Family Practice Grand Rounds

Postmenopausal Osteoporosis and Estrogen Therapy: Who Should Be Treated?

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DR. LOMBARDO F. PALMA *(Robert Wood Johnson Foundation Fellow, Department of Family and Community Medicine)*: The objective of Grand Rounds today is to discuss the cognitive process by which the family physician can make a rational decision about estrogen therapy in postmenopausal women. I will briefly present some facts about osteoporosis, the physiology of menopause and subsequent bone demineralization, the characteristics of women at risk of developing osteoporosis, and the therapeutic alternatives, as well as their risks and benefits. Then we will open the discussion.

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It is estimated that 25 percent of white women by the age of 65 years and 50 percent by the age of 75 years will have vertebral fractures, by far the most common complication in osteoporotic postmenopausal women. Hip fractures have also been related to osteoporosis, and they are at least two times more frequent in women than in men, depending on the age group.[1] In the United States there are about 200,000 hip fractures a year at an estimated cost of over one billion dollars, and 75 percent of those are probably due to osteoporosis. Hip fractures are related to a high death rate in the elderly (16 percent die within six months).[1] This is a public health issue, as there are about four million women in the United States who are symptomatic from osteoporotic fractures.

Menopause is the result of a sharp decline in the production of estrogens in women, a process which occurs in the United States at a median age of 50 years.[2] This produces a sharp increase in two of the gonadotropin hormones, follicle stimulating hormone and luteinizing hormone.[2]

The great majority of women will present some

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symptoms of varying intensity and duration when going through the menopause. Some of these symptoms, such as vasomotor instability, may be due to an unidentified factor in the hypothalamus.[2] Menopausal women may also present psychogenic and metabolic problems. Examples of the latter are demineralization of the bones, myalgia, skin atrophy, senile vaginitis, and hyperlipidemia. Estrogen affects four main target organs: the vagina, the uterus, the breast, and, our main subject today, bone.

Osteoporosis is the result of an imbalance between bone resorption and formation, resulting in net bone loss. The fundamental pathophysiology of the various osteoporoses is still not resolved.[3] The predisposition for osteoporosis in the elderly years has a sexual dimorphism.[3] Women have greater, more precipitous, and earlier bone loss than do men. Postmenopausal estrogen deficiency plays a significant role in women. There is also an ethnic polymorphism as a predisposing factor for osteoporosis.[3] The least pigmented races are more vulnerable, and severe osteoporosis in blacks is almost nonexistent. Total skeletal mass, physical activity, nutrition, and genetic and cultural factors also play a role in the development and progression of osteoporosis.[2]

In 1965, Meema et al compared the total bone mass of women in their reproductive years to that of women after menopause.[4] Their study shows that women have a normal, constant bone mass throughout their reproductive years. However, postmenopausal women start losing bone mass at a rate of 2.7 percent for the first few years and 0.7 percent thereafter.[5] In 1940, Albright, one of the early investigators of osteoporosis in postmenopausal women, in a paper published with coworkers, coined the term "postmenopausal osteoporosis" to describe the pathological exacerbation of this physiologic event.[6] In 1957, Henneman and Wallach[7] studied some postmenopausal patients of Albright and plotted their height, demonstrating how their height decreases between one to five inches in direct proportion to the number of years postmenopause without treatment. When treated with estrogen, height loss was arrested in most cases. The authors also present another group of nonosteoporotic postmenopausal women who were being treated with estrogen for some other reason, before and after the above group was treated. This group did not lose any height.

In 1976, Lindsay et al conducted a study comparing the mean metacarpal mineral content of 63 women followed from three years after oophorectomy and subdivided them into two groups; one group was treated with mestranol, and the other received a placebo.[5] During the five-year study the bone mass of the treatment group did not decrease, even increased slightly, while the placebo group showed a significant decrement in bone mass. This study has been continued, and a second report published, showing that four years after mestranol was discontinued from 14 patients in the treatment group, the bone mass of this new group decreased to the level of 14 controls taking the placebo.[8] It would therefore appear if estrogen therapy for a postmenopausal patient were discontinued, then four years later she would have the same bone mass as a woman who has never been treated. On the other hand, this study indicates that when estrogens are continued, they are effective in preventing bone loss for at least eight years. Although they studied oophorectomized patients, there is no evidence that such a group differs from normal postmenopausal women. However, oophorectomized women are at higher risk of developing osteoporosis and secondary fractures because of decreased androgen and estrogen production.

