AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

The Practical Journal for Primary Care Physicians

Primary Care Reports™

Volume 6, Number 6 **March 20, 2000**

Editor's Note—*The menopause presents a unique set of challenges to both patient and physician alike. Patients must adjust to the physical and psychological changes in their bodies brought on by the fall in estradiol levels, while physicians must go beyond simple reassurance and advise patients on the pros and cons of various forms of treatment.*

Many women are aware of the potential beneficial effects of hormone replacement therapy (HRT) on bone density, but fewer recognize its cardioprotective role in addressing the increased risk of coronary heart disease that accompanies menopause. Any discussion of HRT must take into account these and other advantages but must also not ignore potential disadvantages. With the advent of the Internet, patients' access to many sources of information (and misinformation) has grown tremendously; it is the duty of the primary care physician to provide accurate and reliable recommendations to help women decide whether HRT is right for them. The decision must also factor in the newer agents available to women, including the selective estrogen receptor modulators (SERMs) and phytoestrogens.

In the last issue of Primary Care Reports, an introduction to the physiology and clinical manifestations of menopause was given. Part II continues that discussion with a review of the cardiovascular changes during menopause and the importance of recognizing premature ovarian failure. The authors conclude with an overview of the various options for treatment and a decision-making approach for the primary care physician.

Management of the Menopausal Patient, Part II

Authors: **Redonda Miller, MD**, Assistant Professor of Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; **Katherine K. Chang, MD**, Resident, Osler Housestaff, Department of Medicine, Johns Hopkins Hospital, Baltimore, MD.
Peer Reviewer: **Felice Milan, MD**, Associate Professor of Clinical Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Irvington, NY.

Cardiovascular Effects

Coronary heart disease (CHD) is the leading cause of mortality for women in America; menopause, both natural and surgical, is associated with an increase in the risk for CHD. In fact, the relative risk for CHD in postmenopausal women compared to age-matched premenopausal women is 2.7[1]; estrogen replacement therapy lowers the risk of developing and dying from CHD by 50%.[2]

Cardiovascular Changes with Menopause

With the decline of estrogen levels during menopause,

several changes occur that serve to increase cardiovascular risk. One easily recognizable effect is the conversion to a more atherogenic lipid profile. Within six months of the cessation of menses, total cholesterol, LDL cholesterol, and triglycerides increase significantly. Conversely, HDL cholesterol shows a gradual decline over the two years preceding cessation of menses.[3] HDL has been shown to be particularly protective in women, and low serum HDL levels are strong predictors of CHD death in women, more so than elevated LDL and total cholesterol levels.[4] After adjusting for other cardiac risk factors, women with HDL levels of less than 50 mg/dL have a relative risk of 1.74 for death from CHD.[4]

In addition, a higher level of plasminogen-activator inhibitor type 1 (PAI-1), an essential inhibitor of fibrinolysis, is found in postmenopausal women compared to premenopausal women.[5] Studies have shown that increased plasma levels of PAI-1 are associated with a higher risk of atherosclerosis and subsequent myocardial infarction and stroke.[6]

Finally, both lipoprotein (a) and homocysteine levels are increased in the plasma of postmenopausal women.[7] Each is believed to be an independent risk factor for atherosclerotic disease. Increased plasma homocysteine confers a risk for CHD similar to smoking or hyperlipidemia and powerfully increases the risks associated with smoking and hypertension.[8]

While blood pressure and weight also have an effect on cardiovascular health, these do not change appreciably during the menopause.[9]

Hormone Replacement Therapy and Cardioprotection

Numerous epidemiological studies have found that, in primary prevention settings, a reduced risk of CHD exists in postmenopausal women who use HRT. In patients with existing CHD, the issue is murkier. Estrogen does not seem to have any significant influence on stroke incidence.[10]

