68. Postmenopausal Hormone Prophylaxis

RECOMMENDATION

Counseling all perimenopausal and postmenopausal women about the potential benefits and risks of hormone prophylaxis is recommended. There is insufficient evidence to recommend for or against hormone therapy for all postmenopausal women. Women should participate fully in the decision-making process, and individual decisions should be based on patient risk factors for disease, clear understanding of the probable benefits and risks of hormone therapy, and patient preferences (*see **Clinical Intervention***).

Burden of Suffering

The median age of menopause in American women is 51 years (range 41–59),[1,2] but ovarian production of estrogen and progestin begins to decline years before the complete cessation of menses. Lower levels of circulating estrogen contribute to accelerated bone loss, vulvovaginal atrophy, changes in urethral mucosa and vaginal flora[3] and substantial rises in total and low-density lipoprotein cholesterol (LDL-C) that occur during the perimenopausal and postmenopausal period.[4,5] Hormonal changes produce vasomotor symptoms ("hot flashes") in 50–85% of women by the time of menopause.[1,2,6,7] Hot flashes may be severe in 20% of women, may contribute to sleep disturbances and somatic symptoms, and are present 4 years after menopause in 20% of women.[1,7] Urogenital symptoms (dyspareunia, dysuria, incontinence, and urinary tract infections) are also common in postmenopausal women: up to 45% of women complain of vaginal dryness after menopause,[8] and 10–15% of women over age 60 have frequent urinary tract infections.[9]

The average life expectancy of an American woman reaching menopause is approximately 30 years. Many of the most important causes of morbidity in older women (cardiovascular disease, osteoporosis, and various cancers) appear to be influenced by female hormones. Cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women: nearly half will develop coronary heart disease (CHD) in their lifetime, 30% will die from CHD (more than 230,000 women per year), and 20% will have a stroke.[10–12] An estimated 1.3 million

osteoporosis-related fractures occur each year in the U.S., nearly all in postmenopausal women.[13] A 50-year-old white woman is estimated to have a 16% chance of eventually suffering a hip fracture and a 32% risk of vertebral fracture.[11] In comparison, the lifetime probability of developing endometrial cancer and breast cancer is only 2.6% and 10%, respectively, and the chance of dying from these cancers is only 0.3% and 3%.[12]

Efficacy of Chemoprophylaxis

Controlled trials of the effects of hormone therapy on clinical endpoints are difficult because of the large numbers of subjects and long follow-up required. The recently launched Women's Health Initiative, a multicenter randomized trial with 25,000 women assigned to placebo, estrogen alone (for women with prior hysterectomy only), or combined estrogen-progestin therapy, should provide important new evidence, but results will not be reported for 8–12 years.[14] Additional information may come from secondary prevention trials examining the benefits of hormone therapy in women with CHD or cerebrovascular disease. Numerous cross-sectional, case-control, and cohort studies, however, suggest that postmenopausal estrogen therapy has important effects on a number of major clinical outcomes.[12]

Osteoporotic Fractures. There is good evidence from retrospective studies and clinical trials that oral or parenteral estrogen can reduce the rate of bone loss and improve bone mineral density in postmenopausal women.[15] In epidemiologic studies[16–20] and nonrandomized clinical trials,[21] use of postmenopausal estrogen was associated with a decreased rate of fractures of the hip, forearm and spine. An overview of 11 studies estimated that risk of hip fracture was reduced 25% among women who had used estrogens;[12] greater benefit has been observed with current use (vs. past use), long-term use (>5 years), and therapy begun close to menopause. Since accelerated bone loss resumes when estrogen is discontinued, hormones may be needed indefinitely to provide maximal protection after age 75, when risk of fracture is highest.[22] One model predicted that fracture risk in women ages 75–85 would be reduced 73% in women who took estrogen continuously after menopause, 57–69% in women who began therapy at age 65, and only 23% in women who began therapy at menopause but stopped at age 65.[23] Several studies have reported that past estrogen use provides minimal or no protection to women over age 75 in terms of bone density[24] or reduced risk of hip fracture.[20,25,26]

Coronary Heart Disease and Lipids. Numerous studies have demonstrated significantly lower risks of fatal and nonfatal CHD among postmenopausal women taking estrogen.[12,27] Overviews of these studies have estimated a

37–44% reduction in risk of CHD among ever-users of estrogen.[12,28] In the Nurses' Health Study, one of the largest and best-designed studies, the beneficial effect was most evident in current users of estrogen (relative risk (RR) of major CHD = 0.56) and diminished in former users (RR = 0.83); benefit of estrogen did not increase with long-term use.[29] Studies of women undergoing angiography report less severe coronary stenosis among women taking estrogen,[28,30,31] and one follow-up study of women with angiographically confirmed coronary disease reported reduced mortality in those who had taken estrogen.[32] Generalizing from angiographic studies is problematic, since they do not examine a representative sample of hormone users and non-users.