The typical x-ray films of the dorsal lumbar spine of a white elderly woman with pathologic osteoporosis show biconcavity and codfish type of vertebrae, swelling of the discs, and widening of the intervertebral spaces. Additionally, there is marked decrement of calcification and loss of trabeculae, and frequent compression fractures and wedging can be noted, by far the most common complications of postmenopausal osteoporosis.[3] Radiologic detection of osteoporosis is only possible after a 25 to 30 percent loss of the original bone mass. The laboratory values of serum calcium, phosphate, alkaline phosphatase, and protein electrophoresis are all within normal limits.[3]

As a consequence of fractures of the anterior body of the vertebrae, women lose height very suddenly and develop back pain. Fractures may be caused by walking around, lifting, walking up stairs, or even in the absence of significant physical activity. Eventually, they develop kyphosis or "dowager's hump."

Who are the women at high risk of developing osteoporosis? A number of conditions predispose

women to this malady, including the following:

1. Women who have a small skeleton throughout life have a higher tendency.
2. The more frail the woman is, the higher the chance she will develop osteoporosis.
3. Women who have had an early oophorectomy in life are more susceptible to this disease.
4. Immobilization or sedentary lifestyle, as well as poor diet and decreased calcium intake and malabsorption, can predispose one to osteoporosis.
5. Women who have a small fat cell mass (lean body) are at greater risk. Postmenopausal women produce androgens from their adrenal cortex and ovaries. Androstenedione, specifically, is converted into estrogen in the periphery by the blood, liver, and fat deposits.[3] Therefore, the more fat cells a woman has, the more she will convert her androgens into estrogens. Fat women may continue to produce their own supply of estrogens after menopause for up to 18 months. On the contrary, thin women will be at high risk of developing osteoporosis.
6. Hyperthyroidism, rheumatoid arthritis, and gastrectomy, as well as treatment with glucocorticoids, decrease the mineralization of bones.
7. Alcohol and tobacco consumption are other factors that may increase the risk of developing osteoporosis.

Three questions arise regarding the use of postmenopausal estrogen therapy: Should it be used for the climacteric syndrome ("change of life")? Should it be used for the treatment of recurrent fractures in osteoporotic women? Or should this treatment be used for the prevention of osteoporosis? If it is going to be used for the climacteric syndrome, full replacement doses of conjugated estrogen may be needed (1.25 mg).[2] The treatment course may extend from months to several years. In any case, one should always try to use the lowest dose over the shortest time period possible. In cases of recurrent fractures due to osteoporosis, it is also necessary to use full replacement doses of estrogen.[3] Sometimes androgens are needed for their anabolic effect, along with calcium, vitamin D, and fluorides.[2,3] Prophylactic conjugated estrogen therapy (0.625 mg) can be used in selected women who are at high risk of developing osteoporosis. Calcium in large doses has been found to be somewhat effective for prevention of osteoporosis,[9] calcium carbonate being the most absorbable form of calcium (each tablet of Tums, for instance, contains 500 mg).

The most frequent estrogen therapy used in the United States is conjugated estrogens (Premarin) 0.625 mg per day cyclicly, 25 days out of a month (prophylactic doses). There are some other estrogens on the market, but they all seem to have the side effects of uterine bleeding, breast engorgement or tenderness, weight gain, edema, nausea, and heartburn. Mestranol 20 μg, ethinyl estradiol (Estinyl) 20 μg and stilbestrol 0.5 mg are equivalent to 0.625 mg of conjugated estrogens.[3]

In the United Kingdom, the medical community is surprised at how American physicians are treating postmenopausal women with estrogen alone. It has been shown that progestins decrease the incidence of endometrial hyperplasia by producing endometrial shedding.[10] With this therapy, women with intact uteri continue to have cyclical bleeding. Some women feel very uncomfortable and do not like this. Others are relieved that their symptoms have been alleviated. Progestins are recommended for seven to ten days, in the latter part of the cycle, along with estrogens.[10] Good management of estrogen therapy (either alone or with progestins) includes an annual endometrial biopsy, blood pressure check, and breast examination. Unusual bleeding or discharge also calls for diagnostic measures.

