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INSIDE

Three More Reports from the WHI

SPECIAL REPORT

One year after the cancelation of the estrogen-progestin arm of the WHI, 3 more reports have emerged from this landmark study. Leon Speroff, MD, and Sarah L. Berga, MD provide their analysis as a benefit to OB/GYN Clinical Alert *subscribers.*

THE MAY 28, 2003 ISSUE OF THE *Journal of the American Medical Association* contained 3 reports from the Women's Health Initiative (WHI), 1 on the risk of stroke from the canceled estrogen-progestin arm of the WHI, and 2 from the Women's Health Initiative Memory Study (WHIMS).

WHIMS is a randomized, double-blind, placebo-controlled clinical trial that used the participants in the WHI to assess the risk of all-cause dementia, mild cognitive impairment, and "global cognitive functioning." The WHIMS subjects were all 65 years or older. In the assessment of dementia and mild cognitive impairment, 2229 women received estrogen-progestin (0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone acetate), and 2303 received placebo treatment. In the assessment of global cognitive function, 2145 received hormonal therapy and 2236 placebo. The results were reported after an average of 4 years of follow-up (*see Table 1*).

The WHI concluded that estrogen-progestin therapy increased the risk for probable dementia in women 65 years and older and did not prevent mild cognitive impairment. The WHIMS report on global cognitive function measured the participants annually with an assessment called the Modified Mini-Mental Examination. The results were expressed in rates of change and are best summarized by this conclusion: Cognitive function was no different comparing hormone therapy and placebo, but some of the women on estrogen-progestin treatment experienced a detrimental effect.

The WHI report on stroke was an extension of the initial report in July 2002, based on central adjudication of the diagnoses by neurologists. Eighty percent of all strokes were ischemic strokes; the small number of hemorrhagic strokes limited the power to make a conclusion regarding this type of stroke. The risk of

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ischemic stroke was increased with estrogen-progestin therapy (*see Table 2*) (Shumaker SA, et al. *JAMA*. 2003;289:2651-2662; Rapp SR, et al. *JAMA*. 2003;289:2663-2672; Wassertheil-Smoller S, et al. *JAMA*. 2003;289:2673-2684).

COMMENT BY LEON SPEROFF, MD

The WHIMS trial was impressive in its extensive and rigorous detailed assessment of the participants, using a large battery of measures, as well as an adjudication committee consisting of 2 neurologists and 1 geriatrician that reviewed all diagnoses of dementia and a random sample of the cases of mild cognitive impairment.

The Report on Dementia and Impaired Cognition

A very important demographic characteristic of the WHIMS report is the age of the subjects: 47% were 65-69; 35% were 70-74; and 18% were 75 or older. It seems to me that the critical analysis is revealed in the statistical assessment by age group (*see Table 3*).

Table 1
WHIMS Data

Estrogen-Progestin	Placebo	Hazard Ratio and C.I.
	Probable Dementia	
40 cases	21 cases	2.05 (1.21-3.48)
	Mild Cognitive Impairment	
56 cases	55 cases	1.07 (0.74-1.55)

Table 2
Report on Stroke

Estrogen-Progestin	Placebo	Hazard Ratio and CI
	Ischemic stroke	
125 cases	81 cases	1.44 (1.09-1.90)
	Hemorrhagic stroke	
18 cases	20 cases	0.82 (0.43-1.56)

Table 3
Dementia and Impaired Cognition

Estrogen-Progestin	Placebo	Hazard Ratio and CI
	Age 65-69	
6 cases	2 cases	3.25 (0.66-16.11)
	Age 70-74	
12 cases	9 cases	1.47 (0.62-3.49)
	Age 75 and older	
22 cases	10 cases	2.34 (1.11-4.94)

The only statistically significant finding was increased dementia in elderly women (75 and older) who had been exposed to a relatively short term of estrogen-progestin therapy. After excluding the 265 women at higher risk for developing dementia according to the baseline assessment, the case numbers were down to 24 in the treated group and 10 in the placebo group (HR = 2.64; CI, 1.26-5.53). How many of this small number were 75 or older? Indeed, the report recognized that cases of dementia appeared in the first year of treatment, suggesting that some of the women had cognitive problems at baseline. The report then concluded that hormone therapy hastened the progression to dementia in these women, but in my view it is difficult to make such a conclusion with such a small number of cases.

