 researchers in Hungary looked specifically at the role of proteins responsible for assisting in the body's use of vitamin D, estrogen and calcium in patients with prostate cancer. Their study, which was published in the "Canadian Journal of Urology," showed that individuals with genetically damaged protein binding receptors for estrogen and vitamin D were more likely to develop prostate cancer.

### **Breast Cancer and Vitamin D**

In 2011 researchers at the Roswell Park Cancer Institute in New York published the results of a five-year-long study they conducted looking at levels of vitamin D and estrogen in women with breast cancer in the pretreatment stages. They found that women who had not yet started menopause had significantly low levels of vitamin D, as well as a relationship with malfunctioning estrogen receptors. Their study suggests that there is a strong correlation between vitamin D deficiency, negative estrogen receptors and breast cancer. They note that further research may lead to vitamin D supplements are part of a pretreatment regimen.

### **Genetics and the Vitamin D-Estrogen Connection**

Research, mainly in the areas of cancer treatment and prevention, has looked closely at the relationship between vitamin D and estrogen. It appears that the majority of work supports the idea that genetically determined receptor sites for estrogen and vitamin D work together to make sure that the body is able to ingest and process the minerals and hormones that it needs for maximum health. So while research has established a link between these two compounds, more work will be needed to show the extent and implications of this relationship.<sup>(14)</sup>

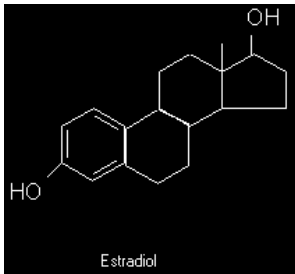
## **Estrogen and electrolytes**

Body fluid volume and electrolyte concentration are maintained at optimal levels by complex behavioral and physiological mechanisms that are integrated and coordinated by the central nervous system. From initial studies of estrogen effects on salt and water intake in the 1970s and later investigations of the role of estrogen in cardiovascular and neuroendocrine function, it has become increasingly clear that body fluid volume and osmotic regulation are affected by estrogen. In the early 1990s, estrogen receptors were identified throughout the central nervous system, in areas including circumventricular organs that detect humoral signals associated with body fluid challenges, and hypothalamic and hindbrain nuclei involved in behavioral, neuroendocrine, and cardiovascular responses to body fluid challenges. Taken together, the body of evidence amassed from more than 40 years of investigations suggests that the central actions of estrogen influence body fluid regulation and, more specifically, compensatory responses to perturbations of osmotic or volume balance in two interrelated ways. Estrogen alter the detection of signals by the central nervous system and, at the same time, act within central pathways to modify neurotransmitter systems that mediate specific responses to osmotic or volume challenges.<sup>(15)</sup>

Estrogen is the second factor people often consider. Especially steroid and prohormone users are often plagued with a serious misunderstanding of estrogen and its effects on adiposity. Most are convinced that estrogen increases fat gain or retards fat loss, when in effect the opposite is true. Estrogens, and especially estradiol (E2), is probably a more effective fat loss aid than is testosterone. Although like testosterone, it may have certain anti-lipolytic effects by increasing  $\alpha 2$  adrenoreceptors in specific female patterning (harder to lose fat in thighs and butt).

First of all, estradiol also reduces LPL, just like testosterone does, so uptake of fatty acids in adipocytes is reduced. Apart from that, its effects can be divided in three categories. Its effect on insulin-related events, its effects on Growth Hormone and its effects on reducing appetite.

Estradiol can cause a reduction in weight, with only a minimal effect in insulin itself, but that does not mean it does not alter the body's reaction to insulin. Estradiol lowers insulin receptor number, and in very high doses even actual insulin sensitivity. It does so in various ways, not in the least by reducing GLUT4 recruitment and translocation in adipocytes, which results in less glucose uptake in fat cells.



This will result in a negative energy balance and a greater activation of lipolysis, right where we want it, in the fat tissue. The effect of estradiol on insulin is quite acute, and clearly evident in the fact that short-term modulation drastically reduces glucose appearance (release) and disappearance (uptake), suggesting a dysfunctional glucose transport system.

The second way in which estradiol may increase fat loss, is its effect on growth hormone. Unlike testosterone, which stimulates the GH/IGF-1 axis, the effect of estrogen may actually be in reducing systemic (liver-derived) IGF-1, which lowers inhibition of Growth Hormone.

In doing so it obviously reduces the anabolic capacity of the body (which is why we don't use estrogen to build muscle) but increases the fat burning capacity since whole-body IGF-1 is reduced, leading to a reduction in adipogenic markers (since IGF-1 and insulin activate the same cascades) and a concurrent increase in Growth Hormone, leading to further decreases in LPL and up regulation of beta-adrenoreceptors. Estradiol may even reduce IGF-1, while increasing IGFBP-3.

This may in effect be the reason why estradiol does not promote growth, since unbound IGFBP-3, which is under normal circumstances the main carrier of IGF-1 in circulation, has been attributed characteristics that inhibit growth. It acts as a pro-apoptotic agent to activate cysteine proteases, much in the same manner that cortisol or TNF alpha would.

