Overview of Estrogen Replacement Therapy: A Historical Perspective (44198)

BRUCE ETTINGER[1]

Division of Research, Kaiser Permanente Medical Care Program, 3505 Broadway, 7th Floor, Oakland, California 94611-5714

Abstract. **In the last 30 years, we have made enormous advances in understanding how estrogen works in multiple physiologic systems and how much it affects the health of aging women. We have also made major improvements in how we prescribe estrogen. As clinicians, we are obliged to provide our patients with acceptable, tolerable, safe therapy which can be continued long enough to provide clinically significant health benefits. Determining optimal long-term hormone replacement therapy is therefore the challenge for the 21st century.** [P.S.E.B.M. 1998, Vol 217]

The year 1991 marked the 50th anniversary of the introduction of Premarin (Wyeth Ayerst Pharmaceuticals, St. David's, PA). This product is still the most widely used form of estrogen replacement therapy (ERT) in the United States. Despite many years of estrogen use by hundreds of millions of women, controversy still rages over the risks and benefits associated with its use. The purpose of this overview and the other articles in this minisymposium is to summarize the remarkable progress made in understanding estrogen's risks and benefits and to predict how ERT will be used in the 21st century.

In the 1920s, most clinicians recognized that menopause (i.e., cessation of menses) was associated with virtual cessation of ovarian estrogen production. At menopause, the ovary runs out of primordial follicles, and none are left to sustain the monthly cycle of hormone production and ovum release. In the 1940s, researchers showed that menopausal symptoms could be relieved by estrogen therapy. This finding led to the fairly widespread marketing and prescription of estrogen (1). The drug was intended to relieve vasomotor symptoms and mood changes associated with menopause. The average prescribed dosage of estrogen during the next two decades was about twice the current dosage, and estrogen was given unopposed by progestin.

In the 1960s, precise measurements of bone density became available. Although a decade earlier Albright *et al.* (2) described postmenopausal osteoporosis and recommended estrogen to treat it, attention was now concentrated on the considerable bone loss that occurred in the immediate postmenopausal period. Just after menopause, women lose bone at a rate of 2%–3% in the radius and 5% in the spine (3). In the 1970s, a series of clinical trials showed decisively that estrogen therapy could prevent this loss (4, 5). Osteoporosis became the postmenopausal disease of the 1980s, and the medical protocol for osteoporosis shifted from treatment to prevention. In fact, most clinicians believed that only prevention of osteoporosis was possible. Further, clinicians optimistically estimated that 5–10 years of postmenopausal ERT would protect women against osteoporosis for life (6, 7). More recent studies have shown that ERT begun soon after menopause and continued lifelong can reduce the risk of osteoporotic fractures by 75% (8). Because most osteoporotic fractures occur 25–30 years after the usual age of menopause, very long-term use has very long-term benefits. However, discontinuation of ERT allows rapid loss of bone (5, 9) and provides virtually no protection against fractures if many years are allowed to elapse after treatment. For example, taking estrogen from age 50–60 has virtually no residual effect on bone density or fracture risk at age 80 (8, 10, 11).

In the 1990s, the belief that osteoporosis could not be treated was dispelled by numerous clinical trials and epidemiologic studies showing both substantial increase in bone density (12) and reduction in fracture risk (13) from taking estrogen for just a few years even well beyond menopause. In fact, the skeletal effect of estrogen is similar in mechanism and magnitude to that of alendronate, considered the major breakthrough in osteoporosis treatment (14).

In the early 1990s, the scientific community and media began to focus on coronary heart disease (CHD) in women. Fueled by the approval of several cholesterol-lowering

[1] To whom requests for reprints should be addressed at Division of Research, Kaiser Permanente Medical Care Program, 3505 Broadway, 7th Floor, Oakland, CA 94611-5714.

0037-9727/98/2171-0002$10.50/0

drugs and the National Cholesterol Education Program (15), national interest in CHD escalated. Studies done in the 1970s showed that ovariectomy without ERT was associated with a doubling of CHD risk and that ERT eliminated this added risk (16). Perhaps endogenous estrogen was cardioprotective. After cholesterol subfractions became measurable, the impact of ERT could be better discerned. Although total cholesterol was only slightly decreased by ERT, analysis of subfractions showed large (10%–15%) increases in HDL and large (10%–15%) decreases in LDL (17). Prior observational studies were used to determine that these lipoprotein changes could reduce CHD risk by 50%. These findings stimulated further research and resulted in numerous articles on ERT and CHD. The epidemiologic literature is remarkably consistent and compelling in showing that the overall effect of ERT is to halve CHD risk among estrogen users (18). Additional research has shown that many mechanisms other than lipoprotein changes may account for estrogen's suppression of CHD; the latest estimates are that only 30%–40% of estrogen's CHD effect is mediated by HDL- and LDL-cholesterol. These mechanisms include estrogen's ability to reduce LDL-cholesterol penetration through the arterial wall, protect LDL-cholesterol against oxidation, enhance intimal repair, decrease platelet aggregation, and, perhaps most importantly, reduce arterial vasospasm.