The average length of follow-up was 4 years, but only 50% of the subjects remained on hormone therapy for 4 years. The report on dementia stated that controlling for adherence did not alter the findings. However, it was revealed that after adjusting for nonadherence, the number of dementia cases was reduced to 21 in the treated group and 6 in the placebo group. The report on cogni-

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tive function concluded that after adjustment for adherence, the more favorable performance in years 3-5 in the placebo group was now only marginal, and thus, not clinically different. These analyses are important because the differences between the treated and placebo groups are not large (in the dementia analysis, the differences were 2, 5, 5, and 8 cases in years 1 through 4, and in year 5 the difference was 5, but this time the excess was in the placebo group). When case numbers are small, a shift in a few cases can change the conclusion. For this reason, it seems to me that adjudication of final diagnoses should be completed before presentation of the results to the public. The central adjudication process resulted in 20% disagreement in the treated group and 24% in the placebo group. The report states that most disagreements resulted in a less serious classification, but the effect on the final conclusions was not shared with us.

The Report on Cognition

The women in this report shared the same demographic characteristics as the report on dementia. The number of subjects that provided the conclusion that there was a small increased risk of a clinically meaningful decline in the hormone-treated group amounted to 6.7% of the women receiving hormone therapy. The confidence intervals are illustrated for these women, and the CIs are very wide, indicating small numbers in these groups. The clinical meaning for all postmenopausal women derived from these few women who experienced a detrimental effect of hormone therapy is by no means certain. What was different about this group of women?

The Report on Stroke

The difference in ischemic stroke was limited to nonfatal cases. An analysis of risk factors could not identify any unique characteristics that would indicate a higher risk group of women. An analysis adjusted for adherence found a similar increase in risk for overall stroke; HR = 1.50 (1.08-2.08). As in the first report from the WHI,[1] the results were re-calculated for multiple end points with the Bonferroni adjustment, producing a confidence interval that was no longer statistically significant (0.93-1.84). What does this mean? Frankly, it is difficult for me to translate this into clinical application. I think Paul McDonough expressed it best when he considered the WHI and said that the statistical results are somewhere between the reported nominal numbers and the reduced numbers after adjustment.[2] If that is the case, is the conclusion clinically meaningful?

The WHI reported that the increased risk of stroke with hormone therapy was observed in women with and without vasomotor symptoms (13 cases in the treated group and 6 in the placebo group in women with vasomotor symptoms), implying that results in women younger than 60 were similar, even in women with vasomotor symptoms. However, even the WHI admits that the number of events in women with symptoms was small, and we know from a recent WHI publication,[3] that only 250 women aged 50-54 were on hormonal treatment. The weakness of the statistical conclusions is emphasized when the analyses of stroke events according to age groups or years since menopause all failed to reach statistical significance. The power to acquire significance was achieved only by lumping all strokes together.

These WHI reports suggest that the central nervous system findings (specifically, that with dementia) are related to vascular changes (specifically, silent strokes causing brain damage). This is a reasonable speculation, but it remains conjecture, especially because the statistical conclusions are limited in their strength.

Answered Questions

1. Will hormone therapy prevent subsequent clinical events in women with existing coronary artery disease? With a great deal of confidence, we can answer no, based upon the series of secondary prevention trials published over the last few years.
2. Will hormone therapy prescribed to elderly women prevent the appearance and progress of dementia? The results of the WHI and a secondary prevention trial in women with Alzheimer's disease[4] indicate that the answer is no.

