

Bio-Identical Hormones and the Menopausal Woman

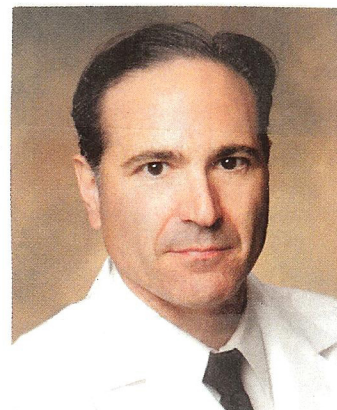
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Over the past several years, the highly publicized Women's Health Initiative (WHI) Study has created quite a stir in the medical community, the media, and the lay public alike, and deserves some attention before we discuss the possible role of bio-identical hormones in the menopausal woman. What we know from the WHI trial is that conjugated equine estrogens (Premarin) taken alone seem to be safe. What appears to be a problem is that when one simultaneously takes medroxyprogesterone acetate (MPA), also known by the brand name Provera, the benefits of hormone therapy are diminished, and in fact the effects can be unsafe. This certainly requires a closer look.

Provera (MPA) is a synthetic molecule that is biomolecularly similar to naturally occurring progesterone. All substances that have progesterone-like activity but are not biologically identical to progesterone are called progestins. There are many progestins, of which Provera is the most commonly prescribed in the menopause. When Provera is ingested orally in pill form, or injected intramuscularly (Depo-Provera), the molecule eventually enters the body's blood stream. Because of its structural similarity to progesterone, these molecules seek and then bind to progesterone receptors throughout the body. At the level of the uterine lining Provera molecules bind to these progesterone receptors, and activate (or stimulate) them. This activation provides a balance to the stimulatory effect of estrogen on the lining of the uterus, and prevents an overgrowth (hyperplasia) or cancer of the uterine lining from occurring. Thus a true physiologic, favorable progesterone-like effect is achieved in the uterus. In fact, Provera, because of its potency, is excellent in this capacity, which is in large part why it became the most popular and widely used menopausal progestin in this country. If this were the entire story, then all would be well with this more traditional synthetic menopausal hormonal treatment. The problem with Provera (MPA) is that although the molecule

has a favorable progesterone-like effect at the uterine level, in virtually every other organ system of the body this is not the case. In fact, Provera produces an unfavorable effect on other organ systems such as the breasts, cardiovascular system, and central nervous system. In these other organs Provera does indeed bind with the familiar progesterone receptors. But instead of

activating these receptors (to provide the natural balance for estrogen), the Provera molecule blocks, jams, or deactivates these receptors. This highly potent molecule thereby prevents any naturally occurring progesterone, or even estrogen from binding to the appropriate receptors at these secondary tissue sites, and eliminates any beneficial or favorable effect that these natural hormones would otherwise have. This deleterious effect of MPA is confirmed by the results of the WHI trial. Again in this trial, menopausal women were able to safely benefit from conjugated equine estrogens (Premarin) when taken alone. But when the synthetic Provera was added (Prempro with MPA), the safety and benefits of therapy were virtually eliminated. The WHI findings demonstrate that the widely used synthetic progestin, Provera, is not an ideal choice for menopausal hormonal replacement. In fact Provera is a rather poor choice for hormonal replacement. But do these findings imply that all hormonal replacement regimens, including bio-identical hormones, are a poor choice? Because there are currently no adequate studies, to help answer this question, we might look further at the natural production and function of female reproductive hormones in the body.



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Female reproductive hormones include estrogen, progesterone, and to a lesser extent testosterone (produced in much larger amounts by men). These reproductive hormones are produced primarily in the ovaries of healthy women of reproductive age. The primary function of this hormone production is to cyclically prepare the reproductive organs (the uterus and breasts) for a potential pregnancy. While these hormones have their main effect on these reproductive organs, they also secondarily effect, to a lesser extent, virtually every other organ system of the body; including the bones, heart, brain, urinary tract, and skin. These secondary effects are of great importance to a woman's long term health. The goal of menopausal hormonal replacement therapy is to achieve the benefits to these "secondary" organ systems, while carefully avoiding improper or over stimulation of the primary reproductive organs (the uterine lining and the ducts and glands of the breasts).

