

**Subcommittee on Human Rights and Wellness
House Committee on Government Reform
“Balancing Act: The Health Advantages of Naturally-Occurring Hormones
in Hormone Replacement Therapy”**

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Sex hormones, including estrogen and testosterone, decline with age, but restoring hormone levels to youthful levels will not restore youth. Hormones as an anti-aging treatment have been promoted for more than a century and were initially aimed at men (Kaptchuk 1998). In the 1920s, grafts of animal testicles were surgically implanted into men (Veronoff 1921). In recent decades, however, hormones have been marketed primarily to women as a preventive against age-related disease.

Hormones are very useful therapies for specific medical conditions. For example, insulin is a vital treatment for diabetes, and many estrogens are effective treatments for hot flashes. However, insulin, estrogens and other hormones don't prevent aging, and, unfortunately, there's no such thing as a harmless hormone.

All hormones, including those that humans create within their bodies, have side effects. Claims that so-called bioidentical, natural, or naturally-occurring hormones are safer than conventional hormones are not backed by science.

The three estrogens that humans make are estriol, estradiol, and estrone, and these are the hormones touted by some compounding pharmacies and physicians as harmless alternatives to conventional hormone therapy. Natural hormone proponents may recommend estriol alone, estriol and estradiol (Bi-Est), or estriol, estradiol, and estrone (Tri-Est), sometimes combined with other hormones. Synthesized versions of these hormones are identical to human versions. But just because humans make a hormone doesn't mean it's good for us.

Breast and Uterine Cancer Risk

Many studies show that women who have naturally higher levels of estradiol and estrone in their bodies are at higher risk of breast cancer than women who have lower levels of these estrogens. A meta-analysis published in the Journal of the National Cancer Institute analyzed nine studies on the subject and concluded that levels of estradiol, estrone, testosterone, DHEA, and other sex hormones were strongly associated with breast cancer risk in postmenopausal women (EHBCCG 2002). More recent studies have also found that naturally higher levels of estradiol and estrone (Zeleniuch-Jacotte 2004, Manjer 2003, Key 2003, Onland-Moret 2003), as well as testosterone, are associated with increased breast cancer risk in women (Onland-Moret 2003, Yu 2003).¹

¹ An increase in breast cancer risk was one of the reasons that the estrogen-progestin arm of the NIH-funded Women's Health Initiative trial on hormone therapy was stopped early (WGWHI 2002). Another randomized trial of hormones in breast cancer survivors was stopped early because of an unacceptably high number of breast cancer recurrences in the hormone-treated group (Holmberg 2004). And an observational study of more than a million women in the UK found that estrogen-progestin hormone therapies were associated with increased breast cancer risk (Beral 2003).

Natural hormone proponents believe that estriol decreases breast cancer risk, and, in contrast to other estrogens, does not increase uterine cancer risk. The belief that estriol prevents breast cancer is based entirely on publications, all more than three decades old, written by Henry M. Lemon. Lemon theorized that estriol had potential in preventing and treating breast cancer. The only non-Lemon-authored support for this idiosyncratic theory is a single commentary that mentions an unpublished study in which Lemon used estriol as a successful treatment in breast cancer patients (Follingstad 1978).

As big a fan of estriol as Lemon was, even he never claimed that estriol was a successful breast cancer treatment. Lemon did publish a review on estriol in which he describes giving estriol to 24 subjects with breast cancer (Lemon 1980), but as the treatment stimulated the growth of metastases in six women – one quarter of the treated population -- the experiment can hardly be considered a success. Two women also developed endometrial hyperplasia (estrogen-stimulated cell growth that precedes uterine cancer). Frighteningly, the author's enthusiasm for estriol appears to have remained undimmed. It is even more frightening that his theory still attracts followers.