Unanswered Questions

1. Will older women who have used hormone therapy for long durations early in their postmenopausal years be protected against dementia? The WHIMS report recognizes, in the discussion, that this hypothesis cannot be tested in this clinical trial. Nevertheless, the conclusion states that hormone therapy should not be prescribed with the expectation that it will enhance cognitive performance in postmenopausal women. It would have been more accurate to limit that statement to "postmenopausal women 75 years and older."
2. Will hormone therapy of long duration initiated early in the postmenopausal years have a beneficial effect on cognition? The WHIMS also cannot answer this question. A prospective study of a homogenous population in Utah (thus minimizing, if not eliminating, the healthy user bias) concluded that a reduction in the risk of Alzheimer's requires long-term treatment, initiated at least 10 years before symptoms of dementia appear.[5]

3. Will hormone therapy reduce the risk of coronary artery disease when administered in a truly primary prevention fashion (for relatively long durations in women of early postmenopausal age with no clinical evidence of atherosclerosis)? Indeed, experimental evidence in women and monkeys indicates that as vascular endothelial cells become involved with atherosclerosis, beneficial responses to estrogen diminish.[6,7]
4. Will the adjudication process produce a shift in cardiac disease case numbers, eliminating the statistical significance of the conclusions already reported by the WHI?

An Emerging Theme

The controversies and recent results from the WHI suggest that it takes healthy target tissue to respond to hormone therapy. If cardiovascular epithelium progressively loses its ability to respond to estrogen in the presence of increasing atherosclerosis, and if neurons lose their ability to respond to estrogen in the presence of the pathology of Alzheimer's disease, then the reported results (lack of effects in secondary prevention) are not surprising, and a truly primary prevention trial may yield a benefit of hormone therapy. The WHI has not tested this hypothesis because it has not studied the appropriate population—the population that forms the great majority of patients prescribed hormone therapy.

The WHI Has Many Limitations

Unfortunately, the individuals involved with the WHI, as well as uncritical supporters, make the leap from conclusions regarding a select group of women to generalizations applied to all postmenopausal women. It is repeatedly stated that the combined WHI results indicate that the risks of estrogen plus progestin outweigh the benefits. In my view, this is true for the specific sets of women studied by the WHI. Important questions remain unanswered, and therefore, hormone therapy initiated in early postmenopausal women and treatment maintained for many years are not precluded by the WHI results.

I continue to emphasize a clinical approach that I believe is acceptable and comforting for patients. Assist each patient to identify her specific goals and objectives. Once identified, an informed discussion can appropriately review the various treatment options to achieve those goals and objectives. This is a process to be repeated at least once a year, incorporating each time the available new knowledge. Approached in this fashion, terms such as short term or long term become meaningless.

COMMENT BY SARAH L. BERGA, MD

The WHIMS study results were unexpected and difficult to reconcile with prior data. While it is typically the case that most study results raise more questions than they answer, this study would seem to be all questions and no answers. What troubles me the most about this study is that there were only 32 cases of Alzheimer's dementia despite the participation of 4532 women older than 65. However, only 803 of the participants were older than 75. This may explain why there were so few cases of AD. As the Cache County study[5] so amply illustrated, rates of dementia do not start to climb in women until after age 80 years. In this study, the risk of developing probable dementia was 12.2 times greater for women aged 75 to 80 years than for those aged 65 to 69 years. Also, as the authors point out, cumulative hazards ratios began to diverge within the first year. Given the small number of cases, one has to wonder if there was a failure of randomization. This suspicion is heightened by the observation that the rates for mild cognitive impairment did not differ between the 2 arms.

