

## Don't Let Your Doctor Give You Horse Urine! There Are Better Treatments For Menopause

By Jonathan Wright MD and John Morgenthaler

No auto mechanic in his right mind would replace worn parts on a Mercedes with new parts made from a Chevy. Unfortunately many physicians (and pharmaceutical companies) seem to have less common sense than the average auto-mechanic when it comes to treating menopausal women.

The "estrogen" replacement most doctors prescribe today for menopausal and premenopausal women is a pill known generically as conjugated equine estrogens (CEE). The best known brand of CEE is Premarin. Many studies suggest that in many women, Premarin does help reduce symptoms of menopause, including hot flashes, vaginal thinning, memory loss and urinary incontinence.

It also appears to reduce the risk of developing postmenopausal cardiovascular disease (the leading killer of women) and osteoporosis (the crippling progressive bone weakness). It also may help to prevent a significant proportion of Alzheimer's disease and senile dementia.

Premarin is horse estrogen derived from horse urine!

So what 's wrong with CEE? Take a close look at the names. Notice the word "equine?" Yes, that equine! Premarin is horse estrogen! It is derived from the urine of pregnant mares, hence its name. Premarin works great in female horse just as Chevy parts work great in Chevys. But replacing human estrogens with horse estrogens may be asking for trouble, and here's why

For the last several million years, the human female reproductive system has been running quite well on three separate estrogens; Estriol, Estrone and Estradiol, which occur in an approximation of 90%; 3%; 7% (1) (Fig 1). Compare that with Premarin, which consists of Estrone (75-80%), equilin (6-15%), Estradiol and two other equine estrogens (5-19%). (2)

Notice that, in addition to having larger proportions of Estrone and Estradiol, Premarin also contains equilin and two other forms of estrogen found exclusively in horses.

The female human body contains all the enzymes and cofactors it needs to process Estriol, Estrone and Estradiol when they occur in their natural human proportions. On the other hand, it has none of the enzymes and cofactors required metabolizing equilin and the other horse estrogens, nor does it have enough of these important substances to deal with the excessively large amounts of Estrone and Estradiol found in Premarin (or in the 100% Estradiol "patch").

Horse, of course, is well equipped to handle CEE. The difference in reproductive hormones is just one of many differences between horse and humans. You may have noticed that horses also have four hooves and a mane, whereas human females don't!

It should come as no surprise then, that the presence of Premarin in the human body induces a hormonal imbalance that can have important adverse consequences. To physicians who prescribe Premarin, this hormonal imbalance doesn't seem to carry much weight. After all, the drug works doesn't it? But, as two leading reproductive physiologists point out, when women take Premarin, "Levels [of equilin] can remain elevated for 13 weeks or more post-treatment due to storage and slow release from adipose [fat] tissue.

In addition, metabolism of equilin to equilenin and 17-hydroxyequilenin may contribute to the estrogen stimulatory effect of [conjugated estrogen] therapy." Another metabolite of equilin, 17-dihydroequilin has been found to be eight times more potent than equilin for inducing endometrial growth, a possible precursor to cancer (3).

As a result, Premarin produces "estrogenic effects" which are much more potent and longer lasting than those produced by natural human estrogens.

This explains why so many women feel "unnatural" on Premarin, why Premarin causes so many side effects and discomforts (see box). It even explains why Premarin has been associated with a significant risk of breast and endometrial cancer, because one of the primary effects of equilin, Estradiol and Estrone is to promote the growth of tissue in the endometrial (uterine) lining and also in the breast. This growth is important for preparing the premenopausal body for pregnancy and lactation, but if some of that tissue becomes cancerous or precancerous, look out!

According to Premarin's official labeling, taking it for a year (without also taking progesterone, see box), increases a women's risk of endometrial cancer by as much as 14% (2).

Most conventional physicians, not to mention the self-serving pharmaceutical industry, are quick to rationalize the cancer and other risks of horse estrogens. Every treatment has its risks, they point out, but the risk of a postmenopausal woman dying of a heart attack or stroke if she doesn't take Premarin are far greater than her risk of dying from cancer or an osteoporosis related fracture if she does.

