

THE **LINDNER** CENTER

AT THE CHRIST HOSPITAL

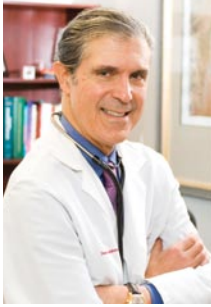
QUARTERLY REPORT



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A message from Dr. Kereiakes

Dear Readers,

Welcome to *The Lindner Center Quarterly Report*, a publication dedicated to providing you with insights to keep you healthy. In this report, the benefits and risks of hormone replacement therapy (HT) in women are discussed by an expert in this field, Dr. Lisa Larkin.

Unfortunately, both medical literature and news reports have offered conflicting information about the safety and efficacy of HT, making it one of the most controversial medical issues in recent history. Dr. Larkin provides both a critical review of this subject and expert commentary, outlining the importance of dose, age and duration of therapy in determining its effectiveness. As she explains, the decision to treat or to be treated with HT must be individualized, and therapy should be tailored accordingly. The appropriate prescription for HT may reduce the risks of cardiovascular disease, which remains the most common cause of death and disability for women.

A significant contributor to cardiovascular disease in women is the occurrence of diabetes mellitus, or the related metabolic syndrome, in epidemic proportion. In this report, Dr. Amanda Denney, an endocrinologist who specializes in the treatment of metabolic syndrome and diabetes, provides valuable insights into what you can do to prevent or treat diabetes before cardiovascular complications arise.

As always, we urge you to discuss these matters with your personal physician. We hope that the knowledge you've gained will make a difference in your life or that of a loved one.

In good health,

Dean J. Kereiakes, MD

Medical Director, The Christ
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THE LINDNER CENTER

AT THE CHRIST HOSPITAL QUARTERLY REPORT

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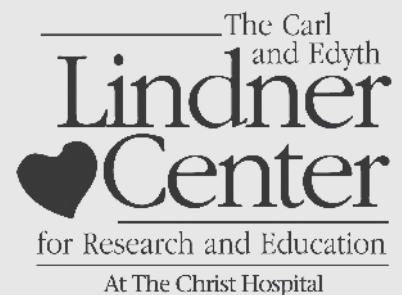
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The Lindner Center Quarterly Report's mission is to educate the Greater Cincinnati and Northern Kentucky community about heart and cardiovascular research, treatment and prevention.

The Lindner Center for Research and Education is affiliated with The Christ Hospital Heart and Vascular Center.

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THE LONG AND WINDING ROAD OF Postmenopausal Hormone Therapy

{ Where are we in 2009? }

BY LISA LARKIN, MD

Few medical issues have attracted more attention or have been the source of more confusion than hormone replacement therapy (HT). Understanding the large volume of recently published studies about hormone use in menopausal women is a daunting task even for physicians, let alone patients. Add to that the often misleading and inaccurate information available to women on the Internet—as well as the media attention given to this subject by celebrities such as Suzanne Somers, Phil McGraw's wife, Robin, and Oprah—it is not surprising that in 2009 women are confused about both the benefits and risks of hormone therapy.

The issue begins at perimenopause, which is the transition time between the reproductive stage of life and the point where a woman no longer ovulates or experiences menstrual bleeding. Typically perimenopause starts in the mid- to late-40s, continues for four to six years and ends at menopause, which is 12 months after the last menstrual period. It's followed by early postmenopause, which is the time period within five years after the final menstrual period.

During perimenopause, hormone production is erratic and often brings unwelcome symptoms and physical changes. Fifty to 80 percent of women will experience the vasomotor symptoms commonly called "hot flashes." Sleep disturbances, mood swings, weight gain, vaginal dryness, decreased libido, palpitations, skin wrinkling and dry eyes are also frequent complaints.

A PROMISING THERAPY

For many years, the magic cure for perimenopausal symptoms was hormone replacement therapy. The medical community's

romance with HT, and the idea that menopause was a condition that required treatment, began with the publication in 1966 of *Forever Feminine* by gynecologist Robert Wilson. His book promoted the notion that menopause was a hormone deficiency state and that estrogen replacement not only could alleviate hot flashes, but also could prevent aging



and preserve female sexuality. In short, Dr. Wilson hailed estrogen as the long-sought-after fountain of youth.

