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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Holly L. Thacker, MD, Chair-Elect, 2007-2008 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Thacker. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Low-dose oral or nonoral EPT does not adversely affect cardiovascular risk in younger postmenopausal women

Casanova G, Radavelli S, Lhullier F, Spritzer PM. Effects of nonoral estradiol-micronized progesterone or low-dose estradiol-drospirenone therapy on metabolic variables and markers of endothelial function in early postmenopause. *Fertil Steril* 2008 [Epub ahead of print]. **Level of evidence: I.**

Short-term, low-dose, oral estrogen-progestogen therapy (EPT) and nonoral EPT have no deleterious effect on endothelial markers and other variables related to cardiovascular disease (CVD) risk in healthy, younger postmenopausal women, according to a crossover, randomized clinical trial conducted in Brazil. Low-dose oral EPT does not increase proinflammatory markers usually found with higher doses and has a favorable effect on body composition, metabolic profile, and markers of endothelial function. Nonoral EPT is not associated with changes in metabolic profile and markers of endothelial function, the study found.

Study participants (N = 40) had their last menstrual period between 6 months and 3 years before the start of the study and were aged 42 to 58 years (mean, 51.2 y \pm 2.7 y). A total of 20 women received oral estradiol (E₂) 1 mg plus

drospirenone 2 mg per day for 2 months. Another group of 20 women received intranasal 17 β E₂ 3 mg per day and then vaginal micronized progesterone 200 mg per day for 14 days during two 28-day cycles. The groups were crossed over for another 2 months. The study aimed to evaluate the impact of EPT in lower dosage and by a nonoral route of administration on variables related to CVD risk in early postmenopausal women. The main outcome measures were markers of endothelial function, inflammation, and anthropometric, metabolic, and hormonal variables before and after EPT.

The mean age at menopause was 49.1 years \pm 2.8 years, and the mean time since menopause was 23.1 years \pm 10 months. Both treatments were effective at relieving menopausal symptoms. Waist circumference and waist-to-hip ratio decreased significantly after the low-dose oral regimen. Total, non-HDL, and LDL cholesterol levels decreased significantly with both the oral and nonoral EPT. HDL-C decreased only after low-dose oral EPT, and triglycerides decreased only after nonoral therapy. Neither treatment affected glucose or insulin concentrations. For markers of inflammation and endothelial function, C-reactive protein, endothelin-1, fibrinogen, and von Willebrand factor did not change after low-

dose oral EPT. After 2 months of nonoral EPT, only von Willebrand factor level decreased.

Comment. It is encouraging to see cardiovascular studies using hormone therapy (HT) administered nonorally at contemporary doses. Over the last decade, postmenopausal estrogen use has dramatically shifted toward lower doses and somewhat away from oral administration. With respect to the cardiovascular system, one plausible reason for making such changes was an attempt to lessen pro-inflammatory, coagulation, or metabolic changes perceived as undesirable (eg, raising thyroglobulin, inducing inflammatory and coagulation proteins, altering bile acid metabolism).

The study at hand shows that treatment with oral E₂ plus drospirenone or 17β intranasal E₂ with vaginal micronized progesterone is mostly beneficial or neutral on a variety of anthropomorphic indices, inflammatory markers, coagulation markers, and lipid concentrations. These data are reassuring but one must not lose track of the fact that although some inflammatory markers are validated cardiovascular risk factors, the changes in inflammatory markers with higher-dose oral estrogen-containing preparations have never been definitively shown to cause adverse cardiovascular outcomes.

New data from the Women's Health Initiative (WHI)¹ revealed that women with abnormal lipid levels had increased risks of HT-mediated coronary heart disease, regardless of high-sensitivity C-reactive protein. In this study by Cassanova et al, disappointingly, lipid concentrations of LDL-C and non-HDL-C were followed instead of lipoprotein concentrations (apolipoprotein B or LDL-particle [LDL-P] measurements). The latter are far better correlated with cardiovascular events than LDL-C and non-HDL-C and one should view with great caution the reductions in LDL-C and non-HDL-C in this study as being indicative of cardiovascular benefit.

Recent data from WHI² demonstrated that HT-induced reductions in LDL-C were not accompanied by desirable reductions in LDL-P,

providing solid evidence that seemingly beneficial changes in lipid concentrations (LDL-C) are not always cardioprotective. Likewise, estrogen affects HDL-P in many complex ways, such as lipidation, delipidation, remodeling, particle number, as well as types of surface apolipoproteins, all of which likely have a more substantial relationship to HDL-P functionality than particle cholesterol content (HDL-C).

