Estradiol

By Ronald Steriti, ND, PhD

The most potent estrogen secreted by the ovary is estradiol. Estradiol is the predominant active estrogen in premenopausal women. 97% of serum estrogen, which is bound, is estradiol.

In the normal menstrual cycle, estradiol levels measure typically <50 pg/ml at menstruation, rise with follicular development (peak: 200 pg/ml), drop briefly at ovulation, and rise again during the luteal phase for a second peak. At the end of the luteal phase, estradiol levels drop to their menstrual levels unless there is a pregnancy. During pregnancy, estrogen levels, including estradiol, rise steadily toward term.

Metabolism

Estradiol is formed in two ways: from testosterone by the enzyme aromatase, and from estrone by the enzyme 17beta-hydroxysteroid dehydrogenase (17ß-HSD).

Figure 1: DHEA.jpg

Increased estradiol is associated with:

> Hepatic cirrhosis, hyperthyroidism, feminization in children (testicular feminization syndrome), estrogen-producing tumors, precocious puberty related to adrenal tumors

Decreased estradiol is associated with:

> Menopause, hypofunction or dysfunction of pituitary and adrenal glands, primary and secondary hypogonadism, Kallman syndrome (Hypogonadotropic hypogonadism, the absent or decreased function of the male testes or the female ovaries with a lack of LH and FSH), anorchia, primary testicular failure

Estradiol In Women

Estrogen (estradiol) mono-therapy unfortunately may induce endometrial hyperplasia in women with an intact uterus. Therefore estrogens are

combined with progesterone. Low doses, however, have been found to be safe in a recent study. (Johansen and Qvigstad 2008)

Breast Cancer

Synthetic estrogens were an integral part in the armamentarium of breast cancer for several decades. High doses of estrogens remained one of the few non-surgical options for breast cancer treatment until the introduction of the anti-estrogen tamoxifen in 1971. (Munster and Carpenter 2009)

A recent study found that low dose estradiol therapy was as effective as high dose for hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer. (Ellis, Gao et al. 2009)

Estradiol has been shown to be an anti-aromatase agent in human breast cancer cells (Pasqualini and Chetrite 2006)

Mental Health

Estradiol may have neuroprotective properties. (Garcia-Segura, Azcoitia et al. 2001) (Behl, Widmann et al. 1995)

Estrogen is considered to play a significant role in women's mental health, with links suggested between the hormone, 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. (Douma, Husband et al. 2005) (Lasiuk and Hegadoren 2007)

Estradiol was found, when in high levels, to act as a genetic initiator in the development of eating disorders during puberty, according to a recent study. (Klump, Keel et al. 2010)

Blood vessels

Estrogen affects certain blood vessels. Improvement in arterial blood flow has been demonstrated in coronary arteries. (Collins, Rosano et al. 1995)

Estradiol In Men

Both excess and deficient estradiol may be harmful in men.

Prostate

The Estradiol-Dihydrotestosterone model of prostate cancer proposes that 17beta-estradiol(E2) is essential for initiating the growth of prostate cancer cells through the formation of telomeres. It also proposes that testosterone is responsible for increasing the expression of proteins that cause apoptosis, or programmed cell death, and that 5alpha-dihydrotestosterone (DHT) is essential for preventing this. (Friedman 2005)

A recent article found that estradiol suppresses tissue androgens and prostate cancer growth in castration resistant prostate cancer. (Montgomery, Nelson et al. 2010)

Estradiol can be used in the treatment of advanced prostate cancer. (Ockrim, Lalani el et al. 2005) (Carruba, Pfeffer et al. 1994)

Bones

A recent study found that decreased estradiol is associated with osteoporosis in aging men. (Clapauch, Mattos et al. 2009)

The GOOD study found that free testosterone is a positive, whereas free estradiol is a negative, predictor of cortical bone size in young Swedish men. (Lorentzon, Swanson et al. 2005)

Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. (Mellstrom, Vandenput et al. 2008)

Heart

Among men with chronic heart failure and reduced left ventricular ejection fraction, high and low concentrations of estradiol compared with the middle quintile of estradiol are related to an increased mortality. (Jankowska, Rozentryt et al. 2009)

Another study found circulating estradiol is an independent predictor of progression of carotid artery intima-media thickness in middle-aged men. (Tivesten, Hulthe et al. 2006)