Whether age or other risk factors modify the cardiac benefits of estrogen is uncertain.[28] Some studies reported a reduced benefit of estrogen (or even increased risk) in smokers,[33,34] while others reported comparable or greater benefits in smokers compared to nonsmokers.[29] Similarly, some studies reported that protective effects of estrogen were lower among older women (over age 60),[29,33] but others observed protective effects of estrogen independent of age[35] and in cohorts of elderly women.[28,36]

The beneficial effects of estrogen on serum lipids are believed to be responsible for some but not all of the observed reduction in the risk of CHD.[35–37] In short-term studies, oral estrogen therapy lowers LDL-C 14–20% and raises high-density lipoprotein cholesterol (HDL-C) 15–20%, but it also raises serum triglycerides 24–38%.[38,39] These effects are mediated through first-pass effects of oral estrogen on hepatic cholesterol metabolism; transdermal and vaginal estrogens, which circumvent this first-pass effect, have less effect on serum lipids.[38] Beneficial effects of estrogen on vascular tone[40,41] or lipid oxidation[42] represent additional mechanisms by which estrogen therapy may reduce cardiovascular risk, independent of effects on serum lipid levels.

Whether or not combined estrogen-progestin therapy has similar effects on CHD remains a matter of considerable debate.[12] The use of progestins attenuates the beneficial effects of estrogen on HDL-C, but effects depend on dose, duration, and type of progestin.[39] The effects of four different hormone regimens on cardiovascular risk factors were examined in the 3-year "PEPI" trial,[43] which randomized 875 women to: placebo; unopposed conjugated equine estrogen (CEE) 0.625 mg daily; daily CEE (0.625 mg) plus cyclic medroxyprogesterone acetate (MPA) (10 mg/day for 12 days each month); daily CEE (0.625 mg) plus daily MPA (2.5 mg); or daily CEE (0.625 mg) plus cyclic micronized progesterone (MP) (200 mg/day for 12 days each month).[43] Compared to placebo, all hormone regimens decreased LDL-C (7–10%), decreased fibrinogen (1–11%), and increased triglycerides (6–7%), without significant effects on blood pressure or insulin responsiveness. Increases in HDL-C were significantly

greater with unopposed estrogen or estrogen with cyclic MP (+9–11%) than with regimens using MPA (+4%).

These results suggest that MPA, the most commonly prescribed progestin in the U.S.,[44] may attenuate the cardiac benefits of estrogen therapy, but the importance of this physiologic effect remains controversial.[12] In a large cross-sectional survey, women taking estrogen and progestins (largely MPA) had lipid levels comparable to women taking unopposed estrogen.[45] In two recent observational studies, estrogen / progestin therapy and unopposed estrogen each were associated with significant and comparable reductions in risk of CHD compared to women who did not use hormones.[46,47] The effects of progestins on other estrogen-sensitive endpoints (vascular tone, lipid oxidation) have not yet been clearly defined.[45,48]

Cerebrovascular Disease. Studies to date have not demonstrated a consistent association between postmenopausal hormone use and cerebrovascular disease.[12] Individual studies have demonstrated significant increases (primarily in smokers)[33] or decreases[49,50] in stroke risk among women who report ever having used estrogen. A pooled estimate of risk from 15 studies calculated that there was no significant effect of estrogen use on risk of stroke among ever-users versus never-users.[12] The failure to distinguish between ischemic and hemorrhagic strokes is a limitation of most studies, since risk factors are distinct for each stroke type. In the Nurses' Health Study, there was no significant effect of current use or past use of estrogen on risk of any stroke, ischemic stroke, or hemorrhagic stroke.[29] This finding is consistent with the observation that serum lipids are weaker risk factors for stroke than for heart disease.[51,52] There are few data on the effects of progestins on stroke. A Swedish cohort study reported significantly lower risk of stroke among women taking combination therapy (and among women taking unopposed estrogen) than in the general population, but it could not adjust for differences in other stroke risk factors.[53]

Other Potential Benefits of Hormone Therapy. Estrogen taken orally, transdermally, or vaginally is effective in relieving vulvovaginal atrophy and urogenital symptoms.[3,7] These benefits may help improve sexual function, but independent effects of estrogen on libido or sexual responsiveness have not been clearly demonstrated.[3] Vaginal estrogen cream reduced recurrence of urinary tract infections in a randomized trial in older women.[54] The effects of estrogen on mood and cognitive function have been inconsistent.[3] In a small randomized trial among women without menopausal symptoms, estrogen significantly improved depression scores but not scores on several other psychological indices.[55] There was no evidence of an effect of past or current estrogen therapy on cognitive function in a large cross-sectional study in a retirement community.[56] Two case-control

studies reported a reduced risk of Alzheimer's disease (AD) among women who were currently using estrogen[57] or had previously used estrogen,[58] but a third study found no association between estrogen therapy and AD.[59]

Potential Risks of Hormone Therapy: Endometrial Cancer. Prolonged use of unopposed estrogens increases the risk of endometrial hyperplasia and endometrial cancer.[60–62] Risk appears elevated at all doses and increases with dose and duration of therapy. A recent meta-analysis of 37 observational studies reported that risk was increased almost 6-fold among women who used estrogen for 5–10 years, and more than 9-fold with use for more than 10 years.[60] Although association was strongest for early stage, noninvasive tumors that have a good prognosis, the risks for invasive cancer (RR = 3.8; 95% confidence interval [CI], 2.9 to 5.1) and for endometrial cancer death (RR = 2.7; 95% CI, 0.9 to 8.0) were also increased among women who had used estrogen.

