

Hormone Replacement Therapy and Cardiac Risk:

Should Menopausal Women Take Hormone Therapy? A Cardiac Risk Assessment of Hormone as Medication

Dejah Judelson

Hearth disease is the leading cause of death and disability among American women.¹ Hence, it is crucial for them to be informed about their options during and after menopause. Conventional wisdom in medicine has held that the risk of heart disease decreased in women who use hormone therapy during menopause, a statement which the 2002 and 2004 clinical studies by the Women's Health Initiative contradicted. The results showed that hormone replacement therapy increases the risks for cardiac diseases, and precipitated a barrage of statements from medical professionals denouncing hormone therapy. A media frenzy ensued and caused millions of women currently on hormone therapy to stop their medication. Yet two facets of this story were not published in the *Los Angeles Times*, women's magazines, or even the *Journal of the American Medical Association* (JAMA). The first is that the WHI findings are not relevant for younger women (40–50 yrs) starting hormones for menopausal symptoms. The second is that menopausal symptoms reemerge for women who stop their medication, severely disrupting their normal lives. Should these women be given hormone therapy to treat their symptoms, despite the reported cardiac risk?

Estrogen and Menopause

Estrogen, the key female hormone, impacts virtually every cell of the body. Many of these effects are beneficial, such as reducing the development of cardiovascular disease, improving lipids processing² and arterial stability,³ optimizing response to stress with artery dilation,⁴ and maintaining healthy arterial walls.⁵ Even though there are some side effects such as increased clot formation and breakdown,⁶ thinning of vessel plaque surfaces,⁷ and alterations in the inflammation of vessel walls,⁸ estrogen's positive effects more than compensate for the negative ones and are thought to delay the onset of cardiac diseases in women.

Estrogen influences the body through estrogen receptors that are present in varying quantities in almost every human cell. These receptors atrophy with age, accelerated by the decrease or absence of estrogen. The concentration of estrogen receptors remains low after an ovariectomy or menopause, giving rise to symptoms of estrogen deficiency.

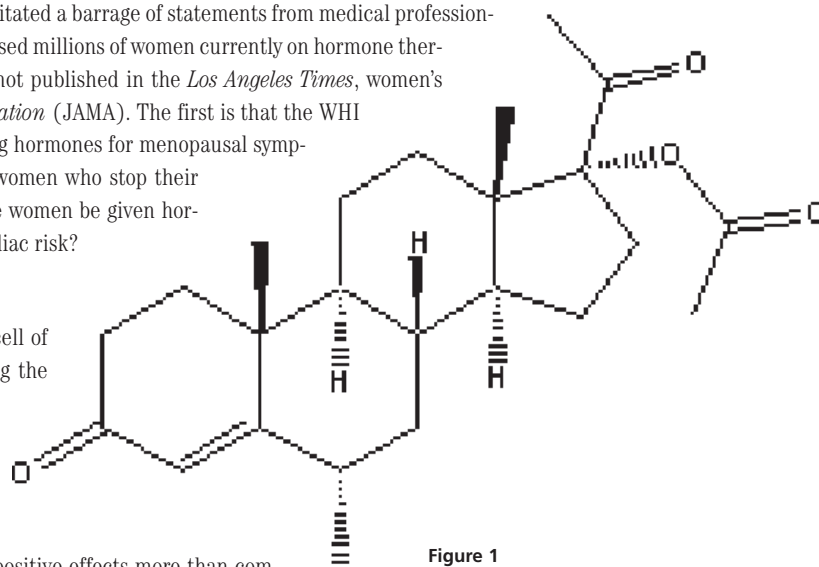


Figure 1

Perimenopause precedes menopause, and starts with the onset of estrogen deficiency symptoms. It is characterized by vasomotor instability symptoms of hot/cold flashes, sleep disturbances, labile mood swings, difficulty in concentration, and an irregular menstrual cycle. Once periods have ceased for a full year, a woman is said to be in menopause.

It is important to note that not all women have estrogen deficiency symptoms or are even aware that their periods have stopped for some time. In particular, obese women tend to have fewer symptoms of estrogen deficiency because estrogen is produced from fat tissues, slowing the rate of estrogen decline.

Most women with estrogen deficiency symptoms seek help from their primary care physician or gynecologist around the time of perimenopause or at the onset of menopause, depending upon how incapacitating their symptoms are.

