

NEWS & Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® program of The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive the complete program by joining the Society (www.menopause.org). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

No increase in endometrial hyperplasia seen with low CEE/MPA doses

Pickar JH, Yeh I-T, Wheeler JE, et al. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: Two-year substudy results. *Fertil Steril* 2003;80:1234-40.

Doses of combined conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) as low as 0.3 and 1.5 mg/day, respectively, provide 2-year endometrial protection similar to that from higher doses, according to this randomized, double-blind, placebo-controlled substudy of the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study. In all, 822 healthy, postmenopausal women with a uterus (mean age range, 51.0-52.5 years) were assigned to either placebo or one of seven doses of continuous-combined CEE/MPA or CEE alone for 2 years. The CEE doses were 0.3, 0.45, or 0.625 mg/day, either alone or combined with MPA doses of 1.5 or 2.5 mg/day. Endometrial biopsies were evaluated at baseline and at years 0.5, 1.5, and 2. After

2 years, no cases of endometrial hyperplasia were seen in the four CEE/MPA groups. Among those receiving CEE alone, the following dose-related increases in incidence rates from baseline were observed: 3.17% (CEE 0.3 mg), 14.93%, and 27.7% (CEE 0.625 mg).

Comment. This 2-year study of different doses of CEE continuously combined with MPA seems to show endometrial protection. After 2 years of use, endometrial biopsies did not reveal any cases of endometrial hyperplasia in any of the four CEE/MPA groups. In the unopposed CEE users, there was a dose-related increase in the incidence of endometrial hyperplasia. In the Women's Health Initiative trial, in which CEE 0.625 mg plus MPA 2.5 mg was used, there was a reduction in endometrial cancer risk at 5.2 years (HR = 0.81; 95% CI, 0.48-1.36), but this dose was not fully endometrial-protective.

Previous studies, (eg., McGonigle, *Gynecol Oncol* 1994) have shown that sequential estrogen-progestogen therapy (EPT) with more than 10 days of progestogen each month is more endometrial protective than continuous-combined EPT regimens. An intended 5-year Scandinavian study of quarterly progestogen was abandoned after 3 years because of increased endometrial hyperplasia (6.2%), including complex hyperplasia and one case of adenocarcinoma of the endometrium (Bjarnason, *Maturitas* 1999). In the current Pickar study, the incidence of hyperplasia was less in the lower-dose unopposed estrogen group, thus, this regimen of continuous-combined EPT using the lower dose of MPA (1.5 mg) should also be more endometrial-protective.

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Comment. This article extends to 2 years' information on the endometrial effects of estrogen therapy (ET) and EPT in postmenopausal women. These data for hyperplasia are consistent with the lack of increase in the incidence of endometrial cancer found during the use of continuous-combined EPT in the prospective, randomized Women's Health Initiative (Anderson, *JAMA* 2003) and case-controlled studies (Hill, *Am J Obstet Gynecol* 2000). The use of a progestin for less than 14 days per month appears to increase the incidence of endometrial cancer (Archer, *Menopause* 2001).

The most important finding is that use of low-dose (0.3 mg/day), unopposed CEE resulted in an increased incidence of endometrial hyperplasia in the second year of use. Other studies have found a similar, but low, incidence of endometrial hyperplasia with either low-dose esterified estrogen (Genant, *Arch Intern Med* 1997) or ethinyl estradiol (Speroff, *JAMA* 1996) when used unopposed for 2 years. The incidence of endometrial cancer has been reported to be increased with the use of unopposed, low-dose ET (Cushing, *Obstet Gynecol* 1998). Current studies limited to 1 year of follow-up have not found a significant incidence of endometrial hyperplasia when MPA is administered for 14 days every 3 or 6 months (Ettinger, *Obstet Gynecol* 1994; Ettinger, *Obstet Gynecol* 2001). Thus, this study supports the importance of using a progestogen on a regular basis in women who have an intact uterus and who might be using low doses of unopposed oral estrogens.

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Interaction observed between calcium and vitamin D in colorectal cancer protection

Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: Results of a randomized trial. *J Natl Cancer Inst* 2003;23:1765-71.