Why not use human hormones for humans?

Well, this reasoning is true as far as it goes, but it ignores one hugely important fact, that horse hormones are not the only choice human females have. What about human hormones? Wouldn't it make sense to replace human estrogens with human estrogens? Mercedes parts with Mercedes parts? Of course, it does! The real question is why has no one thought of this before?

This realization occurred in 1982. All ob-gyn textbooks discussed the naturally occurring human estrogens Estriol, Estrone and Estradiol but completely neglected to recommend their use for treating menopausal symptoms, inexplicably recommending horse estrogens instead!

The approximate circulating levels of the three estrogens were checked in human females. This information was used to design a combination estrogen replacement regimen that closely matched the natural conditions found in premenopausal women. The result is "triple-estrogen", a combination of natural Estriol, Estrone and Estradiol using molecules identical in structure to those produced in the human body in as close to natural quantities and proportions as could be calculated.

Triple estrogen was formulated by a compounding pharmacist friend- Ed Thorp of Kripps Pharmacy, Vancouver BC, and the rest is history. In the 16 years since triple estrogen was first prescribed, thousands of other progressive physicians and their grateful patients have found that it works as well as, or better than conventional ERT regimens, while producing far fewer unwanted side effects.

Estriol, the missing-in-action hormone

You may have noticed that one estrogen, Estriol, is completely absent from Premarin and other forms of conventional estrogen replacement regimens, although it comprises as much as 80-90% of triple estrogen. This is not an insignificant omission. Most conventional physicians and pharmaceutical researchers have long dismissed estriol as a weak and unimportant estrogen. They have considered it to be primarily a metabolite of Estradiol and Estrone, which are far more potent in producing estrogenic effects, such as inducing endometrial tissue growth. "Why go through all the trouble of putting Estriol into a pill if you don't really need it?" seems to be their reasoning.

Well potency isn't everything. In fact, Estriol is vitally important precisely because it is a weak estrogen. A number of studies, published over four decades, have demonstrated that estriol's unique and perhaps most important role, may be to oppose the growth of cancer, including cancer promoted by its more potent cousins, Estrone and Estradiol. We'll talk more about this in a moment.

Estriol plays more than just a defensive role though. European physicians have been open to the potential benefits of Estriol in menopausal women than those in the US. As a result, most of the clinical research evaluating Estriol has been conducted in Europe. In general, these studies show that menopausal women who use natural Estriol to replace their natural estrogen experience a reduction in typical menopausal symptoms like, hot flashes and thinning of the vaginal tissue (vaginal atrophy) (4).

\* In one major trial, 22 practicing gynecologists from 11 large hospitals in Germany treated 911 premenopausal women with Estriol and evaluated them regularly for 5 years. They found Estriol to be "very effective" against common menopausal symptoms and "well-tolerated" with "no significant side effect." (5)

\* A Swedish study evaluated 40 postmenopausal women with urinary incontinence (leaky bladders) for up to 10 years. The researchers found that Estriol treatment resulted in significant improvement in 75% of the women, including eight whose ability to regulated urination completely returned to normal. (6).

\* The same Swedish study found that symptoms of vaginal atrophy disappeared in 79% of the women after just 4 months of Estriol treatment. After 12 months, all but one woman were symptom free (6).

#### Built in cancer protection

There is no doubt that reasonable doses of horse estrogens and 100% Estradiol patches and creams stimulate excessive proliferation of endometrial cells, a precursor to endometrial cancer.

It is to reduce this risk that any woman taking these drugs must also take natural progesterone or a synthetic progesterone substitute (or "progestin") like the Provera (see box). This is in stark contrast to Estriol, which appears to actually antagonize the proliferate effects of Estrone and Estradiol, while having far less tendency to stimulate endometrial proliferation, itself. Studies in experimental animals have shown that the proliferate dose of Estriol (the dose that produces full endometrial growth) is at least double that of horse estrogens and Estradiol (7).

