



# Life After the Women's Health Initiative (WHI): Guiding Women Through the Menopausal Transition

## Background: Pre WHI

In the 1990's, those of us providing health care to mid-life women had it easy. Small clinical trials, animal studies, and observational data indicated that hormone therapy (HT) was the way to go for management of menopausal symptoms and long-term health promotion.

We were sure that HT prevented osteoporosis while offering relief from hot flashes and vaginal dryness. Most providers and women were optimistic that taking hormones after menopause would be the fountain of youth and prevent heart attacks in women. Postmenopausal women presenting to the emergency room with chest pain were often given estrogen immediately. Women with a history of MI were empirically started on HT because of animal studies showing evidence of vascular improvement, and for the well known benefits to the lipid profile.<sup>1</sup> It was thought that maybe HT even helped skin collagen, incontinence, mood disorders, insomnia, decreased cognition, sexual response, management of weight gain, and prevention of Alzheimer disease!

Yes, concerns included an increased chance of endometrial cancer in women with a uterus (without proper progestin dosing). There was also a small thrombotic risk and a slight increase in breast cancer after time. But the benefits of staying young, feeling younger outweighed these risks.

By the mid 1990's, almost 2 in 5 postmenopausal women in the US were taking some form of HT for symptom

control and disease prevention.<sup>2</sup> Still, a large study investigating the non-vasomotor effects of HT had not been done.

## Enter the WHI

In 1991, The National Institutes of Health (NIH) established the largest study of women's health ever undertaken. The Women's Health Initiative (WHI) was designed as a primary prevention study to address the most common causes of death, illness, and impaired quality of life in postmenopausal women. The WHI addressed cardiovascular disease, cancer, and osteoporosis. The WHI was a 15 year multi-million dollar endeavor, and one of the largest U.S. prevention studies of its kind. The three major components of the WHI were:

- a randomized controlled clinical trial (RCT) of promising but unproven approaches to prevention;
- an observational study to identify predictors of disease;
- a study of community approaches to developing healthful behaviors.<sup>3</sup>

In the HT RCTs, women with a uterus were randomized to receive daily conjugated equine estrogens (CEE) .625mg plus medroxyprogesterone acetate (MPA) 2.5mg, or placebo, in what was known as the WHI Estrogen plus Progestin Trial (EPT). This continuous combined hormone regime was the most widely used in the US. Women without a uterus, who

therefore did not require endometrial protection from unopposed estrogen, took either daily CEE .625mg alone or placebo in the WHI Estrogen Alone Trial (ET). Enrollment was begun in December 1993. Ultimately, 161,809 post menopausal women, ages 50-79 were included in the various trials and over 1000 investigators and staff participated in data collection. The WHI was planned to continue for 8.5 years. It was designed to demonstrate “the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women”.<sup>4</sup>

## Related Studies: WHIMS and HERS

### WHIMS

A secondary WHI study looked at the effect of hormones on cognition. The **Women’s Health Initiative Memory Study**, or **WHIMS**, enrolled women age 65 and over to evaluate the role of hormones on the development of dementia.<sup>5</sup>

### HERS

In 1998, while the WHI was in process, startling results from the **Heart and Estrogen/progestin Replacement Study (HERS)** were reported, and they upset conventional wisdom. Although HERS was a part of the overall WHI study, which was intended to be a primary prevention study, HERS was designed for women with existing heart disease, making it clearly a secondary prevention study. Beginning in 1994, 2763 women with prior heart disease were randomized to CEE/MPA daily or placebo. HERS revealed a surprising increase in heart attacks during the first year, with no overall cardiovascular benefit during the duration of the study. The results disappointed and confounded researchers, providers, and the public<sup>6</sup>. Interestingly, regardless of placebo or HT use, women on a statin had no significant difference in coronary heart disease (CHD) events.<sup>7</sup>