Calcium supplementation and vitamin D appear to act together, rather than separately, to reduce the risk of colorectal adenoma recurrence, according to this 4-year, randomized, double-blind, placebo-controlled trial. For this trial, a total of 803 men and women (mean age, 61 years) who had a large-bowel adenoma removed within 3 months of study enrollment were assigned to either placebo or calcium supplements (3 gm calcium carbonate or 1,200 mg elemental calcium). End points were serum levels of vitamin D (25-hydroxy [25-(OH)] and 1,25-dihydroxy [1,25(OH)₂]) and polymorphisms in the vitamin D receptor gene. Follow-up colonoscopies were taken at 1 and 4 years.

Among subjects with baseline 25-(OH) vitamin D levels at or below the median (29.1 ng/mL), calcium supplementation was not associated with colorectal adenoma recurrence (relative risk, 1.05; 95% CI, 0.85-1.29). However, among those with 25-(OH) vitamin D levels above the median, calcium supplementation reduced the risk (RR, 0.71; 95% CI, 0.57-0.89). Furthermore, serum 25-(OH) vitamin D levels were associated with a reduced risk only among those receiving calcium supplements.

Comment. Baron's group had previously shown, in a 4-year, randomized, controlled trial, that calcium supplementation reduced the risk of colorectal adenoma recurrence in patients with recent adenoma removals (Baron, *N Engl J Med* 1999). In this analysis of data from that same study, they show that the calcium benefit is confined to individuals in the upper half of the range of vitamin D repletion (serum 25-OHD levels above 29 ng/mL), and that the vitamin D benefit was con-

fined to those receiving supplemental calcium. Because both vitamin D status and calcium intake have been linked to colon cancer risk, it is perhaps not surprising that one needs sufficiency of both nutrients to realize the benefit of either.

The interaction of vitamin D and calcium in this case is probably not a matter of enhancement of calcium absorption (as would be the case with bone health). Rather, vitamin D helps rapidly dividing cells control their proliferation and differentiation, and unabsorbed, luminal calcium acts as an antipromoter for mucosal neoplastic change. Thus, they function in a complementary way in reducing risk of adenoma recurrence. Given the likelihood that most adults are somewhat vitamin D deficient, special attention needs to be given to assessing serum 25-OHD concentrations and correcting deficiencies when found. Current best estimates place the lower limit of normal at 32 ng/mL (by radioimmunoassay, following extraction)—very close to the median value in this study.

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Hormone therapy benefits BMD and fracture risk, but effects disappear 5 years after stopping therapy

Barrett-Connor E, Wehren LE, Siris ES, et al. Recency and duration of postmenopausal hormone therapy: Effects on bone mineral density and fracture risk in the National Osteoporosis Risk Assessment (NORA) study. *Menopause* 2003;10:412-19.

Current use of postmenopausal hormone therapy (HT) significantly improves bone mineral density (BMD) and reduces the risk of osteoporotic fracture, but those benefits are lost within 5 years of therapy cessation, according to this analysis of data from the National Osteoporosis Risk Assessment (NORA) program, a longitu-

dinal, observational study.

A total of 170,852 postmenopausal women at least 50 years of age (mean age, 63 years) and without known osteoporosis were stratified by use or never-use of HT. Use of HT was further categorized by duration (use up to 5 years, 6-10 years, and >10 years) and recency (current, quit in past 5 years, quit 10 or more years prior to study). End points assessed were BMD changes and the 1-year risk of osteoporotic fracture. At baseline, 40.1% were current users, 13.3% were past users, and 46.6% were never-users.

Current HT users had the highest T-scores at every age. Among those current users, women who had used HT the longest had the highest BMD levels, although even 6 months of HT use increased BMD. Current HT use was more positively associated with BMD than was duration of use, even among women who had used HT for 10 or more years. Women who had stopped HT use more than 5 years before, regardless of duration, had T-scores similar to never-users of HT. For fracture risk, similar results were found. Only current use of HT, regardless of duration, was associated with a significantly reduced risk of fracture. Findings were independent of age, ethnicity, body mass index, lifestyle, years postmenopausal, and site of BMD measurement.

