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Continuous Combined Postmenopausal Hormone Therapy May Protect Against Endometrial Cancer

ABSTRACT & COMMENTARY

Weiderpass and colleagues report the results of a large, nationwide, population-based case-control study in Sweden assessing the effect of adding progestins on the risk of endometrial cancer associated with postmenopausal estrogen therapy. The use of hormone therapy was examined in 709 patients with endometrial cancer compared with 3368 control women. Consistent with previous reports, the use of unopposed estrogen increased the risk of endometrial cancer, reaching a relative risk (RR) of 6.2 for estradiol and other synthetic estrogens and 6.6 for conjugated equine estrogens with five years or longer of treatment, and more than 8 after 10 years. An increased risk of endometrial cancer in users of combined estrogen and progestin was observed only in women using progestins sequentially for less than 16 days per month (most commonly 10 days). Overall, the daily continuous use of a progestin for five or more years was associated with an 80% reduced risk of endometrial cancer (RR = 0.2; CI = 0.1-0.8). The Swedish study observed a greater degree of protection against endometrial cancer with progestins of the 19-nortestosterone category (norethindrone acetate and levonorgestrel are commonly used in Sweden) compared with 17-hydroxyprogestins (like medroxyprogesterone acetate). However, this analysis was limited by a small number of 17-hydroxyprogesterone users. (Weiderpass E, et al. *J Natl Cancer Inst* 1999;91:1131-1137.)

COMMENT BY LEON SPEROFF, MD

Estrogen normally promotes mitotic growth of the endometrium. Abnormal progression of growth through simple hyperplasia, complex hyperplasia, atypia, and early carcinoma has been associated with unopposed estrogen activity, administered either continuously or in cyclic fashion. Only one year of treatment with unopposed estrogen (0.625 mg conjugated estrogens or the equivalent) will produce a 20% incidence of hyperplasia, largely simple hyperplasia; in the three-year

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INSIDE

PEPI trial, 30% of the women on unopposed estrogen developed adenomatous or atypical hyperplasia.[1-3]

Approximately 40 case-control and cohort studies have estimated that the risk of endometrial cancer in women on estrogen therapy (unopposed by a progestational agent) is increased by a factor of somewhere from two to 10 times the normal incidence of one per 1000 postmenopausal women per year.[4,5] The risk increases with the dose of estrogen and with the duration of exposure (reaching a 10-fold increase with 10-15 years of use, and perhaps an incidence of 1 in 10 with long-term use), and an aspect often unappreciated by clinicians, lingers for up to 10 years after estrogen is discontinued.[6] It is important to note that in the current Swedish study, no increase in risk was observed after the cessation of use of combined estrogen/progestin.

Reports of the clinical effect of adding progestin in sequence with estrogen include both the reversal of hyperplasia and a diminished incidence of endometrial cancer.[7-11] The protective action of progestational agents operates via a mechanism that requires time in order to reach its maximal effect. For that reason, the duration of exposure to the progestin each month is critical. While one standard method incorporated the addition of a progestational agent for the last 10 days of estrogen exposure, most have argued in favor of 12 or 14 days. Studies indicate that the minimal requirement is a monthly exposure of at least 10 days duration.[12-14] About 2-3% of women per year develop endometrial hyperplasia when the progestin is administered for less than 10 days monthly.

A case-control study from Seattle reported that the use of combined estrogen-progestin (essentially all sequential and oral) for five or more years was associated with an increased RR of endometrial cancer, even with 10-21 days of added progestin per month.[15] However, the increased risk was confined to those women who had been previously exposed to unopposed estrogen treatment. Remember, after discontinuing unopposed estrogen treatment, the risk of endometrial cancer lingers for up to 10 years, even if a subsequent regimen includes a progestin. In the Swedish prospective cohort in Uppsala, a reduced risk of mortality due to endometrial cancer was observed in women receiving an estrogen-progestin combination; however, there were only two deaths, precluding statistical significance.[16] A case-control study from Los Angeles found no increased risk of endometrial cancer with the continuous combined estrogen-progestin regimen or when at least 10 days of progestin were provided in a sequential regimen.[14]