## Surprise! Initial results from WHI Estrogen plus Progestin Trial

In July of 2002, the Writing Group for the WHI published initial results from the EPT arm of the study. 16,608 women (mean age 63) with an intact uterus had been followed for a mean of 5.2 years (the study intent was 8.5 years). The data and safety monitoring board (DSMB) recommended ending the

trial early “because the test statistic for invasive breast cancer exceeded the stopping boundary...and the global index statistic supported risks exceeding benefits”<sup>8</sup>. The safety threshold for breast cancer set by the DSMB was considered conservative, and the hazard ratio (HR) of 1.26 with a 95% confidence interval (CI) of 1.00-1.59 exceeded the board’s threshold. They had no choice but to end the study, even though the HR was not statistically significant, and the 95% CI included 1.0.<sup>9</sup> This small increase in breast cancer in current users of estrogen was not really a surprise; it had been noted in previous studies.<sup>10</sup>

The investigators found no overall change in coronary heart disease (CHD). Remember that apart from HERS (which studied women with existing heart disease), observational studies had shown that HT was protective. WHI was expected to show a reduction in cardiovascular events. How could this be that HT did not prevent coronary artery disease?. (More about this later when we look at the study participants...)

Although the risks of pulmonary embolism (PE) and stroke were slightly higher in the HT treatment group, this did not exceed the predetermined safety threshold, and had been seen before.

There was some good news. Bones fared well. HT reduced observed hip and clinical vertebral fracture rates by one third compared to placebo. There was a 23% reduction in other osteoporotic fractures and a 24% decrease in total fractures.

Colorectal cancer rates were reduced 37% in the HT cohort.

It is important to note that all cause mortality was not affected during the duration of the trial. Even so, the authors concluded that the risks of taking these hormones were not worth the benefits for primary prevention of chronic diseases. Specifically, CEE/MPA “should not be initiated or continued for primary prevention of CHD”.<sup>11</sup>

The Writing Group discussed several limitations of the study.

1. Only combined daily CEE/MPA was tested. They caution that these results can’t be extrapolated to lower doses of the same drugs, or to other oral or transdermal estrogens or progestins.
2. This trial could not distinguish the effects of estrogen from that of progestin. (One might argue for an even more specific wording here, as in oral CEE from oral CEE with MPA.)

3. There was a high rate of discontinuation in the hormone cohort (40%). The authors point out that perhaps this discontinuation rate led to underestimating the magnitude of negative outcomes including CHD and breast cancer, while at the same time underestimating the benefits of decreases in colon cancer and hip fracture.
4. The duration of the trial made it difficult to estimate long term treatment effects.<sup>12</sup>

Compared to placebo, this first report found that after a mean of 5.2 years of treatment, the women taking daily CEE/MPA in the EPT had no overall change in CHD. There was a slightly increased risk of stroke, PE, and invasive breast cancer. A reduction in the risk of hip fracture (hip fx) and colon cancer were noted.

**Hazard ratios (HR)** (or relative risk, defined as the incidence in exposed individuals divided by incidence in unexposed) were reported as:

CHD	1.29	286 cases
Breast Cancer	1.26	290 cases
Stroke	1.41	212 cases
PE	2.13	101 cases
Colon Cancer	.63	112 cases
Endometrial Cancer	.83	47 cases
Hip Fx	.66	106 cases

**Absolute excess risks** per 10,000 person years (or incidence in exposed minus incidence in unexposed) were calculated as:

CHD	7 more events
Stroke	8 more events
PE	8 more events
Breast cancer	8 more events

**Absolute risk reductions:**

Colon cancer	6 fewer
Hip Fx	5 fewer

Endometrial cancer incidence was not significantly affected.

Taken together, the women taking CEE plus MPA had an “absolute excess risk of events” of 19/10,000 woman years. However, it was felt that “over a longer period, more typical of the duration of treatment that would be needed to prevent chronic diseases, the absolute numbers of excess outcomes would increase proportionately.”<sup>13</sup>

## 2002: The summer of our discontent

The premature end to the WHI EPT was so unexpected that many of us practicing in the field of women’s health in the summer of 2002 remember exactly where we were when we first encountered the media blitz that preceded the actual publication of the initial results. Reporters interpreted data before providers had a chance to digest the study. It was frightening for many of the public unaccustomed to the wording of medical statistics. Did a relative risk of 1.26 for breast cancer mean women on HT had a 26% chance (greater than one in four!) of developing breast cancer?