Although many are convinced of estrogen's cardioprotective effect, its exact magnitude is still being disputed. This dispute will only be settled by randomized clinical trials; results from a secondary prevention trial will be available by 1998, and results from a primary prevention trial will probably be available in 2005.

In the late 1990s, ERT's effect on cognition and Alzheimer's disease received major attention. Case-control studies found that estrogen use was less common among women with Alzheimer's disease than among controls (19). Unlike the epidemiologic studies of estrogen and CHD, these studies found that estrogen was not consistently associated with a lower risk of Alzheimer's disease. A few small, randomized clinical trials of ERT in Alzheimer's disease showed short-term improvement in dementia or slowing of the expected cognitive decline (20), but others failed to show benefit (21). In 1996, two important and positive studies were published. The first, a large cohort study, found the incidence of Alzheimer's disease to be 53% lower among estrogen users than among nonusers (22). The other, a randomized clinical trial of tacrine, a cholinesterase inhibitor believed to help Alzheimer's patients, showed that women estrogen users responded positively to tacrine but that cognition failed to improve in estrogen nonusers who took tacrine (23). The scientific community is now enthusiastically searching for mechanisms that could link estrogen use and improved cognitive function; good candidates are changes in neurotransmitters and growth of synaptic connections.

The history of estrogen use has been marked by low points. In the 20 years between 1953 and 1973, an increase in endometrial cancer rates closely paralleled the increase in ERT. In 1975, the first reports that ERT was associated with increased risk of endometrial cancer appeared (24, 25). At first, many were unwilling to believe the bad news. Some claimed that the apparent association between ERT and cancer occurred because ERT users were more likely to bleed and therefore received different surveillance for endometrial cancer (26). Others said that these cancers were pathologists' misdiagnoses. During the next few years, studies left no doubt that ERT markedly increased endometrial cancer risk, first by causing endometrial hyperplasia, then by promoting atypia and cancer. In fact, long-term (10–15 years) unopposed estrogen use increases the risk of endometrial cancer ten-fold (27). In response to these findings, many women discontinued ERT completely, and physicians reduced the dose for those still being treated. Women in the 1950s and 1960s were typically prescribed 1.25 mg, but by 1980, .625 mg was shown to be sufficient to protect against bone loss.

Scientists in the United States turned to the European approach and began prescribing estrogen plus progestin, also known as hormone replacement therapy (HRT). Unopposed estrogen therapy had never been a popular postmenopausal hormone therapy in Europe. Instead, oral contraceptive-type estrogen and progestin combinations were used; these were not associated with increased risk of endometrial cancer. Addition of progestin to estrogen was at first cyclic (for 7, then 10, then 12–13 days each month), but beginning in the mid-1980s, progestin began to be added continuously. By 1990, most women who were receiving estrogen and who had a uterus were coprescribed some form of progestin. The incidence rate of endometrial cancer declined substantially; however, the risk of endometrial cancer related to estrogen was not completely obviated by cyclic HRT (28) or continuous combined HRT (29). Again, we may have been too optimistic about the safety of HRT.

Further bad news was that progestins have adverse effects on HDL-cholesterol (30) and can counteract some of estrogen's beneficial nonlipid-modifying benefits (e.g., prevent estrogen's antivasospastic effect) (31). Now physicians had a new challenge—how to minimize estrogen-induced endometrial cancer without minimizing estrogen's suppression of CHD. This concern was partly addressed by changing the dose and schedule of progestin therapy. Researchers found that if medroxyprogesterone were used cyclically, the usual 10-mg dose could be reduced to 5 mg without increasing incidence of endometrial hyperplasia (32). In addition, long-cycle regimens using progestin—not monthly, but every 2–3 months—have shown promise (33). Cyclic medroxyprogesterone was shown not to reduce cardioprotection in a large observational study (34). How much *continuous* use of progestin will reduce estrogen's suppression of CHD is unknown. Studies in cynomolgus monkeys with CHD suggest that estrogen alone is much more beneficial than estrogen plus continuous progestin (35).

Most physicians today prescribe continuous HRT because this regimen is believed to enhance acceptance and continuation of treatment because it produces amenorrhea instead of the cyclic bleeding that results from other regimens. In fact, women who begin HRT with continuous progestin are more likely to discontinue treatment in part because of the irregular bleeding associated with this regimen, especially in the first 6–12 months (36).