An attractive idea is that protection against endometrial cancer requires shedding of the endometrium. However, we know that at least one-third and up to one-half of the functioning endometrium is not lost during withdrawal bleeding, and it has not been established that endometrial shedding is essential to protect against cancer.[17] It is just as logical to believe that prevention of growth and development of atrophic endometrium are protective. There is good reason to believe that both the sequential regimens (with appropriate dose and duration of progestin administration) and the continuous combined regimens offer protection against endometrial cancer. The degree of protection and comparable performance will ultimately be determined by the long-term, randomized, currently ongoing, clinical trials.

In the meantime, the results from this Swedish case-control study provide us with the latest epidemiologic assessment of combined estrogen/progestin therapy, and the data indicate an emerging benefit of daily, continuous treatment. Because the use of a daily, continuous, combined regimen is relatively recent in clinical practice (at least in an epidemiologic time frame), it is only now that epidemiologic studies can begin to assess the effect. A protective effect by daily exposure to a progestin is

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not unexpected because a similar experience with oral contraceptives yields the same result. I fully expect that protection against endometrial cancer will become a proven benefit of the estrogen/progestin daily regimens. This will be a powerful piece of information to use when counseling patients who are experiencing breakthrough bleeding on these regimens. ❖

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Assessment of the Revised FIGO Definition for Early Invasive Squamous Cervical Cancer

ABSTRACT & COMMENTARY

Synopsis: *The FIGO definition of early squamous cervical cancer is generally acceptable in its present form.*

Source: Takeshima N, et al. *Gynecol Oncol* 1999;74: 165-169.

Takeshima and colleagues investigated the value of the International Federation of Obstetrics and Gynecology (FIGO) classification (1995) for early cervical cancer. Clinico-pathological analysis was performed in 402 patients with invasive squamous cervical cancer in whom the depth of stromal invasion was 5 mm or less. The incidence of lymph-node metastasis was 1.2% (1 of 82) in patients with 3 mm or less depth of invasion; the node-positive patient was in stage IA1. The incidence of lymph node metastasis was 6.8% (5 of 73) in patients with 3-5 mm depth of invasion; this increased with increasing horizontal spread from 3.4% for 7 mm or less to 9.1% for more than 7 mm. None of the four patients in this series had metastasis to the parametrial tissues. Of four patients with recurrence, three had a horizontal spread of more than 7 mm, and the remaining patient was in stage IA2. Takeshima et al conclude that the FIGO definition of early squamous cervical cancer is generally acceptable in its present form.

COMMENT BY DAVID M. GERSHENSON, MD

The definition of microinvasive cervical cancer has undergone several revisions over the past three decades. In 1973, the Society of Gynecologic Oncologists developed a definition for microinvasion of the cervix that included a lesion that invaded the cervical stroma no more than 3 mm and in which there was no vascular/lymphatic involvement present. FIGO changed its definition of stage IA cervical cancer and then refined the definition in 1994. In the new definition, stage IA1 is defined as the following: measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm. Stage IA2 is defined as the following: measured invasion of stroma greater than 3 mm and no more than 5 mm in depth and no wider than 7 mm. In the present study, one of 72 patients who met the FIGO definition for stage IA1 and who underwent lymphadenectomy had pelvic node metastasis. All were treated with simple hysterectomy. In the entire study, none of the 297 stage IA1 patients recurred. In the United States, the consensus is that the incidence of lymph node metastasis in stage IA1 disease is less than 1%, and the standard treatment is extrafascial hysterectomy (without lymphadenectomy). For young women with stage IA1 disease who have not completed childbearing, even conization is acceptable treatment if the margins are negative and if the patient agrees to close surveillance. Only one patient in this study with stage IA2 disease had a lymph node metastasis, and only one of 33 patients with stage IA2 disease recurred. The standard treatment for stage IA2 disease remains controversial. Some advocate radical surgery, while others believe that extrafascial hysterectomy is adequate treatment. The numbers in this study are too small to make a judgment. We can hopefully resolve the issue of optimal treatment for stage IA2 disease in the near future. ❖

Should all Pregnant Women be Screened for Hypothyroidism?