This implies that as long as we are seeing an increase in estradiol accompanied by an equal or larger increase in testosterone, we are reaping positive effects, on both fat loss and muscle retention since testosterone increases IGF-1, while estradiol prolongs the half-life and effect of the hormone by increasing IGFBP-3 and IGF1-receptor density. Without the testosterone increase, it may however increase muscle loss (and potentially increase fat loss further by enhancing apoptosis of fat cells?).

A third way in which estradiol helps as a fat loss agent is by reducing appetite. It reduces sensations of hunger via modulation of melanin-concentrating hormone. We have discussed the role of orexigenic (hunger inducing) peptides once or twice previously, specifically NPY.

Obviously NPY isn't the only peptide involved. For instance Agouti-related peptide is also involved, as is melanin-concentrating hormone (MCH). When energy intake is restricted, MCH levels sky-rocket, leading to an increased sense of hunger. Estradiol was able to completely abolish this increase in MCH, making it a very potent appetite suppressor during low-calorie diets.

Lastly, estradiol increases both the release of arachidonic acid and the actions of cyclooxygenase in certain cell types. This results in a quick and effective increase in several prostaglandins, including PGF2 and PGI2 which are related to lower body-fat levels. Because these effects can be highly varying in different cell types it should not automatically be assumed that these events do occur, or that they necessarily contribute to fat loss however.

Estradiol can also prevent muscle loss, once again only in the presence of testosterone, by blocking the low affinity glucocorticoid receptors, protecting against the effects of cortisol. Testosterone, or another blocker of the high affinity receptors must be present however, otherwise the blocking of the low affinity receptor would not yield very good results.

On a closing note, as with testosterone, the effects of estradiol are not uniformly positive. It has been shown to enhance PPAR gamma, so modulation of testosterone/estradiol levels should occur in the presence of a PPAR gamma blocker for maximal effects on fat loss. And lastly, estrogen increasing products are often omitted during diets for the simple reason that estradiol increases aldosterone, a hormone that increases sodium retention, and as a result water retention.

Excess levels of estrogen often lead to water retention and a puffed up look. While this does not affect fat loss one iota, and can be addressed quickly, in only 1 or 2 days, it does make it difficult for the dieter to judge his progress accurately. <sup>(16)</sup>

## Estrogen and autophagy

Antiestrogenic therapy is commonly used to treat estrogen receptor (ER) + breast cancers but acquired and de novo resistance limits their overall curative potential. An endoplasmic reticulum stress pathway, the unfolded protein response, and autophagy are both implicated in the development of antiestrogen therapy resistance in estrogen receptor- $\alpha$  (ER) positive breast cancer. Thus, we recently investigated how ER $\alpha$  can regulate autophagy and the unfolded protein response (Cook et al., FASEBJ, 2014). We showed that inhibiting ER $\alpha$  signaling stimulates autophagosome formation and flux. Moreover, we showed that ER $\alpha$  knockdown inhibited the unfolded protein response (UPR) signaling components. Here we support and extend this recent report showing additional data on ER $\alpha$  localization and provide a schematic of the overall signaling implicated by our results. Differential activation of UPR and autophagy highlight the pivotal role of ER $\alpha$  in regulating pro-survival signaling in breast cancer through UPR and autophagy. Furthermore, these data suggest new approaches to successful targeting ER $\alpha$  and preventing the regulation of key pro-survival signaling that confers resistance to endocrine therapies.<sup>(17)</sup>

Glut9 is highly expressed in the human kidney proximal convoluted tubular and plays a crucial role in the regulation of plasma urate levels. The gene effects were stronger among women. Our results show that 17- $\beta$ -estradiol (E2) through ER (estrogen receptor)  $\beta$  down regulates Glut9 protein expression on human renal tubular epithelial cell line (HK2). Intriguingly, E2 does not affect the expression of Glut9 mRNA. ER $\beta$  is linked to PTEN, the PTEN gene negatively regulates the PI3K/AKT pathway, and the PI3K/AKT pathway inhibition may lead to autophagy. Further study indicates that ER $\beta$  may affect the expression of Glut9 through autophagy.<sup>(18)</sup>

Breast cancer is a heterogeneous disease and approximately 70% of newly diagnosed breast cancers are estrogen receptor (ER) positive. Out of the two ER types,  $\alpha$  and  $\beta$ , ER $\alpha$  is the only ER that is detectable by immunohistochemistry in breast cancer biopsies and is the predominant subtype expressed in breast tumor tissue. ER-positive tumors are currently treated with anti-hormone therapy to inhibit ER signaling. It is well known that breast cancer cells can develop endocrine resistance and resistance to anti-hormone therapy and this can be facilitated via the autophagy pathway, but so far the description of a detailed autophagy expression profile of ER-positive cancer cells is missing. In the present study, we characterized tumor cell lines ectopically expressing ER $\alpha$  or ER $\beta$  as well as the breast cancer-derived MCF-7 cell line endogenously expressing ER $\alpha$  but being ER $\beta$  negative. We could show that ER $\alpha$ -expressing cells have a higher autophagic activity than cells expressing ER $\beta$  and cells lacking ER expression. Additionally, for autophagy-related gene expression we describe an ER $\alpha$ -specific 'autophagy-footprint' that is fundamentally different to tumor cells expressing ER $\beta$  or lacking ER expression. This newly described ER $\alpha$ -mediated and estrogen response element (ERE)-independent non-canonical autophagy pathway, which involves the function of the co-chaperone Bcl2-associated athanogene 3 (BAG3), is independent of classical mammalian target of

rapamycin (mTOR) and phosphatidylinositol 3 kinase (PI3K) signaling networks and provides stress resistance in our model systems. Altogether, our study uncovers a novel non-canonical autophagy pathway that might be an interesting target for personalized medicine and treatment of ER $\alpha$ -positive breast cancer cells that do not respond to anti-hormone therapy and classical autophagy inhibitors. <sup>(19)</sup>