Further, if one looks at Table 5 on page 2658 of *JAMA*, 35 of the women diagnosed with probable dementia had not used hormone therapy in the past as contrasted with 19 women in the placebo arm, giving a statistically significant different hazards ratio of 1.98 (1.13-3.47) for not having used HRT. Interestingly, this hazard ratio is similar to that for the risk of probable dementia (of all types) of 2.05 (1.21-3.48) for HRT users in the WHIMS. Does this historical feature explain the difference in dementia rates between the 2 arms? It is difficult to say. There were many variables (shown in Table 5) that differed between the 2 arms. If nothing else, the study illustrates that randomization alone does not guarantee that all relevant attributes will be evenly distributed between the 2 arms. Apparently, there is no study design that can completely obviate bias. I think that we would all agree that the presence or absence of prior hormone therapy is relevant to interpreting the results, but since this variable was not explicitly used as a factor in the randomization process, it is perhaps not completely surprising that the 2 groups differed in their past use of hormones. However, this asymmetry in HRT use is troubling, as the findings of the Cache County study showed that for hormone use to be neuroprotective, it had to be started around the time of menopause and continued for about 10 years. Further, since there were 88 cases of dementia in the Cache County study vs

61 in WHIMS and since having more cases gives greater confidence in the results, one wonders if one ought not to place more stock in the Cache County findings.

If the study results are questionable, where does that leave us, the physicians who must interpret the results to our patients? I was and am reluctant to put much faith in the results, but the headlines on the front page of the newspaper in my town were large and clear: "Hormone Use Doubles Risk of Dementia." One clearly has a lot of explaining to do even if one doesn't trust the results. It is very hard to take a dismissive stance without looking like an intellectual dinosaur. On the other hand, most patients don't really want a thorough statistical explanation of why the results can't be trusted. I found it ironic that Palmer and colleagues just published a study in which they tested various diagnostic tools used for the diagnosis of dementia in the preclinical phase and found that only 18% of 1435 persons who ultimately developed dementia were identified using a 3-step process similar to that used by WHIMS.[8]

The WHIMS results might be real. There might be reasonable biological explanations for why the risk of dementia was doubled in the HRT-treated vs placebo group. In terms of putting the results into perspective, it would help a lot to know what the risk looks like in the estrogen-only arm. However, I am trying to resist the temptation to proffer a biological explanation when I feel like the results may not be "real." I am uncomfortable with offering a biological rationale when the findings may not stand the test of time. It will be impossible to completely ignore these study results. But it is also difficult to base therapy on them. My primary concern is that the results will actually guide clinical decision-making, that estrogen will be found to be neuroprotective, and that many women will decide to stop using HRT in any form because there is so much confusion. ■

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Ethnicity and Insulin Resistance

ABSTRACT & COMMENTARY

Synopsis: *Insulin resistance increases with increasing body weight and is most prevalent in Mexican-Americans.*

Source: Park YW, et al. *Arch Intern Med*. 2003;163: 427-436.

THE PREVALENCE OF THE METABOLIC SYNDROME WAS assessed in the Third National Health and Nutrition Survey. Overall, the metabolic syndrome was present in 22.6% of American women. The prevalence increases with increasing body weight, from about 5% in normal weight individuals to 60% in obese men and women. The prevalence is highest in Mexican-Americans and lowest in Blacks.

■ COMMENT BY LEON SPEROFF, MD

Insulin resistance is defined as a reduced glucose response to a given amount of insulin. Resistance to insulin-stimulated glucose uptake is a relatively common phenomenon, but only 1 component of a condition referred to in the past as syndrome X, now called metabolic syndrome. In addition to insulin resistance, the metabolic syndrome includes at least 2 of the following: hypertension, elevated triglyceride levels, reduced HDL-cholesterol levels, abdominal or overall obesity, and albuminuria. The prevalence of metabolic syndrome in Finland and Sweden has been estimated to be approximately 10% of people with normal glucose tolerance, 40% of people with impaired glucose tolerance, and 85% of people with type 2 diabetes mellitus.[1] In the United States, the overall prevalence was previously estimated to be 24%, higher in women and increasing with age.[2]

Do all anovulatory patients require testing for hyperinsulinemia? Both lean and obese women with polycystic ovaries can be found to have hyperinsulinemia, but not all hyperandrogenic women with polycystic ovaries (lean and obese) have hyperinsulinemia. However, hyperinsulinemia is more common and severe in overweight women and androgenic effects are more intense. Furthermore, lean women with hyperinsulinemia do not appear to have the same risk of future diabetes mellitus, although clinical follow-up may in time document an onset later in life of noninsulin-dependent diabetes mellitus compared to an earlier onset in obese women.

