

COVER STORY

PREMARIN
PREGNANT MARES URINE

The biggest snow job in American history has come to a grinding halt with a study that puts to rest once and for all the notion that a drug made from the urine of pregnant horses will keep women healthy and youthful. It may kill them instead says an NIH study of 8,000 women who took "Prempro", a combination of the drug, Premarin, and synthetic progesterin (medroxyprogesterone acetate). Prempro was supposed to enhance health, not endanger it, but five years into the eight-year study, the monitoring committee put a stop to it, and announced that the side effects weren't worth the risk. Blood clots increased 100%, stroke increased 41%, heart attacks increased 29%, heart disease increased 22%, and most ominously, the risk of invasive breast cancer increased 26%. Prempro now has the dubious distinction of increasing the risk of all of the leading causes of death in older American women. It did reduce colorectal cancer 37%, hip fractures 33%, and other fractures 24%, though.

The NIH study that was halted is part of a huge, government-sponsored trial known as the Women's Health Initiative (WHI). Over 160,000 women are involved in the WHI, which is designed to find ways to prevent heart disease, cancer and broken bones in older women. Although the Prempro portion of the study was stopped, a study on Premarin ("conjugated equine estrogens") is ongoing. Researchers are still hoping the drug will prevent heart attacks—a hope that may be founded more in hype than science. No study has ever convincingly shown that Premarin can prevent heart attacks or heart disease. Small studies

have shown that it can create a better lipid profile, but that has never translated into preventing heart attacks in any meaningful way. The lipid changes Premarin causes are not comprehensive to begin with. Adding synthetic progestins (to protect the uterus from cancer) reverses some of those benefits, leaving a less-than-stellar overall effect.

Heart hype

The notion that Premarin's lipid-lowering effects would prevent heart attacks was tested and rejected decades ago. The WHI Prempro study that was recently halted is not the first Premarin heart study that has been halted. In 1973, a huge, government-sponsored study of 8,000 men was also halted at 5 years so as to "minimize possibilities of subjecting study patients to potential harm." Lung cancer rates in the men taking Premarin were four times higher even though their smoking habits were the same as those getting placebo. Cancer mortality was higher, and the incidence of serious blood clots was much higher. (On the bright side, breast cancer rates didn't go up, and prostate problems decreased).

It may seem odd for men to take estrogen, yet men naturally make this "female" hormone in their bodies just as women make the "male" hormone, testosterone. The study was done because researchers thought at the time that cholesterol was the cause of heart attacks. Since Premarin could lower cholesterol, they assumed it would prevent heart attacks.

Given this study and others showing a big increase in the risk of blood clots and other problems, why would researchers keep pursuing the notion that Premarin would prevent heart attacks? One reason is that observational studies looked promising. The Nurses' Health Study, in particular, gives strong evidence that women who take Premarin and other synthetic estrogens will be protected from heart disease—at least by one group's analysis of the data. Researchers from Harvard took data from the large, ongoing nurses' study, analyzed it and came to the conclusion that synthetic estrogen (with or without progesterin) protects the heart.

Although the analysis was published in The New England Journal of Medicine, it was highly criticized by researchers in the field. Dr. Jacques Rossouw, chairman of the Women's Health Initiative, pointed out that the nurses taking the estrogen-progesterin drugs were of a higher (and equal) socioeconomic class, better educated, had better access to doctors, had higher incomes and took better care of themselves. In other words, they were healthier to begin with. This is not disputed in the report itself which acknowledges that the women who appeared to get heart benefits from Premarin also took multivitamins (including folate), vitamin E, didn't smoke, didn't have a history of diabetes or heart attacks in the family, were younger, leaner, and took aspirin. But because the report was

published in the NEJM, it was widely accepted.

But there is another reason to believe that Premarin might prevent heart attacks. Estrogen is beneficial for blood vessels. Studies show that estrogen drugs like Premarin do help prevent the hardening and lesions characteristic of cardiovascular disease. The problem is-at what price? Natural estrogens without side effects do the same thing without risk. Vitamin K has excellent benefits for blood vessels, and it not only has no side effects, it has other benefits as well. Statin drugs, changes in diet, and supplements like policosanol are much safer choices for lowering lipids.

Although the NEJM report was the most persuasive evidence, it would not be the last. Soon after it was published, serious cracks began appearing in the concept that synthetic estrogen would protect women from heart disease. Researchers in Finland, looked at a chart of side effects from a study called the "PEPI" trial, and saw that women taking estrogen drugs were more likely to have a cardiac "event" than women not taking them. This directly contradicted widespread beliefs about synthetic estrogen. Looking into it further, they reviewed 22 studies of women taking synthetic estrogen, mostly Premarin. In 1997, they published their findings in The British Medical Journal. Their analysis confirmed what PEPI had found: heart problems are more likely to occur in women taking estrogen drugs. Despite its serious implications, their report went virtually unnoticed.