What effects are usually seen with estrogen therapy? There is strong evidence that women with intact uteri, taking estrogens, have a higher risk for endometrial cancer.[11-13] This seems to be related directly to length of treatment, dose, and lack of concomitant use of progestins. Several case control studies have shown a four- to twelvefold higher risk for this disease in women who are taking exogenous estrogens. Of course, women who have undergone hysterectomy are not exposed to this risk. In 1981, it is estimated that 38,000 new cases of endometrial cancer will be reported in this country, and 3,100 deaths will occur due to this cause. The overall five-year survival rate for cancer of the endometrium is about 75 percent, but in the earliest stages this increases to 86 percent. Hulka's paper discusses important concepts relating duration and recency of estrogen use to endometrial cancer risk and latency.[13]

Data relating cancer of the breast to use of estrogens are inconclusive.[12-13] A recent case control study in California[14] shows a higher relative risk, about 2.5, in women with intact ovaries who have

had a total cumulative dose in excess of 1,500 mg of estrogen. This study indicates that women at higher risk were those with benign cystic disease of the breast. There is a possibility of a long latency period before breast cancer becomes manifest, which may be the reason why epidemiological studies have not been able to document it consistently.

Incidence of thromboembolic phenomenon has not been proven to be increased in elderly women taking estrogens.[15] This may be due to smaller doses of estrogen used in postmenopausal years, in comparison with the larger doses contained in the birth control pill. There is controversy regarding increased incidence of cardiovascular disease, but the data are not yet conclusive.[13]

Further investigation is required to determine the possible association of postmenopausal estrogen use and gallbladder disease.[11] One study observed a 2.5 relative risk for the development of surgically confirmed gallbladder disease.

DR. DAVID PIERCE (*Robert Wood Johnson Foundation Fellow, Department of Family and Community Medicine)*: Is it necessary to do an endometrial biopsy every year if you are using progestins along with estrogen therapy?

DR. PALMA: Even when you use progestins along with estrogens, you should do an endometrial biopsy yearly. In England, they do endometrial biopsies in women who are taking combined therapy. If they find endometrial hyperplasia, they administer progestins in two series of 21 days each, separated by seven days free of medication. They find that the incidence of hyperplasia decreases sharply.[10]

DR. KING UDALL (*Assistant Professor, Department of Family and Community Medicine)*: Is there any evidence of calcium and vitamin D alone preventing osteoporosis, or does it always have to be combined with estrogens?

DR. PALMA: Calcium alone, in high doses (2 gm of calcium carbonate per day), has been shown to be somewhat effective in preventing osteoporosis.[9] Vitamin D has not been proven effective for prevention of osteoporosis, unless the woman has a poor natural supply of vitamin D.

DR. GEORGE SMITH (*Psychiatrist, Assistant Professor, University of Utah)*: What is the side effect of high calcium therapy?

DR. PALMA: It may produce hypercalcemia, soft tissue calcification, nephrolithiasis, or calcium nephropathy. These effects occur, however, only if you use large doses for long periods of time.

DR. UDALL: If a 60-year-old patient comes in with obvious severe osteoporosis, do you have any recourse at that point?

DR. PALMA: There is some evidence that estrogens not only inhibit or retard calcium loss, they may also regenerate some of the calcium content of the bone. For this purpose, you may need to treat your patient with full replacement doses of estrogen for a short period of time. Sometimes anabolic steroids are needed for thin elderly women.

DR. SMITH: How do you treat fractures due to osteoporosis?

DR. PALMA: It depends on the type of fracture; in general, the more you immobilize an osteoporotic patient, the more her bones will continue to demineralize. Therefore, as much as possible, try not to immobilize the patient. Treat her with acute doses of estrogen, sometimes androgens, high calcium intake, vitamin D, and pain medication. If there is a hip fracture, the patient will need orthopedic management.

DR. SMITH: What about exercise?

DR. PALMA: It is known that loss of stress-and-strain stimulus on the osteoblasts results in decreased bone formation. Exercise provides this stimulus. Therefore, let your patient be as mobile as she can, and use pain medication as needed.

DR. UDALL: Does anyone have experience with using progestins along with estrogen therapy in postmenopausal patients? (No hands raised in the audience.)

DR. PALMA: The British literature[10] recommends giving progestins, along with estrogen, for the last seven to ten days of the cycle. Explain to your patient that she is going to have cyclical bleeding. Some physicians are reluctant to treat patients with progestins on a monthly basis and decide to give it once every six months to slough off the endometrium that has been promoted by estrogen.

DR. UDALL: What about using norethindrone acetate and ethynil estradiol combination tablets (Loestrin 1/20) for prevention of osteoporosis?

DR. PALMA: Loestrin contains estrogen and progestins for the whole month. The effects of giving oral contraceptives to elderly women are still not known, so I would not recommend this therapy without further information.

DR. PHILIP ZAZOVE *(Third year family practice resident)*: How long after menopause can you wait to start treating your patients? There seem to be differences of opinion regarding the effectiveness of estrogen treatment at varying stages.

