

Hormone Replacement: Individualizing Treatment

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After years of promotional messages about the benefits of hormone replacement therapy (HRT), the results from the recent Women's Health Initiative¹ (WHI) have come as a surprise to patients and health care providers alike, leaving them with more questions than answers. Results from this 5.2-year study of more than 16,000 women clearly indicate an increased risk of breast cancer, heart attacks, stroke, and blood clots from using PremproTM, the most widely prescribed HRT regimen for women. Although some protective benefits from HRT were observed for hip fracture and colorectal cancer, the study was halted three years early on the grounds that the risks outweighed the benefits.

Clearly the conclusions of this study are disconcerting and leave women with a decision that feels no more certain than a roll of the dice. There is no question that an increased number of HRT-supplemented women in the study experienced coronary heart disease, strokes, pulmonary embolism, and breast cancer. Additional studies such as the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II) corroborate these findings, demonstrating that cardiovascular risk occurs primarily in the first year of treatment.²

It is important to bear in mind that the WHI trial tested only one drug regimen—a combination of conjugated equine estrogens (CEE), and medroxyprogesterone acetate (MPA), a synthetic progestin. The study's results do not necessarily apply to the more bio-identical hormones, including estriol, estradiol, and oral micronized progesterone, which appear to have less adverse impact on health, particularly in breast cancer^{3,4} and vascular disease.⁵ Nor do these results apply to regimens utilizing lower dosages or non-oral routes of administration, both of which appear to be safer.^{5,6} It is not clear what the outcome would have been, had the study incorporated less potent hormones, along with a better assessment of the contributing risk factors.

What can we safely conclude from these study results? The answer lies in biochemical individuality. Since disease results from a combination of genetic predisposition and environmental stressors, HRT may be the defining factor in whether a woman who is genetically predisposed to cardiovascular disease or breast cancer actually develops disease. It is probably safe to assume that many women who experience heart attacks, stroke, blood clots, or breast cancer after undergoing HRT are already at risk for these conditions before starting treatment.

The WHI Study highlights the perils of applying "one-size-fits-all" medicine, but also plants the seed for better understanding the specific patients in whom HRT will be beneficial. Our goal is to better understand HRT: to apply it properly, individualize it appropriately, and monitor it thoroughly.

We can do this by carefully evaluating each woman's unique set of genetic, environmental and physiological risk factors. Advanced and specialized laboratory markers are available to help practitioners and their patients

more accurately assess the potential risks and benefits of HRT for each patient. The information gleaned from these laboratory assessments might have helped us understand why some HRT users in the WHI trial developed breast cancer or heart disease, while others didn't (or, for that matter, why so many women *not* on HRT still develop the diseases).

More importantly, these genetic and biochemical evaluations allow health care providers to practice a level of personalized medicine that provides the clinical foundation for individualized approaches to HRT.

1. **PRE-HRT EVALUATION:** To identify women with a high risk of developing negative health conditions from HRT, as well as those most likely to benefit from HRT with minimal associated risks. This allows each woman to make a more informed decision about the use of HRT based on her unique array of personal risk factors. In addition, it ensures that the physiologic systems of women who decide not to use HRT are adequately assessed and supported by other treatment strategies.
2. **HRT-MONITORING:** To monitor the potential safety and efficacy of HRT in women who decide to undergo such therapy. This allows women to be treated for any imbalances, including sex steroid hormones, which could lead to problems if unchecked.

1) PRE-HRT EVALUATION: Weighing the Risks and Benefits of HRT

As many as 85% of women in the perimenopausal period experience vasomotor symptoms and vaginal atrophy.⁷ Although HRT has been proven effective in alleviating these symptoms, a determination of the risks and benefits is necessary to individualize the decision about HRT.

Given the results of the WHI study, it seems clear that a woman with a personal history of heart disease, stroke, or breast cancer should avoid HRT. For women whose individual disease risk is less certain, functional laboratory evaluation of each woman's unique and dynamic physiology (described later in this article) can reveal high-risk, pre-disease imbalances that can lead to a cardiovascular event or cancer. Supportive therapies may be instituted to remedy these imbalances; in severe cases, HRT may be considered a contraindication.

