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REPORT

ESTROGEN Fails the Heart Test

The bubble has burst for estrogen and heart disease. Two studies involving thousands of women show that synthetic hormone replacement increases the risk of heart attack in postmenopausal women.

by Terri Mitchell

Researchers involved in two studies have warned that women should not take synthetic hormones to prevent heart attacks. Almost all of the women in both studies were taking Premarin, which casts further doubt on this best-selling drug. Coupled with its history of causing fatal blood clots and breast cancer, this new finding should be a wake-up call to women currently taking Premarin. Safer alternatives are readily available.



Heart disease is a serious problem. It kills more women over the age of 60 than any other disease. At half a million deaths, it dwarfs breast cancer which will claim about 43,000 lives this year. (Between ages 40 and 60, however, cancer is the biggest killer.)

Because the incidence of heart disease rises sharply in women after menopause, researchers have thought that female hormones are protective. They theorized that this protection could be extended with synthetic replacement. These ideas were strengthened when observational studies showed that women taking estrogen and progesterone had a lower rate of heart disease. In 1995, the Postmenopausal Estrogen/Progestin Intervention trial (PEPI) established that estrogen replacement has a positive effect on lipids and clotting factors. Although it was questionable whether this would translate into fewer heart attacks, it was all some doctors needed to begin prescribing synthetic hormones for heart disease. The warnings of Jacques Rossouw (NIH) and others went unheeded in the belief that synthetic estrogen was the answer to heart attacks in postmenopausal women.

In 1994, a large-scale study was begun at 20 medical centers across the U.S. Called the Heart and Estrogen/Progestin Replacement Study (HERS), it was the second largest study of its type ever attempted. Funded by pharmaceutical giant Wyeth-Ayerst, every expectation was that HERS would prove that synthetic hormones would prevent heart attacks in postmenopausal women. Two thousand women with heart disease were put on "Prempro," a combination of Premarin and medroxyprogesterone acetate (a synthetic progestin). By 1998, the results were in: Prempro substantially increased heart attacks the first year and had no effect on heart attacks in subsequent years. Blood clots were three times higher in the group that took Prempro, and gallbladder disease was also increased.

It won't be easy to explain this study as a fluke: researchers from Duke University have reported the same findings. In that study, 37% of women who began taking synthetic hormone replacement after their first heart attack were hospitalized for heart problems compared to 17% of women who did not take the drugs. Most of the women in the study were on Premarin.

In 1997, it was reported in the British Medical Journal that an analysis of 22 studies shows that synthetic hormones do not prevent heart attacks. Another study concluded that synthetic hormones increase the risk of a blood clot four-fold. Although the risk of blood clots appears to decline after the first year of use, and cardiovascular benefits-if any-may increase after years of use, the overall consensus is that women should not take synthetic hormones for heart attack prevention.

How could something so promising turn out so negatively? Scientists are scrambling for an explanation. Maybe it would work in healthy women, they suggested. Perhaps the study was too short. (Prempro tended to show a better effect after four or five years). The most common argument was that the synthetic progestin cancelled out the good effects of synthetic estrogen. Studies show that adding progesterone to estrogen replacement dampens the lipid-lowering effects of the estrogen. However, this argument doesn't hold up because although synthetic progesterone does reverse some of the beneficial effects of estrogen on lipids, it doesn't completely obliterate them. This has been confirmed in studies that show no difference in heart attack incidence when progestin is

added to synthetic estrogen. Also, it is unlikely that its lipid effects account for estrogen's heart benefits. At least four other mechanisms have been proposed. They include its effects on elasticity of blood vessels, its antioxidant action, its ability to enhance vasodilation, and its effects on clotting factors. Clearly, another explanation for the negative studies has to be found.

One of the issues that has been consistently overlooked in estrogen/heart studies is the type of hormones used. Studies indicate that different brands of hormones may have different effects. The type of estrogen used in the HERS study was Premarin, which had seemed to reduce the incidence of heart attack in a study known as the Nurse's Health Study. (However, that study has been criticized for not taking into account certain factors that could have been responsible for the lower incidence of heart problems, including access to healthcare. Since the nurses were taking homocysteine-lowering supplements, it is likely that they, too, played a role in the lower rate of heart attacks. And, unfortunately, even if the Nurse's Health Study were to still show benefit after statistical corrections, the women who took Premarin would still lose because it was discovered that they had a significantly higher risk of breast cancer.)

Premarin is the brand of synthetic estrogen taken by most of the women in the two recent studies. Known as "conjugated equine estrogens," it is made from horse urine. This type of estrogen has performed poorly in previous heart disease studies, including one on men that had to be stopped because of the increased number of heart attacks at the dose of 5 mg/day, and greater mortality from other causes at 2.5 mg/day. Its manufacturer, Wyeth-Ayerst, has been accused of animal cruelty in the production of the drug, which involves collecting the urine of confined horses. (This type of practice dates back to the 15th century when yellow paint was made from cow's urine. In order to create the salts necessary for the paint, people would feed cows exclusively on mango leaves, which killed them prematurely. The British government finally outlawed it at the turn of the century. Other types of synthetic estrogens do not involve animals, and may have the benefits researchers hoped to find in estrogen.

The "patch" type synthetic estrogens have made a good showing in several studies that measured lipids. And transdermal estrogen has produced good one-year results in an Italian study-no heart attacks or blood clots. Unlike horse urine estrogen, these types of replacement therapies contain 17 β -estradiol, a synthetic form of estrogen made from plants. 17 β -estradiol improves heart function, lowers cholesterol and elevates HDL, the "good cholesterol." 17 β -estradiol estrogens also have a more favorable effect on blood sugar than Premarin. This is important, as disruptions in glucose tolerance have been linked to heart disease. Time will tell whether the plant-derived forms of synthetic estrogen will reduce heart attack risk.