Young women with irregular menses are very likely

to be anovulatory and should be evaluated for hyperinsulinemia. Because of the probable inherited susceptibility for anovulation and insulin resistance, consideration should be given to a glucose tolerance and insulin evaluation for family members of already diagnosed patients. Both brothers and sisters of anovulatory, hyperandrogenism women can be insulin resistant. What about those women who are ovulatory and have no clinical complaints, yet supposedly have an underlying hyperinsulinemic disorder? In my view, if this is real, it is a homeostatic compensatory state, and until appropriate data reveal adverse outcomes in these women, diagnostic and therapeutic interventions are not indicated.

Teenagers who present with persistent anovulation (oligomenorrhea at least 2 years after menarche) are good candidates for hyperinsulinemia testing. During puberty, insulin resistance develops, probably because of the increase in sex steroids and growth hormone, resulting in a secondary increase in insulin and IGF-I. The increase in insulin leads to a decrease in SHBG, which would allow greater sex steroid activity for pubertal development. There is reason to believe that some teenagers fail to normalize the hyperinsulinemia associated with the growth hormone increase in early puberty. It would be important to identify these teenagers who are at an increased risk for the development of diabetes mellitus and are destined to struggle with all of the problems associated with anovulation and polycystic ovaries. All anovulatory adolescents with polycystic ovaries, especially those who are overweight, should undergo periodic screening for abnormal glucose tolerance,[3] but there is a particular group associated with premature adrenarche that deserves special attention.

Premature adrenarche can be due to hyperinsulinemia, and these patients go on to develop the full characteristics of anovulation, hyperandrogenism, and polycystic ovaries. A marker for this unique teenage problem is low birth weight. Furthermore, these individuals are not overweight and insulin resistance and dyslipidemia are present during childhood, indicating that the basic problem is hyperinsulinemia beginning in fetal life, present in childhood, and worse after puberty. Most importantly, treatment with metformin returns the metabolic parameters to normal, and ovulatory menstrual function is initiated.[4] Long-term metformin treatment, therefore, offers the opportunity to prevent cardiovascular disease and the early onset of diabetes mellitus.

Unfortunately, it is not certain what levels of insulin in the fasting state or in response to an oral glucose tolerance test are correlated with clinical outcome. The most accurate assessment, the euglycemic clamp technique, is not practical, requiring considerable time, an experienced technician, intravenous access, and/or multiple venipunctures. Several quick methods based upon the fasting values for glucose and insulin are available, but all are subject to the variability associated with insulin levels. Because there is considerable overlap between normal women and patients with anovulation and polycystic ovaries, it is reasonable to assume that all overweight, anovulatory women with polycystic ovaries are hyperinsulinemic. The measurement of the ratio of fasting glucose to fasting insulin has been advocated in order to provide evidence that lends credence and importance to counseling efforts, with a ratio of less than 4.5 being consistent with insulin resistance.[5]

An important disadvantage of the ratio method is variability among different ethnic groups, and even among populations living in different regions of the United States. In one study from Texas, a ratio less than 7.2 indicated insulin resistance in white women compared with a ratio less than 4.0 in Mexican-American women.[6] In addition to Mexican-American women, insulin resistance appears to be more severe in Black women and Asian women.[7,8] Because of the variability, the fasting glucose to fasting insulin ratio is no longer recommended; a 2-hour oral glucose tolerance test is now the preferred method of assessment.