Hormone Therapy

Hormone replacement therapy (HRT) or hormone therapy (HT) has been the accepted menopause treatment for many years. Since the mid-1960s, millions of women have used HT to reduce symptoms. In the 1990's, it was believed that HT could help prevent chronic illnesses such as atherosclerosis, colon and breast cancer, osteoporosis, and Alzheimer's disease.⁹

Hormone therapy is given to a postmenopausal woman with an intact uterus in prescribed dosages of estrogen and progesterone, either on a continual basis or for ten to fourteen days each month. The most popular HT regimens in the United States had been Premarin with 0.625 mg of conjugated equine estrogen (CEE) used daily for twenty-five days a month, or 5 mg to 10 mg medroxyprogesterone acetate (MPA), also known as Provera, for ten to fourteen days a month. Both medications are manufactured by Wyeth-Ayerst Pharmaceuticals. In the last decade, a combination of 2.5 mg MPA with Premarin 0.625 mg daily was the standard treatment.

The Studies

Observational studies, such as the Nurses' Health Study (NHS) led by Dr. Frank Speizer in 1976, found that HT helped reduce the risk for coronary heart disease (CHD).¹⁰ This result combined with increased advertising for HT drugs helped strongly promote the benefits of HT for post-menopausal women. However, these studies had severe flaws. The most notable intrinsic bias was probably the "healthy-user effect"¹¹ in which women who chose to go on HT tended to have better health care and were better educated than women who did not choose to go on HT. In addition, these studies did not account for the adverse drug-mixing effects, since most subjects in the study were taking other medications.

Randomized clinical trials (RCT) were needed to verify the benefits of HT without the major study flaws in observational and population-based studies. There were three well-conducted studies that were randomized and placebo controlled, with statistically significant sample sizes: Heart and Estrogen/Progestin Replacement Study (HERS), Women's Health Initiative (WHI) with combined therapy, and WHI with CEE alone.



Figure 2.

The HERS trial, published in 1998, was designed to test the validity of previous observational studies that demonstrated the effectiveness of hormone therapy in women with established coronary heart disease (CHD). The study consisted of 2763 women, aged 55 to 80 with an average age of 67 years, with known CHD who had never been on HT, randomized to take HT

or placebo. Overall, HERS found no statistically significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had myocardial infarction or CHD death.¹² The study concluded that treatment with Premarin and Provera did not decrease the likelihood of CHD occurrences in postmenopausal women with previously determined CHD. Therefore, the HERS authors recommended that HT should not be used as a secondary preventative measure against CHD, but the women currently on HT were recommended to continue treatment.

The Women's Health Initiative study enrolled 161,809 postmenopausal women with an intact uterus from the ages of 50 to 79 years into a set of RCTs starting in 1993 and ending in 1998. Its focus was to determine the risks and benefits of various methods to decrease the incidence of heart disease, colon and breast cancer, and fractures due to osteoporosis. A major aspect of the study was to analyze the estrogen and progesterone combination therapy and assess the associated risks and benefits. Another was to either prove or disprove that hormone therapy reduced the risk of CHD. The estrogen plus progesterone component focused on 16,608 women, average age 63 years, predominantly not on hormones, randomized to HT or placebo. However, this component of the WHI study ended almost three years earlier than planned because the predetermined risk level of harmful side effects (breast cancer) had been reached. The investigators thus concluded that the overall health benefits were outweighed by the risks for combined hormone therapy treatment. This was the first RCT using combined hormone therapy that showed an increased risk for breast cancer and a non-significant increase in risk for heart disease.¹³

Parallel to the original WHI study, the investigators conducted a study on estrogen-alone (CEE) treatments with 10,739 women, average age 64 years, predominantly not on hormones, who had undergone hysterectomies. They concluded that using CEE alone for postmenopausal women without a uterus decreased the risk of osteoporosis, increased the risk of a stroke, but had no effect on the rate or incidence of CHD. Again, they recommended that CEE should not be used for disease prevention in postmenopausal women.¹⁴ However, this component of the study demonstrated a reduction in breast cancer risk that almost reached statistical significance and a reduction in risk of heart attack that did not reach significance.

The Media Blitz

The 2002 publication of the WHI turned the medical profession inside-out with its announcement that hormone therapy was associated with an increased risk of myocardial infarction. While this increase was not statistically significant, this incon-

gruity to prior results from observational studies generated numerous articles in medical journals denouncing the use of hormone therapy for all women. Medical organizations published guidelines and urged physicians to stop prescribing hormone therapy. However, little attention was focused on the 40% whose estrogen deficiency symptoms substantially interfered with their quality of life. When these women did not get better on their own or with over-the-counter medications, they sought help from their physicians but were often refused hormone prescriptions.