In GYN practices across the country, phone calls from concerned women were immediate and unrelenting. Clinicians quickly pulled together informational sessions for the public to try to put this data in perspective, even as we struggled to understand the long-term implications. Before the summer of 2002, an estimated 15 million women were taking some form of HT. Within the next year estimates are that up to 50% discontinued therapy, some without a discussion with a provider. 91,000,000 new prescriptions for HT were written in 2001. This dropped to only 57,000,000 in 2003, a 42% decrease.<sup>14</sup> Symptomatic women who had been grateful for hot flash relief on HT were now struggling again. Yet the WHI ET study had not been stopped. Did that mean women might be better served on estrogen alone? It was a confusing time.

## 2003: But... estrogen helps cognition, right? The WHIMS results

### Background

Earlier studies indicated estrogen might protect the brain from cognitive decline. The Cache County Study published in 2002 noted that ten years of HT begun at menopause yielded up to an 83% decrease in the lifetime risk of Alzheimer disease (AD). Those who initiated HT after age 60 and continued for three to ten years had a 112% increase in AD.<sup>15</sup> It was expected that WHIMS would confirm these results.

Again, there was a surprise in store with the release of The WHI Memory Study in May 2003. Unlike earlier studies, a two-fold increase in dementia was reported among women 65 and older. However, all women studied were at least 65 when HT was initiated.<sup>16</sup>

After the WHIMS and WHI EPT results were made known, The US Food and Drug Administration required a black box warning of harm recommending HT not be used to prevent CHD or osteoporosis.<sup>17</sup>

## 2004: The other shoe drops: Results from WHI Estrogen Alone Trial

In April 2004, results from the Estrogen Alone Trial were released. 10,793 healthy women (mean age 63.6) who had undergone hysterectomy had been randomized to receive either daily CEE .625mg or placebo. The goal of this primary prevention RCT (like the WHI EPT) was to determine if the treated cohort showed a reduced risk of heart disease.<sup>18</sup>

This study was terminated early (after a mean of 6.8 years) because of an increased risk of stroke (HR 1.39) in CEE users<sup>19</sup>. In real life, this translates to only 0.12% additional strokes per year of treatment. The decision to end the trial early was reported to be a difficult one, and made by NIH after no consensus was reached by the WHI Data Safety and Monitoring Board. The global index of risk over benefit increased only 1% (HR 1.01 with 95% CI 0.91-1.12).<sup>20</sup>

It is notable that the increased risk of stroke in women taking CEE alone or CEE with MPA is consistent across the HERS, WHI EPT, and WHI ET trials. It is the only statistically significant negative effect of CEE alone and is less pronounced than in the CEE/MPA arm.<sup>21</sup> There was an overall null effect on CHD except in the younger women studied. For those between 50-59 years old, protection from CHD (HR.56) was noted. Is there a theme emerging?

More confusing was a decrease in breast cancer. Overall, CEE users in this study showed a not quite statistically significant reduction in risk. This 23% reduction in breast cancer, HR .77 (0.59-1.01), conflicts with findings from both HERS and the WHI EPT trials in which breast cancer increased about 25%. The younger women (age 50-59) had slightly less breast cancer (HR .72). However, Hully and Grady caution against taking the results of only one study as gospel. “Numerous lines of evidence support an increased risk of breast cancer with estrogen use, including cell culture studies, animal models, many observational studies, and the fact that anti-estrogens reduce the risk of developing breast cancer in healthy women. The reduced risk of breast cancer observed in a single trial, which is not statistically significant and does not fit with prior evidence, is best interpreted, for now, as due to chance.”<sup>22</sup>

As in the combined hormone arm, women taking only CEE trended toward a decreased risk of hip fracture (6 fewer fractures per 10,000 women years, HR .61).<sup>23</sup>

## Is it possible to reconcile WHI and observational studies?

Reassessment of WHI continues. Wasn't it a randomized clinical trial, the gold standard of research? Randomization is the best way to minimize any inherent differences (in lifestyle and other health-related factors) between cohorts. A large number of women were randomly assigned to treatment with hormone or placebo. In observational studies, on the other hand, subjects self-select into treatment groups and the cohorts can be very different from each other.