One mechanism of cardioprotection is through alterations in the lipid profile. Oral estrogen replacement therapy in standard doses reverses the adverse lipid effects of menopause, increasing HDL levels by 13-18% and decreasing LDL levels by 11-19%.[11] Higher daily doses of estrogen do not substantially enhance these effects,[12] which generally occur within six months of beginning therapy. The increase in HDL may account for up to 50% of the CHD risk reduction afforded by estrogen therapy.[13] Transdermal estradiol produces similar, but more moderate lipid profile changes, as would be expected by a route of administration that lacks hepatic first-pass metabolism and its direct effects on cholesterol synthesis. Of note, oral conjugated estrogen therapy does increase serum triglycerides in a dose-dependent manner, which may be of concern in treating women who already have high levels.[11]

Oral conjugated estrogen, either alone or combined with progestin therapy, reduces plasma PAI-1, lipoprotein (a), and total homocysteine levels.[13-15] Estrogen may also have other lipid-independent cardioprotective effects, including vasodilation, alteration of cholesterol metabolism and deposition, and calcium antagonism.

Progestins, as a class, increase LDL and decrease HDL. Accordingly, estrogen's beneficial effect on LDL and HDL is attenuated with the addition of progestins to HRT.[10] Micronized progesterone may be less detrimental than other forms of progestins.[9] Despite the consequences on the lipid profile, observational studies suggest that the cardioprotective effects of postmenopausal estrogen combined with progestins in primary prevention remain.[16]

The role of estrogen in secondary prevention of CHD is more controversial. Observational data have suggested a positive effect of estrogen on survival in established CHD patients.[17] However, the only randomized trial to date looking at combination HRT as secondary prevention for CHD—the recent Heart and Estrogen/Progestin Replacement Study (HERS)—did not show a positive effect.[18] After an average follow-up of four years, researchers found an early increase in cardiovascular events and no overall cardiovascular benefit, leading to a recommendation of not starting HRT for secondary prevention of CHD. Yet, after the initial increase in risk during the first year of therapy, possibly due to an immediate prothrombotic effect, risk decreased in subsequent years, suggesting a possible long-term benefit. This study has tempered enthusiasm for estrogen use in secondary prevention, and it will be important to follow further reports from the HERS group and additional randomized trials to better assess true cardiovascular benefit from HRT.

Primary Care Reports™, ISSN 1040-2497, is published biweekly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

EXECUTIVE EDITOR: Glen Harris.

ASSOCIATE MANAGING EDITOR: Robin Mason.

ASSISTANT MANAGING EDITOR: Neill Larmore.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

POSTMASTER: Send address changes to ***Primary Care Reports™,*** P.O. Box 740059, Atlanta, GA 30374.

Periodical rate postage paid at Atlanta, GA.

Back issues: $23. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robin.mason@medec.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $150).

Multiple Copies
1-9 additional copies: $269 each; 10 or more copies: $239 each.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

For 50 AMA/AAFP Category 1/Prescribed hours, add $100.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 50 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

This program has been reviewed and is acceptable for up to 50 prescribed hours by the American Academy of Family Physicians. Term of approval is for one year from beginning distribution date of January 1, 2000, with option to request yearly renewal.

Questions & Comments

Please call **Robin Mason,** Associate Managing Editor, at (404) 262-5517 or e-mail: robin.mason@medec.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Miller (author) is a consultant, serves on the speaker's bureau, and is involved in research with Hoechst Marion Roussel, is a stockholder for Merck, Pfizer, Inhale Therapeutics, and Emisphere, serves on the speaker's bureau of Novartis, and is involved in research with Proctor & Gamble. Dr. Milan (peer reviewer) reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Premature Ovarian Failure

Premature ovarian failure is defined as loss of ovarian function before the age of 40 and is more common than most physicians realize. Up to 1% of women may be affected.[19] There are many causes of premature ovarian failure, including Turner's syndrome; autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosis, and myasthenia gravis; and physical insults such as surgery, chemotherapy, or radiation therapy. Some cases remain idiopathic. Women who undergo premature menopause have more severe vasomotor symptoms and more significant impairment of sexual functioning. Because these women will spend a significantly larger proportion of their lives without estrogen, they are at markedly increased risk for osteoporosis and heart disease. These women should universally be started on HRT and continued at least until the natural age of menopause (50 years of age) to prevent long-term health consequences.