Both continuous and cyclic regimens of progestins prevent estrogen-induced endometrial hyperplasia.[43,63] In the PEPI trial, incidence of adenomatous or atypical hyperplasia was similar among women taking various combination therapies or placebo (0–2%), compared to 34% among women on unopposed estrogen.[43] Several observational studies and a small trial reported that women taking estrogen with cyclic MPA had a lower risk of endometrial cancer than did women who never took hormones, but several more recent case-control studies observed nonsignificant 2-fold increases in endometrial cancer.[60] One study reported increased risk only when progestins were taken for fewer than 10 days each month.[64] There are few data on cancer risk with other progestin regimens (i.e., daily). For women who do not tolerate daily or monthly progestins, regular endometrial surveillance (annual endometrial biopsy) or less frequent progestin cycles (e.g., every 3 months) have been proposed as alternative ways to reduce risks of estrogen; neither of these methods has been adequately assessed for its ability to prevent endometrial cancer, however.

Breast Cancer. Endogenous estrogen appears to be important in the etiology of breast cancer, but the effect of exogenous estrogens on breast cancer risk remains uncertain.[65,66] More than 40 observational studies, and 6 meta-analyses of individual studies, have examined the association between postmenopausal estrogen therapy and the risk of breast cancer, with varying results.[12,67–71] Although cancer risk was not increased among women who had ever used postmenopausal estrogens, several overviews reported a modest but significant increase in risk among women who were currently using estrogen (RR = 1.2–1.4)[70,71] or had used estrogen for long periods (RR = 1.2–1.3 for durations >10–15 years).[12,69–71] These findings were affirmed in a 1995 report from the Nurses' Health Study, with over

725,000 person-years of follow-up: risk of breast cancer was increased only among current, long-term users (>5 years) of hormones and increased with age. Compared to women who had never taken hormones, breast cancer incidence among current long-term users of hormones was increased 50%.[72] Risk was not increased among past users of hormones, however, even those who took hormones for long periods. There was no clear effect of dose of estrogen on risk in most studies.

A number of studies reported that women who develop breast cancer during estrogen therapy have earlier disease at diagnosis,[73–76] lower rates of metastasis,[75] and longer survival with breast cancer,[74,77,78] compared to women with cancer who had never used estrogen. These findings suggest that some of the apparent increase in cancer incidence among women taking estrogens may be due to earlier diagnosis (i.e., "surveillance bias")[79,80] or effects of estrogen on well-differentiated cancers with better prognosis.[75,76] The effect of hormones on breast cancer mortality is not consistent. There was no association between past or current estrogen use and death from breast cancer in the Nurses Health Study,[72] in long term follow-up of a smaller British cohort,[81] or in 12-year follow-up of 23,000 Swedish women prescribed hormones.[82] Among a subgroup of current long-term users in the Nurses' Health Study, however, breast cancer mortality was increased (RR = 1.45, 95% CI, 1.01 to 2.09).[72] The lack of risk attributable to past hormone use may indicate that hormones promote growth of existing cancers rather than cause new cancers.[77]

There is little evidence that adding progestins to estrogen therapy influences the risk of breast cancer. An early study that reported protective effects of progestins[83] has been largely discounted due to methodologic flaws. In more recent studies, the risks associated with combination therapy are comparable to those observed for estrogen alone.[84–86] Estrogen-progestin therapy was associated with modest but significant increases in risk in three large cohort studies with long-term follow-up (RR =1.2–1.6)[72,76,87] but no increase in a recent community-based case-control study.[87a] In the only long-term controlled trial of hormone therapy, 84 pairs of institutionalized women were randomized to 2.5 mg/day conjugated estrogen plus cyclic MPA, or placebo for 10 years. After an additional 12 years of follow-up, none of 116 women who had ever received hormone therapy (during trial or follow-up) developed breast cancer, compared to 6 of 52 controls who never received therapy ($p < 0.01$).[88] The select nature of the participants precludes generalizing these results to the average perimenopausal woman.

Thrombosis, Gallbladder Disease, Glucose Tolerance, and Other Side Effects. High-dose estrogen has been associated with alterations in clotting factors and an increased risk of thrombosis in studies of early contraceptives and in a trial

of estrogen therapy in men with CHD.[48] There is no clear evidence of an increased risk of clinical thrombosis in women taking postmenopausal estrogens, however.[12,89] High-dose CEE (2.5–5 mg daily) doubled the incidence of gallbladder disease in a trial in men[90] and in a small trial in postmenopausal women.[91] Several larger observational studies report a similar 2–3-fold increased risk of gallstone disease or cholecystectomy among women taking postmenopausal estrogen;[92,93] this effect was not consistently seen in smaller studies.[94,95] Transdermal estrogens, which avoid first-pass effects on the liver, may have less effect on thrombosis and gallbladder disease. In the PEPI trial, neither estrogen nor estrogen / progestin therapy had a significant effect on mean systolic blood pressure or glucose tolerance, and all hormone regimens lowered fibrinogen levels.[43]