Previous data have shown that increases in serum amyloid are induced by conventional doses of oral estrogen but not by transdermal estrogen. Amyloid has a great affinity for the main structural protein of HDLs, apolipoprotein A-I (Apo A-I); HDLs carrying amyloid are dysfunctional.³ It would have been interesting to measure both amyloid and HDL-associated amyloid in this study. Classically, it has been assumed that estrogen or other drugs that increase HDL-C would be beneficial—but such benefits have not been seen, plausibly due to such drugs inducing dysfunctional HDL-P.

Likewise, there are beneficial cardiovascular therapies associated with reductions in HDL-C. Androgenic drugs (such as drospirenone) can reduce HDL-C through a variety of mechanisms (eg, hepatic lipase, Apo A-I production) with no evidence that this is necessarily harmful. Thus, I draw no positive or negative conclusions from the total cholesterol, LDL-C, or HDL-C changes seen in the study.

Lastly, one of the desirable effects of HT seen in the WHI was an improvement in insulin sensitivity (using homeostasis model assessment scores) and reduction of the incidence of type 2 diabetes.⁴ The lower-dose oral or nonoral EPT used in this study had no effect on insulin or glucose.

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Menstrual cycle irregularities early in menopause transition correlate with anovulation

Van Voorhis BJ, Santoro N, Harlow S, Crawford SL, Randolph J. The relationship of bleeding patterns to daily reproductive hormones in women approaching menopause. *Obstet Gynecol* 2008;112:101-108.

Level of evidence: II-2.

Irregularities in menstrual cycle intervals and bleeding duration among women early in the menopause transition correlate with hormonal changes and often with anovulation, according to the Daily Hormone Study (DHS), a substudy of the longitudinal cohort Study of Women's Health Across the Nation (SWAN). Unexpectedly, very heavy bleeding is not associated with hormonal changes but with obesity and leiomyomata, according to findings after 3 years of study. Participants (n = 804; aged 42-52 y; median 47 y) collected first morning voided urine samples daily for either one complete menstrual cycle or for 50 days (whichever came first), once a year for 3 years.

Levels of follicle-stimulating hormone (FSH), luteinizing hormone, estrone conjugates (E1c), and pregnanediol were measured. The women kept daily calendars of menstrual bleeding patterns. Hormone production was correlated

with the bleeding patterns observed in the period immediately after the daily urine collection. The objective was to discover early hormonal predictors of menopause and of the stages of transition, and to elucidate the hormonal basis behind bleeding abnormalities that occur during the menopause transition.

A total of 20% of all cycles were anovulatory, including 44% of short cycles (<21 d) as well as 65% of long cycles (>36 d). Short cycle intervals occurred more often in older women transitioning into early perimenopause. These women had lower daily production of FSH and higher production of E1c. Long cycle intervals were associated with the transition to perimenopause and with greater production of FSH and lower production of progesterone. Short and long durations of bleeding were associated with anovulation as well (18% and 23%, respectively). Women with heavy bleeding were less likely to be anovulatory; heavy bleeding was associated with the reported presence of uterine fibroids and obesity (body mass index [BMI] of ≥ 30). Heavy bleeding was also associated with elevated production of FSH.

Comment. This article, summarizing the most current analysis of the DHS of the SWAN study cohort, provides valuable data to clinicians. Providers get the greatest amount of queries and skepticism from women trying to understand perimenopausal menstrual cycle changes. There is always the question of whether to be conservative, temporizing (hormonal manipulation), or invasive (surgical interventions such as ablation or hysterectomy). The current study clearly tells us that about one fifth of all these cycles are anovulatory. However, women with anovulatory bleeding do not have heavy menstrual cycles. Women with ovulatory bleeding had the heaviest cycles, based primarily on their higher BMI and uterine fibroids.

These findings indicate that anovulatory cycles can either be conservatively managed by watchful waiting or with hormone therapy (oral

contraceptives or low-dose menopausal hormone therapy) to alleviate possible symptoms or to give cycle predictability. The heavy ovulatory cycles can be managed by aggressive surgical therapy if bleeding was not controlled effectively and created significant anemia. Fibroids can also be managed by hormonal manipulation as a first line to abate heavy blood loss. Lifestyle changes (ie, weight loss and exercise) are key, as weight loss also improves vasomotor symptoms.

Short of broadly sketching out an algorithm for treatment, analysis of the DHS group also shows us the bleeding pattern during perimenopause: short interval cycles occur in older women transitioning into early perimenopause, whereas long interval cycles precede menopause later in the transition. The hormonal dynamics are distinct. However, the message I would take away from these observations is not to perform random blood tests to decipher these different categories. Rather, have the patient keep a menstrual and symptom calendar between visits and then proceed accordingly.