Hormone Replacement Therapy Considerations

Advantages of HRT

There are many advantages of HRT (*see Table 1*). The most obvious to the patient is the relief of vasomotor symptoms and vaginal dryness. Perhaps even more important is the role estrogen plays in the prevention of chronic diseases. It is well documented that the use of estrogen at menopause prevents bone loss. In osteoporotic patients, bone density may even increase up to 5% per year for several years, and the hip fracture rate may decline by 50%. Estrogen also affords a 50% reduction in cardiac events, the leading cause of death among women. Each of these is discussed in the earlier sections.

Disadvantages of HRT

Despite the many positive effects of HRT, physicians must also be aware of the disadvantages (*see Table 1*). When confronted with the choice of using HRT, most women claim that their biggest fear is the possible increased risk of breast cancer. Numerous epidemiological studies have tried to address this issue with conflicting results, and no one study is definitive. The Nurses' Health Study[20] suggested that the relative risk of breast cancer for women currently using estrogen is 1.3, which translates into a 30% increase in risk. Risk was related to the duration of use, with use over 5-10 years being more significant. No increased risk was found in past users. On the other hand, the Iowa study found that women with a family history of breast cancer who used HRT did not have a significantly increased incidence of breast cancer, even with use of more than five years.[21] Despite the questionable increased risk, all studies (except one)[20] examining mortality from breast cancer in hormone users have documented lower mortality for women on HRT. This may reflect earlier diagnosis in HRT users who are more likely to have regular mammograms, or that estrogen exposure results in better differentiated tumors that are less aggressive.[21,22]

In women with a uterus, more than two decades of evidence have linked the use of unopposed estrogen with adenocarcinoma of the endometrium. A recent meta-analysis estimated this risk to be 2.3 times that of nonusers. With 10 or more years of exposure, the relative risk climbed to 9.5 and remained elevated five years after discontinuation.[23] Adding a progestin negates this risk to that of placebo[24] and should be considered standard in nonhysterectomized women. While some irregular bleeding is anticipated with initiation of continuous HRT, any woman who continues to have irregular bleeding at 6-8 months should undergo further work-up, including possible transvaginal ultrasound and endometrial biopsy. Likewise, any late-onset uterine bleeding warrants evaluation.

Unlike oral contraceptives, HRT is associated with only a small increase in the risk of venous thromboembolism, predominantly in current users. The risk is estimated to be 2.5-3.5 times that of nonusers.[18,25] This is usually not considered to be a deterrent to HRT use.

Women who use HRT are at a modestly increased risk of gallbladder disease.[18] This is presumed to be related to estrogen's ability to enhance uptake and turnover of cholesterol in the liver. Cholesterol concentration is then increased in the bile, leading to a greater chance of stone formation. Mortality from gallbladder disease is not increased in HRT users.

Minor side effects include breast tenderness and breakthrough vaginal bleeding, which are often short-lived. Less well-substantiated are reports of weight gain, nausea, and headaches.

Despite these disadvantages, the absolute contraindications to HRT are relatively few (*see Table 2*). Most experts would agree that a personal history of breast cancer or acute thromboembolic disease falls into this category. Other conditions formerly thought to be contraindications, however, are being

Table 1. Advantages and Disadvantages of HRT

Advantages of HRT

- relief of vasomotor symptoms
- decrease in vaginal dryness
- stabilization ± increase in bone density
- improved lipid profile
- decrease in cardiovascular risk

Disadvantages of HRT

- breast tenderness
- vaginal spotting
- increased risk of gallstones
- increased risk of thromboembolic disease
- questionable increased risk of breast cancer

Table 2. Contraindications to Hormone Replacement Therapy

Absolute

- Personal history of breast cancer
- Acute thromboembolic disease

Relative

- Strong family history of breast cancer
- Unexplained vaginal bleeding
- Past history of thromboembolic disease
- Chronic hepatitis

re-evaluated in light of the increasingly documented benefits of estrogen.