Estrogen and progestin each can cause unpleasant side effects. Progestin is a more common cause of bothersome side effects, including bloating, headache, irritability, and depression; the most prominent effect of estrogen is breast tenderness. Many of these side effects subside with continued treatment or can be relieved by adjusting dose or timing of administration. Women who have not had a hysterectomy will experience resumption of menses while taking cyclic progestins. Up to 40% of women on continuous progestins will experience erratic and unpredictable bleeding within the first 6 months, but 75–95% have amenorrhea after 12 months.[3,7,96]

Limitations of Epidemiologic Evidence. There are some important limitations in the ability to predict the benefits and risks of long-term hormone therapy from currently available studies: the average duration of hormone use in most studies was relatively short (several years), most long-term users of hormones had specific indications for estrogen therapy (e.g., early menopause, surgical menopause, persistent symptoms, or osteoporosis), and few women had used long-term progestin or regimens other than cyclic MPA.[44] In many studies, differences between hormone users and never-users may have independently influenced the risk of specific diseases or death. Compared to never-users, women who take estrogen are: thinner, better educated, and of higher income; more likely to exercise and drink alcohol; more likely to have had a surgical menopause and less likely to have a family history of breast cancer; in more frequent contact with physicians; and, by definition, compliant with medical therapy.[45,50,97–99] Although "selection bias" (i.e., the greater tendency for low-risk, healthy women to take hormones) may exaggerate the protective effects of estrogen on CHD, it is unlikely to account for the large and consistent effects seen in multiple studies. Confounding, selection bias, and surveillance bias are of greater concern when the observed associations are weak and inconsistent (i.e., breast cancer). The net effect of these different biases is

difficult to predict, and they could plausibly have increased *or* decreased the risk of breast cancer among hormone users in observational studies.

Risk-Benefit Analyses. Several analyses have estimated the net benefit of prolonged hormone therapy for the average postmenopausal woman.[12,100–102] Because CHD is much more common than breast cancer after the menopause,[11] both estrogen and estrogen-progestin therapy are predicted to prolong life expectancy for most women even if the risk of breast cancer is increased up to 50%.[101,102] Predicted benefits exceed those of most other preventive interventions in older women[101] and are particularly large for women at increased risk of CHD (>2-year average increase in life expectancy).[12,101] For women at high risk of breast cancer and low risk of CHD, effects may be small or even adverse, depending on the influence of progestins on these outcomes. These predictions assume that the effects of estrogen are independent of age, race, or underlying risk factors, but data on the effects of long-term hormone use are limited for some important groups of women: women over age 70, black women, and women who are obese. Cost-effectiveness of therapy is highly sensitive to costs of medication and follow-up visits. In a British study, combined estrogen-progestin therapy was predicted to cost roughly $10,000 per quality-adjusted life-year gained, assuming an annual cost of less than $150 for medications and follow-up.[100] A 1995 report of the Office of Technology Assessment estimated that unopposed estrogen would cost up to $25,000 per year of life gained, and that therapy begun at age 65 might be even more cost-effective.[114,115]

Effectiveness of Counseling

Few studies have examined the effectiveness of physician counseling of asymptomatic postmenopausal women to use estrogen. Long-term compliance with estrogen therapy may be limited by side effects, concerns about cancer risk, or inconvenience of taking daily medication.[103] In one study, up to 20–30% of women never had their prescriptions for estrogen filled; of those who began therapy, 20% discontinued the drug within 9 months.[104] The strongest determinants of use in one survey were a clear physician recommendation and knowledge that estrogen deficiency was a risk factor for osteoporosis.[105] Women who have documented low bone density appear more likely to take hormone therapy,[106] but up to 40% of those with low bone density in one study did not comply with recommendations to take hormone therapy.[107] Studies have demonstrated that targeted education and screening for osteoporosis or heart disease prevention can increase the proportion of women remaining on hormone therapy to over 80%.[107,108]

In women without a hysterectomy, breakthrough bleeding or withdrawal bleeding are important reasons for noncompliance;[103,109] more

than half of such women assigned to unopposed estrogen in the PEPI study changed or stopped therapy.[43] Continuous combination therapy, which usually causes amenorrhea, or less frequent progestin cycles (e.g., every 3 months) may improve patient satisfaction. In the PEPI trial, however, compliance did not differ between continuous and cyclic estrogen / progestin regimens.[43]

Recommendations of Other Groups

The American College of Obstetricians and Gynecologists,[110] the American Academy of Family Physicians,[111] the Canadian Task Force on the Periodic Health Examination,[112] and the American College of Physicians (ACP)[113] recommend that physicians counsel all postmenopausal women about the risks and benefits of estrogen replacement and make decisions regarding therapy on an individual basis. The ACP concluded that women with a hysterectomy and those at increased risk of coronary disease are likely to benefit from therapy, but that risks may outweigh benefits among women at increased risk of breast cancer. A 1984 National Institutes of Health consensus conference on osteoporosis recommended that estrogen therapy after menopause should be considered in high-risk women who have no medical contraindications and who are willing to adhere to a program of careful follow-up.[13]

Discussion

Estrogen therapy after the menopause relieves vasomotor and urogenital symptoms, produces clinically important improvements in bone density and blood lipids, and is associated with significant reductions in the risk of heart disease and fracture. Ongoing clinical trials can be expected to provide more reliable estimates of the magnitude of these benefits. Nonetheless, the strength and consistency of the results of observational studies strongly suggest that estrogen therapy can substantially reduce morbidity and mortality from coronary disease and osteoporosis in older women. Although models suggest a net benefit of hormone use in most postmenopausal woman, important questions remain about the appropriate duration of treatment, the benefits and risks in older women (over age 65) and non-white women, the net effect of adding progestins, and interactions with other risk factors. Recommendations about hormone therapy are best made on an individual basis, weighing probable benefits against the costs, inconvenience, and possible adverse effects of estrogen and progestin.

