Coast Compounding PHARMACY

3921 Waring Rd, Ste A
Oceanside CA 92056
Tel 760-433-6233
Fax 760-433-6234

Conjugated Estrogens with or without Progestin Therapies for Pre and Postmenopausal Women

1. What are estrogen and Progesterone formulas and what do they treat?

Estrogen and Progesterone are hormones. Estrogens are given either alone, or in combination with progesterone. Estrogen is used to: reduce hot flashes in menopause, treat vaginal dryness, itching and burning due to menopause, help reduce chances of getting osteoporosis (thin weak bones) in menopause, treat certain conditions in women before menopause if their ovaries do not make enough estrogen, ease symptoms of certain cancers that have spread through the body, in men and women.

2. What is menopause?

The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes menopause (the end of monthly menstrual periods) or the "change of life."

3 What changes do women go through after menopause?

Every woman experiences menopause differently. Some may not experience any noticeable effects at all. As estrogen levels begin to drop, women may experience changes such as: Hot flashes ("hot flushes") - these symptoms can range from feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating. Vaginal changes/vaginal atrophy - the tissues lining the vagina may become drier, thinner and less elastic. Irregular menstruation - the menstrual cycle may become lighter or heavier and then stop. Sleep disturbances or night sweats. Emotional changes - mood swings, irritability.

4. What is the new, important information about all estrogen and estrogen with progestin drug products?

Estrogen and estrogen with progestin drug products remain the most effective products available to treat hot flashes and vaginal symptoms of menopause. The major points arising from the WHI study and WHIMS are: Postmenopausal women should not take estrogen and progestin to protect the heart. Estrogens and progestins may increase the risk of heart attack, stroke, blood clots and breast cancer. Although other doses of Prempro and other estrogens and progestins were not studied, it is important to warn postmenopausal women who take estrogens and progestins about the potential risks, which must be presumed to be the same. When these drugs are being prescribed only to prevent osteoporosis, health care providers are encouraged to consider other treatments before prescribing estrogen or estrogen with progestin. Estrogens and estrogen with progestin should be used at the lowest dose for the shortest duration. The estrogen with progestin combination studied in WHIMS does not prevent dementia or slow progress toward dementia over time. Women treated with combination estrogen plus progestin have a greater risk of developing dementia. There is a higher incidence of mammography abnormalities requiring medical attention.

5 How great are the risks for women taking estrogen with progestin?

The study results show that of every 10,000 women per year taking estrogen with progestin, there would be: 8 more cases of breast cancer; 7 more cases of heart attacks; 8 more cases of stroke; 18 more cases of blood clots in the lungs and legs; 23 more cases of dementia in women over 65 years of age.

6. Are there any risks that were found to be lowered in women taking estrogen with progestin?

The WHI study results show that of every 10,000 women per year taking estrogen with progestin drug products, there would be: 6 fewer cases of colon cancer; 5 fewer cases of hip fracture.

7. Who should not take estrogens and progestins?

Women should not take estrogens and progestins if they: think they are pregnant, have unusual vaginal bleeding, have or had certain cancers, have had a stroke or heart attack in the past year, have or have had blood clots, have liver problems or liver disease.

8. What are some side effects of estrogens and progestins?

Less common but serious side effects include: Breast cancer, Uterine cancer, Stroke, Heart attack, Blood clots, Dementia, Gallbladder disease, Ovarian cancer. Progestins should not be used in pregnancy due increased risk of birth defects. Common side effects include: Headache, Breast pain, Irregular vaginal bleeding or spotting, Stomach cramps, Nausea and vomiting, Hair loss. These are not all the possible side effects of estrogen and estrogen with progestin drug products. For more information, women are encouraged to consult with a health care provider or pharmacist.

