WRITTEN TESTIMONY

JoAnn E. Manson, MD, DrPH, FACP
Professor of Medicine, Harvard Medical School
Chief, Division of Preventive Medicine, Brigham and Women's Hospital

The landscape of hormone therapy in the post-Women's Health Initiative (WHI) era

The hormone therapy component of the WHI consisted of two randomized clinical trials in postmenopausal women who were aged 50-79 years (average age, 63 years) and generally healthy at baseline. The trials were designed to test the effect of estrogen plus progestin (for women with a uterus) or estrogen alone (for women with hysterectomy) on coronary heart disease (CHD), stroke, hip fracture, breast and colorectal cancer, and other health outcomes, and whether the possible benefits would outweigh possible risks. Taken in aggregate, data from observational studies had suggested benefits for osteoporotic fractures, heart disease, and colorectal cancer and risks for breast cancer, stroke, and blood clots in the legs or lungs[1]. Until the WHI, however, no large-scale clinical trial in healthy women had been conducted to confirm or refute these observational findings.

The WHI results not only disprove the theory that supplemental estrogen confers heart protection in women who are on average more than a decade past menopause onset but also indicate that this hormone, when taken in combination with a progestin, may actually increase the risk of coronary heart disease in such women.[2-4] Moreover, the findings suggest that the overall health risks associated with hormone therapy tend to outweigh the benefits in women distant from the onset of menopause.[2, 5] However, because few participants were within 5 years of menopause, the WHI trials could not conclusively determine the balance of benefits and risks in recently menopausal women. Nonetheless, the WHI results are critically important because the study halted what was becoming an increasingly common clinical practice of initiating hormone therapy in older women and those at elevated risk of CHD.

The WHI results have led to revisions of clinical guidelines for hormone therapy use. The U.S. Preventive Services Task Force,[6] American College of Obstetricians and Gynecologists,[7] American Heart Association,[8] Canadian Task Force on Preventive Health Care,[9] and the North American Menopause Society[10] now recommend against the use of estrogen with or without a progestogen to prevent CHD and other chronic diseases. Hot flashes and night sweats that are severe or frequent enough to disrupt sleep or quality of life are currently the only compelling indications for hormone therapy. The WHI results suggest that key factors to consider in deciding whether to initiate hormone therapy in a woman with these symptoms (assuming she has a personal preference for such therapy) are where she is in the menopausal transition and whether she is in good cardiovascular health. A younger, recently postmenopausal woman—one whose final menstrual period was 5 or fewer years ago—at low baseline risk of CHD, stroke, or blood clots is a reasonable candidate for hormone therapy. Conversely, an older woman many years past menopause, who is at higher risk of these conditions, is not. Use of hormone therapy is

best limited to 2 to 3 years and generally no more than 5 years, as breast cancer risk increases the longer hormones, particularly estrogen plus progestin, are used.

The WHI trials will undoubtedly remain the "gold standard" of evidence on the health effects of hormone therapy for years to come, but their limitations must be acknowledged. Although the WHI provided clear data on the benefits and risks of hormone therapy in women aged 60 and older and ended the increasingly common practice of starting hormones in these women for the express purpose of preventing CHD, the overall findings likely overstate the risks for healthy women aged 40 to 59 who begin hormone therapy closer to menopause onset. Moreover, only one type and dose of oral estrogen and progestogen was tested, so the results may not apply to other formulations, doses, and routes of administration. There are few or no trials on alternative hormone medications, particularly custom-compounded "bioidentical" hormones. The lack of data on these agents, however, should not be construed to mean that they are safer or more effective at preventing chronic disease; more research is needed to answer these questions. Until such data are available, the prudent strategy—and one endorsed by all major medical organizations in the U.S.—is to assume all formulations have a similar safety and risk profile.