17 $\beta$ -estradiol (E2) has been shown to have neuroprotective effects in different central nervous system diseases. The mechanisms underlying estrogen neuroprotection in spinal cord injury (SCI) remain unclear. Previous studies have shown that autophagy plays a crucial role in the course of nerve injury. In this study, we showed that E2 treatment improved the restoration of locomotor function and decreased the loss of motor neurons in SCI rats. Real-time PCR and western blot analysis revealed that the protective function of E2 was related to the suppression of LC3II and beclin-1 expression. Immunohistochemical study further confirmed that the immunoreactivity of LC3 in the motor neurons was down-regulated when treated with E2. In vitro studies demonstrated similar results that E2 pretreatment decreased the autophagic activity induced by rapamycin (autophagy sensitizer) and increased viability in a PC12 cell model. These results indicated that the neuroprotective effects of E2 in SCI are partly related to the suppression of excessive autophagy. <sup>(20)</sup>

ER $\alpha$  contributes to the growth of PTC by enhancing an important prosurvival catabolic process, autophagy, in PTC cells. The inhibition of autophagy promotes apoptosis, implicating a novel strategy for the treatment of ER $\alpha$ -positive PTC. <sup>(21)</sup>

### **Autophagy:**

Autophagy is an intracellular degradation system that delivers cytoplasmic constituents to the lysosome. Despite its simplicity, recent progress has demonstrated that autophagy plays a wide variety of physiological and pathophysiological roles, which are sometimes complex. Autophagy consists of several sequential steps—sequestration, transport to lysosomes, degradation, and utilization of degradation products—and each step may exert different function. In this review, the process of autophagy is summarized, and the role of autophagy is discussed in a process-based manner. <sup>(22)</sup>

## Estrogen and infection

The multiple effects of estrogens on infectious processes are only beginning to be understood. The existence of such effects is suggested by gender-related differences in the incidence and severity of some infections and by the association of certain infections with predictable hormonal changes. Current information indicates that estrogens may depress cell-mediated immunity, impair the activity of natural killer cells, and suppress some aspects of neutrophil function. Estrogens potentiate the production of systemic antibody, but local antibody responses may be impaired. Direct effects of estrogens on microorganisms have thus far been best studied in fungi; these hormones may either stimulate or suppress fungal virulence, depending on the species involved. Recent research also suggests responsiveness to estrogens in a wider variety of microorganisms. Studies in cell culture, animals, and humans indicate that pregnancy, estrogen supplementation, and menstrual stage can affect the acquisition and severity of certain bacterial, parasitic, and viral infections. This interaction depends on multiple attributes of both the microbe and the host in a given setting and thus may lead to disparate outcomes; however, there appears to be a predisposition to increased infectious morbidity in certain high-estrogen states. In view of the widespread use of estrogen supplementation, the clinical impact of estrogens on the incidence and outcome of infection needs to be better defined. <sup>(23)</sup>

The effects of estrogen on the risk of urinary-tract infection (UTI) in women has been the subject of many studies in both humans and experimental animals. Often, these studies have come to seemingly contradictory results: some have suggested an increased risk attributable to estrogen and others that estrogens may be preventative. In part, this confusion arises because the physiological effects of estrogen on different anatomic parts of the urinary tract differ depending on the specific effect and the outcome measured. For example, in the absence of estrogen, the periurethral and vaginal microflora, which is usually predominated by hydrogen peroxide-producing lactobacilli and few *Escherichia coli*, changes dramatically to a flora with few or no lactobacilli but many *E. coli*. This change in flora is associated with a markedly increased risk of recurrent *E. coli* bladder infections. In a randomized, placebo-controlled trial of topical intravaginal estrogen cream in such women, both the reestablishment of the normal lactobacillus-dominant vaginal flora and reduced rates of UTI were demonstrated in estrogen-treated women. However, topical vaginal estrogen also reverses the atrophic vaginitis that accompanies menopause, making sexual intercourse more comfortable and likely more frequent in users. Because sexual intercourse is itself a risk factor for UTI in women, this effect may counter the beneficial effects of normalizing flora. Animal models have not been used much to study these particular aspects of estrogen-related susceptibility to UTI, because both the urogenital anatomy and normal flora in small animals differ considerably from those of women. Thus, the preventive effects of estrogen replacement on UTI observed in postmenopausal women, which is thought to be mediated by changes in vaginal flora, are not usually seen in animal studies. As in the study by Curran et al. in this issue of the *Journal of Infectious Diseases*, most animals are in fact inoculated via urethral catheterization in models of experimental infection, which completely bypasses the stage of infection in which the vaginal microbial flora plays an important role. <sup>(24)</sup>

Chronic yeast infections are commonly attributed to lifestyle issues like using tight underwear, use of over-the-counter feminine hygiene products/douches, being overweight or having a diet high in sugar intake, having diabetes, over-use of antibiotics, or having a condition that suppresses the immune system. However, one of the important underlying causes of chronic yeast infection can actually be hormonal imbalance – especially imbalance in sex-hormones like estrogen and progesterone.