3921 Waring Rd, Ste A
Oceanside CA 92056
Tel 760-433-6233
Fax 760-433-6234

I. Background[1,2,3]

a. Estrogens

The body naturally produces three main forms of estrogen: estrone (E1), estradiol (E2), and estriol (E3). Before menopause, E2 is the most physiologically active form of estrogen and is synthesized primarily by the ovaries. Some E1 is converted reversibly from E2 in the liver and small intestine, but E1 synthesis increases significantly after menopause when the adrenal glands replace the ovaries as the primary source of estrogen. However, it should be noted that some E2 may still be synthesized postmenopausally via aromatization of adrenal androstenedione by fat cells. Lastly, both E1 and E2 can be metabolized to E3, which is the primary urinary metabolite. E3 is considered the "weakest" estrogen, but can antagonize the effects of other stronger estrogens on the endometrium and breast if administered at low daily doses.

b. Progesterone versus Progestin

Progesterone (P4) refers to a single molecular structure that is identical to the progesterone molecule the body synthesizes. Progestin, however, refers to synthetic progestogens, or hormones that act like natural progesterone in the uterus. While synthetic progestins may mimic natural progesterone's effects on the endometrium, they may also have a variety of different actions elsewhere in the body depending on their affinity for androgen, progesterone, glucocorticoid, and estrogen receptors.

c. Testosterone and DHEA

Testosterone and dihydroepiandrosterone (DHEA) are androgens that contribute to normal ovarian function, bone metabolism, cognition and sexual behavior. Androgens are primarily produced in the adrenal gland, ovaries, and via peripheral conversion of pro-hormones. Androgens are also essential precursors for estrogen synthesis.[8] There is no consensus as what constitutes biochemical or clinical testosterone deficiency, but mean circulating testosterone levels decline gradually with age, primarily due to decreased production of the precursor androstenedione and decrease in peripheral conversion to testosterone.[9] For example, testosterone levels in women in their 40's are about half of women in their 20's. Because androgen production declines after menopause, it is reasonable to assume that some menopausal symptoms could be due to androgen deficiency. A low testosterone level is closely correlated with reduced coital frequency and loss of sexual desire.[9] The addition of testosterone therapy to estrogen replacement results in women feeling more composed, elated, energetic with an increase in sexual motivational behaviors.[10] Studies have shown that higher doses of testosterone are associated with increased side effects but no additional benefits, so replacement should given at the lowest possible dose to decrease symptoms.[8]

II. Menopause

Menopause marks the end of menstruation, and thus the diminished production of estrogen, progesterone, and testosterone. The physiological effects of each hormone, as well as symptoms of hormone deficiency or excess are outlined in the table below:

HORMONE	PHYSIOLOGIC EFFECTS	SYMPTOMS OF DEFICIENCY	SYMPTOMS OF EXCESS
Estrogen[1,2,4,5]	• *Sexual organs*: growth, blood flow, water retention, breast & endometrial cancer • *Liver*: ↓LDL , ↑HDL & triglycerides, ↑ coagulation factors • *Aging skin*: ↑ turgor & collagen production, ↓depth of wrinkles • *Other:* ↓ osteoporosis	• Hot flashes • Night sweats • Vaginal atrophy	• Breast tenderness • Bloating • Nausea • Migraine • Hypertension • Edema • Mucorrhea • Melasma
Progesterone[1,2,4,5]	• *Kidney:* diuretic (aldosterone antagonism), ↓ pressures in hypertension • *Vasculature:* ↓ arteriosclerosis, vasodilation • *CNS:* mental health, myelin formation, ↓ vasospasm	• Depression • Anxiety • Headache • Irritability • Impaired memory • Insomnia	• Fatigue • Increased appetite • Weight gain • Acne • Hair loss • Hirsutism • Depression • Yeast infection
DHEA & Testosterone[8,9,10]	• *Anabolic effects*:↑ muscle mass/bone density, stimulation of linear growth and bone maturation • *Virilizing effects:* male secondary sex characteristics include maturation of the sex organs and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair.	• Decreased libido • Fatigue • Depression	• ↓HDL* • Acne • Hirsutism • Deepening of voice • Clitoromegaly

*has not been shown to increase overall cardiovascular effect[8]

Bioidentical hormone replacement not only serves as an individualized therapeutic option for managing menopausal symptoms, but also poses several advantages over conventional therapy. For instance, while commercial estrogens (see appendix for list of all available products) have demonstrated an increased risk of blood clots, this trend has not been documented with bioidenticals.[6] Furthermore, progestins such as medroxyprogesterone acetate have been shown to induce hypertension, increase insulin resistance, and enhance estrogen activity, whereas natural progesterone decreases hypertension and edema, can lead to weight loss, and has favorable effects on lipids and mood.[4,6] Testosterone and DHEA has been shown to improve cognitive functiton, feeling of well being, and appetite, and bone density.

