

Estrogen and your heart: Does it help or hurt?

Does estrogen therapy prevent heart disease in menopausal women — or cause it? ‘Today’ contributor Dr. Judith Reichman clarifies the issue

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Updated: 9:02 a.m. ET Nov. 15, 2005

Choosing to take estrogen during menopause is one of the more confusing decisions a woman has to make, with some studies linking it to heart disease and other studies saying it can help prevent heart disease. “Today” contributor and gynecologist Dr. Judith Reichman sheds some light on the issue:

We see the ads, hear the statistics, and even wear red to acknowledge that heart attack and strokes are the leading causes of death in women. In a public health effort to overcome our ongoing female cardiac and brain complacency, we have been exhorted to take charge and:
Not smoke Exercise Not gain weight Treat high blood pressure Lower cholesterol

But what about hormones?

Here's a look at why estrogen, taken in early menopause, may actually help prevent coronary heart disease (CHD), whereas taking it years later may not.

Why the hormonal confusion?

Many of our early studies showed that estrogen prevents heart disease; then along came others that demonstrated that hormone replacement in menopause could increase the risk of heart attack and stroke. The earlier “positive” studies were observational; women who took estrogen were followed and compared to women who did not. Those on high doses of the most commonly prescribed form of estrogen, Premarin (1.25 to 2.5 milligrams a day) had a 50 to 70 percent reduction of CHD. When doses were reduced and progestin added (to protect the uterine lining from cancerous changes), the benefit was still there, but “only” 30 percent. The argument was subsequently made that part of the so-called estrogen benefit came not from taking the hormone but from the fact that women who took it were initially healthier and had a higher socioeconomic status than nonusers. There is some justification for this, however, when the statisticians corrected for these factors, the observed heart benefits of estrogen persisted.

We also know that in women who undergo removal of their ovaries before menopause and do not take estrogen replacement, the risk of heart attack increases dramatically; the younger they are at time of surgery, the higher the risk. Even if a woman’s ovaries are removed in the years just prior to or at the beginning of menopause (50 to 59), lack of estrogen replacement may cause her to be twice as likely to develop atherosclerosis as a woman who has not undergone surgical menopause. When women of the same age but different menopausal status are compared (one menopausal, the other, not) the menopausal woman has a two to threefold increase in her future risk of CHD. In the final analysis: for each year’s delay in menopause, the risk of CHD decreases by 2 percent.

Scientists also like to demonstrate medical conditions and therapies in “controlled” experimental settings. And they have in monkeys — those who have been estrogen deprived as a result of the surgical removal of their ovaries develop atherosclerosis; when given estrogen replacement, the rapid plaque deposition in their arteries does not occur.

The paradox: What about those well known studies that show that hormone replacement can increase the risk of CHD?

The HERS (the Heart and Estrogen/Progesterone Replacement Study) looked at nearly 3,000 women who already had significant heart disease. Their average age was 67. When Premarin and synthetic progestin (MPA or Provera) was given to half of these women, they had more heart attacks during the first year of therapy than the control women who took no hormones. But when the hormone-treated women were followed for an additional four to five years, there was a late benefit: they had fewer heart attacks and strokes than the controls. The study was then continued for two more years (the HERS II trial), at which time hormone replacement did not seem to make a difference (heart attacks and strokes were the same in both groups).

The Women's Health Initiative (WHI) seemed to corroborate these findings. This was a huge trial designed to evaluate hormone therapy in over 16,000 theoretically healthy women who had not undergone hysterectomy. They were randomly divided into two groups: One was given Prempro (a combination of Premarin and Provera) and the other a placebo. The average age of these women was 63 and many were 12 or more years past their menopause transition. The majority of women were overweight or obese (a cause for underlying atherosclerosis) and few had significant menopausal symptoms of hot flashes or night sweats. After less than five years — amidst much media attention — the trial was halted. The treated women had an increased rate of heart attack, stroke, pulmonary embolism, and clots in the deep veins, as well as an increase in the incidence of breast cancer. But there was some good news, the treated women had fewer osteoporotic fractures and were less likely to develop colon cancer.

Was it the Premarin (Prem) or the Provera (Pro) that was to blame for some of these risks?

Possibly it was the Provera. If you add Provera to Premarin when treating female monkeys whose ovaries have been removed, the Provera opposes the ability of the estrogen to limit plaque formation in the arteries. Natural types of progesterones have not been found to have this negative effect. In studies in female humans (not just monkeys), researches have found that Premarin and other estrogens lower bad cholesterol (LDL), increase good cholesterol (HDL), and improve the ability of vessels to dilate so blood flow is facilitated. Provera blunts these cardiovascular benefits.

And while we're discussing side effects of hormone replacement, let's go to the issue of breast cancer. A separate part of the WHI as well as other studies have demonstrated that estrogen therapy alone does not seem to increase risk for breast cancer. The risk appears to increase only with added progestin exposure.

Prempro was the hormone used in these studies. Are other hormones safer?