During the 1970s and 1980s, *Forever Feminine*, in conjunction with a large body of observational and preclinical studies demonstrating the benefits of HT, led to a dramatic increase in prescriptions for hormone therapy. Additional research in the 1980s demonstrated that estrogen could strengthen a woman's bones, so by the mid 1980s, HT was the standard of care for most women and roughly 50 percent of women age 50-59 were taking HT. Because estrogen is also the most effective therapy for hot flashes, night sweats and other symptoms, women who are symptomatic during perimenopause reported a significantly improved quality of life with HT.

In particular, HT was promoted for protecting postmenopausal women from cardiovascular disease. After menopause, women are at much greater risk for coronary heart disease (CHD). Estrogen, however, has many protective properties. It lowers blood pressure, increases insulin sensitivity and improves fat distribution. Estrogen lowers "bad" LDL cholesterol, raises "good" HDL cholesterol and improves the structure and function of the blood vessels.

A major study published in the 1990s provided further evidence of the protective effects of HT. The Harvard Nurses Health Study, a large-scale hormone study of 121,000 female nurses, clearly demonstrated for the first time that women who took estrogen were at a much lower risk of cardiovascular disease. In this study, the women on HT experienced 40-50 percent fewer major coronary events and were 40-50 percent less likely to die from cardiovascular disease. These data led the American Heart Association in 1996 to recommend that all women should be counseled about the benefits of HT for preventing CHD, and that HT should be used as first-line therapy for lowering total cholesterol and LDL cholesterol.

THE CONTROVERSY EMERGES

In this context, how did confusion and controversy over HT arise when the data for years was so convincing about the overall benefits?

Doubts first appeared in 1998 with the publication of the HERS (Heart and Estrogen/progestin Replacement Study) trial. The first randomized double-blind placebo-controlled secondary prevention trial of HT, this study demonstrated that when women with established CHD were randomly assigned to HT, they had the same number of coronary events after four years as those who randomly received a placebo. In fact, during the first year, the hormone users were 52 percent more likely to suffer from coronary events. The HERS trial concluded that not only is HT not beneficial in preventing CHD-related events in women who already

have established coronary artery disease, but it may actually be harmful.

A second randomized, placebo-controlled study, the Estrogen Replacement in Atherosclerosis (ERA) Trial, was consistent with HERS and raised further concerns. In ERA, women with established CHD who were treated with HT had the same degree of progression of their coronary artery disease as those without HT over 3.2 years. The conclusion of HERS and ERA was that hormone therapy has no role in the secondary prevention of cardiovascular disease, and the AHA abolished the 1996 guidelines in support of hormone therapy.

Advocates of HT attempted to negate the findings of the HERS and ERA trials by citing that follow-up was inadequate, secondary prevention was a different objective than primary prevention and that the women enrolled in the HERS trial who had an average age of 67 were too far past menopause and were not representative of early menopausal patients.

In July 2002, the "pro-hormone" era came to a screeching halt with the publication of the Women's Health Initiative (WHI) estrogen and progestin treatment arm. This randomized placebo-controlled study, designed to look at the effects of HT on heart attacks, breast cancer, strokes, colon cancer and hip fractures, began enrolling patients in 1993. By 2002, following the enrollment of 16,000 women, the Prempro treatment arm (the estrogen and progesterone combination most commonly prescribed at the time) was discontinued three years early—after only an average 5.2 years of follow-up—when the results suggested that taking Prempro was harmful compared with placebo.

Much to the disbelief of experts in the field, and in stark contrast to the Nurses Health study and other data, not only did Prempro fail to prevent coronary heart disease events, but it actually appeared to increase cardiovascular risk. The study demonstrated seven additional cases of CHD per 10,000 women (37 compared to 30) in the women taking Prempro versus the placebo. In addition, women in the Prempro group had higher rates of stroke (eight additional per 10,000 women), blood clots (18 additional per 10,000 women) and breast cancer (eight additional per 10,000 women).

Following the study's publication and the news that it had been terminated early by the safety monitoring committee, a media frenzy continued for weeks. Media reports cited "alarming data" that HT presented a 40 percent increase in stroke, a 30 percent increase in heart disease and a 25 percent increase in breast cancer. Although the study also showed a reduction in the incidence of colorectal cancer and hip fractures in the HT group, these facts were barely mentioned. The overwhelming "take home message" to the public was that hormones were dangerous and caused heart disease and cancer.