When Provera and Premarin were first advertised to the public, the advertisement that got the most attention was one starring Lauren Hutton, a supermodel. She was featured on the cover of *Parade* magazine with the following tagline: "My hot flashes and night sweats, gone. I feel great. See your doctor, and say yes to HRT." The public did not know that Hutton was a paid spokesperson for Wyeth. Having such a high-profile role model as a spokesperson for a medicine to treat such a debilitating and common disease helped boost the popularity of the treatment. Moreover, this advertisement was run in 2000, after the HERS study which proved that there were no known cardiac benefits to HT in women with existing coronary heart disease.

Once the 2002 WHI study was published, further proving the risks of HT, there was an outrage concerning the misleading Hutton advertisements. On October 3, 2002, PBS aired a special on how the Hutton advertisement misled the public and how the FDA and NIH planned to hold public forums to verify the newly-released WHI study. Bringing together representatives from the FDA, WHI, Wyeth Pharmaceuticals, and a non-affiliated physician, PBS helped elucidate the confusion regarding the misleading HT advertisement.¹⁵

Wyeth Pharmaceuticals' successful advertisement could be attributed to a four-step campaign: (1) creating awareness through a supermodel presenting a disease on the cover of a popular magazine, (2) generating the fear factor by making the audience think that they are possibly at risk, (3) personalizing the campaign and (4) confirming self-diagnosis. Hence, there was an influx of women rushing to their physicians asking for HRT.

The Controversies

There were many controversies surrounding the studies which claimed that HT was not only ineffective, but was also dangerous and should thus not be taken by women. Media hysteria immediately following the published studies caused women to stop taking hormones that they had already been on for years. Many of those women had symptoms and could not function after they stopped taking their medication, forcing them to return to their doctors for prescriptions—prescriptions that, due to the recent publicity, the doctors were now afraid to write.

Articles started to appear that said, "Go slowly, take it easy and don't jump to conclusions."¹⁶ After HERS, some said, "Let's see what happens when you give the hormones to healthy women." After WHI HRT, some said, "Let's see what happens with WHI ET" (which had a modest but not significant CHD benefit). Still, organizations and guidelines came out that said HRT/ET should not be started or continued for cardiovascular

disease prevention, an indication that the medications never had. Advice was to use the medicines at the lowest dose for the shortest time.¹⁷ These ignored the biology of the estrogen on blood vessel function, lipids, and the maintenance of healthy blood vessel walls.

Limitations of Studies

Although both the NHS and WHI studies were comprehensive, using a large subset of women for an extended period of time, there were many flaws with the studies that produced misleading evidence. First of all, NHS, an observational population-based study, had the intrinsic issue of the "healthy-user bias" not present in a randomized study such as WHI. In addition, by studying nurses who were more educated and were already following a healthy lifestyle, they had a reduced risk of cardiovascular disease, so the results obtained from the study were not an accurate representation of what to expect in the general female population. Observational trials have flaws that overestimate the benefits and underestimate the risks.

However, randomized clinical trials are not without their flaws. The biggest problem that HERS, WHI HRT and WHI ET have is the women that they studied. HERS looked at women aged 55-80 with an average age of 67. WHI HRT studied women from the ages of 50-79, with an average age of 63 years, while WHI ET studied women with an average age of 64. Most women enter perimenopause in their 40s, lasting about four to eight years, and hit menopause around the age of 50. Therefore, the average woman studied started menopause over 13 to 17 years prior to enrolling in the study. In addition, women were excluded from the study if they had estrogen deficiency symptoms (less than ten percent of patients in either WHI had these symptoms). This was to be a study of healthy women, yet women as old as 79 were enrolled without screening cardiac testing, and significant data is now available to show that 60 percent of women have subclinical coronary artery disease by the time they are in their early sixties.¹⁸ The American Heart Association research in heart disease states that heart attacks and cardiac death occur when asymptomatic coronary artery plaque becomes unstable and ruptures, forming a clot that blocks the vessel. Women with coronary artery plaque are much more likely to develop this complication than healthy younger women who have not yet formed much plaque. So what primary benefit did these women gain if they didn't need to be treated for symptoms of menopause? HRT was intended and approved by the FDA to treat symptoms of menopause and, as a secondary effect, osteoporosis. But the majority of the women studied had no symptoms to treat, so there was very little for them to gain from the study. In these cases, the risks almost certainly outweigh the benefits because there were no primary symptoms for these women to cure. In addition, all the risks that are mentioned are relative risks of cancers and chronic diseases. The overall risks for these women were still extremely low; they just had a slightly higher rate of developing cancer or CHD than the placebo group. The youngest women in the study had fewer cardiac events and complications than the older women.¹⁹ In short, the RCT suffered from flaws that caused them to overestimate the risks and underestimate the benefits.

