

Perspectives of Hormone Replacement Therapy

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INTRODUCTION: COMING OUT OF THE CLOSET

- **THE "DARK" AGES**

Lack of information, fear and prejudice are a few of the reasons women in general remain uninformed and often times misinformed about their bodies and choices for maintaining optimal health. Fortunately, due to the courage and persistence of women across the country the veil of secrecy and what some might even call a conspiracy is slowly beginning to "see the light". Hopefully, the day is coming in the not so distant future when a woman can feel comfortable entering into a dialog with her physician regarding options for hormone replacement therapy or not to choose to take hormones of any type. Ideally, the physician will be informed about options for hormone replacement, herbal remedies, nutrition and exercise recommendations. I truly believe this time will come in the not to distant future. To understand our present day dilemma one needs to take a brief recess into the past where attitudes and current day prescribing practices were born.

- **THE BIRTH OF PREMARIN AND FEMININE FOREVER**

In an attempt to develop an inexpensive form of estrogen, Willard Allen extracted an estrogenic product from the urine of a pregnant mare. This proved to be cheap and easy to obtain, it also had fewer side effects than some of the previous hormones extracted from animals. The patents for the "horse urine estrogen" were sold to Ayerst Laboratories. Given the lack of any competition and backed by a massive advertising campaign, Premarin quickly gained a dominance in the market that has been maintained to the present time. The early marketing of Premarin was fueled by gynecologist Robert Wilson, M.D., in his book, *Feminine Forever*, published in 1966. The book was written with the financial backing of the Ayerst laboratories. In his book Wilson promoted menopause as a deficiency "disease", he campaigned to save women from the loss of their femininity. His view was that women were valued solely for their reproductive abilities and this "femininity" was what made them attractive to men. A direct quote from a paragraph in his book provides the general flavor of the book and

attitudes of many at the time.... **“The unpalatable truth must be faced that all postmenopausal women are castrates...From a practical point of view, a man remains a man until the very end. The situation with a woman is very different. Her ovaries become inadequate relatively early in life. She is the only mammal who cannot reproduce after middle age.”** *Feminine Forever* sold over 100,000 copies in seven months. The book was widely promoted in women’s magazines with the effect that by 1975, there were approximately six million women using Premarin. Today, Premarin continues to be one of the top selling drugs in the United States, in spite of the fact that there are other estrogen products, plant derived, readily available.

- **RESEARCH AND THE HORMONE REPLACEMENT CONTROVERSY:**

Currently, studies are ongoing to determine the risk/benefit factor for hormone replacement therapy, however, these ongoing studies are using conjugated (mixed) estrogen compound (Premarin) and the progestin that has already been shown to increase the risk of cancer with long term use, so when the current study is completed in 2005 we will just have more information about the Premarin/Provera regimen. Joel Hargrove, M.D., chief of Vanderbilt University’s menopause center states, “The metabolites of estradiol and progesterone frequently have important metabolic consequences. The metabolic footprint of foreign steroids in the human may be different from that of native sex steroids and may cause a variety of side effects. Estradiol and progesterone evolved with the human; therefore, these steroids would seem preferable for long-term replacement therapy.” (3) In other correspondence, Dr. Hargrove suggests that the most reasonable approach to testing should concentrate on the principal human female sex steroids estrogen and progesterone, providing measured levels of these native steroids. (1,3) Even the **PEPI** study (Postmenopausal Estrogen and Progestin Intervention trial) used only Premarin as the estrogen although the study compared natural micronized progesterone with a synthetic progestin (Provera) for the first time in the U.S. This question begs to be answered: **“Why aren’t studies done using a native human estrogen, specifically estradiol?”**

- **GENDER BIAS AND DOUBLE STANDARDS:**

Decreased libido, a common symptom of perimenopausal and menopausal women, is viewed by many insurance companies as a mental health diagnosis. Subsequently, when drawing serum testosterone levels for the purpose of evaluating the need for testosterone or monitoring therapy, the patient must pay for the cost of the blood test unless the physician is able to fine another way to communicate this symptom to the insurance company. Interesting, given the fact that many insurance companies do pay for Viagra. My personal experience is that generally insurance companies will pay for related hormone levels drawn on men in an effort to evaluate decreased libido. One of the many mysteries of our health care system.