Follow-up studies that have been conducted to help clear up confusion after the WHI

The divergence between earlier observational studies, which suggested that hormone therapy might protect against heart disease, and the WHI trials, which did not, raised concern that the coronary benefit seen in observational studies might simply reflect the fact that women who choose to use hormone therapy tend to be healthier, have greater access to medical care, and embrace health-promoting habits (e.g., eating a nutritious diet and exercising regularly) more readily than women who do not choose to use hormones. Nevertheless, the concordance between observational studies and the WHI for other endpoints, particularly stroke, which have lifestyle determinants similar to those for CHD, suggest that these biases are not the primary explanation for the discrepant CHD results.[11, 12] Instead, a closer examination of available data suggests that the timing of initiation of hormone therapy in relation to menopause onset may affect the association between such therapy and risk of CHD. Hormone users in observational studies typically start therapy within 2-3 years after menopause onset, which occurs on average at age 51 in the U.S., whereas WHI participants were assigned to hormones more than a decade later. These older women likely had less healthy arteries than their younger counterparts.

Small trials conducted prior to the WHI had shown that estrogen therapy has both beneficial and harmful effects on blood and other markers of cardiovascular health. In light of findings from the WHI, as well as findings from clinical trials of hormone therapy among women with preexisting heart disease (e.g., the Heart and Estrogen/progestin Study [HERS][13, 14]), scientists have hypothesized that the clot- and inflammation-promoting effects of supplemental estrogen may be more problematic among women with advanced atherosclerosis who initiate hormone therapy well after the menopausal transition, whereas women with less arterial damage who start hormone therapy early in menopause may benefit most from estrogen's favorable effect on cholesterol levels and blood vessel elasticity.[11, 15]

Animal experiments support the idea that the coronary effect of hormone therapy depends on the initial health of the arteries. In one series of studies, investigators induced menopause in monkeys by surgically removing their ovaries and then attempted to induce atherosclerosis by feeding them an "imprudent" diet high in fats.[16] Some of the monkeys were given hormone therapy immediately upon ovary removal and initiation of the imprudent diet. The remaining monkeys were given hormones only after a 2-year lag (the equivalent of 6 years in a woman) or were not given hormones at all. Compared with the monkeys that didn't get hormones, the monkeys that received the hormones early—and, presumably, before their arteries had advanced fatty deposits—had 70% less atherosclerosis, while the monkeys that didn't get hormones right away had no reduction in atherosclerosis.

The WHI findings have prompted reanalyses of data from existing observational studies and randomized clinical trials to examine whether timing of initiation of hormone therapy affects coronary and other outcomes. Investigators with the Nurses' Health Study, the largest and longest-running observational study of hormone therapy and CHD in the United States, who earlier reported that current use of hormone therapy was associated with an approximate 40% reduction in risk of CHD in the cohort as a whole,[17] recently found that the coronary benefit was largely limited to women who started hormone therapy within 4 years of menopause onset.[18] A 2006 analysis that pooled data from 22 smaller randomized trials with data from the WHI found that hormone therapy was associated with a 30 to 40% reduction in CHD risk in trials that enrolled predominantly younger participants (women under age 60 or within 10 years of menopause) but not in trials with predominantly older participants.[19]

The ongoing Early versus Late Intervention Trial with Estrogen (ELITE) is testing whether there are differential effects of hormone therapy on the development and progression of atherosclerosis according to the age at which therapy is initiated.[20]

It should be noted that the evidence for differential health effects of hormone therapy by age or time since menopause, though strong, is not yet conclusive. Nonetheless, even if differential health effects do not exist, the much lower absolute baseline risks of coronary and other events in younger or recently postmenopausal women means that these women experience much lower absolute excess risks associated with hormone therapy use as compared with their counterparts who are older or further past menopause.