III. Monitoring Therapy: Saliva Testing vs. Plasma Levels

Saliva testing provide a non-invasive way to detect levels of free circulating hormones in the body.[12] This method can be useful if multiple collections are required, or if a patient has cultural, physical or psychological conditions that make them unable to have blood draws. Saliva testing also minimizes hazard associated with blood collection. Saliva differs from serum in that it measures only the free physiologically active hormone in saliva, not the inactive protein-bound form.[12] There have been many discussions about the accuracy of saliva tests. While saliva testing has been used for a number of years as a fast and reliable method to check hormone levels, some studies have shown saliva testing may not be as reliable as once believed due to the body's natural diurnal and monthly fluctuations in hormones.[13] There are still many improvements required to produce a collection device that combines ideal recovery, stability, and reliable correlation to blood levels for out-patient applications.[14] Direct serum levels have been the gold standard to measure hormone levels and monitor treatment, but may be more troublesome due to its invasiveness and requirement for office visits. Regardless of type of testing, BHRT dosing and monitoring should include both relative lab values and patient's reports of symptom frequency and intensity. The goal is to keep hormone levels at the lower end of the normal range to minimize potential side effects while decreasing symptoms and allowing the patient to have the best quality of life during these important years.

III. Conclusion

"Bioidentical" refers to hormones that are identical in chemical structure and effect to hormones produced by the human body. These products are derived from plant sources and differ from synthetically made commercial products which use a different chemical structure from that which naturally occurs. The advantages of bioidentical hormone replacement therapy (BHRT) when compared to commercially available products include decreased side effects, decreased risks for breast cancer, and improved compliance.[7] Since each formulation is custom made for each individual, treatment is based on one's symptoms and laboratory values and can be changed accordingly. This essentially customizes the treatment for the patient instead of attempting to fit the patient to a commercially available treatment. Compounding offers a unique therapy option for women who would like to have individualized treatment of menopausal symptoms. Compounding specialists offer a variety of delivery forms based on each individual preference: creams (transdermal), troches/lozenges (buccal), solution (sublingual), suppositories (rectal/vaginal), and capsules (oral).

References:

1. Harrison TR. Harrison's online. New York: McGraw-Hill Health Professions Division; 1998. Available from: <http://uclibs.org/PID/21201;> <http://uclibs.org/PID/112098>.
2. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. *N Engl J Med*. 2002;346(5):340-52.
3. Wepfer, ST. A Review of Bioidentical Hormone Replacement Therapy. *Intl Journal of Pharmaceutical Compounding*. 2002;6(1):50-54.
4. Wepfer, ST. The Science Behind Bioidentical Hormone Replacement Therapy. *Intl Journal of Pharmaceutical Compounding*. 2001;5(6):462-464.
5. DiPiro JT. Pharmacotherapy : a pathophysiologic approach. New York: McGraw-Hill, 2005.
6. Moskowitz D. A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks. *Altern Med Rev*. 2006;11(3):208-23.
7. Wepfer, S. The Science Behind Bioidentical Hormone Replacement Therapy. International Journal of Pharmaceutical Compounding. 2001: 5; 462-464.
8. Udoff, L. Androgen Production and Therapy in Women. Accessed from www.uptodate.com <http://www.uptodate.com/> on 1/27/09.
9. Davis, S, Tran, J. Testosterone Influences Libido and Well Being in Women. *Trends in Endocrinology and Metabolism*. 2001:12;33-37.
10. Watts, N, Notellovitz, M. Comparison of Oral Estrogens Plus Androgens on Bone Mineral Density, Menopausal Symptoms, and Lipid-Lipoprotein Profiles in Surgical Menapause. *Obstetrics & Gynecology*. 1995: 85; 529-537.
11. Nieman, L. Measurement of Adrenal Androgens. Accessed from www.uptodate.com <http://www.uptodate.com/> on 1/13/09.
12. Hofman, L. Human Saliva as a Diagnostic Specimen. *Journal of Nutrition*. 2001: 131; 1621S-1625S.
13. Lewis, J et al. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in menopausal women. Maturital 2002; 41: 1-6.
14. Groschl, M, Kohler, H. Evaluation of saliva collection devices for the analysis of steroids, peptides and therapeutic drugs. *Journal of Pharmaceutical and Biomedical Analysis*. 2008:47; 478-486.