- **WHAT ARE “NATURAL” OR BIO-IDENTICAL HORMONES**
- **WHAT ARE THE DIFFERENCES BETWEEN THEM AND “SYNTHETICS”**
- **ARE THEY “PROTECTIVE” AGAINST OSTEOPOROSIS AND HEART DISEASE**
- **WHO SHOULD CONSIDER TAKING HORMONE REPLACEMENT THERAPY**
- **WHERE CAN WOMEN GET THE “NATURALS”**

WHAT ARE THE “NATURAL” OR BIO-IDENTICAL HORMONES?

- Steroid hormones produced from plants, usually soybeans or wild yam (*Dioscorea*), are identical to the hormones produced in a woman’s body. A form of chemical processing is used to make the hormones as the human body lacks the ability to synthesize the plant substance into individual hormones.
- Patentable drugs usually refer to “artificial” or substance not found in nature. The exceptions to this include conjugated estrogens (*Premarin*), and micronized estradiol (*Estrace*). Some physicians refer to *Premarin* as being a “natural” hormone. While it is true that *Premarin* does come from a “natural” source (pregnant horse urine) it is certainly not “natural” for women. Other examples of synthetic or patentable hormones are the synthetic progestins. The chemical structure of the progestins is different than progesterone and while natural progesterone has never been shown to have any serious side effects its synthetic counterparts have significant and serious side effects. The brand name most frequently prescribed for hormone replacement therapy is *Provera*, it is generally used in combination with *Premarin* on a cyclic basis or on a daily basis using a lower dose (*Prempro*). Products that are patented which contain hormones ‘natural’ or “native” to a woman’s body, generally have received patents due to a type of unique delivery system. These products are preferable to products foreign to the body. The estrogen patches are other examples of patented hormones. They contain the hormone estradiol, one of the estrogens found naturally in a woman’s body. There are many reasons to choose products “natural” to the body. Native or “natural” sex steroids have proven time and time again both in clinical practice and in research to be better tolerated and to have fewer side effects. (2,3) Many women actually feel a significant improvement in energy levels, sleep patterns, memory and libido.
- Bio-identical or “natural” hormones are not patentable because they are found in nature. These substances can be granted a “process patent” that recognizes the way the material or substance is collected or processed. Because the bio-identical or “naturals” are generally “custom made” for each individual by a compounding or formulary pharmacy, it would be difficult if not impossible to gain patent rights for these products. As a result there has been little interest in promoting these products to the public or to physicians. U.S. physicians are generally educated in the prescribing of patented pharmaceuticals, they are as a group, are generally reluctant to explore treatments that are not in common practice among their peers. For physicians who would be open to acquiring information on alternative forms of medical therapy, the information is not easy to come by, takes time to review and put into clinical practice and possibly more paramount, is the fear of alienation from their peer group. Physicians also fear malpractice, to quote John R. Lee, M.D., from *The Multiple Roles of a Remarkable Hormone* in 1989: “Few people know that the definition of malpractice hinges on whether or not the practice is common among one’s own medical peers and has little (usually nothing) to do with whether the practice is beneficial or not. A doctor willing to study, to learn the ins and outs of an alternative medical therapy, and to put what he has learned into practice in helping patients is potentially exposing himself to serious charges of malpractice...”

ESTROGEN, “THEIR’S” AND “OUR’S”

- The term estrogen actually is a term that is used to refer to a collective group of hormones that produce similar functions. There are three main estrogens' produced in human beings, **estradiol** which is the most potent and the major secretory product of the ovary, **estrone** (produced by oxidation of estradiol and **estriol** (primarily produced by hydration of estrone). Under normal circumstances a woman's circulating estrogen levels fluctuate based on her menstrual cycle and the proportions of the three main estrogen hormones vary, however, the approximate percentages are as follows:
- **ESTRIOL (E3) 60-80%** of circulating estrogens. Thought to be protective against breast cancer. (4,5) Causes little or no built-up of the endometrium (uterine lining). (9) Offers one potential option for symptomatic women at high risk of breast cancer. (10) Very effective in alleviating vaginal and urinary symptoms in postmenopausal women. (11) Does not appear to produce changes in serum lipid levels. (cholesterol, triglycerides, LDL, HDL)
- **ESTRONE (E1) 10-20%** of circulating estrogens. This is primary estrogen produced after menopause.
- **ESTRADIOL (E2) 10-29%** of circulating estrogens. Predominant estrogen produced by the ovary before menopause.