Serum estradiol concentration is inversely associated with carotid atherosclerosis. (Fukui, Kitagawa et al. 2008)

High levels of serum estradiol may be associated with an elevated risk of stroke in elderly men. (Abbott, Launer et al. 2007)

An elevated serum estradiol/testosterone ratio was found in men with primary varicose veins. (Kendler, Blendinger et al. 2009)

The MrOS Study in Sweden found that low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. (Tivesten, Mellstrom et al. 2007)

Diabetes and Obesity

Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. (Vikan, Schirmer et al. 2010)

Serum estradiol is associated with lean mass in elderly Swedish men. (Vandenput, Mellstrom et al. 2010)

Male Infertility

Several studies have noted that sperm counts have been declining in many parts of the world and it has been postulated that this may be related to estrogen exposure in the environment. (Sharpe and Skakkebaek 1993)

Suppression of estradiol production (via aromatase inhibition) in a subpopulation of subfertile men may improve the semen analysis. (Raman and Schlegel 2002)

Miscellaneous

One study found that circulating estradiol in men is inversely related to urinary metabolites of non-persistent insecticides. (Meeker, Ravi et al. 2008)

Estradiol Medications

Estrogen is marketed in a number of ways to address issues of hypoestrogenism. Thus there are oral, transdermal, topical, injectable, and vaginal preparations. Furthermore, the estradiol molecule may be linked to an alkyl group at C3 position to facilitate the administration. Such modifications give rise to estradiol acetate (oral and vaginal applications) and to estradiol cyprionate (injectable).

Oral preparations are not necessarily predictably absorbed and subject to a first pass through the liver, where they can be metabolized and also initiate unwanted side-effects. Thus, alternative routes of administration that bypass the liver before primary target organs are hit have been developed.

Transdermal and transvaginal routes are not subject to the initial liver passage.

A more profound alteration is ethinylestradiol, the most common estrogen ingredient in combined oral contraceptive pills

Natural Therapies

Flaxseed

Flaxseed is known to reduce estradiol and may be beneficial in breast cancer. (Power and Thompson 2007) (Saggar, Chen et al. 2010)

A recent study showed flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. (Bergman Jungestrom, Thompson et al. 2007)

Genistein

The characteristic way that isoflavones bind to estrogen receptors (ERs), mainly to beta-receptors (ERs-β), makes them promising molecules in

replacing hormones for therapeutic purposes. Isoflavones are less potent than endogenous and synthetic hormones, and they have fewer side effects. Genistein and its derivatives are the most active isoflavone, and is also the main isoflavone found in soy seeds. (Campos Mda and Matos 2010)

Lycium barbarum

A recent study showed that Lycium barbarum inhibits growth of estrogen receptor positive human breast cancer cells by favorably altering estradiol metabolism. The MCF-7 cells maintained in 0.7% serum (17beta-estradiol, E2 < 1 nM) exhibited 11%-87% increased growth after treatment with 1nM to 20 nM E2. Growth promotion with 20 nM E2 exhibited 5.2-fold increased estrone (E1), 35.7% increased 2-hydroxyestrone (2-OHE1), 15.4% increased 16alpha-hydroxyestrone (16alpha-OHE1), and eightfold increased estriol (E3) formation. Treatment of E2 stimulated cells with LB exhibited a dose-dependent growth inhibition of 9.5%-42.8% at Day 3 and 33.9%-83.9% at Day 7. The 3-day inhibitory response to 1% LB (maximum cytostatic concentration) exhibited 84.8% increased E1, 3.6-fold increased 2-OHE1, 33.3% decreased 16alpha-OHE1, and 9.2-fold increased E3 formation. Thus, MCF-7 cells retain their mitogenic and metabolic response to E2 and LB downregulates E2-stimulated growth via the formation of antiproliferative 2-OHE1 and accelerated conversion of mitogenic 16alpha-OHE1 to antimitogenic E3. (Li, Sepkovic et al. 2009)

Herba Epimedii

A recent study showed that Herba Epimedii (Horny Goat Weed) water extract decreased the total cholesterol and triglyceride levels ($p < 0.01$). Furthermore, Herba Epimedii water extract significantly increased the serum level of estradiol ($p < 0.01$) compared with the pre-treatment level. (Yan, Liu et al. 2008)

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