Methods of Delivery

There are several methods of delivery of hormone replacement for postmenopausal women (*see Table 3*). Each has unique features that may make one method more attractive than another for the individual patient. In women who have undergone hysterectomy, estrogen may be administered alone without a progestin. Currently available preparations provide oral, transdermal, or vaginal delivery. Orally, conjugated estrogens are the most widely used and studied. These are less potent than the ethinyl estradiol found in oral contraceptives but are adequate to restore physiologic status. Transdermal estrogen provides a convenient option for women since it may be applied only one or two times per week. The drawback of the transdermal route is the less beneficial effect on the lipid profile since first-pass metabolism through the liver is lost. However, this may be desirable in women with chronic liver disease or high triglyceride levels. Vaginally applied estrogens are useful to ameliorate vaginal dryness, but they lack systemic effects and, therefore, do not prevent bone density loss or provide cardioprotection.

In a patient with an intact uterus, estrogen must be administered with a progestin (synthetic progesterone) to prevent endometrial hyperplasia and possible adenocarcinoma.[24] Medroxyprogesterone acetate is commonly used because its androgenic activity is weaker than other progesterone derivatives. The progestin may be added in one of several ways. It may be given in a cyclical fashion, resulting in periodic sloughing of the endometrium. If done in this fashion, it is usually given on days 16-25 of a woman's cycle. In 70-90% of cases, women find the continued monthly menses associated with cycling to be inconvenient. Alternatively, progestin may be delivered on a continuous basis as medroxyprogesterone acetate 2.5 mg q.d. Regardless of method, the addition of a progestin to estrogen counteracts some of the positive effects on the lipid profile. In particular, HDL cholesterol is not increased as much, but significant benefit remains compared to placebo.[9] Micronized progesterone, a newer and less widely available preparation, can be delivered continuously or cyclically, and seems to result in less detrimental changes in the lipid profile. It is well tolerated and still maintains its protective effects on the uterus.[9]

Some physicians have advocated the addition of androgens to HRT for menopausal women, particularly if they experience diminished libido, cognitive difficulties, or low mood. Small studies have suggested some effect,[26] but large randomized clinical trials are lacking. Adding an androgen does not diminish the ability of estrogen to relieve vasomotor symptoms or increase bone density.[27] In contrast to standard HRT, however, HDL cholesterol decreases with the addition of testosterone, which may have a bearing on long-term cardioprotection in women. Other potential side effects include acne, hirsutism, weight gain, and aggressiveness, although these have mainly been reported with higher doses. An oral combination preparation of esterified estrogens and methyltestosterone is now available (Estratest). Progestin must still be given in a woman with a uterus.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are a relatively new class of drugs being used for HRT. These drugs bind to the estrogen receptor and have both agonist and antagonist effects, depending on the target organ.[28] Tamoxifen is a first-generation SERM that was approved by the FDA in 1969. Because it blocks the effect of estrogen on the breast, it has been used extensively as adjuvant therapy for prevention of receptor-positive breast cancer recurrence. Drawbacks include the onset or worsening of hot flashes, endometrial hyperplasia with the attendant risk of neoplasia, and increased risk of thrombosis. Other SERMs under development include droloxifene and toremifene, each with varying levels of estrogen agonist and antagonist properties.

Raloxifene is a newer generation SERM that has received a lot of attention for use as HRT in postmenopausal women. At a dose of 60 mg q.d., raloxifene provides estrogenic effects on the bone and lipid profile, and antiestrogenic effects on the breast and endometrium. Similar to estrogen, raloxifene inhibits bone resorption primarily in cancellous bone. On average, at two years women gain 2-3% in bone mineral density over placebo[29,30] and have a relative risk of vertebral fracture of 0.7 compared with controls.[30] In addition, raloxifene decreases total and LDL cholesterol but has no effect on HDL and triglycerides. No studies have yet documented the vasodilatory effects that estrogen has or whether a long-term benefit on cardiovascular outcomes exists.