Recent WHI findings assessing the role of a woman's age and time since menopause: what it means for the current approach to hormone therapy

To test the hypothesis that timing of initiation of hormone therapy may influence its benefit-risk profile, WHI investigators[21] recently conducted a combined analysis of the two hormone therapy trials of the WHI. We found that women who begin hormone therapy closer to the onset of menopause tend to have more favorable outcomes, in terms of cardiovascular disease and mortality, than women who begin treatment at older ages and when more distant from menopause. Specifically, women who were less than 10 years since menopause when randomized to hormone therapy had a 24% *reduced* risk of heart disease compared with those randomized to placebo, while women 10-19 years past menopause had a 10% *increased* risk and

women 20 years or more past menopause had a 28% *increased* risk (p-value for trend=0.02). When examined by age group, hormone therapy had a neutral effect on risk of heart disease in women aged 50-59 and 60-69, but caused a 28% *increase* in risk among women aged 70-79. We also found that total mortality rates with hormone therapy appeared to be more favorable in younger women (a statistically significant 30% reduction in death rates), while older women had slightly higher mortality rates with hormone therapy than placebo. Overall, the findings suggest that timing of initiation does influence the benefit-to-risk profile of hormone therapy and provide some reassurance for recently menopausal women considering hormone therapy for treatment of menopausal symptoms. However, stroke risks were elevated with hormone therapy among women in all age groups. The results do not change the recommendation that hormone therapy should not be used for the express purpose of preventing cardiovascular disease in women, regardless of age.

Bioidentical or custom-compounded hormone therapy and the new "alternative" protocols

There is very limited research on the efficacy and safety of bioidentical hormone therapies overall and custom-compounded bioidentical hormone preparations in particular. Women may be misled into believing that various "protocols" or regimens are safer or more effective than they may actually be, and they may not be getting objective information and a balanced overview about side effects, long-term risks, and benefits. There is no rigorous scientific research on most, if not all, of these protocols with respect to safety and efficacy—i.e., they have not been tested in large-scale clinical trials with large numbers of women followed for long durations. The data that do exist are primarily anecdotal.

Because of the risks of conventional hormone therapy that were identified by the Women's Health Initiative, there has been growing interest in bioidentical and custom-compounded hormones as potentially safer alternatives. The key question is: are these products indeed safer or more effective than conventional hormone therapy? Unfortunately, there is little evidence to support this notion. Moreover, women aren't getting accurate, unbiased information to help them make an informed choice about whether to use such hormones or not. Some consumer books have blurred the line between science and hearsay and promulgatd protocols that may expose women to serious health dangers[22].

Let's define our terms. Scientists and mainstream healthcare providers use the term "**bioidentical hormones**" to refer to medications that contain hormones that are an exact chemical match to those made naturally by our bodies. Women make three types of estrogen—estradiol, estrone, and estriol—as well as progesterone and other hormones. Thus, bioidentical hormones are medications that provide one or more of these hormones as the active ingredient. Bioidentical hormones are available with a doctor's prescription at commercial retail pharmacies in a range of standard doses. Commercially available bioidentical estradiol comes in several forms, including pills (Estrace & various generics), skin patches (Alora, Climara, Esclim, Vivelle, Estraderm), skin creams (EstroGel & Estrasorb), and various vaginal preparations (Estrace vaginal cream & Estring vaginal ring). Commercially available bioidentical progesterone can be purchased as a capsule (Prometrium, which has a peanut oil base) or a

vaginal gel (Prochieve vaginal gel). Because they are manufactured en masse and sold by retail pharmacies, these bioidentical products are regulated by the FDA.

Many consumers and naturopaths use the term "bioidentical hormones" to refer exclusively to custom-mixed cocktails of these hormones, prepared according to an individualized prescription from a doctor by compounding pharmacies. A more precise term for these preparations is **"custom-compounded"** bioidentical hormones. Although hormone compounding has been popular in Europe for years, interest in the U.S. surged only after the WHI results cooled the ardor for traditional hormone therapy. There are no reliable estimates of how much of the U.S. prescription hormone market is serviced by compounders, but some compounding pharmacies have claimed that as many as 2 million U.S. women rely on customized hormone products.[23]

Advocates of bioidentical hormones—particularly custom-compounded ones—assert that these products are more effective at relieving menopause symptoms, have fewer side effects, and offer a better balance of long-term health benefits and risks than other hormone options. However, we simply don't know whether these claims are valid, because large-scale, scientifically rigorous studies of bioidentical hormones have not been conducted. Until we have solid data that indicate otherwise, virtually all medical authorities (e.g., the North American Menopause Society and the American College of Obstetricians and Gynecologists) agree that a conservative and prudent approach is to assume that all hormone formulations confer a roughly similar balance of benefits and risks.