ORIGINAL TRI-ESTROGEN FORMULA (2.5 MG)

- **ESTRONE (10%) 0.25 MG**
- **ESTRADIOL (10%) 0.25 MG**
- **ESTRIOL (80%) 2.0 MG**

ORIGINAL BI-ESTROGEN FORMULA (2.5 MG)

- **ESTRADIOL (20%) 0.5 MG**
- **ESTRIOL (80%) 2.0 MG**

PREMARIN Quoted from the Physicians' Desk Reference "...contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from **pregnant mares' urine**."

- **ESTRONE 75-80%**
- **EQUILIN 5-6%**
- **ESTRADIOL + OTHERS 5-19%**

Dr. Malcom Whitehead and Dr. Campbell, two leading menopause researchers in England, did studies of the potencies of the different types of estrogens and the effects of the various estrogens on different target organs in the body. While their research raised some serious issues essentially none of these concerns have been addressed with further studies in this country. “Campbell and Whitehead show(s) that the conjugated equine estrogens are about three times more potent in stimulating the liver production of rennin substrate, which is used to make angiotensin in the body, a factor that causes increased blood pressure.” Micronized estradiol (brand: Estrace) and piperazine estrone sulfate (brand: Ogen) did not show this elevation of rennin substrate. These findings correlate with work published by Geola in 1980. He “observed that 1.25 mg of conjugated equine estrogens (brand name: Premarin) daily, caused supraphysiologic (greater than normal) effects on the liver synthesis of rennin substrate, physiological (normal) actions on the vagina lining tissue (epithelium) and subphysiological (less than normal) effects on the brain hormones FSH and LH.” Similar effects have been reported in other research. (19,20,23) AN-OTHER REASON THAT THERAPY MUST BE INDIVIDUALIZED. ONE SIZE DOES NOT FIT ALL.

COMMERCIALY AVAILABLE BRANDS OF ESTRADIOL APPROVED FOR HORMONE REPLACEMENT THERAPY:

- ESTRACE tablets
- ESTRADERM and CLIMARA transdermal patches

WHAT IS THE FUNCTION OF ESTROGEN?

- **Promote development and maintenance of female reproductive structures.** Particularly the lining of the uterus, the endometrium.
- **Responsible for development of female secondary sex characteristics.** Includes fat distribution to breasts, abdomen, hips, broad pelvis, voice pitch and hair pattern.
- **Increase protein anabolism.** Estrogens beneficial affect on postmenopausal osteoporosis is felt to be due more to their renal calcium-retaining effect rather than to a direct anabolic effect on the matrix of the bone. In other words, it appears that estrogen helps prevent bone loss in part through its work with the kidney to prevent loss of calcium in the urine. Estrogen also stimulated the liver to produce proteins that effect other hormones of the endocrine system.
- **Estrogen appears to be cardioprotective.** Exactly how estrogen does protect from heart disease and whether it actually does protect has been the subject of significant study and debate. Generally, it is accepted that it does offer protection for the heart. It is believed that estrogen exerts its affect on lipids by increasing the high-density lipoprotein cholesterol (HDL-C) (“good cholesterol”) and by decreasing low-density lipoprotein cholesterol (LDL-C (“bad cholesterol”). (22) “Furthermore, prospective studies suggest that HDL-C is the best predictor of coronary heart disease risk in women, and that up to half of the apparent cardiovascular benefit observed in estrogen-treated women may be mediated by the higher HDL-C levels.” (22)