Along with the functional assessments, a one-time measurement of genetic susceptibility to disease can help determine the likelihood of these genes being switched "on" or "off" by environmental factors. For a woman with a strong genetic predisposition to problems such as clot formation or inflammation, for example, HRT may be considered too risky a venture. On the other hand, a woman showing high genetic risk for osteoporosis, but low risk in these other areas, may be a good candidate for HRT.

Assessing Genetic Predisposition

Breast Cancer Risk

Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) are pro-inflammatory cytokines that play important roles in regulating estrogen synthesis in peripheral tissues, including breast. Both cytokines tend to increase estrogen production via key enzymes.⁸ Although environmental factors influence the activity of

cytokines such as IL-6 and TNF- α , genetic variations will predispose a woman to their increased activity, raising the risk of associated estrogen-dependent health conditions, such as breast cancer.

How estrogen is metabolized in a woman's body is another determinant in breast cancer risk. Estrogen is metabolized either to 16 α -hydroxyestrone (16 α -OHE1), high levels of which are associated with breast cancer,⁹ or to 2-hydroxyestrone (2-OHE1) which, in turn, is methylated to the more protective methoxyestrone. The ratio between these metabolites is considered an important factor in evaluating estrogen's potential stimulatory effect on target tissues.¹⁰

In addition, research has demonstrated an inverse correlation between intake of dietary folate (a critical cofactor in methylation) and breast cancer risk.¹¹ An inborn defect in this methylation process, as measured by a common genetic variation (or "polymorphism") in the MTHFR enzyme, may predispose a woman to less favorable estrogen metabolism, thus increasing her chances of developing cancer.

Heart Disease Risk

With menopause comes an increase in cardiovascular risk; inflammation is one of the primary mechanisms involved. The activity of certain cytokines can signal this. Increased activity of IL-6 and TNF- α predicts a poor prognosis in patients with acute coronary syndromes.¹² IL-6 is also a powerful inducer of the acute phase response, which leads not only to intimal thickening and plaque disruption but also to increases in fibrinogen, and in C-reactive protein (CRP), a strong predictive risk factor for cardiovascular events.¹³ Furthermore, IL-6 stimulates the hypothalamic-pituitary-adrenal (HPA) axis; chronic overactivation of this system is associated with central obesity, hypertension and insulin resistance—factors that may raise cardiovascular risk in menopause.¹²

Clot Formation Risk

For the women using HRT in the WHI study, the increase in the rate of vascular disorders was higher than that for any other condition. While the route of administration of the drugs may have had a bearing on the results (oral hormones stimulate hepatic production of proteins, including clotting factors⁵), not all of the women on HRT developed clots.

One key point to keep in mind is each woman's genetic susceptibility to blood clotting mechanisms. Polymorphisms in the genes regulating coagulation, such as Factor II and Factor V, may explain why, despite the various cardiovascular benefits afforded by estrogen replacement, a subset of women still show an increase in cardiovascular events after initiating HRT.¹⁴

In general, persons who are heterozygous or homozygous for a Factor V Leiden mutation have 4-7 times and 50-100 times increased risk, respectively, for venous thromboembolism (VTE). The presence of this polymorphism *in combination* with HRT appears to increase the risk of VTE as much as 15-fold compared with non-carriers who use HRT.¹⁵

Treatment with estrogens significantly increases clotting factors, including Factor II, with the degree of elevation correlating with dose.¹⁶ A recent study demonstrated the role of the Factor II mutation in nonfatal heart attacks in women, at least in those with hypertension.¹⁷ Women on HRT who carried the Factor II polymorphism showed an 11-fold increase in risk of non-fatal myocardial infarctions compared with non-carriers and nonusers of HRT. A polymorphism in this gene should be considered a contraindication for HRT.

Osteoporosis Risk

On the *benefit* side of HRT, research has fairly consistently demonstrated estrogen's ability to retard bone resorption.^{18,19} For a woman at low risk of breast cancer, heart disease, and thromboembolism, but at high genetic risk of osteoporosis, the benefits of HRT for bone may outweigh the risks.