It is true that custom-compounded hormones benefit women who for some reason cannot use a commercially available preparation. For example, a patient may be allergic to an ingredient, such as the peanut oil in Prometrium, or may require a specific dose or product mixture not produced by a pharmaceutical company, although this is uncommon given the large and increasing number of options offered by commercial manufacturers. However, there are also unique risks associated with custom-compounded products, as they are not under the oversight of the FDA:

***Quality control is problematic*.** Preparation methods differ from one pharmacy (and pharmacist) to another, so patients may not receive consistent amounts of hormone. In addition, inactive ingredients vary, and contaminants may be present. In 2001, the government purchased and tested 29 products, including hormone preparations, from 12 compounding pharmacies and found that 34% of the samples failed one or more standard quality tests.[24] Additionally, 90% of the failing samples contained less of the active ingredient than advertised. In contrast [to the 34%], the testing failure rate for FDA-approved drug therapies is less than 2%.[25]

The value of saliva and blood testing is unproven. Before custom-compounded hormones are prescribed, a saliva or blood test is typically performed to measure a woman's natural hormone levels. The belief is that the test can determine whether a woman has the "right amount" or "right balance" of hormones and guide adjustment of hormone doses. However, the value of these saliva and blood tests is highly questionable, and there are little scientific data to support their use. Optimal estrogen and progesterone levels in blood or saliva have not been established for postmenopausal women. Hormone levels fluctuate throughout the day as well as from day to

day, and these levels are not clearly linked to the presence or severity of menopausal symptoms, short-term side effects of hormone therapy (e.g., headaches), or, in most instances long-term health outcomes (e.g., heart attack).

Expense is an issue. Many custom-compounded hormone products, as well as the associated blood and saliva testing—which must be done every few weeks or months until hormones are "balanced"—are expensive and are not covered by health insurance. Lab tests cost roughly $100 to $400 per visit, while hormones cost approximately $30 to $100 per month.

Consumers lack reliable product information and can fall prey to misleading advertising claims. Unlike retail pharmacy prescriptions, compounded products are not required to have a package insert that contains information about their benefits and risks, do not have a "black box" warning about side effects, and are subject to fewer checks on advertising claims. Testimonials by patients—including books by celebrities—are commonly used to endorse custom-compounded products, with little or no mention of the known risks of supplemental hormones. Some women may request bioidentical or custom-compounded hormones because they are misled by the following claims often made by their proponents:

- ***"Bioidenticals are not drugs."*** This is false—bioidentical products are indeed drugs that provide hormone doses that are not usually experienced by women after menopause.
- ***"Bioidenticals are 'natural' and are therefore safe."*** Natural is not necessarily safe. Bioidentical estrogen has the same chemical structure as a woman's natural estrogen, but even a woman's natural estrogen confers some health risks. For example, women with higher natural estrogen levels after menopause have a higher risk of breast cancer. Also, women's natural estrogen levels climb during pregnancy and this rise is linked to a higher risk of blood clots in the legs and lungs. The assertion that bioidentical estrogen has no risks is patently untrue, and the assertion that bioidentical estrogen confers less risk than synthetic forms of estrogen is unproven.

How can we determine whether bioidentical hormones are safe and effective or not? By conducting well-designed clinical trials, which are the scientifically rigorous way to gauge the safety and effectiveness of medications. Unfortunately, for many bioidenticals and for all custom-compounded bioidenticals, such trials have not been done. Without clinical trials, the best and most truthful thing we can say is that we simply don't know how safe or effective these drugs are.