It is important to stress that apart from CHD, there is concordance between observational data and WHI regarding hormone therapy and stroke, PE, breast cancer (in the EPT but not ET arm), colon cancer and hip fracture. What makes CHD and breast cancer in the estrogen alone group outliers? And more importantly, where do we go from here? Let's begin by looking at problems presented by observational studies and then criticisms of the WHI itself.

### Methodological issues in observational studies of HT

“Healthy User” effect. In observational studies, women who decided to take hormones were generally healthier to begin with. Given the belief that hormones have long-term benefits, it makes sense that women interested in being proactive would choose to take them. The same women might be more likely to make other choices to protect their health, too. Hormones are by prescription only, requiring some level of contact with a provider, and therefore a higher likelihood of exams, mammography and other health screenings. In addition, HT users in observational studies tended to be more affluent, exercised more, were leaner, and more educated. Again, the healthy user effect.<sup>24</sup>

**Alcohol Use.** The HT users in observational studies reported drinking more alcohol than non-users. Some studies associate alcohol with an increased risk of breast cancer.<sup>25</sup>

**Adherence bias.** Adherence to a HT regime may also correlate with commitment to other health-promoting behavior. Interestingly, some randomized trials of heart disease indicate that placebo users have a lower rate of CVD than those who do not comply with placebo use! If a woman can't adhere to one regime,

perhaps she is less likely to continue an antihypertensive, daily aspirin, or lipid lowering agent, or to stick with an exercise program and healthy eating plan.<sup>26</sup>

**Missing an early adverse event.** Observational studies usually update data only every couple of years, and may have trouble capturing clinical events that occur early. This makes it difficult to pick up early harm with an intervention like HT.<sup>27</sup>

## Criticisms of the WHI

### Biological differences among hormones

The WHI estrogen/progestin study used one specific oral formulation. The only progestin studied was MPA and it was given continuously. It is known that MPA diminishes the beneficial increase in HDL caused by estrogen alone. When micronized progesterone is combined with estrogen, lipid benefits are maintained.<sup>28</sup> Would this have made a difference in the null effect of EPT on CVD? It is true that surrogate endpoints (such as the lipid panel and improved endothelium-dependent vasodilatation) do not always correlate perfectly with disease endpoints (actual CVD), but might another progestin have changed the outcome? Experts are undecided as to whether we can extrapolate benefit or harm from CEE/MPA to other regimes or other formulations (such as lower doses, transdermal delivery, estradiol instead of CEE, and cyclic micronized progesterone instead of MPA). The North American Menopause Society's (NAMS) Position Statement of March 2007 dealing with hormone use states that "in the absence of clinical trial data for each specific product, the clinical results for one agent should be generalized to all agents within the same family."<sup>29</sup> But we have no data to help prove or refute this position.

### Age

The WHI studied mainly older women without severe menopausal symptoms. They were chosen to eliminate the risk of placebo users with hot flashes leaving the study.<sup>30</sup> The mean age of the WHI EPT study was 63.3, the WHI ET trial 63.6, both more than a decade after the average age of menopause, (51 years).<sup>31</sup> The mean age of the HERS participants was even older, 67.<sup>32</sup>

The hazards recorded were events usually seen in older women. According to Hulley and Grady, absolute risk for many diseases doubles for each

decade of life. So, a 50-year-old would have half the risk of a sixty-year-old and a quarter of the risk of a 70-year-old. The absolute risk of CHD is low in younger women compared with those studied in WHI and HERS, and even if the patterns of relative risk were similar in all age groups, the actual risk to newly menopausal women would be low. Therefore, any effect from hormones on chronic diseases would be less.<sup>33</sup>

Most women initiate HT around the time of menopause to treat their symptoms. Yet both WHI and HERS did not include a sufficient number of younger women to determine whether a similar risk pattern in that age group would emerge.

A "critical window" theme is emerging, suggesting that initiating HT close to the age of menopause may be cardioprotective.<sup>34</sup> In later years, estrogen may either lose its protective effect or cause frank harm.<sup>35</sup> Healthy tissue may be needed to allow for an optimal response to estrogen.