Then why did HRT become a focus to prevent CHD? From the observational studies conducted, women were shown to not only be cured of the menopausal symptoms, but also seemed to garner these secondary disease prevention benefits. Thus the focus on studying HT was pushed away from looking at the true reasoning behind the drugs which was to help women in their 40s and 50s withstand menopausal symptoms, and instead became focused on taking healthy women and seeing if giving them drugs would help prevent disease. Because the RCTs were done in older women, too many years after menopause to get the blood vessel benefits that younger women going through menopause have a potential to gain, the possibility of preventing the development of heart disease if given when the natural production of hormones decreases remains unknown. These studies are needed to answer questions for women approaching menopause. With multiple versions of hormone therapy available, if the choice of drug makes a difference, we can see that difference.

Fact Circulation — Getting the Word Out Effectively

The most important lesson learned by the controversies surrounding HT is that randomized clinical trials need to be focused on the group that the drug was intended to treat. In addition, one should not apply data from RCT to patients that are different from those that were studied. If it were explained who was in the study and why, then much of the media hysteria could have been prevented.

To prevent future cases like this from occurring, there are a number of ways that fact circulation as seen today can be improved. First of all, the FDA needs to be more active in the mainstream media and prevent media leaks before they are ready to publish their findings. A large problem of the WHI study was that the information was leaked to the press before the FDA had completely analyzed the data and prepared a statement, so the organization was caught unprepared and proved unable to provide accurate recommendations to the public when prompted. In addition, the FDA should have a spokesperson to respond to all statements made in newspapers and major magazines. If they assume that responsibility, instead of leaving it up to the drug companies and doctors, then a more uniform attack can be made on misleading or contradictory information. The one strong area for women's issues that drug companies and the FDA use well is health-based magazines, especially those focused on women's issues, because women tend to turn to them and trust them more than mainstream media. To accurately get information passed to physicians, the FDA needs to use well-read journals such as the *New England Journal of Medicine* or the *Journal of the American Medical Association*. Most doctors read them on a regular basis and they could be the most efficient way to relay data and information, unlike the postal mail or the *Physician's Desk Reference*, which is only published once a year.

Despite all the ways facts and information could be processed and published more rapidly, it is clear that there are few time-related issues in relaying information to the public. Immediately following the WHI study, sales of HT drugs dropped as a result of the negative publicity.²⁰ Many women dis-

continued use or switched to a lower dosage as a quick response to the clinical evidence and amended guidelines for use. That was a good indicator that the public became aware of the issue quickly. Now the medical community, and especially the FDA, needs to use the comments suggested above to reverse the negative publicity and let the public know the truth. One way to do this would be to hold a large scale RCT with the correct age and risk factor group for menopause. Conducting a large scale trial with clear results should help to reverse some of the negative and misleading press HT has received over the past three years.

Recommendations

Overall, HRT needs to be highly individualized for each patient. Each woman is a different case and needs to discuss her options with her physician. There is no magic formula, no ideal type of woman that should or should not be on HT. There are some general guidelines that can be followed to help determine whether a woman should consider HT or not.

Above all, the most consistent fact from all the studies is that HT should not be used for primary prevention of coronary heart disease or cardiovascular disease in older women, for which it was never approved. In addition, while HT is approved for osteoporosis, there are other treatments which produce similar effects without the detrimental side effects, especially for older women at increased risk of heart disease complications. If these medications aren't sufficient, then HT can be tried. However, if a woman has symptoms and is using HRT/ET and receives a cardiac benefit, is that a problem? Do not use HT for symptoms if there is a high risk for CHD or CVD and those risk factors are not being treated or are being exacerbated.

Older women, those who are more than five years post-menopausal, should not start on HT unless they have been screened for heart disease. Doctors need to see studies to tell patients if they can continue HT long-term if they do not have any complications from it. If women are nervous and want to discontinue therapy, then they should try to reduce the dosage gradually, under the supervision of a physician, instead of quitting cold turkey. One thing we know from these studies is that there are no major benefits to beginning HT late post-menopause.

For women who are just entering menopause, there are two categories: non-symptomatic and symptomatic. Non-symptomatic women should avoid HT drugs as a CVD/CHD preventative measure and use other measures to reduce their heart disease risk such as statin drugs, low dose aspirin, and blood pressure medications. They should not be on estrogen/progesterin therapy if they are not encountering menopausal symptoms.