But a major study published in The Journal of the American Medical Association (JAMA) got people's attention when it reported that not only did Premarin not protect against heart attacks, it produced life-threatening side effects in women with heart disease. Women taking Prempro were no less likely to have a heart attack, and three times more likely to have a blood clot or gallbladder disease than women who didn't. Those adverse effects tapered off the longer a woman stayed on the drug, but that was small comfort for the ones who had been hospitalized with life-threatening blood clots. The study's authors concluded "we do not recommend starting this treatment for the purpose of secondary prevention of coronary heart disease." (See Life Extension magazine, June, 1999). The hoopla around this study was restrained, mostly because the women participating in it already had heart disease. But there was more to come.

Snake oil salesmen with millions

The WHI Premarin/Prempro trial has cost taxpayers millions of dollars. With all the adverse findings on the Premarin drugs-the strokes, the cancer, the gallstones, and all the side effects that cause most women to stop taking them-why are we spending millions to do more tests? And how has a drug that is supposed to cure hot flashes become the panacea for every ailment an adult woman can get? The answer to both questions is advertising. More than thirty-seven million dollars were spent pushing Premarin in the year 2000 alone. That's \$100,000 a day and it's been going on for decades. Contributions and "inducements" to physicians and big physician organizations; "incentives" to insurers and pharmacists to only reimburse for Premarin, "direct-to-consumer" ads designed to target empathy, personalize the message and improve patients' motivation have made Premarin the white noise of women's health. The truth hasn't been able to penetrate the million dollar babble.

Wyeth-Ayerst has been cited repeatedly by the FDA for falsely advertising its products. In one ad, the company reduced by two-and-a-half times the bone density achieved by a competing drug (Evista). In another, it omitted the information that Premarin could harm a fetus. In another, important side effects like blood clots, nausea and vomiting were omitted. But the most enduring lie, and the one that is taking millions of taxpayer dollars to dispel, is the notion that Premarin is the panacea for everything that can plague an older woman. The FDA warned the company in 1998 that Premarin's advertising "is misleading because it implies that Premarin can be used for a broader indication than that supported by substantial evidence." That's a delicate way of telling a snake oil salesman that his cure-all elixir doesn't. The company was told to "immediately withdraw" this direct-to-consumer advertisement in question. Wyeth-Ayerst has been reminded repeatedly that the only approved uses for Premarin in most women are hot flashes and osteoporosis. The company has also been given notice of violation for its osteoporosis ads. The Food and Drug official pointed out that contrary to the ads, it's not necessary for a woman to gain bone density to avoid osteoporosis, only to maintain it.

New Labeling for Premarin

- Within weeks of the announcement that the WHI studies on Prempro/Premphase had been halted, Wyeth-Ayerst announced that it was changing the package inserts for Premarin and related drugs. The modifications are extensive, and reverse popular misconceptions about Premarin - misconceptions that federal authorities repeatedly warned the company to quit fostering. The new warnings make clear, for the first time, that the benefits of these drugs may not outweigh the risks. Doctors who have prescribed the drugs for decades may be shocked by what they read.
- The new labeling makes everyone aware of the findings of the Women's Health Initiative study which was halted after 5 years. "Because of the potential increased risk of heart attack, stroke, breast cancer, and blood clots, use of Premarin, Prempro, or Premphase should be limited to the shortest duration consistent with treatment goals and risks for the individual woman and should be discussed with her physician

In 1999, the company was again cited for violating federal law with regard to its advertising, the FDA official noting that the Premarin ads contained "false or misleading" statements. Again the company was told to quit advertising Premarin for everything under the sun. "These advertisements," the official wrote, "promote Premarin for unapproved uses by implying or stating that Premarin is useful in a broad range of undefined health problems."*

Continued on Page 2 of 2

[Back to the Magazine Forum](#)

regularly." In other words, the old days of putting a woman on Premarin for life are over.

- The second new warning advises women to consider other treatments for osteoporosis even though Premarin is approved for this use. In other words, the risks may outweigh the benefits. There are safer alternatives.
- In addition, the new labeling will reiterate the approved uses of Premarin. Because of Wyeth-Ayerst's massive advertising campaign, many doctors and patients alike, have come to believe that Premarin is good for all sorts of things that haven't been proven. The new warnings make it clear that the approved uses of Premarin drugs are limited to: moderate to severe hot flashes, night sweats, vaginal dryness and the prevention of osteoporosis.
- The label will also contain a reminder that Premarin may cause endometrial carcinoma, and that Prempro or Premphase (Premarin combined with progestin) should be used in women who have a uterus. Women are also reminded that they should not take Premarin if they have ever had a stroke, blood clot, heart attack, and liver disease, or a known or suspected estrogen-sensitive cancer, including breast cancer, or pregnancy.
- The most common side effects of Premarin drugs are hair loss, weight gain, headache, bleeding and breast pain.

Carefully coiffed pop stars singing the praises of Premarin, are conspicuously absent from this new information campaign.

