



Red River Pharmacy Services

Texarkana's Problem Solving Pharmacy

Compounding medications to meet patient's specific needs

Dear Doctor,

As you know, the National Institute for Health has recently released information about The Women's Health Initiative, which has resulted in much national publicity. The institute's investigators abruptly ended the largest study on synthetic hormone replacement therapy. The Data and Safety Monitoring Board of The Women's Health Initiative cited the main factor for discontinuing the combination therapy arm of the study was an increased risk of invasive breast cancer as compared to placebo. This factor was based on an average follow up of 5.2 years. The active drug arm also had an increase in cardiovascular events. The Board determined that these risks outweigh the benefits, which include a decrease risk of colon cancer and hip fractures.¹

It is important to differentiate between synthetic hormone replacement therapy cited in the study and bio-identical hormone replacement therapy offered by compounding pharmacies. A compounding pharmacist, pursuant to a doctor's prescription can prepare customized bio-identical hormone replacement therapy for women as an alternative to synthetic hormone replacement therapy. The medications compounded by our pharmacists are "bio-identical", which means they represent the chemical structure exact to those produced by the female body. These formulas include: estradiol, estrone, estriol, micronized progesterone and testosterone. In fact, we provide these hormones in proportions that closely mimic the amount produced by premenopausal women.

Sincerely,

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Bio-Identical Progesterone and The Medical Literature

It has been established that bio-identical progesterone prepared by compounding pharmacies protect against endometrial hyperplasia due to estrogen replacement therapy. The Postmenopausal Estrogen / Progesterone Interventions (PEPI) Trial investigated 875 healthy postmenopausal women receiving estrogen and progesterone replacement therapy.² The primary objective of the trial was to assess the effect of estrogen/progesterone regimens (including Premarin® and Provera®) on selected heart disease factors. The investigators concluded: "In women with a uterus, conjugated equine estrogens (Premarin®) given along with bio-identical progesterone had the *most favorable* effect on HDL cholesterol and no excess risk of endometrial hyperplasia. Provera® was also shown to decrease the risk of endometrial hyperplasia, however, did not produce as favorable results on the cardiovascular profile.² The dose of progesterone used in the study was 200mg per day for the first 12 days of the cycle.²

While it is known that Provera® has an anti-proliferative effect on the endometrium, progesterone has an anti-proliferative effect on breast tissue and the endometrium. A study printed in the April 1995 issue of Fertility & Sterility evaluated the effect of topically applied hormones on the proliferation of breast epithelium.³ The investigators concluded that the data suggests that progesterone may have a therapeutic value to prevent breast epithelial hyperplasia when used more than 10 days per month at appropriate substitutive doses.³

In 1981, researchers from John Hopkins University conducted an epidemiological study in an effort to determine breast cancer incidents in women with a history of progesterone deficiency.⁴ The researchers followed 1,083 Caucasian women who were separated into 2 groups based on their endogenous progesterone levels. The women were followed for 13 to 33 years. Results showed an increase in breast cancer incidence that was 5.4 times greater in women with low progesterone levels. Women in the progesterone deficient group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to women with normalized progesterone levels.⁴

A third study evaluated the protective effects of progesterone and Tamoxifen in estrogen-induced mammary carcinogenesis in W/FU rats.⁵ The investigators concluded that progesterone and Tamoxifen demonstrated a protective effect against estrogen-induced mammary carcinogenesis in ovariectomized rats.⁵

These studies suggest that bio-identical progesterone may exhibit a protective role against breast cancer. These findings have become even more significant in light of the recent information released from the Women's Health Initiative study, which was abruptly ended due to the increased incidence of breast cancer in those patients on synthetic estrogen and progesterone therapy.

References:

- 1) 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; 288:321-333.
- 2) Writing Group for the PEPI trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA*. 1995; 273: 199-208.
- 3) Chang K, Tigris L, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vitro *Fertility and Sterility*. 1995; 63(4): 785-791.
- 4) Cowan LD, Gordis L, et al. Breast cancer incidence in women with a history of progesterone deficiency. *Am. J. Epidemiology*. 1981; 114(2), 209-217.
- 5) Inoh A, Kamiya K, et al. Protective effects of progesterone and Tamoxifen in estrogen induced mammary carcinogenesis on ovariectomized W/FU rats. *Jpn. J. Cancer Res*. 1985; 76: 699-704

For a copy of any of the above referenced articles
contact Gena at (903) 792-7435 or (903)-824-0319

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May 27, 2003

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This letter is in response to your inquiring about the cardiovascular effects of Bio-identical Hormone Replacement Therapy (BHRT). I will briefly summarize the articles and trials I am familiar with. I have also included a copy of these journal articles so that you can assess to them and formulate your own opinion

Red River Pharmacy is a specialized compounding facility, which prepares many different dosage forms to deliver BHRT. Most commonly we prepare BHRT in oral capsule form or as a topical cream, however, occasionally we will prepare troches, sublingual drops and vaginal suppositories and creams. Bio-identical hormone replacement therapy is called such because we use hormones that are identical in structure (and therefore function) as those sex hormones, which are native to the human body. There are three "native" estrogens used in BHRT; Estrone, Estradiol and Estriol. The major difference between our formulas of ERT and commercially available estrogens as I see it is the addition of estriol. Evidence supporting the addition of estriol is largely related to its effects in breast cancer. I have found no conclusive evidence that estriol has any added benefits in the prevention of CVD. Our compounded BHRT also may include; progesterone, testosterone and DHEA-s.

The cardiovascular advantages of BHRT over most commercially available combination HR prescriptions are seen with a comparison of the effects of medroxyprogesterone acetate (MPA) versus bio-identical progesterone. MPA and other synthetic progestin's are most commonly used in hormone-replacement regimens to decrease the risk of endometrial hyperplasia in women receiving estrogen replacement who have