While data is accumulating on synthetic estrogens, natural estrogens are safe and available. Soybeans and other plants appear to protect against heart disease without the side effects of synthetic estrogens, which carry with them a four-fold increased risk of blood clots and a 30% increased risk of breast cancer. Instead of creating life-threatening conditions, phytoestrogens and other plant substances appear to protect against them. Phytoestrogens are part of a group of substances known as phytochemicals-beneficial substances from plants.

One of the ways phytochemicals may protect against heart disease is by scavenging free radicals. Free radicals oxidize fat. People with heart disease have abnormally high amounts of oxidized fat in their arteries. The antioxidant protection of phytochemicals also decreases DNA damage to mitochondria. This is important because mitochondria are the power source for the heart. When they break down, heart muscle suffers.

Phytochemicals are broken down into categories. Flavonoids are a type of phytochemical that has been shown to lower the risk of heart attack, as well as lower mortality from heart disease. This protection is above and beyond that provided by antioxidants C and E. Antioxidant reserves are low after a heart attack, and should be replaced. A study in rats shows that vitamin E supplements improve cardiac function after a heart attack. So does curcumin, a phytochemical from a root similar to ginger. Lycopene, a carotenoid that gives tomatoes their red color, is also heart-protective.

There are over 4,000 flavonoids. They are found in tea, grapes, onions citrus fruit, and many other plant products. Two of them, quercetin (onions, red wine, broccoli) and catechin (tea) greatly reduce free radicals created by diets high in poly and monounsaturated fats. The American diet is rich in n-6 polyunsaturated fat, present in oils such as corn and safflower. The latter fat type, when combined with a lack of antioxidant vitamin E, has adverse effects on arteries. In Israel, where n-6 polyunsaturated fat in the diet is even higher than in the U.S., there is high incidence of cardiovascular disease and cancer in women. Quercetin and catechins can reverse this effect by conserving vitamin E. Tea contains phytochemicals known as polyphenols that protect against heart disease. In a study from Harvard Medical School, drinking one or more cups of tea a day slashed heart attack risk in half.

It has been demonstrated that the antioxidant power of single phytochemicals such as equol (from soy) and coumestrol (from clover and alfalfa sprouts) is as strong, or stronger, than 17 β -estradiol. Several plant substances, including a flavonoid in apples, appear to have both the estrogenic and the antioxidant power of 17 β -estradiol. Apples were a main source of flavonoids in two studies showing that flavonoids reduce heart disease in humans. The heart-protective effects of flavonoids are apparent in a study on doxorubicin ("dox"). Dox is used as chemotherapy in breast cancer, but it's toxic to the heart. Researchers in the Netherlands have shown that flavonoids protect mice from dox cardiotoxicity almost completely.

The most well-studied phytoestrogens are from soy, genistein and daidzein. Genistein possesses strong antioxidant action, and

lowers cholesterol. The best study to date on soy and heart disease was done on monkeys. It found that soy greatly reduced atherosclerosis. Soy also decreased lipid peroxidation, improved insulin sensitivity, and improved lipid profiles. When genistein and daidzein were removed from the soy, its beneficial effects were greatly reduced. Adding 17b-estradiol to the soy diet caused weight reduction and reduced stomach fat.

Phytoestrogens produce effects similar to what drugs offer. Dozens of studies document genistein's calcium channel blocking action. Genistein also increases the sensitivity of the heart to beta-blockers, inhibits blood clotting factors, and helps blood vessels relax. We can only guess at what other benefits soy has that have not yet been discovered.

Synthetic estrogens have been promoted for maintaining strong bones. Their long-term effects are not known, however. Soy, on the other hand, has a thousand-year track record with proven benefits for bone. In a study from Japan, genistein improved bone strength and density, while daidzin prevented bone loss. Daidzin also prevented atrophy of the uterus caused by removal of the ovaries. Soy is so effective at preserving bone that it rivals calorie restriction in its effects. It has been proven that the bone loss associated with meat-based diets can be substantially reversed with soy.

Some women have expressed concern that phytoestrogens might increase their risk of breast cancer just as synthetic ones do. However, the opposite appears to be true. According to Dr. Richard St. Clair of Wake Forest University, phytoestrogens decrease, rather than increase, the proliferation of breast and uterine cells. Dozens of studies show that phytoestrogens actually inhibit breast cancer cell growth. St. Clair also points out that in Asia, where soy consumption is high, breast cancer incidence is much lower than in the U.S. where soy consumption is low.

Phytoestrogens provide estrogenic benefits without the dangerous side effects of synthetic hormones. Coupled with the lack of benefit for heart disease, the side effects of Premarin make it a poor choice for hormone replacement. Until more is known about the 17b-estradiol synthetic estrogens, the best choice for heart health is a combination of flavonoids, phytoestrogens and other natural factors proven to have a beneficial effect.

While eating a diet high in fruits and vegetables may theoretically provide enough flavonoids and phytoestrogen for heart protection, the vast majority of women do not consistently "eat right" day-in and day-out. Supplements ensure that beneficial heart factors are consistently available to the body. Postmenopausal women who exercise, eat a good diet and take supplements should feel secure that they're doing everything possible to forego America's number one killer, heart disease-without adverse side effects.

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