### **Effect of estrogen on infection causing yeast (Candida)**

Over the last many years, researchers have consistently found an effect of estrogen on the growth of the yeast, *Candida*. For example, a study published in 2000 by researchers from Iowa clearly showed that estrogen (specifically, 17- $\beta$ -estradiol) increased the growth and survival of *Candida*.

*Candida* exists in two forms – oval form and filamentous form. A change from the oval to the filamentous form is necessary for infection establishment. Research at the University of Illinois found that 17- $\beta$ -estradiol, the predominant type of estrogen during reproductive years, supported the conversion of oval form to the filamentous form. On the contrary, 17- $\beta$ -estradiol, which is similar to 17- $\beta$ -estradiol but lacks its activity, did not have the same effect. Similarly, neither Estriol (produced in significant amounts during pregnancy), nor Ethynyl estradiol (a derivative of Estradiol commonly used in oral contraceptive pills) had any effect on conversion to filamentous form.

Many women notice an increase in vaginal yeast infections before their periods or around menopause. This is because of the changes in estrogen levels – high before periods and low closer to menopause. Lower estrogen levels cause vaginal dryness which can lead to more injuries to the vaginal tissue and increase the chances of infection.

### **Effect of Estrogen on vaginal immunity against infections**

A review article published in 2010 describes the role of sex-hormones in immunity of reproductive tract against infections. The vaginal cells have an immune system of their own to prevent infection. However, the reproductive tract also needs to be able to support fertilization and maintain the fetus which, being genetically different, is foreign to the woman's body. This balance is achieved by the changing levels of sex-hormones with the stage of the menstrual cycle. Thus, lower estrogen levels are protective against infections while an increase in estrogen suppresses the immunity against infections. This immunosuppressive effect of estrogen also seems to be responsible for yeast infections as shown by research published in 2012 by researchers from Arizona.

You might wonder that if it is natural and normal for a woman to have fluctuating levels of estrogen, shouldn't the lower levels of estrogen in the non-ovulating phase then take care of the infection? Yes, you are right, it should. Obviously, something else is happening that makes the yeast infection chronic.

A study carried out in mice by an expert from Sharjah, published in 2014, showed that giving estrogen externally to mice predisposed them to severe and persistent vaginal yeast infections.

Several prevalence studies have shown that *Candida* infections are more common in pregnant women during the second or third trimester of pregnancy. This would correlate directly with the increased levels of estrogen in the second and third trimester. As we have learnt, the higher levels of progesterone during this time should prevent infections. So what is happening in pregnant women who get yeast infection? <sup>(25)</sup>

There is a close relationship between hormones, cytokines, neuropeptides, and neurotransmitters that modulate the host immune response by several effector mechanisms, including both cellular and humoral immunity. Disruption of this communication balance results in disease or in a higher susceptibility to infections. The relationships between parasites and hosts are complex and there is substantial interaction, communication and biochemical co-evolution. The role of certain hormones in parasitic infections has been demonstrated, and there are documented direct effects of hormones on parasites. Many parasites induce the secretion of molecules that influence the physiological and immunological responses in hosts, including intermediaries and vectors. Conversely, the parasites secrete many factors that alter hormone host levels. In some cases, hormones have positive or negative effects on the parasites status. In other cases, effects are mediated indirectly via the host's immune system. In vertebrates, the parasite presence also has a major influence on the host's endocrine status and the normal suite of processes governed by hormones. These processes include host development, establishment, metamorphosis, and reproduction. Thus, understanding the mechanisms involved in immunoendocrine modulation and its effects on parasites is essential for developing new drugs, finding vaccine targets and devising new therapies for several infectious diseases. <sup>(26)</sup>

Female mice are more susceptible to *Taenia crassiceps* (TC) infection than males. However, after a month parasite load increases massively in both genders reaching thousands of parasites per host. The possibility of hormonal changes in the infected mice was envisaged. Sex hormones levels were assayed after different periods of infection, the parasites present in the peritoneal cavity were collected and gonads, uterus and seminal vesicles were weighed. In male mice, serum estradiol increased to levels 200 times their normal values whilst those of testosterone decreased 90% relative to controls. The weight of seminal vesicles was significantly diminished. Infected female mice also showed a slight increase in estrogen blood levels after 8 weeks of infection and the weight of the uterus was significantly increased relative to controls. Serum estradiol and testosterone were almost undetectable after gonadectomy. Cytokines such as IL-6 are capable of stimulating aromatase activity and we found that splenocytes from infected mice produced amounts of IL-6 higher than control as measured by ELISA. In conclusion *T. crassiceps* infection triggers a feminization process in the infected hosts. The gonads are required for the parasite to induce higher estrogen synthesis. IL-6 could be involved in the immunoendocrine mechanism used by the parasite to maintain a highly permissive environment for its rapid growth. <sup>(27)</sup>