All anovulatory women who are hyperandrogenic should be assessed for glucose tolerance and insulin resistance with measurement of 2-hour glucose and insulin levels after a 75 g glucose load (*see Table*). ■

Table

Evaluation of Anovulatory Women with a 2-Hour, 75 g Glucose Tolerance Test

Interpretation of the Glucose Response
Normal→less than 140 mg/dL
Impaired→140-199 mg/dL
Noninsulin-dependent diabetes mellitus→200 mg/dL and higher
Interpretation of the Insulin Response
Insulin resistance very likely→100-150 mU/mL
Insulin resistance→150-300 mU/mL
Severe insulin resistance→greater than 300 mU/mL

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'Tamponade Test' in the Management of Massive Postpartum Hemorrhage

ABSTRACT & COMMENTARY

Synopsis: *This diagnostic test rapidly identifies those patients with postpartum hemorrhage who will require a laparotomy. Even when results are positive, life-threatening hemorrhage is arrested and time is also allowed to correct any consumptive coagulopathy.*

Source: Condous GS, et al. *Obstet Gynecol*. 2003; 101(4):767-772.

Although homicide surprisingly is now the leading cause of maternal mortality, postpartum hemorrhage has always remained near the top of the list. Attempts to mechanically cause uterine tamponade have been reported mainly in the Japanese and European literature, but very recently, an article appeared in *Obstetrics and Gynecology* that got my attention.

The paper by Condous and colleagues described a simple method of stopping intrauterine bleeding with an inflated balloon (the Sengstaken-Blalock esophageal catheter). Although somewhat similar techniques were described by other authors to quell postpartum hemorrhage in a few patients, Condous and colleagues used the method as a "tamponade test" to see which patients would require surgery (if the balloon failed to accomplish hemostasis).

Sixteen patients with intractable postpartum hemorrhage were studied. Fourteen of the 16 had uterine atony, but 5 also had retained products and 3 had DIC. There were no known cases of accreta.

The tamponade method simply consisted of gently inserting the S-B catheter into the uterus, after cutting off the protruding end of the catheter so that it was flush with the superior margin of the balloon. Between 70 and 300 cc of saline were infused into the balloon until the uterus, palpated abdominally, "felt like a well contracted uterus," and, at the same time, appeared within the cervix.

Fourteen of the 16 had complete cessation of the bleeding (a positive test) and, therefore, did not require surgery, while 2 continued to bleed and required surgery. The success rate probably might have been even better since 1 patient requiring surgery had an unrecognized cervical extension of a cesarean incision and in the other case Condous et al admitted they probably had not applied the balloon correctly.

COMMENT BY JOHN C. HOBBINS, MD

In the overwhelming majority of cases, postpartum bleeding can be stopped with uterine massage and oxytocics (oxytocin, Methergine, and/or prostaglandins such as 15-methyl F2α). However, when hemorrhage is not countered by these methods, some patients may lose much of their blood volume while attempts are being made to establish the cause of the bleeding and to institute rescue therapy through interventional radiological techniques or surgery.

This technique, which really represents a kinder, gentler means of intrauterine packing, can either stop the bleeding by itself, or enable the operators to tread water, without disastrous interval blood loss, while preparations are being made for further interventions.

These catheters could be stocked on labor and delivery floors and brought out for occasional use immediately upon request. The expense of this esophageal catheter, compared with a Foley catheter, which has only been tried on a few occasions, could be easily justified based on the success of the above study.

Unfortunately, it seems that the most common step undertaken in the United States, after oxytocics fail to stop postpartum hemorrhage, is to take the patient "back" where she is put in stirrups and a D&C is done to determine if retained products are the cause of the bleeding. While preparing for the D&C, and during the procedure itself, the patient can lose a substantial portion of her blood volume.

Actually, this often-used step is unnecessary in the majority of cases. A simple transabdominal ultrasound examination at the bedside will tell the provider in a minute whether or not retained tissue is present. This would allow the balloon to be placed at the bedside without delay if no tissue is found or to do a gentle removal of the tissue with sponge forceps under ultrasound direction if there is retained tissue.

Various interventive methods to stem intrauterine bleeding have been described, which include embolizing the arterial circulation to the uterus, applying various stitches to compress the uterine cavity, occluding the uterine or hypogastric artery, or, the ultimate therapy, performing a hysterectomy.