Through the course of the next year, women by the millions (an estimated 52 percent) stopped taking their HT without consulting with their physicians. In addition, 50 percent of women reported having lost trust in their physicians because of the new WHI data. The confusion and mistrust was heightened by media personalities such as Anna Quindlen, who accused physicians in a *Newsweek* op ed piece of deciding “willy-nilly” to prescribe hormones to every female patient because it was the “easiest” path to pursue. In the wake of the WHI report, physicians themselves became fearful of prescribing HT, and prescriptions for HT fell by 68 percent between 2002 and 2003.

Two years later, in 2004, the second arm of the WHI study was also terminated early (after 6.8 years average follow-up) due again to increased risk of stroke in the patients prescribed HT. This arm of the study compared estrogen-only therapy (Premarin) to placebo. Similar to the Prempro treatment arm, patients treated with estrogen showed an increased risk of stroke compared with placebo. However, estrogen appeared to reduce the risk for heart disease and breast cancer. Once again, results that appeared to be conflicting delivered a frustrating mixed message.

In the wake of these confusing and contradictory study results, both patients and physicians were unsure whether HT was safe or effective. At the same time that many physicians stopped prescribing or even discussing HT with their patients, many of the women who had abruptly stopped their hormones after the media blitz on the WHI results had recurrence of their menopausal symptoms. Confused about what to do, and largely abandoned by the medical community, many of these women turned to alternative medicine physicians, diet supplements, the Internet and other resources such as Suzanne Somers' book *Ageless*. The bioidentical and compounded HT business grew rapidly during this time to fill the HT void.

MAKING SENSE OF THE DATA

Although the initial landmark HT studies (WHI and NHS) appeared to be contradictory, further analysis has shed some light. Physicians now believe that these two studies cannot be directly compared because their patient populations are so different. The observational NHS was a study of young, healthy nurses and thus suffers from what is known as a “healthy user” bias. NHS participants were healthier, thinner, more educated, more physically fit, largely Caucasian and had more frequent physician contact than patients in the general population. Conversely, WHI subjects were older than typical menopausal patients. The average age of WHI participants was 63, and the majority of them were at least 10-15 years post-menopause. In fact, neither NHS nor WHI evaluated the typical 50-year-old perimenopausal women who are most likely to consider HT for treatment of menopausal symptoms.

Additional research also helped the medical community understand that a woman's age and time since menopause are critical factors in determining the relative risk and benefit of HT. When data from both treatment arms of WHI (Prempro and Premarin) were pooled and analyzed by age, the results were more consistent with the results of the NHS. For example, when younger patients (age 50-59) are analyzed separately from older patients, HT users are at both a lower risk of coronary heart disease (10 percent risk reduction) and a lower risk of death (30 percent risk reduction), although there remains an increased risk of stroke with HT.

An extension of the WHI Premarin treatment arm (WHI-Coronary Artery Calcification Study) also supports this finding. In the WHI-CACS study, women age 50-59 on estrogen alone demonstrated a lower mean coronary calcium score than women taking placebo (83 compared to 123), which suggested that they had less plaque in their coronary arteries.

Collectively, these data suggest that HT may be beneficial for younger women who are closer to menopause, but may be harmful for older women who are farther past menopause. Our current understanding is that estrogen therapy in younger women who are close to menopause may delay and even prevent the development of atherosclerosis. But years later, when atherosclerosis has already begun to develop and estrogen receptors in the body have already diminished, estrogen appears to speed up plaque formation and may actually trigger dangerous blood clotting. In addition, recent studies suggest that the method of HT administration is also important. The transdermal delivery of HT (patch or gel) may offer specific advantages by bypassing the liver during absorption.

Thus, in 2009, we now understand that HT does not prevent coronary heart disease in all women and that it is no longer appropriate to prescribe HT routinely to all women as was standard in the 1980s. *The Position Statement of the North American Menopause Society (NAMS) on Hormone Therapy* states that women who initiate HT within 10 years of menopause have decreased CHD risk, while women who initiate HT more than 10 years from menopause have increased risk.