Whether current postmenopausal hormone regimens increase the risk of breast cancer remains uncertain. Although there is little evidence of harm from short-term use of postmenopausal estrogen, overviews suggest that continued, long-term use of hormones may increase the risk of breast cancer in

older women. The reported association is biologically plausible and could alter the balance of risks and benefits for some patients, but it has not been consistent in all studies. Moreover, the absolute increase in breast cancer mortality from hormone therapy (if any exists) is likely to be small: a 30–40% increase in mortality would increase the lifetime risk of dying of breast cancer by only 1% (i.e., from 3% to 4%). Regular mammography may further reduce any risk, but patients will have to make their own decisions regarding possible risks vs. potential benefits of therapy.

Despite many areas of uncertainty, clinicians play an essential role in helping women decide whether or not to begin hormone therapy. Clinicians can elicit symptoms related to estrogen deficiency (e.g., vasomotor or urogenital symptoms), assess other potential indications (major risk factors for osteoporosis or heart disease) or contraindications (prior breast cancer, liver diseases, or estrogen-related complications) for estrogen therapy, and explain the probable benefits and risks of prolonged therapy. Although direct evidence is not available, the asymptomatic women most likely to benefit from estrogen therapy include those with early or surgical menopause, those with other cardiac risk factors (especially adverse lipid profile; see Chapter 2), and women at high risk of osteoporosis or fracture (women who are thin, smoke, or have a family history of fracture).

The balance of benefits and risks of estrogen therapy in women at increased risk of breast cancer is not known. Since the risk of cardiovascular disease is much higher than the risk of breast cancer for most postmenopausal women, benefits may outweigh any harms even in women with a family history of breast cancer. Fear of breast cancer is particularly high in these women, however, and many may be reluctant to do anything that might increase risk. Patients should also understand that current estimates are based on available (often incomplete) knowledge and may change with new information. Because many of the benefits of estrogen may require continuing therapy indefinitely, clinicians should clarify the reasons for recommending hormone therapy and periodically assess patient concerns about side effects or risks of treatment.

CLINICAL INTERVENTION

Clinicians should counsel all women around the time of menopause about the possible benefits and risks of postmenopausal hormone therapy and the available treatment options (“B” recommendation). Counseling should include asking about presence and severity of menopausal symptoms (hot flashes, urogenital symptoms), as well as assessing risk factors for heart disease, osteoporosis, and breast cancer. Women should be advised of the probable benefits of hormone therapy on menopausal symptoms, myocardial infarction, and fracture; the increased risks of endometrial cancer with unopposed estrogen; and a possible increased risk of breast cancer.

Each woman should consider the relative importance of these benefits and risks, the possible side effects of treatment, and her willingness to take medication for an indefinite period.

Women considering estrogen therapy should be counseled about the available estrogen and progestin preparations and routes of administration. The minimum effective dose of estrogen is 0.625 mg conjugated estrogen or the equivalent once a day. For women who have not had a hysterectomy, progestin therapy or regular endometrial surveillance is recommended to reduce risk of endometrial cancer. The most common progestin regimens include a continuous regimen of daily administration of 2.5 mg medroxyprogesterone acetate (MPA) or equivalent, or a cyclic regimen of 5–10 mg MPA daily for 10–14 days each month. Transdermal estrogen preparations are effective in relieving menopausal symptoms and preventing osteoporosis, but they have less effect on lipids and are of undetermined benefit against heart disease.

All women should receive information about potential alternatives to hormones for treating menopausal symptoms (e.g., vaginal lubricants for dyspareunia, etc.), for preventing osteoporosis (see Chapter 46) and for reducing their risk of heart disease, including screening for high cholesterol (see Chapter 2) and hypertension (see Chapter 3) and counseling to prevent tobacco use and promote physical activity and healthy diet (see Chapters 54–56).

See also relevant background paper: Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992;117:1016–1037.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by David Atkins, MD, MPH, and Robert B. Wallace, MD, MSc, based in part on material prepared for the American College of Physicians by Deborah Grady, MD, MPH, Susan M. Rubin, MPH, Diana B. Petitti, MD, MPH, Cary S. Fox, MS, Dennis Black, PhD, Bruce Ettinger, MD, Virginia L. Ernster, PhD, and Steven R. Cummings, MD.