There are many alternative estrogens that are FDA approved for treatment of menopausal symptoms. Most are composed of estradiol (the estrogen made by our ovaries) and are plant-derived. Estrogen can be delivered through the skin as a patch (products include Climara and Vivelle) and as a gel or a skin emulsion (EstroGel and Estrosorb). It can also be absorbed into the body through the vagina (Fem Ring). Several types of progestins that are more like that which our ovary makes (progesterone) are also plant-derived. Prometrium is an FDA-approved formulation of progesterone. It has *not* been found to blunt the positive effects of estrogen on the vessels in the heart.

There may be a difference in side effects depending on whether estrogen enters the body in pill form or via patches, gels or rings. (I know the latter sounds weird; no we are not discussing

jewelry!) Many researchers feel that oral estrogen pills or capsules, which pass through the gastrointestinal tract, are immediately metabolized in the liver where they increase factors that are *pro-inflammatory*. We now know that inflammation causes damage to blood vessels and increases the risk of heart attack and stroke. One such inflammatory factor is called C-reactive protein (CRP) which, when found to be elevated in women is correlated with an increased risk of these cardiovascular events. It's possible that the higher incidence of CHD in the first years of the HERS and WHI trials was partially due to an increase in inflammatory factors. Switching to non-oral estrogens that go through the skin or vagina will, to some extent, bypass this initial effect on the liver, and may reduce this inflammatory "insult."

When it comes to progestin, doctors are trying to figure out how to diminish its effect on breast tissue. Lower and lower doses are now prescribed and progestins that are considered "heart healthy" are often used. Some form of progestin is usually given to protect the uterine lining, but it should achieve this goal when given every few months for 12 to 14 days. Progesterone can also be given as a vaginal gel called Prochieve. There are physicians who, after discussions with their patients, don't prescribe progestin at all and simply monitor the uterine lining with pelvic ultrasound and/or endometrial biopsies. Obviously women who have had a hysterectomy do not need any form of progestin.

Does estrogen have a different effect on the hearts (and minds) of younger versus older women?

Most likely. When estrogen is given to monkeys immediately after their ovaries are removed, there is a 50 percent to 70 percent decrease in the development of plaque in their coronary arteries, but there is no benefit if estrogen is given years later. Because WHI was begun on older women who were more than a decade past menopause, they were likely to already have plaque in their arteries, and estrogen's inflammatory effect might have made this plaque "vulnerable." This likely increased the risk that the plaque would rupture or that pieces would shear off and be carried to small arteries, block them, and cause a heart attack or stroke.

When we put all these facts and theories together, estrogen's effect on coronary heart disease is thought to be as follows: In our reproductive years, hormones protect our vessels from plaque formation. Once we become menopausal there is an early window of opportunity to reduce this plaque formation with estrogen. If hormone therapy is delayed and is started years after menopause when plaque has already formed, it may initially cause the plaque to erode or rupture, but years later there could be a benefit in that cholesterol levels are improved. In scientific terms, this is a triphasic effect: First good, then not good, then better.

Are there new thoughts and recommendations regarding estrogen and hormone replacement in heart disease?

The official American Heart Association recommendation states that hormones should not be prescribed for the purpose of preventing heart disease. Currently The American College of Obstetricians and Gynecologists as well as the North American Menopause Society state that hormone replacement should not be initiated in women known to have coronary heart disease. Two of the WHI investigators (Drs Phillip and Langer) recently published their own recommendation in the Journal of Fertility and Sterility. They stated that they believed "that based on all the data now available, **the benefits of hormone therapy outweigh the risks.** Hormone therapy should be started at menopause in most women and failure to initiate treatment near menopause may foster damage to the vasculature [blood vessels], bone and other organs

systems that cannot be repaired by initiating treatment later." They go on to say that blood vessels may experience paradoxical harm with delayed treatment and that we should consider forms of progestin other than Provera.

The current state of knowledge is still in flux. Obviously we have to continue to abide by all our other attempts to safeguard our hearts with appropriate behavioral changes and medications to treat high blood pressure and abnormal cholesterol.

Many physicians feel that the WHI should not be considered the last or only word with regard to the many forms of estrogen and hormone replacement therapy available to women, especially to younger women who are just becoming menopausal and who are more likely to suffer from significant symptoms. A new National Institute of Health (NIH) sponsored study called ELITE (Early vs. Late Intervention Trial with Estradiol) has recently begun at the University of Southern California. Menopausal women will be given estradiol or a placebo and followed for two and a half years. They will have extensive checks of their arteries, heart function and cholesterol levels as well as mammograms, pelvic exams and mental function tests (all free of charge). The investigators want to find out if use of this estrogen in early or even late menopause has a clinically demonstrable protective effect on the vessels, hearts and minds of these women. Menopausal women can learn more about this study and enroll by going online at www.usc.edu/medicine/aru or calling the toll free number (866) 240-1489.

The results of the ELITE study will help us better counsel women on the possible cardiac benefits of early estrogen therapy.

Dr. Judith Reichman, the "Today" show's medical contributor on women's health, has practiced obstetrics and gynecology for more than 20 years. You will find many answers to your questions in her latest book, "Slow Your Clock Down: The Complete Guide to a Healthy, Younger You," which is now available in paperback. It is published by William Morrow, a division of HarperCollins.

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