ABSTRACT & COMMENTARIES

Synopsis: *A recent study concluded that undiagnosed hypothyroidism in pregnant women may adversely affect neuropsychological development in the fetus, and that screening for hypothyroidism early in pregnancy may be worthwhile, even in asymptomatic women.*

Source: Haddow JE, et al. *N Engl J Med* 1999;341: 549-555.

Normal maternal thyroid function is known to play an important role in fetal neurologic development. To determine if maternal hypothyroidism effects neuropsychological development in the fetus, Haddow and associates measured serum thyrotropin (TSH) in blood samples from 25,216 women collected in the second trimester as part of a screening program for open neural tube defects and Down's syndrome. Forty-seven women were identified with TSH levels at or above the 99.7th percentile and 15 with values between the 98th and 99.6th percentiles in combination with low thyroxine levels. These women were matched with 124 women whose values were normal. Serum TSH levels averaged 13.2 mU/liter in women with hypothyroidism as compared with 1.4 mU/liter in controls. Serum thyroxine and free thyroxine concentrations were also significantly lower in hypothyroid women. Of note, antithyroid antibodies were found in 77% of women with hypothyroidism vs. 14% of controls. None of the children of the hypothyroid women were hypothyroid at birth. At 7-9 years of age, all children were tested to evaluate intelligence, attention, language and reading skills, school performance, and visual-motor performance. The study subjects were matched for their parent's educational level and occupation, maternal age of delivery, and sex of the infant. Overall, the children of hypothyroid mothers did significantly less well in word discrimination and measurements of sustained vigilance and attention. Of the 62 women with hypothyroidism, 15 had a diagnosis made prior to pregnancy and 14 were being treated. When the evaluations of the 48 children of untreated women with hypothyroidism were compared to those of control women, a reduction of 7 IQ points was observed while there was no significant difference found for the children of treated women with hypothyroidism. Nineteen percent of the children of women whose hypothyroidism was not treated had an IQ score of 85 or less as compared with 5% of the control children.

Haddow et al conclude that undiagnosed hypothyroidism in pregnant women may adversely affect neuropsychological development in the fetus. They propose that screening for hypothyroidism early in pregnancy may be worthwhile, even in asymptomatic women. They suggest that testing be performed at the first prenatal visit, preferably in the first trimester, and that women with a positive screen receive timely follow-up and treatment as needed.

COMMENT BY STEVEN G. GABBE, MD

If your practice is like mine, your patients have heard about this study and have begun requesting testing for hypothyroidism. Should this become part of our routine prenatal battery? I don't think so. Only one in 400 women were found to have elevated TSH levels and hypothyroidism. And, of the 62 women identified with hypothyroidism in this study, 15 were known to have this disorder prior to pregnancy. The children of mothers known to be hypothyroid and treated prior to pregnancy were found to have no neuropsychological deficits on testing at 7-9 years of age, even though their mothers had elevated TSH levels and lower serum thyroxine concentrations. In contrast, the children of the 48 women with untreated hypothyroidism had lower IQ scores. It should be noted that all of the children born to hypothyroid women in this study had normal neonatal thyroid screening tests.

Should all pregnant women be screened for hypothyroidism? Before this question can be answered, we need more information. Haddow et al have not provided data on the costs of screening and the benefits expected, or on the occurrence of pregnancy-related complications associated with hypothyroidism such as preeclampsia and preterm delivery.