## **Sex-Associated Hormones and Immunity to Protozoan Parasites**

Numerous epidemiological and clinical studies have noted differences in the incidence and severity of parasitic diseases between males and females. Although in some instances this may be due to gender-associated differences in behavior, there is overwhelming evidence that sex-associated hormones can also modulate immune responses and consequently directly influence the outcome of parasitic infection. Animal models of disease can often recreate the gender-dependent differences observed in humans, and the role of sex-associated hormones can be confirmed by experimentally altering their levels. Under normal circumstances, levels of sex hormones not only differ between males and females but vary according to age. Furthermore, not only are females of reproductive age subject to the regular hormonal cycles which control ovulation, they are also exposed to dramatically altered levels during pregnancy. It is thus not surprising that the severity of many diseases, including those caused by parasites, has been shown to be affected by one or more of these circumstances. In addition, infection with many pathogens has been shown to have an adverse influence on pregnancy. In this article we review the impact of sex-associated hormones on the immune system and the development and maintenance of immunity to the intracellular protozoan parasites *Toxoplasma gondii*, *Plasmodium* spp., and *Leishmania* spp.

The literature is full of observations that both the incidence and severity of natural parasitic infections are different between males and females of many species, including humans. These differences are undoubtedly due to many factors, including the different exposure of the sexes to various parasite infective stages. However, under controlled laboratory conditions, a clear dichotomy in the susceptibility of males and females can also be observed. Such experiments demonstrate that physiological differences between males and females play an important role in determining susceptibility to parasitic infection. Moreover, a dichotomy in the incidence and severity of many diseases of noninfectious etiology is a further indication that the physiology of males and females is an important factor in determining disease susceptibility. These studies have prompted investigation into the ability of sex-associated hormones to influence the immune system. It is now widely accepted that many hormones, including the sex-associated hormones, directly influence the immune system and thus susceptibility to disease. Herein, we review the effects of sex- and pregnancy-associated hormones on the immune system in general and in particular immunity to selective protozoan parasitic diseases. <sup>(28)</sup>

## **Estrogen and urinary schistosomiasis**

About 200 million people across 75 of the poorest countries in the world are now infected by the blood parasite *Schistosoma hematobium* (*S. hematobium*). The infection causes severe urogenital disease, but also causes bladder cancer in a number of patients and why this occurs is not clear.

Now a group of Portuguese scientists believe they have the answer – their research shows how the parasite’s eggs can make human bladder cells behave as cancerous cells. And the key to that – according to the first author of the work Mónica Botelho– are catechol estrogens, a molecule derived from estrogen (the sex hormone) that was found by the researchers in the eggs and is known to be highly carcinogenic (causes cancer).

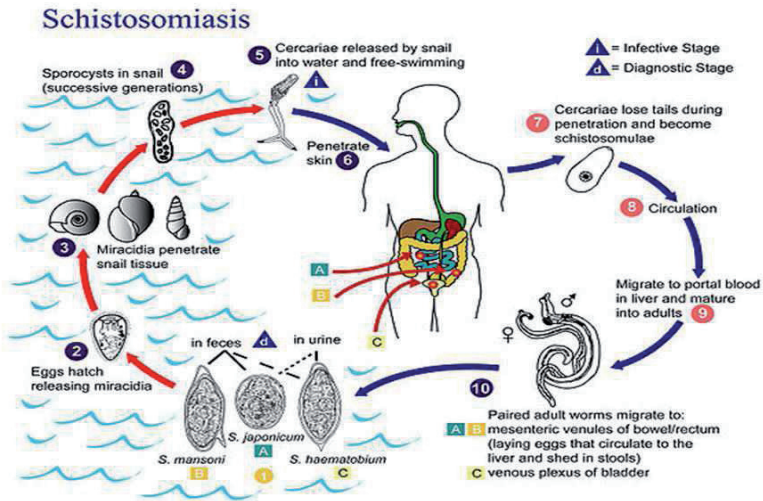
The research, a collaboration of the CECA/ICETA from the University of Porto, the National Institute of Health in Porto, Portugal and the George Washington University, US could be a first step towards one day be able to identify *S. hematobium* infected patients at risk of bladder cancer or even prevent the cancer by targeting catechol-estrogens. Schistosomiasis is also associated to fertility problems and the newfound molecules might hold the key to also understand this.

Schistosomiasis, despite the numbers infected, remains a neglected tropical disease that affects the world’s poorest with a socioeconomically impact in the developing world only second to malaria. The disease is transmitted to humans by freshwater snails from contaminated waters, with the worms entering our blood stream to release eggs that become embedded in the bladder wall where they cause chronic inflammation and, in some patients, lead to bladder cancer.

How common is this carcinoma among parasite-infected patients is difficult to know because the most affected countries are also the world’s poorest with scarce or even non-existing disease recording.

Nevertheless, in Egypt, disappearance of *S. hematobium* saw the type of tumors associated with the infection going from being almost 80% of all diagnosed bladder cancers, to less than 27 %, suggesting that the infection leads to a significant number of cancer cases.

## S. hematobium life cycle



Botelho and colleagues have been investigating this relationship for many years, and shown already that extract from the adult worm could make animal cells acquire cancer-like characteristics and even form tumors if injected into mice with no immune system, further proving the parasite-cancer link.

Following the finding that Schistosomiasis' patients had higher than normal levels of estrogens Botelho and colleagues also discovered new estrogenic molecules released by *S. hematobium*. These molecules down-regulate estrogen receptors effectively blocking the host's estrogens (that act through these receptors). This, as Botelho explains "was an important clue because we know that estrogen receptors are reduced when cancer becomes more invasive".

