

**WOMEN IN BALANCE INTERVIEWS**  
**KENNA STEPHENSON, M.D.**

**First-Year Results of the CHOIICE Study are In**

Dr. Kenna Stephenson recently presented the first-year results of her CHOIICE (Compounded Bioidentical Hormones: Immune, Inflammatory, and Cardiovascular Biomarker Effects) study to the American Heart Association 2008 Scientific Sessions. Dr. Stephenson did her research under the auspices of the University of Texas Health Science Center. She has had a distinguished academic career that includes clinical research and professional publications on women's health, cardiovascular pharmacology, aging, prevention, and holistic medicine. She is a Fellow in the American Academy of Family Physicians, and is board certified in Family Medicine. She appears as the health expert for the local CBS television affiliate, KYTX, in *Eye on Health* and is a sought-after speaker on the subject of natural hormones in clinical practice. Stephenson is currently an Associate Professor of Family Medicine at The University of Texas Health Science Center in Tyler, Texas.

**WIB:** Taking on a study like this involves an enormous commitment of time, energy and fund raising. What inspired you to take on this task?

**KS:** I started using compounded [natural] hormones in clinical practice about a decade ago and observed an oftentimes dramatic benefit and very few side effects or problems. I wasn't entirely comfortable prescribing them because of the paucity of clinical studies, especially long term, with specifically compounded hormones. I wanted to make up for that deficit in the U.S. research literature in a prospective, 36-month, long-term study to look at clinical outcomes with the compounded hormones as well as potential for harm.

I was really spurred on after the Women's Health Initiative [WHI] when all hormones were condemned equally. My thinking in looking at the clinical literature, epidemiological studies and experimental studies is that hormones are not all equal as it relates to their pharmacology and physiology, and that there are distinct differences with the compounded hormones. This needed to be explored further instead of just saying, "Hormones are dangerous, hormones are bad, we can't use them anymore, we've got to look at non-hormone therapies for hormone-related symptoms."

We started recruiting for the CHOIICE study in 2005. The second arm of the WHI, the Premarin-only study, was halted in 2004. I think the timing was good in that there were women who had been off hormones for awhile because of the fear-based knee jerk response by a lot of physicians and patients, and yet women were suffering and looking for relief.

WIB: What were the criteria for women entering the study? Did you choose women suffering from specific menopausal symptoms?

KS: We did not seek out women that were having menopausal symptoms. We looked at women who were perimenopausal and postmenopausal, between the ages of 30 and 70, and who were free of any severe chronic diseases. They could not be on a statin or other cholesterol-lowering drugs, they could not be on a COX-2 inhibitor, they could not be on any hormones, and had to be cancer-free for five years. Those are the inclusion/exclusion criteria.

We documented their symptoms at baseline and on followup. There were a few women that did not have hormone-related symptoms because that was not an inclusion criteria, but part of our hypothesis is that if women have depleted levels of sex steroid hormones, and those levels are vital to multiple systems in the body, then it would benefit them to have those levels restored. Maybe they don't feel it as it relates to having a hot flash or a night sweat, but does it reflect on say, cardiovascular markers? Does it behoove them perhaps in a preventive way, in a proactive way, to have their hormones evaluated and then restored if they're deficient?

WIB: How many women total are in the study?

KS: Seventy-five in the interventional group, and then 75 in the control group. The control group are women in the clinics at our facility that are receiving conventional care. They're ethnic and age-matched controls. Those women are receiving, let's say, statins, antidepressants, anxiolytics [drugs for anxiety] and conventional hormone therapy from their providers.

This is a three-year study. The data that we reported at American Heart Scientific Sessions last month [November 2008] was the 12-month data.

WIB: What were the markers that you chose to measure?

KS: Our high interests were in thrombotic [stroke/blood clot] factors because there is a large body of clinical and experimental evidence demonstrating that conventional hormone therapy does increase thrombotic risk when given orally. Then there have been statements by entities such as the North American Menopause Society that progesterone should be inferred to have the same thrombotic risk as medroxyprogesterone acetate [e.g. Provera], yet there's not evidence of that—but again there was no lack of evidence either.

We had a high interest in what was happening with hemostatic factors. We looked at factor VII, factor V, factor VIII, antithrombin III, fibrinogen activator inhibitor and fibrinogen. These factors may be reduced or elevated in patient populations and then lead to risk of stroke or heart attack, pulmonary embolism or venous thrombosis.

Both the PremPro arm and the Premarin arm of the WHI were stopped early because of increased thrombotic risk, so we measured all of these factors and did not see any

significant changes that would be pro-thrombotic, and we saw, with several of the factors, a statistically significant beneficial change. That change was most pronounced in the postmenopausal women.

We also looked at other biomarkers for cardiovascular disease: the inflammatory factors such as C-reactive protein [CRP] and we looked at clinical measures of systolic blood pressure, diastolic blood pressure, pulse pressure, fasting blood glucose, fasting insulin, fasting triglycerides. Then we looked at a mood scale for depression, anxiety, as well as the Greene Climacteric Scale, a numerical index that scores 21 menopausal symptoms. We looked at a depression and anxiety scales scale because of data from the POWER study and the ATTICA study—both demonstrate that when women have a mood state of anxiety or depression, they have an increase in both pro-thrombotic and pro-inflammatory factors irrespective of whether they're on psychotropic drugs, they smoke, or their BMI [body mass index, or weight]. A woman's emotional state will affect these biomarkers, so it was important for us to quantify that.

WIB: How did you decide which hormones to put the women on?