COMMENT BY SARAH L. BERGA, MD

This is an interesting study with important results. Haddow et al conclude that asymptomatic maternal hypothyroidism can adversely affect the offspring's later neuropsychological development. They cite a similar, but smaller, study showing that lower maternal-free thyroxine in the first trimester was associated with impaired psychomotor development at 10 months of age.[1] Thyroid hormone is also important for the later stages of fetal brain development when neuronal migration and organization occur. Thus, a mechanism for the deleterious consequences of maternal hypothyroidism in the second and third trimester is provided. In an accompanying editorial, Utiger and associates point out that the mother is the sole source of fetal thyroxine in the first trimester, but also the predominant source in the second and third trimesters.[2] Thus, the

fetus remains critically dependent upon maternal thyroidal function throughout gestation. Haddow et al suggest that maternal screening should be considered, but Utiger et al point out the prevalence of maternal hypothyroidism in the United States, as estimated from another survey, was only 2.5%. Still, screening for hypothyroidism involves only a serum TSH test, the cost of which is generally around $30. This determination could easily be made from the blood that is routinely obtained at the first prenatal visit. Utiger et al also caution us to remember that iodine deficiency is the only preventable cause of maternal hypothyroidism. Since 15% of women of childbearing age are iodine-deficient, Utiger et al suggest that iodine deficiency in pregnancy is best prevented by adding extra iodine to prenatal vitamins, or increasing the amount in table salt and other foods. The latter strategy would benefit others as well.

There is one other less common cause of hypothyroidism that needs to be considered in this discussion. Women with functional hypothalamic amennorrhea (FHA), particularly those with anorexia nervosa, have what can best be thought of as "hypothalamic hypothyroidism." This is because stress-related increases in cortisol secretion lead to reduced TSH and TRH secretion. This is true whether the stress is performance pressure, excercise, or inadequate nutrition. In our study population of women with FHA of normal body weight who were without overt eating disorders, thyroxine levels were roughly 25% lower than those of the eumenorrheic comparison group.[3] The reduction of thyroxine in FHA is comparable to the reductions seen in the present study, which were in the range of 30%. Ovulation induction in women with FHA overcomes the decrease in gonaddotropin-releasing hormone and gonadotropins that are the proximate cause of anovulation, but ovulation induction does not correct the underlying concomitant metabolic deficits, including the relative hypothyroidism due to decreased hypothalamic drive. Are the offspring of women who undergo ovulation induction for FHA and conceive at increased risk for poor neuropsychological development? I know of no study that has addressed this issue, but the present data certainly heightened my sense of alarm. At the least, women with stress-related anovulation need to be counseled about this possibility. Since FHA is theoretically reversible with lifestyle management, clearly that type of intervention is warranted before ovulation induction is undertaken. Should we give thyroxine to women with FHA undergoing ovulation induction? I suppose that is another possibility, but that strategy also has limitations. First, there are metabolic alterations other than thyroid that would persist and might have fetal consequences. Second, the hypothalumus has made an "executive decision" in shutting down hypothalmic-pituitary-ovarian and hypothalmic-pituitary axes and it seems cavalier to think we are smart enough to intelligently overide this mechanism. ❖

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Special Feature

Treatment Options for the Prevention of Osteoporosis

By Leon Speroff, MD

There is little controversy surrounding the active treatment of osteoporosis. Our focus is now on preventing osteoporosis-related fractures, and the pain and disability that accompany those fractures. Because the number of treatment options is ever increasing, decision-making is becoming more difficult. I would like to share with you my own "game plan" for making treatment choices.

Lifestyle Modifications

Lifestyle can have a beneficial effect on bone density. Physical activity (weight-bearing), as little as 30 minutes a day for three days a week, will increase the mineral content of bone in older women. To be effective, exercise must exert a load on bone, especially the spine. In other words, weight lifting is better for the spine than ordinary walking, although running probably helps hip bone mass. The activities that are beneficial include running, weight training, aerobics, stair climbing, and sports other than swimming. The effect of weight-bearing exercise on bone density is additive when combined with hormone therapy. Although ordinary walking has little effect on bone density, it is still reasonable to expect walking to have an overall beneficial effect on the risk of fracture. Walking improves the cardiovascular status of patients and reduces body mass. These changes, plus the exercise itself, will improve balance and decrease the risk of falling. For these reasons, walking, even after adjusting for bone density, is associated with a reduced risk of hip fracture.