Comment. Multiple observational studies and short-term clinical trials have shown that bone loss after HT discontinuation is very similar to what occurs in the early years of menopause. However, these studies have been either too small or too short (or both) to determine the effect of duration and discontinuation of HT on fracture risk. The NORA study provides data on a large cohort of women to evaluate the BMD and 1-year fracture risk stratified by duration and recency of use. The main criticisms of the NORA results are that they are observational, self-reported data (only hip fractures were partially validated) and peripheral BMD was used rather than central meas-

urements. The women were also healthier and at lower risk than the general population. Regardless, the results suggest that only *current use* of HT, independent of duration, is associated with a reduced risk of fracture, and it is not affected by other variables.

The fracture reduction observed in the NORA study is similar to what was reported in the Women's Health Initiative (WHI) participants who were assigned to HT. Additionally, in NORA, after 5 years off HT any prior favorable effect of HT on BMD was lost. Given the reduction in HT use seen since the WHI results were published, the current study reinforces the need for clinicians to be vigilant in their assessment of women at risk for osteoporosis.

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Call for Manuscripts

In this issue of *Menopause Management*, Peter F. Schnatz, DO, shares with our readers his experience—and that of his colleagues—in creating The Women's Health Center, a center devoted to the care of midlife women ("The Women's Health Center: Menopause Clinics Help Provide Quality Care and Education," page 18).

Do you have a similar experience you'd like to share with our readers? If so, the editorial staff of *Menopause Management* wants to hear from you. We are currently accepting manuscripts* on topics related to starting new practices devoted to the care of midlife women, and revising existing practices to better meet the needs of women as they transition through menopause and beyond.

Please contact managing editor Laura A. McKeown at lmckeown@menopausegmt.com (phone: 732-282-0703; fax: 509-463-0447) with your article ideas.

*Publication of manuscripts is subject to the approval of the Editor-in-Chief and the Menopause Management Editorial Advisory Board.

The Women's Life Center

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related to hormonal therapy, and other important topics. Along with the opportunity to provide important clinical experience and education, it has opened the door to encourage research in this important and expanding field.¹²

Our Center is open one afternoon per week, and although we initially saw many new patients, we currently have about seven follow-up visits per session in addition to several new patients. We close the center on the fourth Friday of each month, and reserve this time for educational sessions that are open to all perimenopausal and postmenopausal women. We have used this time to address many of the topics identified through our survey (Table 2, page 21). During these sessions we provide lunch to the participants, along with a presentation by an expert in the area of discussion. Some recent sessions have included discussions on cardiovascular health, bone health, hormonal therapy, sexuality, nutrition, exercise, and breast disease. We allow ample time for what usually turns into a very informative question-and-answer session.

We also offer free bone density screening via peripheral ultrasound testing at least four times a year, which helps to raise awareness and provides opportunities to educate our patients about osteoporosis. Other additions to our education sessions have included breast exams on plastic models and cholesterol screening.

Patients' financial concerns have been addressed by providing a sliding scale payment schedule based on financial need. Also, we have arranged discount laboratory charges to cover the costs for our needy patients. These measures, along with the availability of several translators, have helped address the major issues that had kept our patients from receiving care (Table 3, page 22). Although many of our patients have not received medical care in years, or have no insurance, we seem to have good conti-

Table 5. Practical Benefits of the Women's Life Center

- Specialized and focused menopause consultation by team members certified in internal medicine, OB/GYN and menopause management
- Multidisciplinary approach to education
- Student, resident and nurse practitioner education
- Monthly educational sessions for patients
- Ready availability of translation services
- Broad range of ancillary services and consultants available through the center and the hospital
- Free services and cost-containing measures

nity due to the individual attention and respect patients receive, as well as the educational sessions, the grant funding, and the coordination of services.

Conclusions

Our experience with the incorporation of a specialty menopause center was very smooth. The ease of this transition is due, in part, to the issues considered and steps taken during the planning stage (Table 4, page 22).

In our experience, incorporating a menopause specialty service into an existing women's health center had definite advantages over starting a stand-alone menopause center. This model helps minimize costs, staffing needs, resources, planning, and resistance from personnel (since there are no major changes being made to existing services). Furthermore, this arrangement not only strengthens the existing service, but also draws from its strengths. The detailed planning and preparation we conducted was extremely helpful. We highly recommend having consultants receive certification as menopause clinicians and surveying the population to determine their specific needs.

In the first two years of clinical work,
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