Ovarian hormone production is balanced and efficient during a woman's peak reproductive years. This balance may be altered during times of extreme mental or physical stress, including starvation or excess physical exertion, as the body reflexively shuts off ovarian egg production, and alters the coincidental hormonal production. At the extreme ages of reproductive potential, ovarian function also is less efficient and hormonal production is less well balanced. For example, in her mid to

late forties, before the ovaries cease functioning (menopause), they will essentially malfunction. Eggs partially ripen in the ovary, but do not ovulate. Estrogen is produced, but it is not properly balanced by progesterone. This condition, also known as perimenopause is often characterized by irregular, heavy and painful menstrual periods, mood swings, headaches, breast tenderness and other familiar symptoms characteristic of hormonal imbalance.

Perimenopausal symptoms are essentially the result of a progesterone deficiency, while menopausal symptoms are caused by a complete lack of ovarian hormone production. At menopause, menstrual periods cease, and symptoms can include hot flashes, night sweats, sleeplessness, insomnia, memory loss, anxiety, depression, weight gain, urogenital atrophy, and loss of libido.

The best treatment for perimenopausal symptoms is to shut the "malfunctioning" ovaries off, by providing just the right amount of estrogen/progestin to induce suppression. This is often best achieved in the form of an ultra-low dose oral contraceptive, containing 20 micrograms of ethinyl estradiol combined with one of the newer and much safer progestins. As yet there is no oral contraceptive containing bio-identical estrogen and progesterone. To achieve strengths sufficient to

completely suppress the ovaries, a bio-identical pill would need to be about the size of a golf ball, and clearly that would not be a desirable or practical product. Fortunately there is plenty of information supporting the safety of the current low and ultra low dose oral contraceptives. And my hope is that we will soon have an effective bio-identical form of oral contraceptive.

Because much lower amounts of hormone are required to treat the menopause, bio-identical hormones can be used. In contrast to synthetic agents, bioidentical hormones will bind and activate all appropriate receptors throughout the body. As such, in balanced, low dosages, these compounds should safely produce the desired effects at both primary and secondary tissue receptor sites. There are commercially available forms of natural estrogen, progesterone and testosterone, and in many cities and towns local pharmacists will compound bio-identical hormone replacement therapies upon request. Some pharmacies now even specialize in compounding hormonal therapies. These preparations are all plant derived (phyto-hormones) from natural precursors found in soybeans and yams. When compounded, the dosage can be titrated to the specific need of the individual.

Ideally, bio-identical estrogen includes estrone, estradiol, and estriol in a 10/10/80 proportion. While this preparation can be compounded, at present there is no commercially available preparation in this physiologic proportion (estradiol alone is commercially available). Short term estrogen use will diminish menopausal vasomotor symptoms such as hot flashes and night sweats, improve vaginal lubrication, decrease vaginal bacterial infection, and improve libido. Long term benefits of estrogens may include improved bone calcium metabolism with prevention of osteoporosis, decreased genitourinary tract atrophy, and improved skin elasticity. Other long term estrogen effects currently under investigation include cardiovascular health, memory and cognitive functioning, including Alzheimer's disease, and improved bladder function and continence.

Oral micronized progesterone, a bio-identical phyto-hormone is commercially available in the form of Prometrium. Bio-identical progesterone can also be compounded. Natural progesterone provides biological balance to estrogen, and

indeed augments the beneficial effects of estrogen. Progesterone causes smooth muscle to relax which is important in allowing the uterus to expand in pregnancy. Progesterone also causes smooth muscles in the blood vessels to relax, causing vasodilatation, and improved blood flow to the body's organs. Menopausal women often complain of difficulty sleeping. This is a direct result of progesterone deficiency. Natural progesterone has a sedating and relaxing effect on the central nervous system, allowing better sleep. In fact, when bio-identical progesterone is compounded, because the sedating effect is so pronounced, most compounding pharmacies will add a precautionary label (warning that the medication may cause drowsiness if taken during the day). Of course this is exactly what the menopausal woman wants to occur as she is going to bed at night. Therefore, it is important to take bio-identical hormones in the evening. None of the synthetic progestins will have this effect, but rather because of their receptor blocking action in the CNS, they will further impair a menopausal woman's ability to sleep. Finally, for a sexually active menopausal woman, the addition of a small amount of natural testosterone will help increase sexual desire, enhance energy levels and muscular tone, and may help with an overall feeling of well-being.

Certainly we need trials like the WHI that specifically evaluate the safety and efficacy of bio-identical hormones. To date the WHI trials have only compared conjugated equine estrogen alone (Premarin) to a combination of conjugated equine estrogen and the synthetic progestin, MPA (Provera). Until such trials include bio-identical hormones, a woman of menopausal age along with her physician will have to make an individual decision regarding hormonal replacement, whether it be with more traditional compounds or with bio-identical preparations.

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