REFERENCES

1. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14:103–115.
2. Barbo DM. The physiology of the menopause. Med Clin North Am 1987;71:11–39.
3. Greendale GA, Judd HL. The menopause: health implications and clinical management. J Am Geriatr Soc 1993;41:426–436.
4. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspectives from the Framingham Study. Am Heart J 1987;114:413–419.
5. van Beresteijn ECH, Korevaar JC, Huijbregts PCW, et al. Perimenopausal increase in serum cholesterol: a 10-year longitudinal study. Am J Epidemiol 1993;137:4:383–393.
6. Oldenhave A, Jaszman LJB, Haspels AA, et al. Impact of climacteric on well-being. Am J Obstet Gynecol 1993;168:772–780.
7. Belchetz PE. Hormonal treatment of postmenopausal women. N Engl J Med 1994;1062–1071.

8. Oldenhave A, Netelenbos C. Pathogenesis of climacteric complaints: ready for the change? Lancet 1994;343:649–653.
9. Romano JM, Kaye D. UTI in the elderly: common yet atypical. Geriatrics 1981;36:113–115.
10. Kuhn FE, Rackley CE. Coronary artery disease in women: risk factors, evaluation, treatment and prevention. Arch Intern Med 1993;153:2626–2636.
11. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles' or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med 1989;149:2445–2448.
12. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992;117:1016–1037.
13. Consensus conference: osteoporosis. JAMA 1984;252:799–802.
14. Rossouw JE, Finnegan LP, Harlan WR, et al. The evolution of the Women's Health Initiative: perspectives from the NIH. J Am Med Wom Assoc 1995;50:50–55.
15. Johnston CC, Melton LJ Lindsay R, et al. Clinical indications for bone mass measurements: a report from the Scientific Advisory Board of the National Osteoporosis Foundation. J Bone Min Res 1989;4 (Suppl 2):1–28.
16. Weiss NS, Ure CL, Ballard JH, et al. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. N Engl J Med 1980;303:1195–1198.
17. Hutchinson TA, Polansky SM, Feinstein AR. Post-menopausal oestrogens protect against fractures of hip and distal radius: a case-control study. Lancet 1979;2:705–709.
18. Paganini-Hill A, Ross RK, Gerkins VR, et al. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981;95:28–31.
19. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. Ann Intern Med 1985;102:319–324.
20. Kiel DP, Felson DT, Anderson JJ, et al. Hip fracture and the use of estrogens in postmenopausal women: the Framingham Study. N Engl J Med 1987;317:1169–1174.
21. Lindsay R, Hart DM, Forrest C, et al. Prevention of spinal osteoporosis in oophorectomized women. Lancet 1980;2:1151–1154.
22. Ettinger B, Grady D. The waning effect of postmenopausal estrogen therapy on osteoporosis. N Engl J Med 1993;329:1192–1193.
23. Ettinger B, Grady D. Maximizing the benefit of estrogen therapy for prevention of osteoporosis. Menopause 1994;1:19–24.
24. Felson DT, Zhang Y, Hannan MT, et al. The effect of postmenopausal estrogen therapy on bone-density in elderly women. N Engl J Med 1993;329:1141–1146.
25. Paganini-Hill A, Chao AA, Ross RK, et al. Exercise and other factors in the prevention of fracture: the Leisure World study. Epidemiology 1991;2:16–25.
26. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. Ann Intern Med 1995;122:9–16.
27. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA 1991;265:1861–1867.
28. Stampfer MJ, Colditz GA. Estrogen replacement and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991;20:47–63.
29. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten year follow-up from the Nurses' Health Study. N Engl J Med 1991;325:756–762.
30. Sullivan JM, Vander Zwagg R, Lemp GF, et al. Postmenopausal estrogen use and coronary atherosclerosis. Ann Intern Med 1988;108:358–363.
31. Hong MK, Romm PA, Reagan K, et al. Effects of estrogen replacement therapy on serum lipid values and angiographically defined coronary artery disease in postmenopausal women. Am J Cardiol 1992;69:176–178.
32. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease: effect on survival in post-menopausal women. Arch Intern Med 1990;150:2557–2562.
33. Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. N Engl J Med 1985;313:1038–1043.
34. Mann RD, Lis Y, Chukwujindu J. A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. J Clin Epidemiol 1994;47:307–312.
35. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program follow-up study. Circulation 1987;75:1102–1109