Regarding its antiestrogenic properties, raloxifene has no effect on endometrial thickness as measured by transvaginal ultrasound,[29] and the incidence of uterine bleeding appears to be less with raloxifene than with estrogen. Recent data demonstrated the protective effect of raloxifene on breast tissue in postmenopausal women. In a randomized, placebo-controlled trial, the risk of invasive breast cancer was reduced by 76% over three years in women on raloxifene.[31] Trials are currently under way comparing tamoxifen and raloxifene for prevention of breast cancer recurrence. Not surprisingly, raloxifene's antiestrogenic effect on the breast leads to less breast tenderness than estrogen.

Drawbacks of raloxifene include the lack of relief of vasomotor symptoms, with persistent (and possible worsening of) hot flashes in menopausal women, and the failure to raise HDL cholesterol. The risk of venous thromboembolic disease is also increased threefold, similar to estrogen.[28]

Overall, raloxifene provides many benefits to postmenopausal women, but, at this time, estrogen remains the first choice for most women in the perimenopause (*see Table 4*). Increases in bone density are significant but do not appear to be as great as with estrogen, and long-term cardiac benefits are not yet known. A direct comparison between raloxifene and estrogen has not been published. Thus, raloxifene should serve as a useful alternative for women who cannot tolerate or prefer not to take estrogen.

Phytoestrogens

Phytoestrogens are naturally occurring plant-based substances with weak estrogenic effects. The most common forms are isoflavones, found in soybeans and soy products, and lignans, found in flaxseed, vegetables, legumes, and cereals. The clinical importance of the estrogenic effects of these compounds is debated, although more data suggesting some efficacy are accumulating. A recent study found that perimenopausal women given a daily dietary soy supplement had a 45% reduction in daily hot flushes at 12 weeks compared to a 30% reduction in the placebo arm.[32] Regarding potential benefits on the lipid profile, a meta-analysis of 38 controlled clinical trials found that the consumption of soy protein rather than animal protein resulted in significantly decreased levels of total cholesterol, LDL cholesterol, and triglycerides.[33] One concern with these compounds is whether high intake may result in endometrial hyperplasia in women with a uterus, similar to the effect of unopposed estrogen. More data are needed before these compounds can be recommended as a replacement for long-term HRT.

Table 3. Forms of Hormone Replacement Therapy

Form of HRT	Dose	Comments
Estrogens	conjugated: 0.625 mg p.o. q.d. esterified: 0.625 mg p.o. q.d. estradiol: 1 mg p.o. q.d. estropipate: 0.625 mg p.o. q.d.	• use only in hysterectomized women • initial breast tenderness • benefits: improvement in vasomotor sxs; relief of vaginal dryness; cardioprotection; osteoporosis prevention
Cyclical estrogens and progestin combination	estrogen: one of the above preparations on days 1-25 AND medroxyprogesterone: 10 mg p.o. q.d. on days 16-25 OR miconized progesterone: 200 mg p.o. q.d. on days 16-25	• monthly withdrawal bleeding • benefits comparable to estrogen alone
Continuous conjugated estrogens and progestin combination	estrogen: one of the above p.o. q.d. AND medroxyprogesterone: 2.5-5 mg p.o. q.d. OR miconized progesterone: 100 mg p.o. q.d.	• vaginal spotting • benefits comparable to estrogen alone
Transdermal estrogen	estradiol: 0.05-0.1 mg topically 1-2 × per week	• use only in hysterectomized women or must add a progestin • easier for compliance • less benefit on lipid profile • less risk in patients with liver disease
Estrogen and androgen combination	esterified estrogens and methyltestosterone: 0.625/1.25 mg p.o. q.d.	• ? benefit on libido • must add a progestin in women with a uterus

Table 4. Estrogen vs. Raloxifene for HRT

	Estrogen	Raloxifene
Hot flashes	↓	0 or ↑
Breast tenderness	↑	0
Uterine hyperplasia and bleeding	↑	0
Cholesterol:		
HDL	↑	0
LDL	↓	↓
Bone mineral density	↑↑	↑
Venous thromboembolism	↑	↑

Deciding with Individual Patients

For each menopausal woman, the choice of whether to pursue HRT is a personal one. They should be aware that, despite the many benefits of HRT, up to 20% of women prescribed estrogen for the first time discontinue it during the first year, 10% use it intermittently, and up to 30% never have the prescription filled.[34] Common reasons for discontinuation include intolerance of side effects such as breast tenderness and vaginal spotting, as well as fear of breast cancer.