Secor offers further support for the critical window theory of HT. She presents studies associating estrogen with increased levels of metalloproteinase (MMP). This enzyme breaks down the protective fibrous cap covering arterial plaques. If the cap is disrupted, the plaque destabilizes and ruptures. Thrombi that form at the site may cause a stroke or myocardial infarction. It is theorized that when older women (who have more arterial plaque) take estrogen, plaque stability is compromised because of increased MMP.<sup>36</sup> These older women are beyond the critical window of estrogen benefit.

The fully adjudicated data published from WHI in 2006 showed that younger women (in their 50's) on CEE had a significant reduction in CHD.<sup>37</sup> This is good news, and is supported by numerous studies of monkeys by Clarkson and others that show that ET begun immediately after surgical menopause inhibits progression of coronary artery atherosclerosis by 70%. Is it possible that the effects of hormones may vary with the stage of reproductive life?<sup>38</sup>

## Screening the study population

Women reported their experience with hot flashes to investigators prior to being accepted into the WHI trials. Those who had mild to moderate symptoms were warned that they could be randomized to the placebo arm, and therefore their flashes might

continue for the duration of the study. They were, in effect, discouraged from participating. Those reporting severe symptoms were excluded.<sup>39</sup> In real life, hot flashes are an early herald of estrogen decline, and a reason most women seek HT. So WHI was not studying a typical population?<sup>40</sup>

## Breast Cancer

The WHI investigators themselves noted that the reduction in breast cancer in the ET group is counterintuitive and inconsistent with observational data. Ganz suggests this is more likely related to biology than chance. 39% of the women in the WHI ET had a hysterectomy before age 40. 40% of that group underwent bilateral oophorectomy at the time of surgery. If we believe the extensive epidemiological literature correlating breast cancer with the number of years of menstrual life, oophorectomy at a young age would reduce the background risk. Even after menopause, ovaries produce androgens, some of which will be converted to estrogen. Oophorectomy before age 40 reduces a woman's exposure to endogenous estrogen. Ganz hypothesizes that the WHI ET cohort consisted of two groups of women with different risks of breast cancer (those with and those without oophorectomy). As a whole, the group would exhibit a reduction in breast cancer. This theory helps reconcile the WHI ET results with observational studies.<sup>41</sup>

## Was WHI truly a primary prevention study?

Let's look at of **cardiovascular disease and breast cancer**. Subjects in primary prevention studies should be free from any conditions that might affect the outcomes. We know that obesity, hypertension, high cholesterol, and history of heart disease increase the risk of CVD. Over 35 % in the EPT cohort and over 47% in the ET arm were being treated for hypertension. Many were taking statins or using aspirin daily and some had a history of MI and angina. Over one third of the women enrolled in the WHI had a BMI greater than 25, and at least another third had a BMI greater than 30. Kuhl maintains that the weight factor alone renders the studies unsuitable for evaluating the risk of breast cancer.<sup>42</sup> In addition 49% of the women enrolled had smoked or currently smoked. 70% of the women were 60-79 years old. Wouldn't these conditions contribute to adverse outcomes?<sup>43</sup>

## Drop out rate and unblinding

Higher than anticipated dropout rates were seen in both the EPT (42%) and ET (53.8%) studies. 40.5% of the women on hormones and 6.8% of the placebo takers in the EPT were unblinded. Neither of these facts enhances the study results.<sup>44</sup>

## 2007: A WHI secondary analysis attempts to look at age and CVD

Because of the inability of the WHI to focus on the effects of HT on younger, newly menopausal women, Rossouw et al., analyzed the data to see if cardiovascular risk changed according to age or years from menopause. Including years from menopause would encompass those with premature ovarian failure or early surgical menopause. But, there were too few younger women studied in WHI to provide enough power to analyze the arms separately, so in order to increase validity, data sets from both the EPT and ET arms were combined. Results were not statistically significant, but showed higher risks in women age 70 or older, and those 20 or more years from menopause. In fact, the increase in CHD was most pronounced in women taking hormones that were aged 70-79 and had moderate to severe menopausal symptoms. Interestingly, HT (nonsignificantly) reduced CHD in younger women and those less than 10 years from menopause. Total mortality was also decreased by (a nonsignificant) 30% for those age 50-59 and there was no increased risk of stroke in women in their fifties.<sup>45</sup>