An association between estrogen therapy and increased risk of breast cancer was found (37, 38), and this association is certainly biologically plausible. Epidemiologic studies indicate that women exposed to more endogenous estrogen are more likely to develop breast cancer. Both early menarche and late menopause are associated with increased breast cancer risk, and ovariectomy is associated with decreased risk. Until the mid-1990s, epidemiologic studies showed no association between postmenopausal ERT and risk of breast cancer, but these studies were based largely on short-term use (i.e., less than 5 years). Data from several studies of long-term use showed a consistent pattern—after 10–15 years of use, breast cancer risk increases 30%–40% (37, 38). The annual increase in breast cancer related to aging is fairly linear before menopause but shows a break point at menopause—the slope of increase per year of age becomes less steep than prior to menopause. If estrogen use merely continues the age-related rate of increase, then a cumulative 30%–40% increase in incidence might be observed after 10–15 years. Of greater concern is that if women follow current recommendations for lifelong ERT use, their ultimate risk of breast cancer could double.

Since the mid-1980s, use of estrogen has increased about 10% annually. At Kaiser Foundation Health Plan, Northern California, we found that nearly half the women age 50–59 received some HRT in 1995 (unpublished data). Even among women age $\geq$70 yr, incidence of HRT was close to 20%; however, most women who start HRT do not continue it long term because of safety concerns and adverse effects. Treatment discontinuation would be greatly reduced if women could be offered a product with a greater risk:benefit ratio.

How will estrogen be used in the 21st century? In the next 30 yr, the number of postmenopausal women will double as our population ages. Women today are intensely interested in reducing breast cancer risk and are seeking alternate ways of avoiding aging of the vascular and nervous systems. In the 1990s, advances in research on estrogen receptor physiology showed that estrogen receptors in various parts of the body differ markedly in their response to estrogen and to estrogen analogs (39). Thus, an estrogen analog may exist that could stimulate estrogen receptors in some tissues and not stimulate, or even block, estrogen receptors in other tissues. Tamoxifen is an excellent example of an agent with this selectivity. Tamoxifen blocks estrogen receptors in breast tissue but stimulates estrogen receptors in liver tissue, in uterine tissue, and probably in bone. Tamoxifen has an estrogenic effect on cholesterol metabolism by the liver, lowers LDL-cholesterol, and reduces CHD risk (40). Tamoxifen exerts an antiestrogenic effect on breast tissue and reduces breast cancer recurrence (41). Although it reduces bone loss (42), tamoxifen increases risk of endometrial cancer (43). Moreover, tamoxifen seems to worsen vasomotor symptoms.

Tamoxifen's clinical profile is unacceptable for postmenopausal women who are not being treated for breast cancer; however, selective estrogen receptor modulators (SERM) with better profiles than tamoxifen will soon be available. Raloxifene is the SERM with the most advanced clinical trial experience. Raloxifene does not cause endometrial proliferation, and it reduces LDL-cholesterol level and enhances bone density (44). Breast tenderness has not been reported by women in the raloxifene trial, which is also assessing this SERM's effects on cognitive function, on nonlipid-modifying cardioprotective mechanisms, and on urogenital health.

The future of ERT is bright. We will probably be able to offer postmenopausal women hormone therapy that can significantly enhance their health and improve the quality and duration of their lives. In the last 30 yr, enormous advances have been made toward understanding how estrogen works in multiple systems and how much it enhances health in aging women. In addition, striking improvement has been made in the way we prescribe estrogen. As clinicians, we must provide acceptable, tolerable, and safe therapy that can be continued long enough to provide clinically significant health benefits. The challenge of the 21st century is to determine the optimal HRT regimen.

The Medical Editing Department, Kaiser Foundation Research Institute, provided editorial assistance.

1. Coney S. The Menopause Industry: How the Medical Establishment Exploits Women. Alameda (CA): Hunter House Inc., 1994.
2. Albright F, Smith PH, Richardson AM. Postmenopausal osteoporosis: its clinical features. JAMA **116:**2465–2474, 1941.
3. Cann CE, Genant HK, Ettinger B, Gordan GS. Spinal mineral loss in oophorectomized women: determination by quantitative computed tomography. JAMA **244:**2056–2059, 1980.
4. Lindsay R, Hart DM, Aitken JM, MacDonald EB, Anderson JB, Clarke AC. Long-term prevention of postmenopausal osteoporosis by oestrogen: evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet **1:**1038–1041, 1976.
5. Christiansen C, Christensen MS, McNair P, Hagen C, Stocklund KE, Transbøl I. Prevention of early postmenopausal bone loss: controlled 2-year study in 315 normal females. Eur J Clin Invest **10:**273–279, 1980.
6. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. Ann Intern Med **95:**28–31, 1981.
7. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. N Engl J Med **303:**1195–1198, 1980.
8. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med **122:**9–16, 1995.