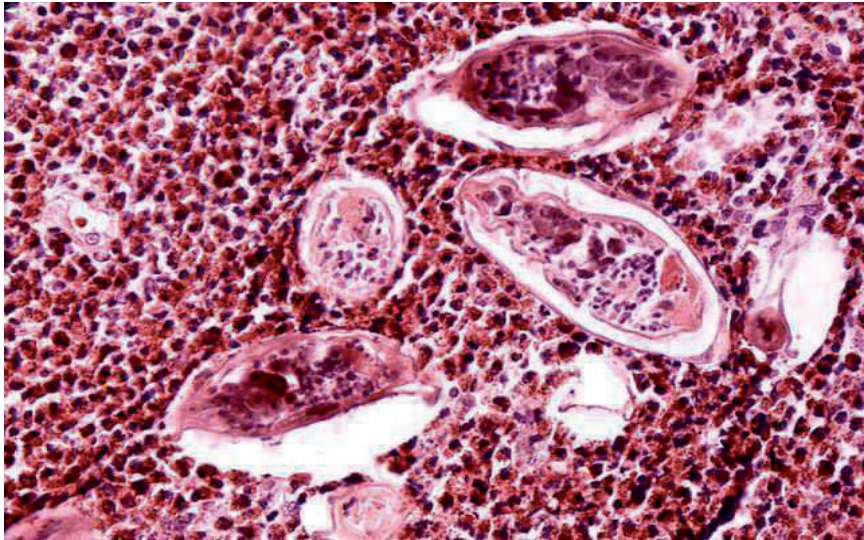
The new molecules were later identified as a combination of DNA and catechol estrogen-quinones (a derivative of estrogen). Catechol estrogens have been linked to several types of cancer, including breast and prostate cancer, suggesting that the new molecules could be the link between schistosomiasis and bladder cancer.

The research now published follows these results looking at the effect of *S. hematobium* eggs (the parasite stage associated with the cancer development) on normal human bladder cells. For that Botelho and colleagues exposed the cells to extract from the eggs and found that treated

cells, when compared with normal control cells, divided much more, died much less and showed signs of oxidative stress.

Uncontrolled cell division and resistance to die are hallmark characteristics of cancer, and oxidative stress is known to be implicated in cancer formation.

To confirm that these changes were linked to cancer Botelho and colleagues next looked for DNA lesions. If DNA - the cell's "instruction book" - becomes damaged and is not properly repaired, it will start giving wrong "instructions", which can lead to the abnormal behavior typical of cancer (uncontrolled cell multiplication, "immortality", etc.). And in fact, exposure to parasite's eggs was linked to a visible increase in DNA lesions in the cells. The eggs were confirmed to contain the same new estrogenic molecules found in adult worms.



**S. hematobium** eggs embedded in the bladder wall (Image from CDC Public Health Image Library)

Based on the new data, Botelho and colleagues are now proposing a mechanism for the Schistosomiasis-bladder cancer connection.

As Botelho explains, "What we think happens is that the parasite releases estrogen molecules into the host. These are metabolized into catechol-estrogen quinones, which are known to have high affinity for DNA and as result from estrogen-DNA adducts that can lead to the bladder cancer."

In fact, adducts, defined as pieces of DNA covalently bonded to a cancer-causing chemical, are known to interfere with normal cell division increasing the chance of DNA mutations and, consequently, of cancer. The carcinogenic effect of this estrogen-DNA adduct could then explain the link between *S. hematobium* infection and the carcinoma.

Botelho and colleague's work have several implications – the possibility of using the new identified estrogenic molecules as biomarkers for bladder cancer in Schistosomiasis patients, or even as therapy targets for a start.

This is important because although at the moment it is suggested that there are about 4 cases of cancer for 100 000 Schistosomiasis-infected individuals what does not seem much, but we must remember that 200 million people are believed to be infected, and even those numbers, like the Egypt case suggests, are probably a gross underestimation. The reality is that carcinoma of the urinary bladder is the most common malignancy in the Middle East and parts of Africa where schistosomiasis is a major problem.

Not only that but, and despite the existence of a cheap and effective drug, the disease (which is asymptomatic until very late) seems to be increasing and spreading. This is probably due to the large numbers of economic migrants from developing countries, as well as the wars in these areas of the globe, that create large displacements of people.

Another interesting potential implication for Botelho's results is the possibility that the new identified estrogenic molecules could have a role in other cancers associated with infection and estrogenic changes, such as cholangiocarcinoma, a liver cancer linked to an infection by a parasitic liver fluke.

A question remains though - why does the parasite produce estrogenic molecules? An option, according to the researchers, could be that uses them to reduce the density of the bladder wall (a known effect of reduced estrogen receptors). After all *S. hematobium* eggs must cross the bladder mucosa to be excreted in order to survive and continue its life cycle. Another possibility is that the parasite is manipulating the host's hormonal environment to improve its own living conditions.<sup>(29)</sup>

## **Estrogen and cancer**

For years, estrogen has been a suspected carcinogen, since strong epidemiological evidence associates the hormone to breast, endometrial, and uterine cancers. Women who begin menstruating early, or who start menopause late, produce more estrogen over their lifetimes and have a higher risk of breast cancer. Recently, the clinical trial of estrogen plus progestin treatment therapy was terminated because of an increased risk of breast cancer.