Cardiologist and researcher Karas criticized Rossouw's secondary analysis. He believes it is faulty design to combine data collected from the ET and HT groups. He points out that another problem arises in assessing the time of menopause. Women with hysterectomy in the ET arm had varying patterns of oophorectomy and previous hormone use, which confuses the data. And women without hysterectomy were asked to "recall" the date of their menopause, which may be imprecise. However, Karas believes that the risks widely associated with HT "appear confined to older women at the time of therapy initiation and in particular to (those) with severe menopausal symptoms".<sup>46</sup>

But, the presence of menopausal symptoms does not seem to correlate with increased risks in younger women. Although the WHI protocols excluded women with moderate to severe hot flashes, women

with mild hot flashes had a lower risk of CHD (RR .95) than those reporting no vasomotor symptoms. Some researchers question whether HT might confer cardioprotection only when arteries are vasoreactive. In theory, if hot flashes happen when arteries dilate in response to a drop in estrogen, the arteries are demonstrating an ability to react to stimulus. The resolution of hot flashes may mean that arteries can no longer respond (to hormonal fluctuations, hypoxemia, or other stresses).<sup>47</sup> Further research is needed to see if hot flashes can serve as a marker for the window of opportunity to obtain cardiovascular benefits from HT.

## June 2007: Even More From WHI

Manson et al found that younger menopausal women (aged 50 – 59) who received CEE .625 mg daily had less coronary artery calcification at the end of the study than those who took placebo. Coronary artery calcification is one marker of artery plaque.<sup>48</sup>

## Now what? Where does all this leave clinicians and menopausal women?

Over 45.5 million American women are currently postmenopausal, and that number is expected to increase as life expectancy lengthens.<sup>49</sup> These women seek help from clinicians both for management of menopausal symptoms and long term health protection. HT remains the most effective option for symptom relief, but is it worth the risk? For how long? How do we offer counsel to women who trust us? It is difficult when published articles present conflicting data. The ground seems to shift frequently.

There is no single right answer. More evidence is needed to clearly define the benefits and risks involved in order to guide decision making for individual women. To this end, in 2007 The NAMS revised its '04 evidence based Position Statement on the Use of Estrogen and Progestogen in Peri and Postmenopausal Women.<sup>50</sup>

NAMS Position Statements are written by an Advisory Panel of clinicians and researchers in the field of women's health, who consider all evidence and attempt to reach consensus. The findings are then reviewed and approved by the NAMS Board of

Trustees. Position Statements provide “practical clinical recommendations” based on all current evidence. The Statements have become a good resource for clinicians.<sup>51</sup>

In the '07 revision dealing with menopause, the Panel negates the one size fits all method of menopause management, and instead supports individualized decision making based on an assessment of the cause of menopause, time since menopause, symptoms, quality of life issues, and risk of cardiovascular disease.<sup>52</sup>

The NAMS Advisory Panel of clinicians cautions that “no trial is perfect and no single trial should be used to make public health recommendations... which should be limited to women for whom the studies are relevant.”<sup>80</sup>

## Current recommendations include:

### For symptom management:

Hot flashes are the most common symptom of menopause. They begin to peak in the months just before the last menstrual period and may be quite intense through the next year or more.<sup>53</sup> For some women, they are debilitating. The majority of women report that their hot flashes resolve within 4-5 years.<sup>54</sup>

Treatment of moderate to severe vasomotor symptoms is the primary indication for systemic HT.<sup>55</sup> Behavioral adaptations such as maintaining cool ambient room air, practicing paced respiration, trigger identification and avoidance, exercise, and stress reduction may help. Isoflavones from soy or red clover have not been shown to be beneficial. In some trials, black cohosh provided improvement for mild hot flashes, but here is no safety data for this product beyond six months of use.<sup>56</sup> A recent double blind RCT found neither black cohosh, multibotanicals with black cohosh and nine other herbs, nor soy dietary counseling with multibotanical use provide relief from hot flashes<sup>57</sup>. Selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to help some women, especially breast cancer survivors.<sup>58</sup> In a RCT, the anticonvulsant gabapentin reduced hot flashes.<sup>59</sup> SSRIs, SNRIs, and gabapentin have a significant side effect profile (including blunting of libido) and require careful counseling prior to initiation.