Estriol apparently accomplishes its protective role by benignly binding to estrogenic receptors in the uterine lining and possibly the breast. Unlike the more potent estrogens though, it does not stimulate growth nearly as much. At the same time, receptors covered by Estriol are shielded from more carcinogenic Estrone and Estradiol (4).

This is thought to be the same mechanism by which other weak estrogens, such as those found in soy products, protect against cancer. In laboratory animal studies totaling more than 500 rat-years, Estriol has been shown to be the most protective estrogen ever tested against cancers of the breast induced by several potent carcinogenic agents, including radiation (8,9).

There is important evidence dating back to the 1960's suggesting that Estriol may protect against breast cancer as well. At that time, Henry Lemon, MD, who was head of the division of gynecologic oncology at the University of Nebraska College of Medicine, hypothesized that some women who develop breast cancer have too little Estriol relative to Estradiol and Estrone circulating in their bodies.

To test this hypothesis, Dr. Lemon ran a preliminary study in which he employed a urinary estrogen quotient (EQ), which was simply a measure of the ratio of Estriol to the total of Estradiol and estrogen in the urine over a 24-hour period. The higher the quotient, the more Estriol there is relative to Estradiol and Estrone (10).

In a small study of 34 women with no signs of breast cancer, Dr. Lemon found the EQ to be a median of 1.3 before menopause and 1.2 after menopause. Only 21% of the women had an EQ <1.0 (I.E. ESTRIOL WAS LESS THAN ESTRADIOL AND ESTRONE COMBINED). FOR 26 WOMEN WITH BREAST CANCER, HOWEVER, THE PICTURE WAS QUITE DIFFERENT. THEIR MEDIAN EQ WAS 0.5 BEFORE

MENOPAUSE AND 0.8 AFTER MENOPAUSE; 62% OF THESE WOMEN HAD AN EQ <1.0.

Thus, the women with breast cancer seemed to be making substantially less Estriol relative to the other estrogens, compared with the women without breast cancer.

Over the years some researchers have published work disputing Dr. Lemon's findings, while others have supported him. The issue is complicated by the fact that a woman's level of Estriol when breast cancer becomes apparent may not be as important as a deviation from the norm in her Estriol levels as a young woman.

Clearly, much more research, including large-scale, long-term human trials are needed to answer the many unanswered questions regarding estriol's role in cancer. In the meantime, there can be little doubt that an estrogen replacement regimen that includes the three human estrogens in triple estrogen, (Estriol, Estrone and Estradiol) in identical-to-natural proportions is a superior choice for premenopausal and postmenopausal women. Especially when compared with the horse estrogens and 100% Estradiol patches and creams the pharmaceutical industry promotes.

This sentiment was echoed in a 1978 editorial in the Journal of the American Medical Association titled, "Estriol, the forgotten estrogen?" in which Alvin H. Follingstad, MD, bemoaned the lack of large clinical trials on Estriol that would earn it an FDA stamp of approval. "Do we as clinicians have to wait the years necessary for the completion of these trials before Estriol becomes available to us?" he asked. "I think not, enough presumptive and scientific evidence has been accumulated that we may say that orally administered Estriol is safer than Estrone and Estradiol." (11)

Two decades later, we are still waiting for those clinical trials, and what Dr. Follingstad said then is even truer today. There's nothing to be gained by waiting. If a woman is concerned about her risk of cancer from estrogen replacement (and who isn't?), then the logical choice is an estrogen formula containing a majority of Estriol, in other words, triple estrogen.

Especially when you consider both modern scientific research and hundreds of thousands of years of human experience producing and metabolizing estrogens).

Natural hormone formulations like triple estrogen are normally available in the US only from compounding pharmacies with a physician's prescription; they can not be found at standard pharmacies. You can also order triple estrogen cream from some overseas pharmacies (ed., - note that IAS has the precise 90/7/3 natural estrogen cream researched and formulated by Jonathan Wright MD, it is called ESNATRI).

