October 7, 2003

Statement of
The American College of Obstetricians and Gynecologists
on Hormone Therapy for the Prevention and Treatment of Postmenopausal Osteoporosis

for the FDA Endocrinologic and Metabolic Drugs Advisory Committee

The American College of Obstetricians and Gynecologists (ACOG), representing over 45,000 health care professionals dedicated to women's health, is pleased to offer this statement to the U.S. Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee on the use of hormone therapy for the prevention and treatment of postmenopausal osteoporosis in women.

Last week, Cauley et al published an updated final analysis of fracture end points in the Women's Health Initiative (WHI) randomized controlled trial (1). They found that use of conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) reduced the risk of hip fracture by 33% (hazard ratio [HR], 0.67; nominal 95% confidence interval [nCI], 0.47-0.96). Subgroup analyses showed that use of estrogen plus progestin resulted in a statistically significantly reduced risk of hip fracture in women who had experienced menopause at least 20 years previously, who had a body mass index of less than 25, who had had at least 2 falls in the past year, who reported a daily calcium intake of at least 1,200 mg/d, who had no history of fracture, and who had used hormone therapy for either less than 5 or at least 10 years. Similarly, hormone therapy also reduced the risk of total fractures by 24% (HR, 0.76; nCI, 0.69-0.83).

Benefits were seen in bone mineral density (BMD) as well. The change in BMD from baseline was higher in hormone users in both hip and spine and at every interval of follow up reported. After 3 years, the percentage difference was 4.5% for lumbar spine and 3.6% for total hip.

This final analysis confirms the previously reported data from the WHI, which demonstrate that estrogen plus progestin is protective against both fractures and loss of BMD (2). It is concordant as well with a wealth of other randomized controlled trials and observational

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studies (3-9). The evidence is strong and consistent: use of conjugated equine estrogen and medroxyprogesterone acetate helps prevent osteoporosis by slowing bone loss and is valuable in treating this condition as well.

The WHI reports, however, calculate a global index to quantify overall benefit versus risk of estrogen-progestin therapy. Because Cauley et al calculated the global index HR to range from 1.23 to 1.03, depending on a woman's risk of fracture, they concluded that there was no evidence of a net benefit and recommended that treatment with estrogen plus progestin not be used for prevention or treatment of osteoporosis in women without vasomotor symptoms. We cannot agree with this global index approach because we believe it to be biased.

In our analysis of the original WHI data on BMD and fractures, ACOG offered the following guidance (10):

> "The decision about use of hormone therapy requires evaluation of the risks and benefits for each individual woman. For women currently using hormone therapy, it is important to assess their reasons for use and to evaluate potential risks, benefits and alternatives. ... For patients with osteoporosis, other preventive therapies such as bisphosphonates and selective estrogen receptor modulators are available. For women at risk of osteoporosis who also have vasomotor menopausal symptoms, hormone therapy can be of benefit. ... Periodic reassessment of the need for hormone therapy is recommended at least at every annual visit or more frequently if indicated."

We continue to support the judicious, individualized use of estrogen and progestin for bone protection and believe that it is inappropriate to withhold this treatment option from those who need it and would benefit from it. While we noted that there are other agents approved for prevention and treatment of osteoporosis, each of these agents has its own contraindications and side effects. Some actually increase hot flashes, and they would not be a choice of women with vasomotor symptoms.

In offering the global index HR, the WHI investigators attempted to estimate overall benefit versus risk. Although this concept is potentially useful from a public policy perspective, it falls short as guidance for care of individual patients. Ultimately, this weighing of benefit and risk must be done by each individual physician with each individual patient.

ACOG continues to educate its Fellows and their patients on the current understanding of benefits and risks of hormone therapy and participated with the FDA in its recently launched menopausal hormone therapy educational campaign. We look forward to continuing to work with the FDA on this issue.

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