Adverse habits, such as cigarette smoking or excessive alcohol consumption, are associated with an increased risk of osteoporosis. The magnitude of bone

loss associated with cigarette smoking is consistent with a 40-45% increase in the risk of hip fracture. Studies have indicated that estrogen is associated with lesser protection against fractures in smokers. However, this may be correctable by titering the blood level of estrogen with the dose administered. The lower blood levels of estrogen in smokers have been correlated with an earlier menopause and a reduced bone density, therefore, the standard dose of estrogen may not totally counteract the predisposition of smoking toward osteoporosis. The titration of estrogen dosage with circulating blood estradiol levels in smokers makes clinical sense, allowing the use of higher hormonal doses to maintain bone density. Monitoring of bone response with bone density measurements or urinary markers would further aid in achieving the maximal effects of therapy.

Clinicians should always remember that exposure to excessive thyroid and glucocorticoid hormones is associated with osteoporosis and an increased rate of fractures. The bone loss associated with glucocorticoid treatment is significantly prevented by estrogen/progestin as well as alendronate therapy, and excessive thyroid effects can be avoided by annually monitoring treatment dosage with TSH levels. Specific treatment should also be offered to patients using anticonvulsants.

A high coffee intake has been reported to be associated with an increased risk of osteoporosis. However, this increase in risk is dependent upon dietary calcium intake. In women who drank at least one glass of milk (300 mg calcium) per day throughout most of their lives, increasing caffeinated coffee intake was not associated with a lower bone density. Repeatedly, we see the importance of teaching children and adolescents the merits of an adequate calcium intake. Drinking nonfat milk throughout life is good for you. An adequate calcium intake compensates for "calcium robbers," such as caffeine and soft drinks. A British study concluded that an increase of only 300 mL of milk per day in adolescents increases bone density without an increase in weight or body fat.

Calcium Supplementation

Calcium absorption decreases with age because of a decrease in biologically active vitamin D and becomes significantly impaired after menopause. A positive calcium balance is mandatory to achieve adequate prevention against osteoporosis. Calcium supplementation (1000 mg/day) reduces bone loss and decreases fractures, especially in individuals with low daily intakes. However, estrogen acts to improve calcium absorption (by increasing the levels of 1,25-dihydroxyvitamin D) and makes it possible to use effective supplemental calcium in lower doses. In order to remain in zero calcium balance, women on estrogen therapy require a total of 1000 mg of elemental calcium per day. Because the average woman receives about 500 mg of calcium in her diet, the minimal daily supplement equals an additional 500 mg. Women not on estrogen require a daily supplement of at least 1000 mg calcium.

Vitamin D Supplementation

It is now recommended that individuals older than age 70 should add 800 units of vitamin D to calcium supplementation. Because adequate and active vitamin D depends upon cutaneous generation mediated by sun exposure, women who live in cloudy areas during the winter months are relatively vitamin D deficient and lose bone. In far northern and southern areas, the winter sunlight is inadequate to stimulate dermal activation. Vitamin D supplementation is recommended for these women as well but only during the winter and at a lower level, 400 units daily (usually available in over-the-counter multivitamins or in combination with calcium). The benefit of vitamin D supplementation is clear in older women, and the lack of side effects with low doses encourages the use of vitamin D supplementation as part of the overall program for osteoporosis prevention in younger women.

Postmenopausal Hormone Therapy

With estrogen therapy, one can expect a 50-60% decrease in fractures of the arm and hip, and when estrogen is supplemented with calcium, an 80% reduction in vertebral compression fractures can be observed. This reduction is seen primarily in patients who have taken estrogen for more than five years. Protection against fractures wanes with age, and long-term estrogen use is necessary to maximally reduce the risk of fracture after age 75. For maximum effectiveness, estrogen requires initiation within five years of menopause and for current use to extend into the elderly years. The protective effect of estrogen rapidly dissipates after treatment is stopped because estrogen withdrawal is followed by rapid bone loss. Maximal protection against osteoporotic fractures requires lifelong therapy, and even some long-term protection requires 10 or more years of treatment. Standard doses of estrogen administered transdermally (50 μg) appear to protect against fractures as well as standard oral doses.