KS: For each patient that met the strict inclusion/exclusion criteria and entered the study, we performed baseline hormone profiles. We looked at estrogen, progesterone, testosterone, DHEAS, and we also looked at their cortisol circadian rhythms. We used saliva testing, which our research team feels is the best measure of bioavailable hormones. Then, if the patients had sub-optimal levels of progesterone they were given progesterone during the first eight weeks. If they had sub-optimal levels of both estrogen and progesterone they were given both of those for the first eight weeks. The first eight weeks did not include any androgens [male hormones]. Then we retested the patients and at that point if they had low androgens we added in androgen therapy. All of our hormones were given transdermally [through the skin, via cream].

There is a myth out there that androgens are harmful to women, but some of that may come from the fact that very high doses of oral synthetic androgens have been shown to have adverse effects. And of course that's distinctly different than the transdermal low dose compounded androgens that were given to our patients.

WIB: How did you decide the amounts of hormones to give them?

KS: We used the formulary for health care professionals that's published in my book, *Awakening Athena*. I used that formulary in clinical practice for nearly a decade. Then the prescriptions were titrated to physiologic reference ranges because women have different responses to hormone therapy. Some women may be rapid metabolizers, some slow metabolizers, so that's why it was important that we monitor and retest them. One patient may need 20 mg of progesterone to get her to target, and another may need 40 mg or 60 mg.

We've looked at the patients collectively as it relates to risk and benefit and the type of hormone therapy. But as far as the dosing, women have to be treated individually, and

they need individual dosing. It is not good enough to just categorize them based on their uterine status or symptoms. Each patient received her specific hormone dose based on her saliva test profile results. It sounds complex but it's really not, and it sure saves a lot of time in the long run.

WIB: And the women sure feel better!

KS: We proved that I think. Our hypothesis was that we would not see the elevated thrombotic factors, but we were very surprised to see this global benefit in all domains. We felt that we would see some, but it was quite surprising to us to see the statistically significant beneficial changes across the board.

WIB: Very exciting. Would you give us a general overview of the results?

KS: Cardiovascular disease is the leading cause of death and disability in American women. Our concern is that there are hormonal factors involved, and our research suggests that if we address those hormonal factors primarily, then there's a downstream effect on the cardiovascular biomarkers showing a benefit. The WISE [Women and Ischemic Events] studies by the NIH Heart, Lung and Blood Institute and others over the last decade suggest that there is a gender-specific pathophysiology as it relates to cardiovascular disease. This clustering effect in peri-menopausal and post-menopausal women of an elevated fasting glucose, elevated triglycerides, elevated CRP and elevated pulse pressure, all contribute strongly to cardiovascular disease risk, along with psychosocial factors of anxiety and depression.

We saw benefit in all of these domains both at eight weeks and at 12 months. We saw improvement in their depression and anxiety scores, we saw a decrease in fasting glucose and fasting triglycerides, we saw a decrease in CRP, we saw a decrease in systolic pressure and pulse pressure.

WIB: Do you plan to continue to follow these women when the study is over?

KS: Funding is the issue. It's been quite a struggle to do this study on a shoestring. We're competing with Big Pharma studies that are very generously funded, where there's want of nothing. We'll probably survey the women, but I don't know that we'll be able to afford much more than that.

WIB: Do you have any insights that you can share from your own clinical practice?

KS: I think the most compelling thing that I can share as it relates to women's health and assessing women in this age group, is that when they are pre-hypertensive and pre-diabetic, by clinical criteria, it is vital to know their hormone profile. Starting treatment with pharmacotherapy [drugs] to lower blood pressure, triglycerides or blood sugar may create problems with drug interactions or side effects, or not have a global protective effects. By knowing a woman's hormone profile and her hormone status, and by testing

that first, you may see a significant improvement in her blood pressure, her lipids and her glucose.

WIB: So doctors can use a treatment that's safe and effective, is replacing what's depleted, and addresses the whole body, rather than treat specific symptoms with a pharmaceutical drug approach. You're treating an underlying cause rather than a symptom.

KS: Yes. That is what I try to emphasize with the medical students and the residents. Metabolic syndrome is so prevalent and is increasing in this patient population. Hormone factors are the priority.

WIB: How do you treat women whose cortisol is out of balance and indicating tired adrenals?

KS: First I want to know what's happening with her progesterone. If the progesterone is low, then I prescribe transdermal progesterone along with nutritional and lifestyle counseling. That's my primary approach.

WIB: Does the nutritional/lifestyle counseling include getting more sleep, eating less sugar, stress management and exercise?

KS: Yes. We counsel women with low adrenal function to pay attention to the glycemic indices of food, to take the time to restore and recharge. Even if she's working two jobs. Some of my patients are working three jobs. They need to find somewhere, even if it's just a twenty-minute break, to help de-stress. Maybe she can take 30 minutes on an hour lunch break to do some yoga work or aerobic type exercise. That's what I counsel the patients initially. And then if the adrenal depletion is more profound or severe, I will oftentimes have them take supplements.

WIB: What types of supplements do you recommend?

KS: I primarily use James Wilson's protocols and supplements. [[www.adrenalfatigue.org](http://www.adrenalfatigue.org)].

WIB: Thanks so much for your time and attention, Dr. Stephenson. This is a beautifully thought-out and executed study, and it will change how doctors approach women's health. We look forward to talking with you next year about the results of the second year of the study.

Dr. Stephenson will be a featured speaker at the upcoming Women in Balance Educational Conference ([add link](#)) in Dallas, TX on February 7<sup>th</sup>. These seminars are for all women who want to learn more about creating hormone balance from some of the top experts in the field.