A new study by Mailman researchers shows that more than one sequence of steps is necessary before estrogen can cause cancer. In addition to a hormone receptor-mediated process, a second process is also required, says the study's lead author, Dr. Hari Bhat, assistant professor of environmental health sciences. Their results suggest that blocking the second pathway could prevent estrogen-induced cancers. But they also suggest that even non-carcinogenic estrogens can cause cancer given the right conditions. This research was published in the April 1 Proceedings of the National Academy of Sciences.

Estrogen was originally believed to cause cancer by helping cells proliferate. After the hormone binds to its receptors in a cell, it turns on hormone-responsive genes that promote DNA synthesis and cell proliferation. If a cell happens to have cancer-causing mutations, those cells will also proliferate and have a chance to grow into tumors.

"But if cell proliferation via receptor-mediated processes is the only mechanism, then all estrogens should cause cancer," Dr. Bhat says. "So it is hypothesized that estrogen metabolism may play a key role in estrogen-induced cancers because different estrogens differ in how they're broken down in the cell."

The cell uses a series of reactions to rid itself of estrogen. In metabolizing carcinogenic estrogens, the reactions produce intermediates capable of producing oxygen radicals that can damage the cell's fats, proteins, and DNA. Unrepaired DNA damage can turn into a mutation, which can later promote cancer.

To see if cancer-causing estrogens need oxygen radicals to produce tumors, Dr. Bhat implanted pellets of the hormone in hamsters that are susceptible to estrogen-induced kidney cancer. This model is widely used as an animal model of hormonal cancer. As expected, when the carcinogenic 17beta-estradiol (E2) was used, nearly all hamsters with the pellets developed cancer within seven months. E2 promotes cell proliferation and produces oxygen radicals when metabolized by the cell.

Also, as expected, none of the hamsters developed kidney cancer when a non-carcinogenic estrogen, 17alpha-ethinylestradiol (EE) was implanted. EE acts through estrogen receptors to create new cells like E2, but unlike E2, is poorly broken down and does not produce oxygen radicals.

But when EE was combined with a non-estrogen molecule that generates oxygen radicals, 30 percent of the hamsters developed kidney cancer within seven months. The non-estrogen used, menadione, did not produce tumors when used alone.

"That we found tumors in the EE plus menadione treated hamsters clearly suggests that estrogen receptor activity and oxidative stress are both needed for estrogen to produce cancer," Dr. Bhat says.

In other experiments, Dr. Bhat and his colleagues confirmed that the oxidative damage suffered by the cancerous kidney cells was caused by the metabolic breakdown of E2. "That's why E2 acts as a complete carcinogen," Dr. Bhat says. "It's a potent estrogen and it can also produce oxidative stress."

The more complete knowledge of how the estrogen increases the risk of cancer could lead to new anti-oxidant therapies to treat or prevent cancer.

But it also suggests that reputedly "safe" estrogens that are touted as replacements for the estrogens in hormone replacement therapy may not be so safe after all. "If we have oxidative stress in cells from other chemicals, then women are at risk for cancer even with estrogens that are considered non-carcinogenic," Dr. Bhat says. "The therapy may be safer if taken with antioxidants, but more research is needed to make safe and more effective antioxidants."<sup>(30)</sup>

### **High level of estrogen**

The body's hormones are like a seesaw. When they're perfectly balanced, your body works as it should. But when they're unbalanced, your body may begin experiencing problems.

Estrogen is known as the "female" hormone and testosterone is known as the "male" hormone. Although they're identified with a specific gender, both hormones are found in women and men. Women have more estrogen and men have more testosterone.

In women, estrogen helps initiate sexual development. It also regulates a woman's menstrual cycle and affects the entire reproductive system.

High estrogen or estrogen dominance can happen if estrogen levels are too great. These higher levels can occur naturally. Too much estrogen can also be the result of medication. For example, estrogen replacement therapy, a popular treatment during menopause, may cause the hormone to reach problematic levels. The body may also develop too little testosterone, which can upset the balance.

#### **Symptoms of high estrogen**

When your body's estrogen and testosterone levels aren't in sync, you may begin developing certain symptoms. Symptoms of high estrogen include:

- bloating
- swelling and tenderness in the breasts
- decreased sex drive
- irregular menstrual periods
- headaches
- mood swings
- fibrocystic developments in the breast
- weight gain
- hair loss
- cold hands or feet
- feeling tired or lacking energy
- difficulty with memory
- trouble sleeping
- increased symptoms of premenstrual syndrome or PMS.

High levels of estrogen can put you at a higher risk for other conditions. For example, elevated estrogen levels are a risk factor for breast cancer. According to the National Cancer Institute, high levels of estrogen over a long period of time can also cause endometrial cancer. <sup>(31)</sup>

## Measurement of estrogens

Estrogen tests are used to detect a deficiency or excess in a woman and to help diagnose a variety of conditions associated with this imbalance. They may also be used to help determine the timing of a woman's ovulation and may be ordered to monitor the health status of the developing baby and placenta during pregnancy. In a man, estrogen testing may be performed to detect a hormone excess and its cause.

Estrogen tests measure one of three components: estrone (E1), estradiol (E2), or estriol (E3). These tests each have different uses.