- “Estrogen has a relaxing factor in the smooth muscle cells which determine the flow of blood through the body. This allows the arterial walls to remain flexible. It is also an antioxidant effecting LDL (prevents oxidation) and prevents destruction of vitamin C,E, and beta-carotene. It also has the ability to inactivate nitric oxide, which is known to increase blood flow and pressure and is associated with plaque formation on the arterial walls.” HEART DISEASE IS THE MOST COMMON CAUSE OF DEATH IN WOMEN IN NEARLY ALL INDUSTRIALIZED COUNTRIES.
- **Antidepressant affect.** “Dr. E.L. Klaiber and Co-workers evaluated a series of premenopausal women with regular menstrual cycles who suffered from a major depressive illness and higher levels of plasma MAO activity (which breaks down and inactivates catecholamines and serotonin) than did nondepressed women. Dr. Klaiber interpreted these abnormalities as further evidence of norepinephrine/serotonin insufficiency consistent with current biological theories depression. His study did not attempt to evaluate the therapeutic effectiveness of estrogen therapy, but all to the patients who received estrogen therapy reported “moderate to marked” improvement in their moods.” (19) In another study, Dr. Klaiber’s group found that oral estrogen therapy was significantly effective in improving mood in women who had not responded to more traditional antidepressants medications. These and other studies support the role of PMS-perimenopausal and menopausal mood disorders. (19, 29, 27) Mood disorders in this group of women has long been thought to be a “syndrome” not related to hormones or their fluctuation.

POTENTIAL SIDE EFFECTS OF ESTROGEN

- Nausea
- Fluid retention
- Irregular bleeding
- Breast tenderness
- Increased chance of gallstones
- Headaches in susceptible women
- Increased blood clotting (this is mainly seen with higher doses of estrogen)
- May enlarge fibroids and worsen endometriosis (some disagreement with this, studies are ongoing)

PROGESTERONE, NATURAL VS. SYNTHETIC “PROGESTINS”

- **BIO-IDENTICAL OR NATURAL PROGESTERONES.** Progesterone is produced by the ovary, in the premenopausal female, as a consequence of ovulation. Small amounts are also produced by the adrenal gland. Natural progesterone has a chemical structure identical to that produced in humans. Oral progesterone has never been shown to be toxic or harmful. (21, 22) Side effects, although uncommon when given in physiologic dosages, include drowsiness, headache, nausea and dizziness. These reported side effects generally have occurred when using oral micronized progesterone to treat premenstrual syndrome. (7,8)

- **SYNTHETIC PROGESTINS.** These products are analogues or synthetic copies of progesterone. They have been developed to produce a progesterone that is longer lasting, stronger, and of course, patentable. Common labels for these products include: *progestins, progestogens or progestational agents*. Unfortunately, literature and common usage often interchange the synthetic terms with the word progesterone, creating much confusion. Since these synthetic products are unique chemicals, foreign to the human body, they create diverse and significant side effects at usual doses. Migraine headache, weight gain, mood swings, depression, irritability, acne, menstrual irregularities and fluid retention to name a few. The **PEPI** study (22) demonstrated that medroxyprogesterone acetate caused “significant” losses in HDL-C, “the most important readily measure determinant of cardio-protection in woman,” when it is added to estrogen therapy, decreasing the “protective” benefit of estrogen therapy. Natural progesterone however, “appears to spare the endometrium and to preserve the bulk of estrogen’s favorable effects on risk factors including HDL-C.” (22) The list of possible adverse reactions is extensive. Side effects are a frequent cause for discontinuation of hormone replacement therapy.

ADMINISTRATION

- Natural progesterone can be administered as a oral micronized capsule, as a lozenge or troche, transdermal preparation, vaginal or rectal suppository or intramuscular injection. They are available by prescription. There are a number of different progesterone creams available over the counter (without a prescription) however, these products vary considerably as to their actual progesterone content. It is important to remember that these non-prescription products are drugs. Hormones play multiple, complex roles in the body as they interact with one another, caution is advised in using these and other products without professional advise.
- Synthetic progestins are available in tablet and injectable form. The most common progestin used for hormone replacement therapy is medroxyprogesterone acetate. A few common brand names are Provera®, Cycrin®, and Amen®. Depo Provera® is the brand name of the injectable form of medroxyprogesterone acetate, it is commonly used as a contraceptive and in some instances for the temporary management of dysfunctional uterine bleeding.