The results from the first randomized trial with hormone therapy have only recently been reported. The results are consistent with the large amount of case-control and cohort data, a 71% reduction in nonvertebral fractures in the hormone-treated group within five years,

better than either the placebo group or the Vitamin D treated group.

Two more controversial issues with hormone therapy are the role of lower estrogen dose treatment and the effect of starting treatment later in life. The idea of postponing treatment to prevent osteoporosis until later in life has merit. Changes in bone density in the early postmenopausal years have no major effect on fractures later in life, except in individuals who already have low bone density. This amounts to only 5% of women in their early postmenopausal years, and most of this 5% will have risk factors such as smoking, fracture at a younger age, a thin body, and excessive alcohol consumption. However, the effect of initiating therapy later in life has not been adequately assessed. Indeed, a large cohort study could detect no significant impact on nonspinal fractures. Until we have better data, we should continue to promote early onset and prolonged use of hormone therapy.

We now know that any amount of estrogen can have an effect, although it is likely that some degree of protection is lost when doses are less than the equivalent of 0.625 mg conjugated estrogens. A lower dose of 0.3 mg daily of conjugated estrogens or 0.5 mg estradiol prevented loss of vertebral trabecular bone when combined with calcium supplementation (to achieve a total intake of 1500 mg daily). Major concerns with lower doses include the possibilities that there will be a significant percentage of nonresponders and some cardiovascular benefit will be sacrificed. Nevertheless, a lower dose of estrogen may be more acceptable (fewer side effects) in elderly women. Patients electing to be treated with lower doses should have follow-up assessments for response with measurements of either bone density or urinary biochemical markers. After six months to one year, patients on lower doses should be urged to move up to a standard regimen.

Alendronate

In women with osteoporosis, alendronate administration (10 mg daily) reduced the risk of subsequent nonvertebral fractures by at least 30% (and probably 50%) and vertebral fractures by 90% in the first three years of treatment. In normal postmenopausal women, alendronate increased bone density in both the spine and the hip, and the 5 mg dose (the preferred dose for preventive treatment) was more effective than 2.5 mg. The increase in bone density with the 5 mg dose is slightly less than that observed with estrogen-progestin therapy. It is unlikely that a difference of a few percentage points in bone density gain has an effect on the number of fractures ultimately experienced.

In the most recent data available, derived from an average follow-up of 4432 women for 4.2 years, a statistically significant reduced risk of fracture was demonstrated only in women with initial T-scores of -2.5 or less, a 36% reduction in all fractures, and a 50% reduction in vertebral fractures. Treatment obviously benefits women who already have a low BMD or previous vertebral fractures. If alendronate benefits women who do not already have osteoporosis, it will take more than four years of treatment to observe the effect.

The Early Postmenopausal Interventional Cohort (EPIC) study concludes that over a four-year period of time, alendronate and hormone therapy in the United States produces similar bone density results. Calcium and vitamin D supplementation with alendronate treatment has no added effect as long as women have a minimal intake of 800 mg of calcium daily.

Combining alendronate and hormone therapy produces an added gain in bone density. By no means is it certain that this difference will translate into a difference in the incidence of fractures later in life. Indeed, it is unlikely. Furthermore, there is a theoretical concern that oversuppression of resorption can ultimately yield more brittle bones.

Compliance with alendronate has been overrestimated by the clinical trials. It is well recognized that participants in clinical trials are better motivated, better supported, and perform better. In the Kaiser Permanente Medical Care Program in California, about one-third of patients had acid-related complaints, one in eight required treatment. About 50% of patients do not comply with instructions, and about 50% discontinue therapy by one year. Bone marker or bone density measurements are recommended to assess compliance.