In Europe, estriol is available as a pharmaceutical and is commonly prescribed by conventional physicians for treating menopausal symptoms. It is quite a weak estrogen and it was thought for many years that there was no need to use a progestin with estriol to protect the uterus². However, we now know that estriol is associated with endometrial hyperplasia (Granberg 1997) as well as endometrial cancer. Women who had ever used estriol had twice the risk of developing endometrial cancer as never-users, and five years of oral estriol tripled the risk (Weiderpass 1999).

Cardiovascular Risk

Data from randomized controlled trials have shown no protection of estrogen alone (Anderson 2004) or an estrogen-progestin combination (WGWHI 2002) in preventing heart attack or stroke³. Is there reason to believe that the estrogens promoted by compounding pharmacies protect against heart disease or stroke?

² Used alone, estrogen increases the risk of endometrial (uterine) cancer. A progestin (medroxyprogesterone acetate/ Provera, progesterone, etc.) is used with estrogen in women with a uterus to prevent estrogen-induced stimulation of the uterus, which can cause uterine cancer or endometrial hyperplasia (thickening of the uterus, a risk factor for endometrial cancer).

³ In July 2002, the combined estrogen-progestin arm of the Women's Health Initiative (WHI), a large, NIH-funded randomized controlled trial, was stopped early because the treated group experienced higher rates of breast cancer, cardiovascular disease, and overall harm (WGWHI). In February 2004, the estrogen-only arm of the WHI was halted early because of an increase in stroke among the treated group, and because estrogen failed to show any cardiovascular benefit (Anderson 2004). Neither preparation prevented dementia (Shumaker 2003, Shumaker 2004), and hormones improved quality of life only in women with hot flashes (Hays 2003).

No. In fact, estradiol has been tested in trials. A randomized, placebo-controlled trial tested estradiol in 664 postmenopausal women after a recent stroke or transient ischemic attack (“mini-stroke”). Estradiol did not protect against stroke, cardiovascular events or death (Viscoli 2002). In ESPRIT (the oEstrogen in the Prevention of Reinfarction Trial), 1017 postmenopausal women with a previous heart attack were given estradiol or placebo for two years. There was no difference between groups in frequency of heart attack or death (Cherry 2002).

Uniquely Unregulated

Although promoters of bioidentical hormones claim that their products are unique and have no relationship to synthetic hormones or commercial pharmaceutical preparations, both claims are misleading. Most bioidentical hormones are synthesized. And bioidentical hormones are commonly available as commercial pharmaceuticals in the United States. Estradiol is available in branded preparations as tablets, patches, vaginal cream, vaginal tablets, and a vaginal ring; the pills and patches are also available as low-cost generic forms. Estrone is available in branded tablets. Branded estriol tablets are not commercially available in tablets or capsules in the U.S., but In the U.K., estriol is marketed by Organon under the brand name Ovestin.

No safety or efficacy studies have been published on bi-estrogen or tri-estrogen preparations. We have plenty of information on the adverse health effects of health risks of pharmaceutical estrogens, but we also have information on documented benefits. And the quality of drugs made by pharmaceutical manufacturers is regulated.

To quote Sarah Sellers, PharmD:

“Hormone creams, gels, troches, capsules, patches, injections, and surgically implanted hormone pellets are compounded with little or no substantiation that the dosage forms can be safely administered and the active ingredients are actually bioavailable...Much concern is currently focused on the importation of drugs from other countries that may not match our gold standard system of regulation for pharmaceuticals, while we have within our own borders a flourishing, unregulated drug industry that manufactures, markets and sells substandard products throughout the United States.” (Sellers 2004).

Conclusion

In summary, human studies have shown that

- Naturally high levels of estrone and estradiol are associated with increased breast cancer risk.
- Estriol pills increase uterine cancer risk.
- Estradiol does not protect against heart disease or stroke.

All of these effects are consistent with what is known about commercially marketed pharmaceutical hormones. The quality of commercially available

pharmaceuticals, in contrast to compounded drugs, is regulated. Claims that the hormones in compounded hormone prescriptions are safer than commercial pharmaceuticals can only be made by those unfamiliar with or resistant to scientific data. Compounding pharmacies should be regulated to ensure the quality of compounded preparations and to prevent them from making misleading and dangerous claims. To do otherwise risks the health of consumers.