I would like to see a description of endometrial histology among the ovulatory but heavy bleeding group from these studies. Since this subgroup is still ovulatory (with a lower FSH but higher E1c), are they more prone to hyperplasia? When should such individuals be biopsied? Furthermore, with regard to the anovulatory cycles with production of progesterone, despite lack of heavy bleeding, do these deserve biopsy also? Another segment of the study should ascertain endometrial thickness in a subgroup of these two categories and give the provider an idea of when to use office biopsy or hysteroscopy for expected hyperplasia.

We all look forward to more publications of this valuable multicultural database. The amount of work that goes into following and analyzing this database is enormous, and the investigators are to be congratulated. It is valuable information that providers need in their offices.

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Low-fat dietary pattern does not lower risk for diabetes

Tinker LF, Bonds DE, Margolis KL, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled Dietary Modification Trial. *Arch Intern Med* 2008;168:1500-1511. **Level of evidence: I.**

A low-fat dietary pattern, in and of itself, does not lower the risk for type 2 diabetes mellitus in healthy postmenopausal women. Any reduction in incidence is instead from weight loss, found the randomized, controlled Dietary Modification Trial of the Women's Health Initiative (WHI). The trial included 48,835 healthy postmenopausal women (aged 50-79 y; average, 62 y) from across the United States, who were randomized to either a low-fat diet intervention group or a usual-diet comparison group. The low-fat diet aimed for 20% of energy intake from fat, but did not promote reduced overall energy intake, a weight loss goal, or a physical activity goal. Diet was monitored via a food frequency questionnaire; the women were followed for 8.1 years. The objective of the trial was to measure the effect of a low-fat diet alone, without the goals of exercise or weight loss, on the incidence of diabetes in healthy postmenopausal women.

At baseline, there were no differences in dietary intake between the two groups. At 1 year, the intervention group reported lower dietary fat as a percentage of energy and a higher intake of vegetables, fruits, and grain. In addition, weight, body mass index (BMI), waist circumference, systolic and diastolic blood pressures, and serum glucose levels were lower

in the intervention group ($P < 0.001$) at 1 year. After 6 years, weight and BMI remained lower in the intervention group ($P < 0.001$). At study's end, 7.1% of women in the intervention group and 7.4% in the comparison group reported a new diagnosis of diabetes (hazard ratio, 0.96; 95% confidence interval, 0.90-1.03; $P = 0.25$). There was a significant effect of percentage of energy from fat on incidence of diabetes ($P = 0.04$), but after adjustment for weight change, the effect on incidence was no longer significant. Women in the intervention group lost a mean of 2.2 kg after the first year, with a 0.8-kg weight loss maintained by the end of the study. The comparison group lost a mean of 0.1 kg.

Comment. The incidence of type 2 diabetes has increased dramatically in the United States, tripling to 1.4 million new cases in 2005 compared to 493,000 in 1980.¹ This rise has been clearly linked to the increase in overweight and obesity, as even small increases in weight within the normal ranges of BMI result in an increased risk of developing type 2 diabetes.^{2,3} Evidence shows that modest weight loss, as little as a 5% to 10% reduction in body weight, reduces incidence of type 2 diabetes in those with impaired fasting glucose.^{4,5}

What is less clear is whether a certain macronutrient composition will affect the incidence of diabetes independent of weight loss. Studies are conflicting on the effect of dietary fat. These studies, as in the Tinker study, are often confounded by weight loss, which mitigates the effect of macronutrient composition. Complicating the issue is the differential effect of the type of fat—incorporation of mono- and polyunsaturated fats in place of saturated and trans fat appears to have a protective effect on the development of diabetes. In the Prevencion con Dieta Mediterranea study,⁶ investigators showed fasting glucose, fasting insulin, and insulin resistance to be significantly reduced in a Mediterranean diet fortified with olive oil or tree nuts versus a low-fat diet despite an insignificant change in weight and BMI between the intervention groups, suggesting that the

macronutrient content of diets may be important in the management of diabetes.

The Tinker study control group did not change percentage of fat intake from baseline (36.9% vs 37.7%), whereas the intervention group reduced fat intake to 28.6% but notably did not meet the goal of a 20% low-fat dietary pattern. The intervention group did have reduced incidence of diabetes, which was not significant when adjusted for the weight lost. The conclusion made by the authors was that weight loss rather than macronutrient composition is the dominant predictor of reduced risk of type 2 diabetes. The inability of the intervention group to reach the target despite intensive nutritional and behavioral modification training argues against the long-term feasibility of a 20% low-fat dietary intervention.