The business of menopause

If triple estrogen is so much better than Premarin, why have so few people heard about it? The answer to this question can be summed up in one word, patentability. Premarin is

patentable, and hence, can be sold exclusively only by its manufacturer and licensees, whereas triple estrogen is a natural product, like vitamin C, and can be sold by anyone.

Patentability has made Premarin a huge moneymaker for its manufacturer, Wyeth-Ayerst Pharmaceuticals. For nearly 30 years, it has been at or near the top of the drug best seller list. In just the first half of 1997, pharmacists filled 22.1 million prescriptions for Premarin, amounting to revenues of \$388.2 million in the United States alone! Add in the rest of the world's women, and you get a sense of the high stakes involved in the business of menopause.

These enormous financial resources have provided Wyeth-Ayerst the muscle to practically corner the estrogen market. Through advertising, sponsorship of clinical trials, and conferences, free samples and other common marketing techniques, they have created an atmosphere in which physicians virtually equate estrogen replacement with Premarin.

Most physicians, who have little enough time to keep up with the world of double blind, placebo-controlled drug trials reported in medical journals (which are supported largely by pharmaceutical advertising) are completely in the dark about the use of triple estrogen and other natural hormones. Their use is not taught in medical schools, nor do any large pharmaceutical companies promote it

With no money available to pay the enormous costs, the large, definitive studies that might demonstrate the efficacy and safety of these natural hormone regimens will likely never be done.

What makes a hormone natural?

The word "natural" gets thrown around a lot in discussions of hormone replacement therapy. Premarin, for example, is widely considered to be a "natural hormone." So is the Estradiol in the estrogen "patch" and "cream" products. Triple estrogen is also considered to be a "natural" estrogen product. Are they are natural? Does it really matter? The answers depend on how you define "natural."

Triple estrogen consists of three separate estrogens. Estriol, Estrone and Estradiol, all of which are derived from a plant, the wild yam (*Dioscorea composita*). How can a hormone that got its start in a vegetable be considered "natural" in the human body? The wild yam is rich in "precursor" molecules that can be easily converted by biochemists into estrogens and other steroid hormones.

The molecular structure of these hormones is indistinguishable from that of the "natural" hormones produced in the human body, and as a result, they function exactly like those the body produces, especially when used in their natural proportions. Thus, the crucial variable defining "natural" is not the origin of the hormone or how it is produced, but whether its chemical structure matches that of the hormone it is intended to replace.

Premarin is natural for horses but not for humans!

Premarin is widely considered by physicians to be a "natural" hormone product, because it is derived from horse urine and is not synthesized in a laboratory. But is it really natural? Certainly, it's natural in horses. But when placed in the human body, the hormones in Premarin are as foreign as any synthetic drug, because the body lacks the enzymes and cofactors to metabolize them safely.

What about estrogen "patch" and "cream" products? These are composed of 100% Estradiol, the most potent and most carcinogenic of all the estrogens. The Estradiol is derived from the same source as the Estradiol in triple estrogen, the wild yam, so in that sense, these products can be considered "natural." However, because they are 100% Estradiol, with no Estrone and most importantly, no Estriol, these products must be considered unnatural once inside the human body.

The human physiology is designed to work with three forms of estrogen, Estriol, Estradiol and Estrone, in a ration of about 90:7:3. Exposing the body to 100% Estradiol creates an unbalanced, and therefore, unnatural and potentially dangerous situation.

Natural Progesterone protects against cancer, heart disease and osteoporosis. Women who replace estrogen also need to replace progesterone. This may seem obvious to anyone who has studied human reproductive physiology, because estrogen and progesterone are closely linked in the normal menstrual cycle. Each month, as estrogen levels rise, progesterone levels fall, and vice versa. Unfortunately, it wasn't always so obvious to physicians and pharmaceutical companies.