36. Henderson BE, Paganini-Hill A, Ross RK. Estrogen replacement therapy and protection from acute myocardial infarction. Am J Obstet Gynecol 1988;159:312–317.
37. Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement therapy in postmenopausal women. In: Manson J, ed. Progress in cardiovascular diseases. Philadelphia: WB Saunders, 1996 (in press).
38. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 1991;325:1196–1204.
39. Lobo RA. Clinical review 27: effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. J Clin Endocrinol Metab 1991;73:925–930.
40. Rosano GMC, Sarrel PM, Poole-Wilson PA, et al. Beneficial effect of estrogen on exercise-induced myocardial ischemia in women with coronary artery disease. Lancet 1993;342:133–136.
41. Gilligan DM, Quyyumi AA, Cannon RO, et al. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. Circulation 1994;89:2545–2551.
42. Sack MN, Rader DJ, Cannon RO. Estrogen and inhibition of oxidation of low-density lipoproteins in postmenopausal women. Lancet 1994;343:269–270.
43. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. JAMA 1995;273:199–208.
44. Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992. Obstet Gynecol 1995;85:6–10.
45. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. N Engl J Med 1993;328:1069–1075.
46. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Arch Intern Med 1994;154:1333–1339.
47. Falkeborn M, Persson I, Adami HO, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. Br J Obstet Gynaecol 1992;99:821–828.
48. Psaty BM, Heckbert SR, Atkins D, et al. A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. Arch Intern Med 1993;153:1421–1427.
49. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991;151:75–78.
50. Finucane FF, Madans JH, Bush TL, et al. Decreased risk of stroke among postmenopausal hormone users. Results from a national cohort. Arch Intern Med 1993;153:73–79.
51. Atkins D, Psaty BM, Koepsell TD, et al. Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. Ann Intern Med 1993;119:136–145.
52. Dyken ML, Wolf PA, Barnett HJ, et al. Risk factors for stroke. A statement for physicians by the Subcommittee on Risk Factors and Stroke of the Stroke Council. Stroke 1984;15:1105–1111.
53. Falkeborn M, Persson I, Terent A, et al. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med 1993;153:1201–1209.
54. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 1993;329:752–756.
55. Ditkoff EC, Crary WC, Cristo M. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynecol 1991;78:991–996.
56. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. JAMA 1993;269:2637–2641.
57. Henderson VW, Paganini-Hill A, Emanuel CK, et al. Estrogen replacement therapy in older women. Comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol 1994;51:896–900.
58. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1994;140:256–261.
59. Brenner DE, Kukull WA, Stergachis A, et al. Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: a population-based case-control study. Am J Epidemiol 1994;140:262–267.
60. Grady D, Gebretsadik T, Kerlikowske K, et al. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995;85:304–313.
61. Brinton LA, Hoover RN, and the Endometrial Cancer Collaborative Group. Estrogen replacement therapy and endometrial cancer risk: unresolved issues. Obstet Gynecol 1993;81:265–271.
62. Shapiro S, Kelly JP, Rosenberg L, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 1985;313:969–972.

63. Williams DB, Moley KH. Progestin replacement in the menopause: effects on the endometrium and serum lipids. Curr Opin Obstet Gynecol 1994;6:284–292.
64. Voigt L, Weiss N, Chu J, et al. Progestogen supplementation of exogenous oestrogens and risk of endometrial cancer. Lancet 1991;338:274–277.
65. Key TJA, Pike MC. The role of oestrogens and progestogens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol 1988;24:29–43.
66. Kelsey JL, Gammon MD. Epidemiology of breast cancer. Epidemiol Rev 1990;12:228–240.
67. Armstrong BK. Oestrogen therapy after the menopause—boon or bane. Med J Aust 1988;148: 213–214.
68. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. Arch Intern Med 1991;151:67–72.
69. Steinberg KK, Thacker SB, Smith J, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991;265:1985–1990.
70. Sillero-Arenas M, Delgado-Rodriguez M, Rodrigues-Cateras R, et al. Menopausal hormone replacement therapy and breast cancer: a meta-analysis. Obstet Gynecol 1992;79:286–294.
71. Colditz GA, Egan KM, Stampfer MJ. Hormone replacement therapy and risk of breast cancer: results from epidemiologic studies. Obstet Gynecol 1993;168:1473–1480.
72. 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 1995;332:1589–1593.
73. Brinton LA, Hoover R, Fraumeni JF. Menopausal oestrogens and breast cancer risk: an expanded case-control study. Br J Cancer 1986;54:825–832.
74. Strickland DM, Gambrell RD, Butzin CA, et al. The relationship between breast cancer survival and prior postmenopausal estrogen use. Obstet Gynecol 1992;80:400–404.
75. Bonnier P, Romain S, Giacalone PL, et al. Clinical and biologic prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. Obstet Gynecol 1995;85:11–17.
76. Schairer C, Byrne C, Keyl PM, et al. Menopausal estrogen and estrogen-progestin therapy and risk of breast cancer (United States). Cancer Causes Control 1994;5:491–500.
77. Colditz GA, Stampfer MJ, Willett WC, et al. Type of postmenopausal hormone use and risk of breast cancer: 12-year follow-up from the Nurses Health Study. Cancer Causes Control 1992;3:433–439.
78. Bergkvist L, Adami HO, Persson I, et al. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. Am J Epidemiol 1989;130:221–228.
79. Henrich JB. The postmenopausal estrogen / breast cancer controversy. JAMA 1992;268:1900–1902.
80. Brinton LA, Schairer C. Estrogen replacement therapy and breast cancer risk. Epidemiol Rev 1993;15: 66–79.
81. Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. Br J Obstet Gynaecol 1990;97:1080–1086.
82. Yuen J, Persson I, Bergkvist L, et al. Hormone replacement therapy and breast cancer in Swedish women: results after adjustment for "healthy drug-user" effect. Cancer Causes Control 1993;4:369–374.
83. Gambrell RD Jr, Maier RC, Sanders BI. Decreased incidence of breast cancer in post-menopausal estrogen-progestogen users. Obstet Gynecol 1983;62:435–443.
84. Bergkvist L, Adami HO, Persson I, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989;321:293–297.
85. Kaufman DW, Palmer JR, Mouzon J, et al. Estrogen replacement therapy and the risk of breast cancer: results from the case-control surveillance study. Am J Epidemiol 1991;134:1375–1385.
86. Yang CP, Daling JR, Band PR, et al. Non-contraceptive hormone use and risk of breast cancer. Cancer Causes Control 1992;3:475–479.
87. Persson I, Yuen J, Bergkvist L, et al. Combined oestrogen-progestogen replacement and breast cancer risk. Lancet 1992;340:1044.
87a. Stanford JL, Weiss NS, Voigt LF, et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995;274:137–142.
88. Nachtigall MJ, Smilen SW, Nachtigall RD, et al. Incidence of breast cancer in a 22-year study of women receiving estrogen-progestin replacement therapy. Obstet Gynecol 1992;80:827–830.
89. Devor M, Barrett-Connor E, Renvall M, et al. Estrogen replacement therapy and the risk of venous thrombosis. Am J Med 1992;92:275–282.
90. The Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism: experience in the Coronary Drug Project. N Engl J Med 1977;296:1185–1190.

91. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al. Estrogen replacement therapy II: a prospective study in relationship to carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 1979;54:74–79.
92. Grodstein F, Colditz G, Stampfer MJ. Postmenopausal hormone use and cholecystectomy in a large prospective study. Obstet Gynecol 1994;83:5–11.
93. LaVecchia C, Negri E, D'Avanzo B, et al. Oral contraceptives and non-contraceptive estrogens in the risk of gallstone disease requiring surgery. J Epidemiol Community Health 1992;46:234–236.
94. Scragg RKR, McMichael AJ, Seamark RF. Oral contraceptives, pregnancy and endogenous estrogen in gallstone disease—a case-control study. BMJ 1984;288:1795–1799.
95. Kakar F, Weiss NS, Strite SA. Non-contraceptive estrogen use and the risk of gallstone disease in women. Am J Public Health 1988;78:564–566.
96. Udoff L, Langenberg P, Adashi EY. Combined continuous hormone replacement therapy: a critical review. Obstet Gynecol 1995;86:306–316.
97. Barrett-Connor E. Post-menopausal estrogen and prevention bias. Ann Intern Med 1991;115:455–456.
98. Petitti DB. Coronary heart disease and estrogen replacement therapy: can compliance bias explain the results of observational studies? Ann Epidemiol 1994;4:115–118.
99. Cauley JA, Cummings SR, Black DM, et al. Prevalence and determinants of estrogen replacement therapy in elderly women. Am J Obstet Gynecol 1990;163:1438–1444.
100. Daly E, Roche M, Barlow D, et al. HRT: an analysis of benefits, risks, and costs. Br Med Bull 1992;48:368–400.
101. Zubialde JP, Lawler F, Clemenson N. Estimated gains in life expectancy with use of postmenopausal estrogen therapy: a decision analysis. J Fam Pract 1993;36:271–280.
102. Gorsky RD, Koplan JP, Peterson HB, et al. Relative risks and benefits of long-term estrogen replacement therapy: a decision analysis. Obstet Gynecol 1994;83:161–166.
103. Wren BG, Brown L. Compliance with hormonal replacement therapy. Maturitas 1991;13:17–21.
104. Ravnikar VA. Compliance with hormone therapy. Am J Obstet Gynecol 1987;156:1332–1334.
105. Ferguson KJ, Hoegh C, Johnson S. Estrogen replacement therapy—a survey of women's knowledge and attitudes. Arch Intern Med 1989;149:133–136.
106. Rubin SM, Cummings SR. Results of bone densitometry affect women's decisions about taking measures to prevent fractures. Ann Intern Med 1992;116:990–995.
107. Ryan PJ, Harrison R, Blake GM. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. Br J Obstet Gynaecol 1992;99:325–328.
108. Coope J, Marsh J. Can we improve compliance with long-term HRT? Maturitas 1992;15:151–158.
109. Hahn RG. Compliance considerations with estrogen replacement: withdrawal bleeding and other factors. Am J Obstet Gynecol 1989;161:1854–1858.
110. American College of Obstetricians and Gynecologists. Hormone replacement therapy. Technical Bulletin no. 166. Washington, DC: American College of Obstetricians and Gynecologists, 1992.
111. American Academy of Family Physicians. Age charts for periodic health examination. Kansas City, MO: American Academy of Family Physicians, 1994. (Reprint no. 510.)
112. Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Canada Communication Group, 1994:620–631.
113. American College of Physicians. Guidelines for counselling postmenopausal women about preventive hormone therapy. Ann Intern Med 1992;117:1038–1041.
114. U.S. Congress, Office of Technology Assessment. Effectiveness and costs of osteoporosis screening and hormone replacement therapy, vol. I: cost-effectiveness analysis. Washington, DC:U.S. Government Printing Office, 1995. (Publication no. OTA-BP-H-160.)
115. U.S. Congress, Office of Technology Assessment. Effectiveness and costs of osteoporosis screening and hormone replacement therapy, vol. II: evidence on benefits, risks, and costs. Washington, DC:U.S. Government Printing Office, 1995. (Publication no. OTA-BP-H-144.)