Menopausal women that are symptomatic should consider going on HT for the shortest time necessary to get desired effects, continuing if new clinical trials support that it is safe to use in healthy women who are going through menopause. The biggest benefit of HT is the improvement of quality of life. All women who need to get up in the morning and have a productive day will benefit from HT if they are sufficiently symptomatic. For many of these women, the benefits associated with living a relatively normal life outweigh the risks of potentially

developing cancer and heart disease later in life. These women need to be able to function and work now so they don't mind taking risks that could possibly shorten their life by a couple of years.²¹ Women claim that HT helps them stay productive and retain the capability to function on a day-by-day basis, which they were unable to do prior to hormone therapy.

Conclusion

Hormone replacement therapy or estrogen therapy does have benefits, if used properly. Doctors need to be aware of who

should take the drugs and for whom they are intended, weighing the risks and benefits to decide whether or not to prescribe the medication. Patients need to also be aware of risks and benefits to decide if it is worth taking a risk to reduce menopausal symptoms. In addition, large and well-conducted studies need to be held analyzing the correct group of women that are affected by menopause and that can be helped by various forms of hormone therapy. Only then can a decision and judgment be made as to whether this line of therapy is beneficial or harmful to women.

References

- Heart Disease and Stroke Statistics—2004 American Heart Association, <http://www.americanheart.org/downloadable/heart/1079736729696HDSStats2004UpdateREV3-19-04.pdf>, last accessed 10/20/2004.
- The Writing Group for the PEPI Trial. "Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial." *Journal of the American Medical Association (JAMA)* 1995; 273: 199-208.
- Clarkson T. "Lack of Effect of Raloxifene on Coronary Artery Atherosclerosis of Postmenopausal Monkeys." *Journal of Clinical Endocrinology and Metabolism*. 1998;83: 721-726.
- Ganz P. "Vasomotor and vascular effects of hormone replacement therapy." *American Journal of Cardiology*. 2002; 90 (1A): 11F-16F
- Williams JK. "Regression of Atherosclerosis in Female Monkeys." *Arterioscler Thrombosis Vascular Biology*. 1995; 15: 827-836
- Zegura B et al. Double blind, randomized study of estradiol replacement therapy on markers of inflammation, coagulation and fibrinolysis. *Atherosclerosis* 2003; 168: 123-9
- Wingrove CS et al. 17beta-oestradiol enhances release of matrix metalloproteinase-2 from human vascular smooth muscle cells. *Biochim Biophys Acta* 1998; 1406: 169-74.
- Pradhan AD et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA* 2002; 288: 980-7
- Freundlich N. "Menopause: What Every Woman—And Man—Needs to Know." *Business Week*, 8/30/2004; 3897: 148
- Grady D et al. "Hormone Therapy to prevent disease and prolong life in postmenopausal women." *Annals of Internal Medicine*. 1992; 117: 1016-1037.
- Nananda F et al. "The Discrepancy between Observational Studies and Randomized Trials of Menopausal Hormone Therapy: Did Expectations Shape Experience?" *Annals of Internal Medicine*. 2003; 139: 923-929.
- Hulley S et al. "Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women." *JAMA*. 8/19/1998; 280: 605-613.
- Writing Group for the Women's Health Initiative Investigators. "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial." *JAMA*. 7/17/2002; 288: 321-333.
- Women's Health Initiative Steering Committee. "Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial." *JAMA*. 2004; 291: 1701-1712.
- Women's Health Debate on 10/3/2002. http://www.pbs.org/newshour/bb/health/july-dec02/hormone_10-3.html. Last accessed 10/20/2002.
- Laurance J. "Specialists seek to calm fears over comparison of HRT to thalidomide," *The Independent*. Health, 10/9/2003
- Nelson H. "Assessing Benefits and Harms of Hormone Replacement Therapy," *JAMA*. 8/21/2002; 288: 882-884.
- Raggi P et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101: 850-5
- Naftolin F et al. The Women's Healthy Initiative could not have detected cardioprotective effects of starting hormone therapy in the menopausal transition. *Fertility and Sterility* 2004;81: 1498-1501.
- Hersh A et al. "National Use of Postmenopausal Hormone Therapy: Annual Trends and Response to Recent Evidence." *JAMA*. 1/7/2004; 291: 47-53.
- Roan, S. "Hormone users take the chance; A major study prompted many menopausal women to toss their estrogen pills, but for some, the quality of life with the drugs far outweighs the benefits of quitting." *The Los Angeles Times* [HOME EDITION] Los Angeles, Calif.: Mar 31, 2003. pg. F.1

For this paper, I spoke extensively with Dr. Debra Judelson of the Women's Health Institute and the Cardiovascular Medical Group of Southern California.