Polymorphisms related to bone can not only help determine which women are at high risk of osteoporosis, but also which women *with* high risk are most likely to benefit from HRT. For example, a polymorphism in the vitamin D receptor gene indicates a higher risk of osteoporosis. HRT, however, increases bone mineral density substantially more in women who have the polymorphism in both chromosomes (homozygotes) than in those who only have the polymorphism in one chromosome (heterozygotes).²⁰

Genomics Assays

The following evaluations can be used to examine inborn, genetic risk of cardiovascular disease, breast cancer, and osteoporosis in women considering HRT:

- **Immuno Genomic Profile**—Measures a variety of cytokines related to inflammation (relevant to breast cancer, cardiovascular disease, and osteoporosis), including IL-1 β , IL-1RN, TNF- α , IL-4, IL-6, IL-10, and IL-13
- **Cardio Genomic Profile**—Measures genetic predisposition to cardiovascular problems, including coagulation defects (Factors II and V), methylation impairment (MTHFR), lipid defects, atherosclerosis, hypertension, and oxidative stress
- **Osteo Genomic Profile**—Examines genetic predisposition to osteoporosis, including type I collagen, calcitonin receptor, vitamin D receptor, parathyroid hormone receptor, IL-1RN, and TNF α

Once genetic susceptibility to cardiovascular problems, breast cancer, and osteoporosis has been assessed, functional assays in these areas can be used to evaluate current health status. Similar to the genetic testing, such assays can help determine risks in advance of HRT; however, they are also valuable in monitoring health risks during therapy. With the added clinical insight these evaluations provide, practitioners have the opportunity to treat pre-disease imbalances developing from HRT before they progress to overt disease.

2) HRT-MONITORING

How can the women who decide to use HRT feel safe?

HRT has primarily been prescribed for symptoms such as hot flashes. Many of the 17 million women currently using HRT experience significant relief from these symptoms and may be reluctant to stop. Some of these women on HRT already have osteoporosis and/or a family history of the disease, and therefore choose to take advantage of the bone-preserving benefits of HRT. How can these women feel safe?

Breast Cancer

Hormone levels can serve as very important indicators of breast cancer risk during HRT. Several studies have linked high levels of bioavailable estrogen or testosterone with increased incidence of breast cancer.²¹ Estrogens are believed to promote breast cancer by encouraging cell proliferation in the breast. On the other

hand, estradiol bound to sex hormone-binding globulin (SHBG) is associated with a *lower* risk,²² presumably because of the lower amount of bioavailable hormone. SHBG concentrations, as well as aromatase activity (converting androgens to estrogens), are modified by numerous environmental factors. Monitoring levels of SHBG and sex steroids can alert the practitioner to advise adjustments in diet, lifestyle, and HRT regimens to restore hormonal balance.

As mentioned above, some of the risk associated with estrogen is dependent upon how this hormone is metabolized. The ratio of the primary estrogen metabolites 2-OHE1 to 16 α -OHE1 correlates highly with breast cancer risk.^{10,23} The ratio is often easily modified by various dietary and lifestyle factors. Monitoring these metabolites in serum or urine can reveal how endogenous or exogenous estrogen is being broken down, so that the physician can better gauge how the body's breakdown of the hormones used in HRT may be affecting the patient's breast cancer risk.

Cardiovascular Disease

The inflammation that drives the synergistic process of cardiovascular disease is reflected by acute-phase markers such as CRP. Although estrogen replacement decreases cell adhesion molecules that promote fatty plaque build-up in the arteries, it also increases CRP, which stimulates their expression.²⁴ This paradoxical effect illustrates the importance of monitoring CRP during estrogen therapy. It is possible that estrogen-induced high concentrations of CRP—signifying heightened inflammation—could explain the increased number of cardiac events observed in the WHI study.

Monitoring estrogen's effect on cholesterol metabolism is also crucial. Although estrogen replacement generally favorably influences lipids by lowering LDL-cholesterol, the risk associated with LDL depends upon its composition. A predominance of small, dense LDL particles—associated with hyperfibrinogenemia in postmenopausal women—is linked to a 2- to 3-fold increase in coronary heart disease risk.²⁵ LDL particles that are larger and more buoyant do not seem to be as potentially detrimental to cardiac health.²⁶

Lipoprotein a (Lp(a)) is an independent hereditary risk factor for heart attack and stroke.²⁷ Studies such as the Postmenopausal Estrogen/Progestin Intervention (PEPI) have demonstrated the ability of estrogen therapy to produce reductions in both Lp(a)²⁸ and homocysteine²⁹ concentrations in postmenopausal women.