In the early days of ERT, tens of thousands of women developed endometrial cancer as a result of taking Premarin in the absence of progesterone. In the absence of progesterone, the estrogen in Premarin can cause excessive proliferation of endometrial tissue, which, in an alarming number of instances, can turn malignant. Progesterone largely prevents this excessive growth. But conventional medicine being what it is, most physicians do not prescribe natural progesterone for their menopausal patients. Instead, they prescribe a synthetic progesterone-like drug, or "progestin," called Provera (medroxyprogesterone), or one of its clones.

Synthetic progestins are not the same thing as progesterone. Thanks to the pharmaceutical industry's promotional abilities, few physicians ever make that distinction.

Women who take Provera pay a high price for the protection it affords against Premarin-induced endometrial cancer. That price includes an increased risk of cardiovascular disease (CVD), because progestins strip away most of the protection against CVD that they gain from estrogen replacement. Since this protection is one of the main reasons they take Premarin in the first place, and since Provera causes a long list of unpleasant side effects. Including breast tenderness, weight gain, depression, and breakthrough bleeding, to name just a few, you have to wonder whether they wouldn't be better off not taking anything!

Natural progesterone, which comes from the same source as the natural estrogens in triple estrogen, is a completely different story. Because it is structurally and functionally identical to the progesterone the body produces, replacing missing progesterone with natural progesterone puts back the same hormone the body is accustomed to.

As a result, when used properly, natural progesterone affords the same protection against endometrial cancer as synthetic progestins, but does not interfere with estrogen's ability to protect against CVD. This was most clearly demonstrated in a large scale federal government sponsored clinical trial, known as PEPI (Postmenopausal Estrogen / progestin Interventions) (12).

In the PEPI trial, 875 postmenopausal women were randomly placed in one of four treatment groups. (A) Placebo (B) Estrogen (i.e. Premarin) only (C) Premarin and Provera or (D) Premarin and natural progesterone (oral). The relevant measure was the level of HDL-cholesterol, which is known as the "good" cholesterol, since it protects against CVD. The results clearly demonstrated that when Provera was added to Premarin, HDL levels dropped to nearly baseline. By contrast, when natural progesterone was added to Premarin, there was no significant loss of HDL-based CVD protection.

If this weren't enough to recommend natural progesterone, there's also the protection it provides against osteoporosis. This ability has been most clearly shown by the work of John R. Lee, MD (13,14).

Osteoporosis is the bone thinning disease that commonly occurs following menopause. It appears to be due to a loss of both estrogen and progesterone. Replacing estrogen will usually help slow or even halt the thinning process, but it does nothing to restore bone that has already been lost.

Dr. Lee took regular bone mineral density measurements of 62 postmenopausal women who were taking Premarin plus progesterone (in a cream base) or progesterone alone for a period of at least 3 months. The women also took calcium supplements and maintained a diet and lifestyle designed to minimize bone loss. He found that natural progesterone replacement resulted in a remarkable increase in bone mineral density.

Some of Dr. Lee's patients increased the density of their lumbar vertebrae by 20-25% in the first year! Over the 3 years of the study, the mean increase in bone mineral density was 15.4%. According to other studies, including PEPI, a 4-5% decrease in bone density would have been expected in women not using natural progesterone. Not surprisingly, Provera appears to provide no protection against osteoporosis and definitely does not enhance bone growth.

#### IAS comments

This excellent article has been contributed by Jonathan Wright, MD and John Morgenthaler and is extracted from their must read book -Natural Hormone Replacement for Women over 45. It is available from Smart Publications in the USA at a cost of \$9.95 plus \$3.95 shipping and handling (US addresses only). California residents must add

7.5% sales tax, foreign orders call Smart Publications for airmail rates, Their telephone number in the USA is 707 769 8308 (fax 707 763 3944). Their complete details are listed under PROFESSIONAL PEOPLE AND ORGANIZATIONS.

Working with this latest clinical research, IAS can offer a natural triple estrogen cream of 90% Estriol, 7% Estradiol and 3% Estrone called ESNATRI.

IAS can also offer the natural progesterone listed as progesterone.

It is important to stress that your physician must guide a natural hormone replacement therapy (NRT). DO NOT start any NRT program if you have ever suffered from cancer.

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