However, based on the current evidence, we cannot conclude that if this target were achieved, it would not protect against type 2 diabetes. It is fair to state that weight loss should be the main goal of medical nutrition therapy for the primary prevention of type 2 diabetes. What is not yet supported by the literature is whether a certain macronutrient composition, namely a 20% low-fat dietary intervention, has a significant effect on the incidence of diabetes.

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Incidence of metabolic syndrome increases in menopause transition

Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. *Arch Intern Med* 2008;168:1568-1575.

Level of evidence: II-2.

Metabolic syndrome incidence progressively increases in the 6 years before and 6 years after the final menstrual period (FMP), found the Study of Women's Health Across the Nation (SWAN). The increase occurs independent of aging and other known cardiovascular disease (CVD) risk factors, and hence is attributable to the dominance of testosterone during this period, the study reports. SWAN is a longitudinal cohort study of the natural history of the menopause transition in 3,302 women (aged 42-52 y) at seven sites in the United States.

The current study focused on 949 women in SWAN who had reached natural menopause and who did not have diabetes or metabolic syndrome at baseline. Participants were followed for 9 years and had annual exams that included interviews, anthropometric measurements, questionnaires, and blood draws to assess

sociodemographic factors, CVD risk factors, and reproductive hormone levels. The primary outcome measure was the presence of metabolic syndrome using National Cholesterol Education Program Adult Treatment Panel III criteria. The study sought to determine the impact of the menopause transition on metabolic syndrome incidence, independent of age and other CVD risk factors, and whether testosterone can be associated with its development.

The mean age at FMP was 50.9 years (range, 42-58 y), and mean body mass index (BMI) was 26.9. At the time of the FMP, 13.7% of the cohort had a new onset of metabolic syndrome. The odds of developing metabolic syndrome were 1.45 (95% confidence interval [CI], 1.35-1.56) per year during perimenopause and 1.24 (95% CI, 1.18-1.30) per year in postmenopause ($P < 0.001$). The change in bioavailable testosterone level was significantly related to the change in metabolic syndrome. For every one standard deviation increase in bioavailable testosterone level, the odds of developing metabolic syndrome increased by 10%. Analyses were adjusted for age at menopause, ethnicity, study site, marital status, education, BMI, smoking, and aging.

Comment. The SWAN study of the association of perimenopause and menopause to metabolic syndrome is provocative. The 9-year longitudinal observation demonstrating the increase in metabolic syndrome in relation to menopause validates prior cross-sectional study reports.

The authors state that testosterone "dominates the hormonal milieu during menopausal transition," and hypothesize that testosterone is associated with the development of the metabolic syndrome and an increase in CVD risk. They further indicate that the prior belief that estrogen exerted a positive beneficial effect on CVD risk has been disproven by "clinical trials showing that replacement of estrogen does not protect against CVD."

The authors did not have the more recent Women's Health Initiative (WHI) reports, which demonstrate a cardioprotective effect of hormone therapy (HT) in women who initiate HT within 9 years of menopause.¹ The authors were also likely unaware of the WHI report of decreased diabetic incidence and insulin level improvement in HT-treated women.² They probably were aware of the HERS study report of decreased diabetes incidence in treated versus placebo subjects.³ Perhaps if these reports had been available, the conclusions of this study might be different.

The theory remains viable that estrogen decline leads to loss of cardioprotective benefits in women. Estrogen deprivation causes a decrease in sex hormone-binding globulin (SHBG), which results in an increase in free testosterone. Estrogen deprivation produces muscle loss and insulin resistance with central fat accumulation. The insulin-resistant state produces all the markers of the metabolic syndrome. Estrogen replacement prevents the centripetal fat accumulation and preserves lean body mass. It might be postulated that hormonal effects that preserve muscle and spare the waist result in maintaining insulin sensitivity, thereby preventing the metabolic syndrome and perhaps avoiding the microvascular disease associated with insulin resistance.

The woman who had a bilateral oophorectomy and has low levels of testosterone is afforded similar protection from insulin resistance and central obesity by estrogen replacement. Her CVD risks, when untreated, are increased despite her lower testosterone; we have indication that those cardiovascular risks are decreased with HT.

Evidence that testosterone reduction improves oophorectomized women's CVD risk is lacking. This study is valuable and offers the factual basis for our understanding of the physiology of menopause and perimenopause. How we synthesize those facts into a working hypothesis can impact the well-being and comfort of our menopausal patients. An alternative conclusion for this paper might be that estrogen decrease in the transition from perimenopause to postmenopause results in skeletal muscle decline, an increase in central obesity, decreased SHBG, and an increase in free testosterone. The metabolic syndrome and its associated microvascular dysfunction may be secondary to these changes. HT during the early years of the menopausal transition may prevent these deleterious changes.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

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