Individual evaluation of lipid fractions and independent risk factors for cardiovascular disease, such as CRP, fibrinogen, Lp(a), and homocysteine (and the related MTHFR polymorphism), enables the practitioner to weigh the potential cardiac risks and benefits associated with HRT.

Monitoring key markers of fat and blood sugar metabolism is also important. The menopausal transition is often associated with an increase in abdominal and visceral adipose tissue accumulation.³⁰ Increased visceral fat appears to play a major role in the pathogenesis of insulin resistance, which increases the risk of type 2 diabetes and cardiovascular disease,³¹ as well as breast cancer.³² Although estrogen replacement appears to attenuate some of these tendencies toward central fat and insulin resistance,³⁰ additional or alternative measures may be required for some women. Monitoring glucose and insulin dynamics can help in making this determination.

Osteoporosis

HRT is recognized for its ability to inhibit the increased rate of bone resorption at menopause. The clinical impact of HRT on bone tissue can be easily monitored with biochemical markers of bone turnover such as Deoxypyridinoline (Dpd). Urine levels typically decline within about 30 days of starting estrogen therapy³³ and correlate over time with increases in bone mineral density (BMD).³⁴

As with other interventions, however, HRT is likely to be more effective for some women than for others. Photon absorptiometry can indicate changes in BMD over time. However, these measurements should only be used infrequently, so a significant amount of bone may be lost between them. Research also suggests that bone turnover may be a better indicator of fracture risk than bone density.³⁵ Periodic measurements of Dpd in the urine enable the practitioner to more accurately gauge the patient's response to treatment.

Functional Assessments

For a woman taking HRT, the following assessments are useful in monitoring her health status over time. If HRT is observed to increase her risks, or if supportive therapies fail to compensate for observed imbalances, then a decision may be rightly made to stop HRT.

- **Comprehensive Cardiovascular Profile 2.0**—Provides a comprehensive serum assessment of total cholesterol, LDL and HDL cholesterol (including fractionation), Relative Risk Indices, ratios, and the independent risk factors Lp(a), homocysteine, CRP, and fibrinogen
- **Estrogen Metabolism Assessment**—Provides a urinary or serum evaluation of estrogen metabolism, including 2- and 16 α -OHE1, 2:16 α -OHE1 ratio, and Estrogen Metabolism Index
- **Women's Hormonal Health Assessment**—Provides a comprehensive serum assessment of sex steroid hormones and their metabolism. Includes a serum Estrogen Metabolism Assessment, estradiol, estrone, estriol, progesterone, DHEA-S, testosterone, SHBG, and ratios
- **Metabolic Dysglycemia Profile**—Provides blood measurements of fasting and 2-hour post-prandial glucose and insulin, along with other hormonal factors influencing fat and blood sugar metabolism
- **Bone Resorption Assessment**—Provides urinary measurement of pyridinium crosslinks, including bone-specific deoxypyridinoline.

Should HRT be the goal?

Results from the WHI study suggest that HRT offers fewer protective health benefits than previously thought. Although ovarian function declines with menopause, a healthy woman continues to produce small amounts of hormones, mostly from adrenal precursors and aromatization in adipose tissue. Some women are able to move through menopause with a minimum of symptoms. With proper attention to evaluation and therapeutic support, many women can avoid symptoms associated with menopause.

Although HRT issues are complex, advanced diagnostic tools enable practitioners to implement a personalized medicine approach to women's healthcare—one that promises to more effectively address each patient's individual needs and concerns about HRT.

Questions?

For more information, or to order the tests described above, please call our Clinical Support Department at (800) 522-4762, or email us at cs@gsdl.com.

You can find detailed information on the functional assessments by visiting our website: www.gsdl.com. For information on the genomic profiles, log on to www.genovations.com.

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