Distressing **vaginal symptoms** (dryness, dyspareunia, and atrophic vaginitis) are reported by almost half of all postmenopausal women. Good response is seen from both systemic and local estrogen treatments. Local estrogen treatments (an estradiol releasing ring, tablet, or cream) are effective, and may be even better than systemic, with between 80 to 100% of women reporting relief.<sup>60</sup>

Initial absorption of **vaginal estrogen** may be enhanced as it passes through the thin walls of an atrophic vagina. This may increase serum levels, but once the vaginal epithelium has thickened and stabilized, systemic absorption becomes negligible. There is insufficient data at present to offer absolute assurance of safety to those women who need to avoid all estrogen exposure. No progestogen protection for the endometrium is required when local estrogen is used in standard doses.<sup>61</sup> An alternative to estrogen for vaginal dryness and atrophy is Replens, an over the counter polycorbophil-based vaginal product which has been shown to be efficacious in lowering the vaginal pH and promoting comfort. Other over the counter lubricants may also be helpful.<sup>62</sup>

Some studies suggest that **transdermal** systemic estrogen might be preferred to oral, although the long-term benefits have not been proven in RCTs.<sup>63</sup> Delivery through the skin avoids the gastrointestinal system and may be better for women with reflux or malabsorption syndromes. Studies show that, unlike oral estrogens, transdermal products have a neutral or beneficial effect on triglycerides and inflammatory markers for heart disease such as C-reactive protein. There is no first-pass metabolism in the liver, which may be why some studies indicate a decrease in Venous Thromboembolism (VTE) with transdermal estrogen.<sup>64</sup> Because the hormones are absorbed directly into the bloodstream, another benefit is steady serum levels, which may allow for lower dosing. Transdermal estrogen may be better for libido. Studies confirm that if estrogen is not metabolized in the liver, it does not increase in sex hormone binding globulin (SHBG). Oral estrogen, on the other hand, is known to increase SHBG, which binds to testosterone and may have the unwelcome effect of lowering libido.<sup>65</sup>

## Compounded and bio-identical products

In recent years, many women who were worried about the safety of commercially available therapies, have turned to the use of specially compounded bio-identical hormones. These are derived from plant products and made up specifically for an individual woman per her physician specifications. In November 2005, ACOG issued a Committee Opinion that pointed to the lack of scientific evidence regarding their safety and effectiveness. In addition, risks may also be related to the compounded process. *Reference: ACOG News Release, 10/31/05.* The FDA in January, 2008 sent warning letters to seven pharmacies who were compounding these non-FDA approved hormonal preparations. Specifically, the “FDA is concerned that the claims for safety, effectiveness, and superiority that these pharmacy operations are making mislead patients, as well as doctors and other health care professionals. Compounded drugs are not reviewed by the FDA for safety and effectiveness, and FDA encourages patients to use FDA-approved drugs whenever possible. The warning letters state that the pharmacy operations violate federal law by making false and misleading claims about their hormone therapy drugs.”<sup>66</sup>

*Reference: DHHS, FDA news, FDA takes action against Compounded Menopause Hormone Therapy Drugs January 9, 2008 1-2.*

## Discontinuing hormones

The decision to stop HT should be individualized. Women need to know that symptoms recur 50% of the time, independent of age and duration of use. Tapering slowly over time may help those whose symptoms had been severe. Data are inadequate to inform whether lengthening the time between doses or decreasing the amount given works best.<sup>67</sup>

## Conclusions about current knowledge

### Age

Clearly, the WHI was not designed to study hormones in the symptomatic newly menopausal woman. Conclusions should not be extrapolated from WHI to this age group.<sup>68</sup>

### Breast Cancer

The absolute risk of breast cancer in the WHI EPT was rare. There were only 4-6 additional cases of invasive cancer per year, per 10,000 women, after 5 or more years of use.<sup>69</sup> Women in the WHI ET arm had no increased risk after 7.1 years of use, with fewer than 8 cases per 10,000 women per year. However, the population studied may have had a

diminished background risk on entry to the trial.<sup>70</sup> Limited observational data suggests that the use of ET for more than 15 years may increase the risk, although there is little change in mortality from breast cancer in hormone users.<sup>71</sup>