This new understanding of hormone use and heart disease risk is reassuring for physicians who prescribe hormones to younger symptomatic women entering the menopause transition. We can now tell our patients confidently that HT initiated during perimenopause for menopause symptom control does not increase the risk of coronary heart disease and may in fact decrease the risk.

We still do not know, however, if HT initiation in younger women closer to the time of menopause affects other outcomes, such as dementia. Currently the KEEPS study (Kronos Early Estrogen Prevention Study) is underway in women age 42-58 and will hopefully answer more of these important questions.

WHAT ABOUT BREAST CANCER?

Menopausal women in their 50s are far more concerned about breast cancer risk than they are about risk of coronary heart disease, and it is this concern that often drives them away from HT. Unfortunately, data regarding HT and its relationship to breast cancer risk is concerning. Many studies have suggested that the increased risk of breast cancer is largely, if not entirely, related to progestin use and not estrogen. Data from the WHI Prempro arm (combination estrogen and progestin) suggested a small but measurable increased risk of breast cancer that correlates with the duration of use.

This risk was cited in the media as being a “25 percent increase in breast cancer.” Although the statistic prompted many women to discontinue HT, it must be clarified that the “25 percent increase” in breast cancer did not mean that 25 of 100 women would develop breast cancer with HT. Rather, WHI demonstrated a 25 percent relative increase in the incidence of breast cancer (38 women per 10,000 on Prempro compared with 30 women per 10,000 on placebo). This increase of eight patients per 10,000 translates into a 25 percent increase in relative risk, but the absolute risk remains small for the individual patient. The *NAMS 2008 Position Statement* indicates that post menopausal HT is associated with a small but measurable increase in breast cancer risk, which appears related to both duration of HT use as well as dose. Estrogen alone appears to be safer than combination

HT (estrogen plus a progestin). Furthermore, vaginal estrogen therapy for treatment of vaginal symptoms does not appear to have any increased risk of breast cancer.

WHAT'S A WOMAN TO DO?

Should a woman take HT when she enters menopause? Unfortunately, despite all of the data and analyses, there still is no simple answer. The decision to take HT must be evaluated for each woman based on her symptoms, personal medical history, family medical history and personal feelings about HT.

In 2009, menopause is no longer perceived as a “deficiency” state or a “disease” but rather a natural stage of life that does not always require treatment. Women who transition to post menopause with few symptoms may not require any therapy. Women who are mildly symptomatic in menopause may respond to non-hormonal therapies (soy, black cohosh, etc.) and lifestyle changes (wearing layered clothing and avoiding alcohol and caffeine). For women with severe menopausal symptoms and no contraindications to HT, treatment is often highly effective and is a reasonable option. It provides significant relief of hot flashes and vaginal dryness and may improve both sleep and mood.

However, women with a personal history of breast, uterine or ovarian cancer should not take HT. Women with a strong family history of breast or ovarian cancer should also consider other non-hormonal options. Furthermore, women who are more than 10 years past menopause should not routinely start HT in the context of our current understanding of heart disease risk and HT when initiated late after menopause.

Finally, although there are no current specific guidelines, women with significant cardiovascular risk factors (diabetes, high blood pressure, smoking) should first try to manage menopause symptoms with non-hormonal therapies. If these measures fail to control symptoms, women can proceed cautiously with HT in the lowest effective dose.

In most cases, the bioidentical FDA approved hormone estradiol should be considered, preferably in the patch or gel form, and HT duration should be for the shortest time possible (in general two to three years) because research suggests that prolonged use of HT increases a woman's risk of breast cancer, endometrial cancer and stroke. Most women's menopausal symptoms will have resolved by this time, and they can successfully stop HT without further issue. Up to 10 percent of women may have persistence of menopausal symptoms for more than 10 years after menopause, and for those women, extended HT use must be considered based on individual risks and expected benefits. ■

Metabolic Syndrome in Women

BY AMANDA DENNEY, MD

In addition to the controversy about hormone replacement therapy, the perimenopause period brings another issue: an increased susceptibility to developing metabolic syndrome. Metabolic syndrome is a cluster of risk factors related to underlying insulin resistance, which has been shown to increase the risk of cardiovascular disease (CVD), which is the leading cause of death in women.