References

- Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004 Apr 14;291(14):1701-12.
- Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003 Aug 9;362(9382):419-27.
- Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, Lokkegaard E, Pedersen AT, Heitmann BL, Jovanovic Z, Keiding N, Hundrup YA, Obel EB, & Ottesen B. (2003). Relation between hormone replacement therapy and ischaemic heart disease in women: prospective observational study. *BMJ*;326(7386):426.
- Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002 Apr 17;94(8):606-16.
- Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004 Jun 23;291(24):2959-68.
- Follingstad AH. Estriol, the forgotten estrogen? *JAMA* 1978;239(1):29-30.
- Granberg S, Ylostalo P, Wikland M, Karlsson B. Endometrial sonographic and histologic findings in women with and without hormonal replacement therapy suffering from postmenopausal bleeding. *Maturitas* 1997;27(1):35-40.
- Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, Aragaki AK, Shumaker SA, Brzyski RG, LaCroix AZ, Granek IA, Valanis BG; Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. 2003 May 8;348(19):1839-54.
- Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, Furberg CD, Kowalchuk GJ, Stuckey TD, Rogers WJ, Givens DH, & Waters D. (2000) Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*;343(8):522-9.
- Holmberg L, Anderson H; HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. *Lancet*. 2004 Feb 7;363(9407):453-5.
- Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Key TJ, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sieri S, Pala V, Venturelli E, Secreto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Kuller LH, Cummings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR, Longcope C; Endogenous Hormones Breast Cancer

Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst.* 2003 Aug 20;95(16):1218-26.

Kaptchuk TJ. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull Hist Med* 1998;72:389-433.

Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients with oestrogens; the role of oestriol in the prevention of mammary carcinoma. *Acta Endocrinologica* 1980;Suppl 233:17-27.

Manjer J, Johansson R, Berglund G, Janzon L, Kaaks R, Agren A, Lenner P. Postmenopausal breast cancer risk in relation to sex steroid hormones, prolactin and SHBG (Sweden). *Cancer Causes Control.* 2003 Sep;14(7):599-607.

Onland-Moret NC, Kaaks R, van Noord PA, Rinaldi S, Key T, Grobbee DE, Peeters PH. Urinary endogenous sex hormone levels and the risk of postmenopausal breast cancer. *Br J Cancer.* 2003 May 6;88(9):1394-9.

Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, Gass ML, Stefanick ML, Lane DS, Hays J, Johnson KC, Coker LH, Dailey M, Bowen D; WHIMS Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003 May 28;289(20):2663-72.

Sellers 2004. Testimony submitted to Subcommittee on Human Rights and Wellness, House Committee on Government Reform "Balancing Act: The Health Advantages of Naturally-Occurring Hormones in Hormone Replacement Therapy", July 22, 2004.

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004 Jun 23;291(24):2947-58.

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN 3rd, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J; WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003 May 28;289(20):2651-62.

Voronoff S. Rejuvenation by grafting. Adelphi Company NY. Circa 1921.

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, & Horwitz RI. (2002). A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*;346(12):942-3.

Weiderpass E, Baron JA, Adami H-O et al. Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 1999;353:1824-1828.

Writing group for the Women's Health Initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-333.

Yu H, Shu XO, Shi R, Dai Q, Jin F, Gao YT, Li BD, Zheng W. Plasma sex steroid hormones and breast cancer risk in Chinese women. *Int J Cancer.* 2003 May 20;105(1):92-7.

Zeleniuch-Jacquotte A, Shore RE, Koenig KL, Akhmedkhanov A, Afanasyeva Y, Kato I, Kim MY, Rinaldi S, Kaaks R, Toniolo P. Postmenopausal levels of oestrogen, androgen, and SHBG and breast cancer: long-term results of a prospective study. *Br J Cancer.* 2004 Jan 12;90(1):153-9.