9. Christiansen C, Christensen MS, Transbøl I. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet **1:**459–461, 1981.
10. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PWF, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med **329:**1141–1146, 1993.
11. Schneider DL, Barrett-Connor EL, Morton DJ. Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo Study. JAMA **277:**543–547, 1997.
12. Ettinger B, Grady D. Maximizing the benefit of estrogen therapy for prevention of postmenopausal osteoporosis. Menopause: The Journal of the North American Menopause Society **1:**19–24, 1994.
13. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, Judd HL, Caplan RH, Riggs BL. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med **117:**1–9, 1992.
14. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med **333:**1437–1443, 1995.
15. Bachorik PS, Ross JW, for the National Cholesterol Education Program Working Group on Lipoprotein Measurement. National Cholesterol Education Program recommendations for measurement of low-density lipoprotein cholesterol: executive summary. Clin Chem **41:**1414–1420, 1995.
16. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. N Engl J Med **316:**1105–1110, 1987.
17. Lobo RA, Speroff L. International consensus conference on postmenopausal hormone therapy and the cardiovascular system [editorial]. Fertil Steril **61:**592–595, 1994.
18. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernstler VL, Cummings SR. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med **117:**1016–1037, 1992.
19. Henderson VW, Paganini-Hill A, Emanuel CK, Dunn ME, Buckwalter JG. Estrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol **51:**896–900, 1994.
20. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Low-dose estrogen replacement therapy for Alzheimer disease in women. Menopause: The Journal of the North American Menopause Society **1:**125–130, 1994.
21. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol **140:**256–261, 1994.
22. Tang M-X, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet **348:**429–432, 1996.
23. Schneider LS, Farlow MR, Henderson VW, Pagoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology **46:**1580–1584, 1996.
24. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med **293:**1167–1170, 1975.
25. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med **293:**1164–1167, 1975.
26. Horwitz RI, Feinstein AR. Alternative analytic methods for case-control studies of estrogens and endometrial cancer. N Engl J Med **299:**1089–1094, 1978.
27. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol **85:**304–313, 1995.
28. Beresford SAA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet **349:**458–461, 1997.
29. Goodman L, Awwad J, Marc K, Schiff I. Continuous combined hormonal replacement therapy and the risk of endometrial cancer: preliminary report. Menopause: The Journal of the North American Menopause Society **1:**57–59, 1994.
30. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA **273:**199–208, 1995.
31. Sullivan JM, Shala BA, Miller LA, Lerner JL, McBrayer JD. Progestin enhances vasoconstrictor responses in postmenopausal women receiving estrogen replacement therapy. Menopause: The Journal of the North American Menopause Society **2:**193–199, 1995.
32. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. The Menopause Study Group. Obstet Gynecol **84:**987–995, 1994.
33. Ettinger B, Selby J, Citron JT, Vangessel A, Ettinger VM, Hendrickson MR. Cyclic hormone replacement therapy using quarterly progestin. Obstet Gynecol **83**(5, Pt 1):693–700, 1994.
34. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med **335:**453–461, 1996 [published erratum appears in N Engl J Med 1996 **335:**1406]
35. Williams JK, Honoré EK, Washburn SA, Clarkson TB. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. J Am Coll Cardiol **24:**1757–1761, 1994.
36. Ettinger B, Li D-K, Klein R. Continuation of postmenopausal hormone replacement therapy: comparison of cyclic versus continuous combined schedules. Menopause: The Journal of the North American Menopause Society **3:**185–189, 1996.
37. Steinberg KK, Smith SJ, Thacker SB, Stroup DF. Breast cancer risk and duration of estrogen use: the role of study design in meta-analysis. Epidemiology **5:**415–421, 1994.
38. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med **332:**1589–1593, 1995.
39. Yang NN, Venugopalan M, Hardikar S, Glasebrook A. Identification of an estrogen response element activated by metabolites of 17β-estradiol and raloxifene. Science **273:**1222–1225, 1996.
40. McDonald CC, Alexander FE, Whyte BW, Forrest AP, Stewart HJ, for the Scottish Cancer Trials Breast Group. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. BMJ **311:**977–980, 1995.
41. Nease RF Jr., Ross JM. The decision to enter a randomized trial of tamoxifen for the prevention of breast cancer in healthy women: An analysis of the tradeoffs. Am J Med **99:**180–189, 1995.
42. Ward RL, Morgan G, Dalley D, Kelly PJ. Tamoxifen reduces bone turnover and prevents lumbar spine and proximal femoral bone loss in early postmenopausal women. Bone Miner **22**(2):87–94, 1993.
43. Neven P, De Muylder X, Van Belle Y, Campo R, Vanderick G. Tamoxifen and the uterus [editorial]. BMJ **309:**1313–1314, 1994.
44. Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Arnaud C. A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res **11:**835–842, 1996.