As mentioned above, trials of relatively small size and short duration should suffice to prove or disprove whether such hormones are effective at treating hot flashes, night sweats, or other symptoms of menopause. However, a research effort on the scale of the WHI—which followed 27,000 women for 5 to 7 years to determine the risks and benefits of conventional hormones—will be needed to substantiate or refute the claim that bioidentical—and custom-compounded—products are safer than conventional hormone therapy or that they offer an acceptable balance of long-term health benefits and risks.

Available evidence does suggest that patch estrogen may have an advantage over pill estrogen in that it may be less likely to cause blood clots. There are also data to suggest that bioidentical progesterone may have an advantage over synthetic progesterone in that it may be

less likely to interfere with the ability of supplemental estrogen to boost HDL (good) cholesterol levels and to dilate arteries (improve blood flow). But no large-scale trials have been undertaken to provide head-to-head comparisons of bioidentical versus traditional hormones in terms of their effects on hard clinical outcomes such as heart attack, stroke, or breast cancer.

Studies that are needed to shed light on bioidenticals and their potential place in menopause management

To shed light on bioidenticals, we need to conduct well-designed randomized clinical trials, which are the scientifically rigorous way to gauge the safety and effectiveness of medications. As noted above, for many bioidenticals and for all custom-compounded bioidenticals, such trials have not been done. Without clinical trials, we simply don't know how safe or effective these drugs are.

Trials of relatively small size and short duration should suffice to prove or disprove whether such hormones are effective at treating hot flashes, night sweats, or other symptoms of menopause. However, a research effort on the scale of the WHI—which followed 27,000 women for 5 to 7 years to determine the risks and benefits of conventional hormones—will be needed to substantiate or refute the claim that bioidentical—and custom-compounded—products are safe (i.e., offer an acceptable balance of long-term health benefits and risks).

There is evidence suggesting that patch estrogen (available only in bioidentical form) may have an advantage over pill estrogen (available in both bioidentical and conventional forms) in that it may be less likely to cause blood clots.[26] There are also data to suggest that bioidentical progesterone may have an advantage over synthetic progesterone in that it may be less likely to interfere with the ability of supplemental estrogen to boost HDL (good) cholesterol levels and to dilate arteries and improve blood flow.[27] The ongoing Kronos Early Estrogen Prevention Study (KEEPS) is a clinical trial comparing the effect of conventional vs. bioidentical hormones (oral vs transdermal) on the development and progression of atherosclerosis, cognitive function, and quality-of-life outcomes in recently menopausal women.[28] But no large-scale trials have been undertaken—or are currently planned—to provide a head-to-head comparison of bioidentical versus traditional hormones in terms of their effects on hard clinical outcomes such as heart attack, stroke, or breast cancer.

Dangers with over-the-counter products

Over-the-counter products that contain bioidentical hormones may carry real health risks and should not be used without supervision by a qualified clinician. Among such products are skin creams that contain bioidentical progesterone. Doctors routinely prescribe progesterone for women who take estrogen to protect against possible overstimulation of the uterine lining, which could lead to uterine cancer. Existing data on progesterone skin creams are not consistent as to how much progesterone is absorbed; moreover, such preparations are often not standardized. Thus, it's hard to know exactly how much progesterone one may be getting. Progesterone skin creams may not adequately protect the uterine lining and should not be used for this purpose.