These risk factors that make up metabolic syndrome include high blood pressure, obesity, dyslipidemia and impaired sugar metabolism. Unfortunately, as the obesity epidemic worsens, so does the incidence of metabolic syndrome. It affects 40-50 million people in the United States, including 23 percent of U.S. women. Its prevalence increases significantly with age, occurring in 20 percent of people 40-49 years old and 45 percent of people 60-69 years old.

There are two specific times when women are more susceptible to the development of metabolic syndrome. Menopause is associated with a 60 percent increase in the risk of developing metabolic syndrome, partly due to the effect of decreased estrogen on cholesterol levels, but also due to physical inactivity and less lean body mass. Younger women are more likely to develop metabolic syndrome if they also have polycystic ovarian syndrome (PCOS). Affecting 10-20 percent of women of child-bearing age, PCOS is also associated with insulin resistance, irregular or absent menstrual periods, signs of excess male pattern hormones and infertility.

The criteria for diagnosing metabolic syndrome have evolved over time. Under the current and most commonly used definition, a patient may be diagnosed with metabolic syndrome if he or she has three of the following five risk factors: waist circumference of 35 inches or greater (for women); triglycerides at or above 150mg/dL; HDL cholesterol (the “good” cholesterol) less than 50mg/dL (in women); blood pressure at or higher than 130/85 mm; and fasting sugar at or greater than 100mg/dL (see Table on next page).

Several studies have confirmed that metabolic syndrome is an accurate predictor for CVD in women; in fact, women with metabolic syndrome are at twice the risk of CVD. And the

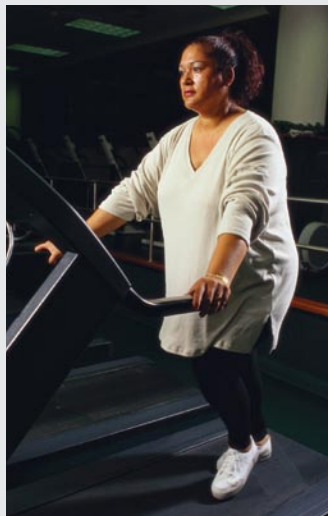
more of those five risk factors that are present, the higher the risk for CVD. Metabolic syndrome has even been found to be a predictor of nonfatal heart attacks in young women under 45 years old.

In both men and women, lifestyle modification is the key to managing metabolic syndrome. The overall goals are to decrease the risk of CVD and to prevent or delay the development of type 2 diabetes. Studies have shown that a 7-10 percent reduction in body weight can have a significant impact on

improving insulin resistance and preventing diabetes. In the Diabetes Prevention Program (DPP), a major clinical study, people with prediabetes who lost about 7 percent of their body weight, showed a 60 percent reduction in the development of diabetes. Similarly, another study in postmenopausal women showed that about 10 percent body weight loss resulted in significantly improved markers for insulin resistance, fasting blood sugar and cholesterol. Importantly, lifestyle modification seemed to have a greater impact on reducing risk factors in women who had either stopped estrogen therapy or who were never on estrogen therapy as compared to women who were maintained on hormone therapy.

Although many women would love to get back to their “high school weight,” this may not be necessary. A woman who is 200 lbs, for example, only needs to lose 20 lbs to cut her risk of diabetes by 60 percent! To achieve this degree of weight loss in these trials, participants followed a low-calorie, low-fat diet and incorporated 150 minutes per week of moderate-intensity physical activity, such as brisk walking.

Other modifiable risk factors for cardiac disease should be considered as well. People with metabolic syndrome may also need medicines to treat elevated cholesterol, high blood pressure and diabetes. Smokers should be counseled about tobacco cessation. Aspirin therapy may also be warranted in patients at higher risk. Although the use of medicines to improve insulin resistance is controversial, metformin (an insulin sensitizer used for people with diabetes and PCOS) was associated with a 30 percent reduction in type 2 diabetes among individuals participating in the DPP. ■





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Clinical Identification of the Metabolic Syndrome

(Taken from NCEP/ATP III Guidelines)

Risk Factor	Defining Level
ABNORMAL OBESITY (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
TRIGLYCERIDES	>150 mg/dL
HDL-CHOLESTEROL	
Men	<40 mg/dL
Women	<50 mg/dL
BLOOD PRESSURE	>130/85 mmHg
FASTING GLUCOSE	>100 mg/dL

RESOURCES:

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285(19): 2486-2497.

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