DR. PALMA: The effect of estrogen therapy is greater when given within three years after menopause. Even after that, there is evidence that the bone loss can be retarded or arrested.[4]

DR. ZAZOVE: But if you stop using estrogens, four years later your patient will have lost that bone mass.

DR. PALMA: It is not known how long after cessation of treatments of varied duration it will take for bone mass to reach the norm of that age group.[8] If your statement were true, as suggested by Lindsay's study, we would have to continue therapy for a very long time, even for life, to avoid the danger of osteoporosis.

DR. PIERCE: Is there evidence concerning the optimal frequency of progesterone use to instigate shedding of the endometrium, say every month or every six months, in reducing endometrial carcinoma?

DR. PALMA: I do not think that has been studied yet. The British literature recommends that progestin therapy be given monthly. For example, although the minimum effective dose for the suppression of estrogenic stimulation has not been determined, 5 mg of medroxyprogesterone acetate (Provera), given during the last seven to ten days of the cycle, produces a sloughing of the endometrium promoted by estrogen in the great majority of cases. Patients receiving progesterone therapy should be monitored for undesirable side effects and complications of such therapy. Lack of withdrawal seems to be related to endometrial hyperplasia and, subsequently, to endometrial cancer. In England, they have combined pills that have estrogen throughout the cycle and progestins for the latter part of the cycle only.

To summarize, menopause is associated with a sharp decline in estrogen production. This frequently leads to osteoporosis. Fractures are very frequent in osteoporotic women, and those with fractures of the hip have very high mortality. Estrogen treatment is effective for the menopausal symptoms, the treatment of recurrent fractures due to osteoporosis, and the prevention of osteoporosis. Some women are at higher risk of developing osteoporosis. Women who take exogenous estrogens are at high risk of developing endometrial cancer; therefore, it is advisable to perform a yearly endometrial biopsy. No general recommendation regarding treatment or prophylaxis can be made that is applicable to all postmenopausal women. The decision about therapy should be individualized in agreement with a patient who is well informed about the risks and benefits of estrogen therapy.[11-13,16]

References

1. Alfram P: An epidemiological study of cervical and trochanteric fractures of the femur in an urban population. Acta Orthop Scand (suppl) 65:9, 1964
2. Aakoff AE, Nowrooze R: The female climacteric. In Greenblatt RF (ed): Geriatric Endocrinology. Aging, vol 5. New York, Raven Press, 1978, pp 165-190
3. Gordon GS: Age-related bone loss with special reference to postmenopausal osteoporosis. In Greenblatt RB (ed): Geriatric Endocrinology. Aging, vol 5. New York, Raven Press, 1978, pp 191-200
4. Meema HE, Bimker ML, Meema S: Loss of compact bone due to menopause. Obstet Gynecol 26:333, 1965
5. Lindsay R, Hart DM, Aitken JM, et al: Long-term prevention of postmenopausal osteoporosis by oestrogen. Lancet 1:1038, 1976
6. Albright F, Bloomberg E, Smith PH: Postmenopausal osteoporosis. Trans Assoc Am Physicians 55: 298, 1940
7. Henneman PH, Wallach S: A review of the prolonged use of estrogens and androgens in postmenopausal and senile osteoporosis. Arch Intern Med 100:715, 1957
8. Lindsay R, MacLean A, Krazzewski A, Hart DM, et al: Bone response to termination of estrogen treatment. Lancet 1:1325, 1978
9. Horsman A, Gallagher JC, Simpson M, Nordin BEC: Prospective trial of estrogen and calcium in postmenopausal women. Br Med J 2:789, 1977
10. Thom MH, White PJ, Williams RM, et al: Prevention of endometrial disease in climacteric women receiving oestrogen therapy. Lancet 2:455, 1979
11. Gastel B, Cornoni-Huntley J, Brody JA: Estrogen use and postmenopausal women: A basis for informed decision. J Fam Pract 11:851, 1980
12. Schiff I, Ryan JJ: Benefits of estrogen replacement. Obstet Gynecol Surv 35:400, 1980
13. Hulka BS: Effect of exogenous estrogen on postmenopausal women: The epidemiologic evidence. Obstet Gynecol Surv 35:389, 1980
14. Ross RK, Paganini-Hill A, Gerkins VR, et al: A case-control study of menopausal estrogen therapy and breast cancer. JAMA 243:1635, 1980
15. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al: Estrogen replacement therapy II: A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 54:74, 1979
16. Weinstein MC: Estrogen use in postmenopausal women—costs, risks, and benefits. N Engl J Med 303:308, 1980