Some naturopaths and medical authors (most notably the late Dr. John Lee, whose hormone books have been recent best-sellers) advocate using progesterone cream alone, without estrogen, to relieve hot flashes and other menopausal symptoms. However, there has been little research on whether it's effective in doing so, and, more importantly, no research on potential long-term risks of this approach. I, along with the majority of doctors, don't recommend it. Of concern, such products are widely available without a doctor's prescription over the Internet. Although classified as a cosmetic by the FDA, progesterone skin creams may produce similar exposure levels in the body as prescription oral progesterone (research is limited and contradictory on this point) and may confer similar long-term health risks, although no rigorous research has been conducted on this subject. It's a dangerous practice to use this product, or any hormone product, without a doctor's supervision

An over-the-counter product marketed as "wild yam cream" contains an inactive precursor of progesterone that cannot be metabolized by the human body. Given that it contains no active hormones, wild yam cream is not likely to cause harm—but it won't help with menopause symptoms and it can be expensive.

Summary

The prudent policy recommended by all major medical organizations is, in the absence of data from well-designed studies of various hormone therapies, to operate on the assumption that all postmenopausal hormone formulations confer similar risks and benefits. However, many proponents of custom-compounded bioidentical hormones are making unsupported claims of superiority that run directly counter to this policy. Given this pervasive and misleading marketing, I have a deep concern that women—and even some of their doctors—are not getting the objective information necessary to make well-informed choices about hormone therapy. There is an urgent need for (a) increased FDA oversight of custom-compounded bioidentical hormones as well as (b) clinical trials testing the safety and efficacy of these products.

.

References

1. Manson JE, Bassuk SS, Harman SM, et al. Postmenopausal hormone therapy: new questions and the case for new clinical trials. Menopause 2006;13(1):139-47.
2. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321-33.
3. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523-34.
4. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, Pettinger M, Heckbert SR, Greep N, Crawford S, Eaton CB, Kostis JB, Caralis P, Prentice R. Conjugated equine

estrogens and the risk of coronary heart disease: the Women's Health Initiative. Arch Intern Med 2006; 166:357-65.

5. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701-12.
6. US Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med 2005; 142:855-60.
7. American College of Obstetricians and Gynecologists. Executive summary. Hormone therapy. Obstet Gynecol 2004; 104:1S-4S.
8. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith SC, Jr., Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E, Wenger NK. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007; 115:1481-501.
9. Wathen CN, Feig DS, Feightner JW, Abramson BL, Cheung AM. Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ 2004; 170:1535-7.
10. North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 Position Statement of The North American Menopause Society. Menopause 2007; 14:168-182.
11. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. N Engl J Med 2003; 348:645-50.
12. Michels KB, Manson JE. Postmenopausal hormone therapy: a reversal of fortune. Circulation 2003; 107:1830-3.
13. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605-13.
14. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, Knopp R, Lowery M, Satterfield S, Schrott H, Vittinghoff E, Hunninghake D. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288:58-66.
15. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science 2005; 308:1583-7.
16. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. Cardiovasc Res 2002; 53:605-19.
17. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933-41.
18. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health 2006; 15:35-44.

19. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med 2006; 21:363-6.
20. Hodis HN. Early versus Late Intervention Trial with Estrogen (ELITE) website. 2007.
21. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Effects of postmenopausal hormone therapy on cardiovascular disease by age and years since menopause. JAMA 2007; 297:1465-1477.
22. Schwartz E, Schwarzbein D, Rosensweet D, Randolph CWR, Jr., Northrup C, Murray J, Leonetti H. Letter to Suzanne Somers. 2006.
23. Parker-Pope T. Popular menopause hormones made from plants come under scrutiny. Wall Street Journal: October 25, 2005; Page D1.
24. FDA Center for Drug Evaluation and Research. Report: Limited FDA Survey of Compounded Drug Products, January 2003, 2003.
25. American College of Obstetricians and Gynecologists. ACOG Committee Opinion: Compounded bioidentical hormones. Obstet Gynecol 2005; 106:1139-1140.
26. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007; 115:840-5.
27. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. Jama 1995; 273:199-208.
28. Harman SM, Brinton EA, Cedars M, Lobo R, Manson JE, Merria GR, Miller VM, Naftolin F, Santoro N. KEEPS: The Kronos Early Estrogen Prevention Study. Climacteric 2005; 8:3-12.