This balloon method seems to represent the simplest step, as it may work by itself, as shown in the study, or can help to ameliorate blood loss (while correcting a DIC) until more drastic intervention can be arranged. ■

CME Questions

1. **The following statements are true regarding insulin resistance *except*:**
   a. Most overweight, anovulatory, hyperandrogenic women are insulin resistant.
   b. Only older women with insulin resistance requiring annual surveillance for impaired glucose tolerance.
   c. Hispanic women have an increased prevalence of insulin resistance.
   d. Metformin treatment offers the possibility of preventing the long-term consequences of insulin resistance.

2. **The following statements are true regarding the published results of the Women's Health Initiative *except*?**
   a. The Women's Health Initiative is mainly a study of elderly women.
   b. The published results of the Women's Health Initiative thus far reflect only the daily use of 0.625 mg conjugated estrogens combined with 2.5 mg medroxyprogesterone acetate for an average duration of 4 years.
   c. Hormone therapy caused a decline in cognitive function in older women.
   d. Ischemic stroke may be a risk for hormone therapy in women with existing clinical atherosclerosis.

Answers: 1 (b); 2 (c)

Special Offer to Subscribers

Clinicians are familiar with the writings of Leon Speroff, MD, especially as the senior author of *Clinical Gynecologic Endocrinology and Infertility* currently in its 6th edition. Now Dr. Speroff's writing has taken a new direction, a biography entitled *Carlos Montezuma, M.D., A Yavapai American Hero, The Life and Times of an American Indian, 1866-1923*. The book is the culmination of four years of research and work, a product of the same enthusiasm and dedication as his medical writing. Look for this historical narrative about a remarkable man, one of the first Native-American physicians, available this summer from Arnica Publishing, Inc. A special pre-publication purchase price is available for readers of *OB/GYN Clinical Alert* at www.arnicapublishing.com. ■

PHARMACOLOGY WATCH

HRT, Estrogen, and Postmenopausal Women: Year-Old WHI Study Continues to Raise Questions

The Women's Health Initiatives (WHI) was halted 1 year ago, but fallout from this landmark study continues. The study was designed to identify the risks or benefits of estrogen plus progesterone vs placebo in healthy postmenopausal women. More than 16,000 women were randomized to a fixed dose of conjugated estrogen 0.625 mg plus medroxyprogesterone 2.5 mg daily. The second arm of the study randomized women who had undergone hysterectomy to conjugated estrogen alone vs placebo. The combination estrogen/progesterone wing of the study was halted prematurely and results published in July 2002 when the overall risk of intervention with combination estrogen/progesterone was found to outweigh benefits. Specifically, the risk of breast cancer hit a predetermined threshold in the intervention group, and study was halted after only 4 years. The main outcomes included increased risks of coronary heart disease, stroke, and venous thromboembolic disease, as well as an increased risk of invasive breast cancer. The hormone combination did result in a lower risk of colorectal cancer and a decreased risk in hip and vertebral fractures. All-cause mortality was the same in both groups (*JAMA*. 2002;288:321-333). The second wing of the study, looking at estrogen alone, is continuing with implication that the same level of adverse events was not seen in this arm of the study. The total duration is planned to be 8.5 years.

WHI and Dementia

WHI data continue to be analyzed and published. Most recently, combined estrogen/progesterone was found to increase the risk of probable dementia in women aged 65 and older and did not prevent mild cognitive impairment in the same group. Another study in the same journal found that estrogen/progesterone did not improve cognitive function in women 65 and older, and in fact led to a clinically meaningful cognitive decline in some women on the combination therapy. A third study in the same journal confirmed findings published last July that combination estrogen/progesterone increases the risk of ischemic stroke in generally healthy postmenopausal women (*JAMA*. 2003;289:2651-2662,2663-2672,2673-2684).

Alternative Therapies

Concern that oral fixed dose conjugated estrogen/medroxyprogesterone may have more deleterious effects than benefits has sent primary care doctors and their patients scrambling for alternatives. Currently, most experts are recommending hormone replacement therapy only for severe menopausal symptoms and

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only for a short interval after menopause. But many questions remain. What should be done with women who have had a hysterectomy and are on unopposed estrogen? Are other estrogen/progesterone combinations safer than conjugated estrogen/medroxyprogesterone? Is transdermal estrogen safer? Or should all hormones be avoided and alternatives sought?