FUNCTIONS OF PROGESTERONE

- In the absence of pregnancy or implantation of a fertilized ovum, it’s role is to effect secretory transformation of the endometrium to produce orderly shedding of the uterine lining. Inadequate amounts of progesterone in the presence of estrogen (in premenopausal quantities) can lead to heavy irregular bleeding.
- Decreases the number of estrogen receptors, accounting in part for its antiestrogenic or protective properties against endometrial (uterine lining) cancer. The same process appears to provide protection against breast cancer. (3, 12, 13, 14, 15, 21, 27)
- Functions as a diuretic (16)
- Builds bone density (17, 18)

- Promotes glucose utilization (16)
- Improves libido
- Improves sleep patterns

ANDROGENS, THEIR ROLE IN HORMONE REPLACEMENT THERAPY

- **RESTORING THE “BALANCE”** In keeping with the intent to restore hormones in a bio-identical manner one must assess the androgen levels and if found to be deficient they should also be replaced. Not to do so is to leave the woman’s therapy incomplete. We can not improve upon human physiology. Estrogen, progesterone, DHEA and testosterone are involved in a complex symphony and to leave out one or more “instruments” could change the beauty of the final arrangement. Which “instruments” are needed and which “notes” they play must be individually determined with and for each woman. Hence, the “art” and “science” of medicine.
- **WHAT ARE ANDROGENS?** Testosterone and dehydroepianandrosterone (DHEA) which is actually an androgen precursor hormone. Androgens are metabolically active in skin, muscle, and bone and are thought to have an important role in maintaining libido. (3) Androgens help maintain muscle mass and strength. In the skin, they support collagen and help maintain oil production. Estrogens and androgens are necessary to maintain the optimum integrity of the musculoskeletal system.
- **WHAT HAPPENS TO ANDROGENS AFTER MENOPAUSE?** After “natural” menopause a woman’s ovaries continue to produce androgens. However, the majority of the androgens produced in the body even before menopause, come from peripheral conversion of DHEA. As the body ages, production of DHEA declines so that by the time a woman goes through her transition into menopause, and is in need of support from her adrenal glands, the production of DHEA is often inadequate. Symptoms provoked by this potential deficiency vary substantially, again, this is unique to each individual. Replacement must be provided for to maintain physiologic levels. (normal in this instance is defined as comparable to the replacement levels of estrogen and progesterone used) (3, 25)
- **REPLACEMENT OPTIONS.** Bio-identical or “natural” testosterone with or without DHEA when given at physiologic replacement levels, is generally well tolerated. (3) In contrast, methyltestosterone, commonly used as a part of some hormone replacement programs, (brand name: Estratest®, Estratest® H.S.) has dose-related negative effects on HDL (good) cholesterol. On rare occasions it may also prove hepatotoxic. (26)

ARE “NATURAL” HORMONES PROTECTIVE?

- “Customized” prescriptions provide assurance of most appropriate dosing for each individual. “...attempting to establish reasonable hormone replacement based solely on management of symptoms defies logic.” (19) Estradiol levels can be kept at levels that are currently known to be protective against osteoporosis and cardiovascular disease. (3,19)

Natural Progesterone is superior to synthetic progestins in preventing cardiovascular disease. Natural progesterone does not adversely affect lipid levels. (22)

Hormone replacement therapy using native hormone therapy has proven to have fewer side effects, subsequently women are more willing to continue therapy. (19, 28) It is estimated that only about 10% of women started on “standardized” hormone replacement therapy will remain on it. Many times discontinuing therapy without discussing it with their physicians.

WHO SHOULD CONSIDER HORMONE REPLACEMENT THERAPY?

Any woman who is having symptoms severe enough to affect the quality of her life. Symptoms can include, but are not limited to: vaginal dryness, decreased libido, fatigue, decreased concentration and memory, irregular or heavy menstrual cycles, insomnia, irritability, depression or persistent sadness, palpitations or hot flashes.

Any woman who has had a hysterectomy. This is particularly important for women who have had their ovaries removed. Women who have had hysterectomies but still have their ovaries should be monitored for evidence of early menopause. Hormone levels should be monitored and treatment initiated when estradiol levels fall below 50pg/ml and FSH levels are greater than 50mIU.

Women who have strong family histories of heart disease, osteoporosis or Alzheimer’s disease.

Breast and endometrial cancer are not definite contraindications to hormone replacement therapy. (3, 27)

ALL WOMEN ON ESTROGEN SHOULD BE ON PROGESTERONE REPLACEMENT AS WELL!

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