### Coronary Heart Disease

Both HERS and WHI indicated that HT has an overall null effect on CHD risk, but these studies did not test the same populations as observational data. Observational studies support the reduction of CHD with systemic HT. The timing of HT initiation may play a role. Current data do not advise using HT for either primary or secondary coronary protection. WHI results support the findings from observational studies that young healthy women who initiate HT in close proximity to menopause for relief of menopausal symptoms are most likely to receive cardiovascular benefits. For these women, Hodis believes HT is “as effective and safe as other primary prevention therapies such as lipid lowering therapies and aspirin.” Many researchers agree with Hodis that “WHI is not the end-all trial concerning HT and CHD prevention but a step in providing data for hypotheses for the next generation of trials.”<sup>72</sup>

### Stroke

The WHI revealed an increase in stroke in both the EPT and ET arms (8 per 10,000 women years with EPT and 12 in the ET cohort). Other RCTs do not agree. The absolute risk is much lower in women in their 50's (1 in 10,000 for ET and 3 in 10,000 for EPT). The NAMS Panel concluded that HT should not be used for primary or secondary prevention of stroke, and should be avoided in the presence of an increased baseline risk of stroke.<sup>73</sup>

### Thromboembolism (deep vein thrombosis and pulmonary embolism)

The risk of thromboembolic events increase twofold in women on HT, according to the WHI, HERS, other RCTs, and observational studies. This risk appears early (in the first two years) and decreases over time. It is lower in younger women.<sup>74</sup> Some studies show a higher risk for ET than E alone.<sup>75</sup>

### Cognition and Dementia

Starting HT after age 65 may increase the risk of dementia during the following 5 years. It is not known if earlier initiation has a helpful or harmful

role<sup>76</sup>. One meta-analysis found symptomatic women had improvements in verbal memory, reasoning, vigilance and motor speed.<sup>77</sup>

## Current recommendations for counseling women

- Younger recently menopausal women should not fear HT to treat symptoms, but clinicians should simply and clearly explain the documented risks.
- Women with established or increased risk of heart disease, stroke, DVT history, or breast cancer should not take HT.
- Women should try lower than standard doses first, and increase if need be.
- Transdermal and local products (including vaginal estrogen in low doses) may offer better options, and should be discussed.
- Treatment should be continued for as short a time as possible (less than four years if ET, and less than seven for E) to minimize risk of breast cancer.
- If a woman has stopped HT but is having trouble with symptoms and wants to restart, it might be reasonable to do so if she is at low risk of CVD and is within 5 years of menopause. If she is 5-10 years post menopause and at low risk for CVD, consider her risk of breast cancer versus protection from osteoporosis. Avoid restarting HT in women more than 10 years after menopause.<sup>78</sup>
- Women discontinuing systemic therapy should be counseled on the likelihood of vaginal dryness and proactively consider local estrogen.
- Even given the emerging data on the window of opportunity theory for HT and CVD protection, we still should prescribe HT only for symptom management, not for protection from CVD.<sup>79</sup>

## Coming soon...

We await the results of future trials. Hodis looks forward to the **Kronos Early Estrogen Prevention Study (KEEPS)**, which is evaluating different delivery modes of estrogen in younger postmenopausal women.<sup>81</sup> The **ELITE** study (Early Versus Late Intervention Trial with Estradiol) was designed after the WHI in 2002. It is funded by the National Institute on Aging, and looks at cognition and the progression of atherosclerosis in postmenopausal women relative to the timing of initiation of HT.<sup>82</sup>

In summary, the best choices are made when a clinician partners with a woman to make decisions about HT that are based on her individualized needs. These choices should be revisited as time passes. Incorporating evidence from well-designed trials into clinical practice is necessary, but no one trial holds the key for all women. “Compassionate clinical

practice”, as Thacker says, “requires attention to the art as well as the science of medicine. Not only RCTs, but observational and cohort studies can be balanced with common sense, patient preferences, values, and stage of life.”<sup>83</sup> Stay tuned!

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