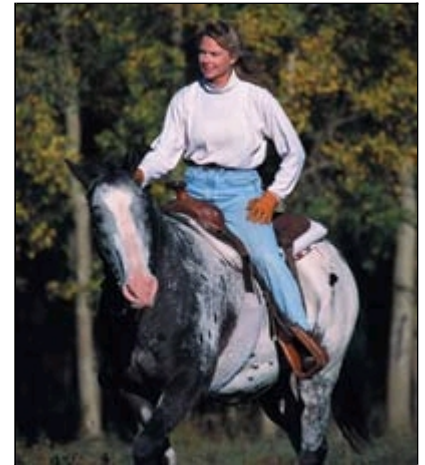
COVER STORY

PREMARIN PREGNANT MARES URINE

Confusion about estrogen

Premarin has created a big problem. Because of its huge sales, the drug has become synonymous with "estrogen". Even researchers have confused this estrogen-like product with estrogen.** Others have mistakenly referred to Premarin as "hormone replacement therapy" (HRT) as if this one drug is all there is to HRT. There are many hormones that decline with age (horse estrogen in humans not being one of them). HRT can be achieved with any number of hormones-growth hormone, testosterone, progesterone, etc. To limit hormone replacement therapy to Premarin is like limiting a fireplace to one brick.

Premarin has created another problem. According to its manufacturer, Premarin is a very unique estrogen-like product, unlike any other estrogen on the market. This argument, repeated for decades to the FDA, has kept a cheaper generic off the market. Because Premarin is in a class by itself, so unique that a generic cannot even be made without that manufacturer also keeping thousands of pregnant horses in stalls and collecting their urine, then it's important to realize that any effects or benefits Premarin has cannot be extrapolated to any other estrogen product. This means that all so-called HRT studies on Premarin products are nothing more than drug trials for Wyeth-Ayerst. The results cannot be applied to other estrogens, which leaves Americans, for the most part, without any meaningful studies on estrogen or hormone replacement. And there are dozens of possibilities-everything from natural progesterone to supplements, to herbs and other drugs.



This means that all so-called HRT studies on Premarin products are nothing more than drug trials for Wyeth-Ayerst.

What next?

Since the bubble has burst, some women have argued that they take Premarin, and feel fine. They also say that if they try to stop taking it, they get severe hot flashes or other negative symptoms. In response, it should be pointed out that if a woman taking Premarin or related drugs is diagnosed with breast cancer, the first thing her physician will do is take her off of it. One day it's safe, the next day, it's not. That's something to consider. In addition, "feeling fine" is no indication of health. Many women diagnosed with breast cancer or a stroke, felt fine the day before. Women should take the new warnings for Premarin, Prempro and Premphase to heart. Those warnings make it clear that women should take the drugs the shortest amount of time possible, and that in many cases, the risks outweigh the benefits.

A couple of other things are worth noting. A recent study in Archives of Internal Medicine reports that if a woman is taking hormone replacement therapy, and she finds a lump in her breast, she is more likely to be reassured by her doctor that it is a fibroid, not cancer. Researchers don't know why yet.

On a similar note, synthetic estrogen and progestin drugs make breast tissue dense, and harder to read on mammograms. Harder-to-detect cancer coupled with false assurances about lumps add up to the fact that a woman taking hormone drugs is less likely to get diagnosed with a disease she's more likely to get. That doesn't mean that every woman taking the drugs is going to get serious side effects. Most do not. The problem is that nobody knows which women will and which women won't.

Switching from Premarin

Some women have reported difficulties in stopping Premarin and related drugs. They report getting severe hot flashes and other side effects if they try to stop. This has never been scientifically investigated, but there is some evidence that the body adjusts to Premarin, and that sudden withdrawal may cause a reaction. Premarin increases the number of estrogen receptors-meaning that it makes physical changes on cells. It's also been reported that the drug activates or deactivates at least 32 genes in the rat uterus. What this means for women is not known. But if it does something similar in humans, the sudden withdrawal of the drug could produce side effects.



"Feeling fine" is no indication of

health. Many women diagnosed with breast cancer, or a stroke, felt fine the day before. Women should take the new warnings for Premarin, Prempro and Premphase to heart.

There isn't any official documentation of women having problems switching from Premarin drugs to something else, so the extent of the problem, if any, is unknown. The best advice to a woman who wants to replace Premarin with something else is to reduce the amount of drug slowly while at the same time increasing the amount of the replacement, allowing the body to adjust and detoxify. This can take months for some women. Women need to realize that there's no one hormone-replacement strategy that works for everybody. Women who successfully move from Premarin to

something else keep trying various combinations until they find something that works.

Do you need it at all?

Finally, women should be aware of something that's very important to the entire discussion of hormone replacement therapy. It may surprise many to learn this, but millions of women all over the world don't get menopausal symptoms. Menopausal symptoms are not "a natural part of aging" in other cultures. Hot flashes, osteoporosis and the like occur rarely if at all. Surprised? To find out more about this, read our companion report on natural hormone replacement.

Some of the FDA enforcement letters to Wyeth-Ayerst are available on its website at www.fda.gov. See enforcement letter. We define "estrogen" here as that made by the human body.

References

- Grodstein F, et al. 1996. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *NEJM* 335:453-61.
- Hemminki E, et al. 1997. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 315:149-53.
- Hulley S, et al. 1998. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 280:605-13.
- Stampfer MJ, et al. 1991. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *NEJM* 325:756-62.
- Writing Group. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 288:321-333.

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.