Oral Estrogen and CRP Levels

A recent study suggests, for example, that oral, but not transdermal, estrogen elevates levels of C-reactive protein (CRP), which has been associated with myocardial infarction and other adverse outcomes. In a small study, 21 postmenopausal women were randomized to 8 weeks of daily treatment with transdermal estradiol 100 mg or oral conjugated estrogen 0.625 mg or placebo in a crossover fashion. Transdermal estrogen had no effect on CRP or insulin-like growth factor, while oral estrogen more than doubled CRP levels and significantly reduced levels of insulin-like growth factor. The authors suggest that since CRP is synthesized in the liver, oral estrogen may stimulate its production, whereas transdermal estrogen, which bypasses enterohepatic circulation, does not elevate CRP. They further suggest that since CRP is a powerful predictor of adverse prognosis in otherwise healthy postmenopausal women, the route of administration of estrogen should be considered when prescribing HRT (*J Am Coll Cardiol*. 2003;41:1358-1363). And while the WHI showed an increase in vascular events in women on conjugated estrogen/medroxyprogesterone, it was the increase in the rate of breast cancer that led to the early termination of the study. New data suggest that the progestin in the combination of hormones may be associated with a greater risk of breast cancer than estrogen. A review of the records of nearly 30,000 Swedish women in the early 1990s revealed that combined continuous HRT was associated with a 4.6-fold increase in the risk of breast cancer compared to women who never took HRT (95% CI, 2.39-8.84). The breast cancer rate for estrogen-only HRT was 1.89 (not significant; 95% CI, 0.80-5.56) (*Cancer*. 2003;97: 1387-1392). The eventual publication of the estrogen-only wing of the WHI, which is ongoing, will help to further elucidate this important issue.

Discontinue Unless Used Short-Term

Meanwhile, most national experts are recommending discontinuing estrogen/progesterone unless it is being used in a short-term fashion to treat severe vasomotor symptoms. Many postmenopausal women have elected to follow these recommendations, and many women entering menopause are electing not to start HRT in the first place. The vasomotor symptoms, especially hot flashes, are the most consistently bothersome postmenopausal symptom, but unfortunately there are no non-HRT treatments that are consistently effective. Some patients try "natural" remedies such as isoflavones found in soy protein, or black cohosh. And while there is no doubt that isoflavones have some estrogenic activity, the risks vs benefits of these products are still unknown. Newer options include SSRI antidepressants—especially paroxetine, fluoxetine, and sertraline. A recent paper from the Mayo clinic even suggests that gabapentin may be helpful (*Mayo Clin Proc*. 2002;77:1159-1163).

Alendronate Viable Option for Bone Loss

Many women who recently discontinued HRT were taking it specifically for protection against osteoporosis. Studies have shown that bone loss accelerates within the first year of stopping HRT. Alendronate may be a viable option for some women according to a new study sponsored by Merck. The study enrolled 144 women who were on HRT for least 1 year, had been postmenopausal for at least 3 years, and had discontinued HRT within the last 3 months. Patients were randomly assigned to alendronate 10 mg/d or placebo. Treatment with alendronate was associate with 82.3% mean increase in spine bone mineral density (95% CI, 1.7-3.0) compared with the mean loss of 3.2% in patients receiving placebo (95% CI, -4.6 to -1.7). Increases in hip and total body bone mineral density were also observed with alendronate, which was well-tolerated (*Arch Intern Med*. 2003;163:789-794). Other options for preventing and treating osteoporosis in postmenopausal women include the other bisphosphonate risedronate, calcitonin nasal spray, the selective estrogen receptor modulator (SERM) raloxifene, the recently approved parathyroid hormone-like agent teriparatide, and the old standbys of vitamin D and calcium. ■