Results with Raloxifene

The increase in bone density associated with raloxifene is slightly less than that seen with alendronate. The Multiple Outcomes of Raloxifene Evaluation (MORE) study of raloxifene administration to osteoporotic women has now accumulated results from two and three years of follow-up. Women with low T-scores or previous vertebral fractures have approximately a 50% reduction in vertebral fractures with raloxifene treatment. However, there has been no evidence of a reduction in hip fractures. Thus, the reduction in vertebral fractures is similar to that seen with alendronate. However, why is there no decrease in hip fractures, despite a bone density response that is only slightly less than that associated with alendronate? And like alendronate, we have no fracture data in treated women who originally had normal bone densities.

Treatment Options: Summary

Reassuring data are available for the prevention of osteoporosis and osteoporosis-related fractures for hormone therapy and alendronate. The absence of an effect on hip fractures after three years of raloxifene is of concern. For tibolone, calcitonin, and especially phytoestrogens, fracture data are not available. Based on bone density responses, we can predict that tibolone and calcitonin should have an effect on fracture incidence. We should keep in mind that the fracture data associated with alendronate are derived from women with osteoporosis.

Not all women will maintain or gain bone density on postmenopausal hormone therapy. In one study, 12% of treated women lost bone despite apparently good compliance. In the PEPI three-year clinical trial, where compliance rates were probably maximal, 4% of treated women lost bone in the spine and 6% in the hip. It is worthwhile to measure the bone density in treated women when they are in their late 60s to detect this high-risk group.

The reason why some women fail to respond is unknown. It is unknown whether these patients will respond to added treatment, such as calcitonin or a bisphosphonate, but it is worth special evaluation, treatment, and surveillance. In a woman demonstrated to be losing bone despite hormone therapy, the following steps are recommended:

- Check compliance and dose by measuring blood estrogen levels.
- Rule out other causes of bone loss (e.g., eating disorders).
- **Drugs:** Heparin, anticonvulsants, high intake of alcohol.
- **Chronic Disease:** Renal and hepatic.
- **Endocrine Diseases:** Excess glucocorticoids, hyperthyroidism, estrogen deficiency, hyperparathyroidism.
- **Nutritional:** calcium, phosphorous, vitamin D deficiencies.
- Add alendronate.
- Follow with markers or bone density measurements.

The treatment of choice for the early postmenopausal years (ages 50-65) is hormone therapy, because of its broad spectrum of benefits, most notably symptomatic relief and protection against cardiovascular disease. Furthermore, we have no data confirming that alendronate and raloxifene given to women with normal bone densities will prevent fractures in old age, and if they do, how they compare to hormone therapy. Around age 65, I recommend measurement of bone density. Low bone density should be treated with the specific drug chosen during a clinician-patient dialogue reviewing the advantages and disadvantages of each drug. ❖

References

Available upon request

Correction

An error appeared in the September 1999 issue of *OB/GYN Clinical Alert*. In Dr. Speroff's abstract and commentary, *Postmenopausal Hormone Therapy and Benign Breast Cancer,* the last sentence on page 37 should have read: "Dupont et al concluded that postmenopausal hormone therapy does not increase the risk of invasive breast cancer in women with true benign breast disease, and that hormone therapy should not be contraindicated in these women." We regret any confusion this may have caused. ❖

CME Questions

20. The following statements are true regarding postmenopausal hormone therapy and the risk of endometrial cancer *except*:

a. Sequential postmenopausal hormone regimens should use more than 10 days of progestin monthly.
b. The increased risk of endometrial cancer associated with the use of unopposed estrogen treatment is dissipated five years after cessation of use.
c. Protection against endometrial cancer does not require hormonal withdrawal shedding of the endometrium.
d. Synthetic estrogens and conjugated equine estrogens have the same increased risk of endometrial cancer when used without a progestational agent.

21. Which of the following is the FIGO definition of stage IA2 cervical cancer?

a. Depth of invasion < 3 mm, width of invasion < 7mm.
b. Depth of invasion < 3 mm, width of invasion > 7 mm.
c. Depth of invasion 3-5 mm, width of invasion < 7 mm.
d. Depth of invasion 3-5 mm, width of invasion > 7 mm.

In Future Issues:

The Effects of Famine on Prenatal Development