In Girls and Women:

Estradiol (E2) and/or estrone (E1) testing may be ordered to:

- Help diagnose early-onset puberty, when a young girl develops secondary sex characteristics sooner than expected; or delayed puberty, when a girl shows delayed development of secondary sex characteristics or start of menstruation
- Investigate menstrual abnormalities, such as lack of menstrual periods (amenorrhea), infertility, and abnormal vaginal bleeding
- Evaluate the function of the ovaries and detect ovarian failure
- Monitor follicle development in the ovary in the days prior to in vitro fertilization by making serial measurements of estradiol
- Monitor hormone replacement therapy that is given to assist fertility
- Monitor menopausal hormone replacement therapy that is given to alleviate symptoms associated with estrogen deficiency
- Detect estrogen-producing tumors
- Monitor anti-estrogen therapy, as in breast cancer

Estriol (E3) testing:

- May sometimes be ordered serially to help monitor a high-risk pregnancy; when it is used this way, each sample should be drawn at the same time each day.
- An unconjugated estriol test is one of the components of second trimester maternal serum screening. Decreased levels have been associated with various genetic disorders, including Down syndrome, neural tube defects, and adrenal abnormalities.

## In Boys and Men

Estradiol (E2) and/or estrone (E1) testing in boys or men may be ordered to:

- Help diagnose delayed puberty
- Help diagnose the cause of enlarged breasts (gynecomastia) or other signs of feminization
- Detect a relative estrogen excess that is due to a testosterone or androgen deficiency
- Detect estrogen-producing tumors

When is it ordered?

## In Girls and Women

Estradiol (E2) and/or estrone (E1) testing in girls and women may be ordered when:

- A girl's sex organs develop earlier or later than normally expected
- A woman has symptoms such as abnormal vaginal bleeding after menopause or abnormal or lack of menstrual cycles
- A woman is experiencing infertility; a series of estradiol measurements over the course of a woman's menstrual cycle may be done to monitor follicle development prior to in vitro fertilization techniques (timed with a surge in estradiol).
- A woman is having symptoms of menopause, including hot flashes, night sweats, insomnia, and/or irregular or lack of menstrual periods
  
- A menopausal woman is taking hormone replacement therapy; her health practitioner may periodically order estrone levels to monitor treatment.

Estriol (E3) testing in women may be ordered:

- During pregnancy, a health practitioner may order serial estriol samples to look for a trend, whether there is a rise or fall in the estriol level over time.
- Unconjugated estriol is often measured in the 15th to 20th week of gestation as part of the triple/quad screen.

## **In Boys and Men**

Estradiol (E2) and/or estrone (E1) testing in boys and men may be ordered when:

- A boy has delayed puberty, characterized by delayed development of muscle mass, lack of deepening of the voice or growth of body hair, slow or delayed growth of testicles and penis
- A man shows signs of feminization, such as enlarged breasts

What does the test result mean?

Normal estrogen results depend upon the sex and age of the person being tested. With women, it also depends upon their menstrual cycle or whether they are pregnant. Reference ranges will vary somewhat between laboratories, both in normal values listed and in units used.

Increased or decreased levels of estrogens are seen in many metabolic conditions. Care must be used in the interpretation of estrone, estradiol, and estriol results because the levels vary on a day-to-day basis and throughout a woman's menstrual cycle.

A health practitioner who is monitoring a woman's hormones will be looking at trends in the levels, raising or lowering over time in conjunction with the menstrual cycle or pregnancy rather than evaluating single values. Test results are not diagnostic of a specific condition but give the health practitioner information about the potential cause of a person's symptoms or status.

Below are conditions with which one might see an increase or decrease of estrogen levels.

Increased levels of estradiol (E2) or estrone (E1) are seen in:

Girls and Women:

- Early (precocious) puberty
- Tumors of the ovary or adrenal glands

Boys and Men:

- Enlarged breasts (gynecomastia)
- Tumors of the testicles (testicular cancer) or adrenal glands
- Delayed puberty

Both Women and Men:

- Hyperthyroidism
- Cirrhosis

In women, decreased levels of estrogen are seen in:

- Turner syndrome, an inherited condition in women caused by a missing or abnormal X chromosome and characterized by underdeveloped female sex characteristics
- Low level of pituitary hormones (hypopituitarism)
- Dysfunction of the ovaries (female hypogonadism)
- Failing pregnancy (estriol).
- Eating disorders such as anorexia nervosa
- After menopause (estradiol)
- PCOS (Polycystic ovarian syndrome, Stein-Levanthal syndrome)
- Extreme endurance exercise.

Blood and urine results are not interchangeable. Your health practitioner will choose which estrogen and sample type to test. In addition to blood and urine, estrogen testing is occasionally also performed on saliva or on amniotic fluid.

Beyond daily and cycle variations, illnesses such as high blood pressure (hypertension), anemia, and impaired liver and kidney function can affect estrogen levels.

Some drugs, such as glucocorticosteroids, ampicillin, estrogen-containing drugs, phenothiazines, and tetracyclines, can increase estrogen levels in the blood. Glucose in the urine and urinary tract infections can increase levels in the urine. Drugs that may decrease levels include clomiphene and oral contraceptives.<sup>(32)</sup>

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[info@omniscrptum.com](mailto:info@omniscrptum.com)  
[www.omniscrptum.com](http://www.omniscrptum.com)

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