HRT should not be a universal recommendation. The benefits and risks associated with HRT are different for each woman, and they must be weighed on an individual basis. A distinction must also be made as to whether the woman is interested in short-term use for relief of vasomotor symptoms or long-term use to prevent chronic conditions such as osteoporosis and CHD. Short-term use is fairly riskfree and requires less discussion.

Regarding long-term use, a woman with significant risk factors for osteoporosis or CHD may benefit from long-term HRT. A woman with a personal or strong family history of breast cancer may not. Many attempts have been made to quantify the risk associated with each condition to aid clinicians in their counseling endeavors. The Nurses' Health Study provided information regarding the use of HRT and all-cause mortality. Current hormone users were found to have a lower risk of death (relative risk, 0.63) than nonusers. This reduction was largest in women with cardiac risk factors. The benefit decreased with use of more than 10 years (due to breast cancer deaths) but still remained significant.[35]

Another study used decision analysis to examine the effect of long-term HRT on life expectancy, taking into account the risk of CHD, breast cancer, and hip fracture.[36] The results indicated that HRT should increase life expectancy for nearly all women. Women with at least one cardiac risk factor would benefit, even if a first-degree relative had breast cancer. In this model, the risk of HRT outweighed the benefit only in women without risk factors for CHD or hip fracture, but who had two first-degree relatives with breast cancer.

Clearly, each woman will have her own risk/benefit profile regarding HRT, as well as personal preferences about methods of delivery and tolerance of side effects. Discussion of these factors and close communication between physician and patient are essential in order for the menopausal woman to make an informed decision.

Additional Information

Patients frequently request additional sources of information for further reading. Listed below are several resources particularly helpful to patients.

- *Menopause Guidebook*. Obtained through: The North American Menopause Society, P.O. Box 94527, Cleveland, OH 44101-4527.
- www.menopause.org
- www.discoveryhealth.com
- www.drkoop.com
- www.nof.com
- www.mediconsult.com

References

1. Gordon T, et al. Menopause and coronary heart disease. *Ann Intern Med* 1978;89:157-161.
2. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
3. Jensen J, et al. Influence of menopause on serum lipids and lipoproteins. *Maturitas* 1990;12:321-331.
4. Bass KM, et al. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med* 1993; 153:2209-2216.
5. Gebara OC, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation* 1995;91:1952-1958.
6. Juhan-Vague I, et al. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation* 1996;94:2057-2063.

7. Wouters MG, et al. Plasma homocysteine and menopausal status. *Eur J Clin Invest* 1995;25:801-805.
8. Graham IM, et al. Plasma homocysteine as a risk factor for vascular disease: The European Concerted Action Project. *JAMA* 1997;277:1775-1781.
9. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208.
10. Stampfer MJ, 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.
11. Walsh BW, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991;325:1196-1204.
12. Bush TL, et al. Cardiovascular mortality in noncontraceptive use of estrogen in women: Results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987;75:1102-1109.
13. Koh KK, et al. Effects of hormone-replacement therapy on fibrinolysis in postmenopausal women. *N Engl J Med* 1997;336:683-690.
14. Espeland MA, et al. Effect of postmenopausal hormone therapy on lipoprotein(a) concentration. *Circulation* 1998;97:979-986.
15. Mijatovic V, et al. Postmenopausal oral 17ß-estradiol continuously combined with dydrogesterone reduces fasting serum homocysteine levels. *Fertil Steril* 1998;69:876-882.
16. Grodstein F, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-461.
17. Sullivan JM, et al. Estrogen replacement and coronary artery disease. Effect on survival in postmenopausal women. *Arch Intern Med* 1990;150:2557-2562.
18. Hulley S, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-613.
19. Davis SR. Premature ovarian failure. *Maturitas* 1996; 23:1-8.
20. Colditz GA, 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.
21. Sellers TA, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997;127:973-980.
22. Bonnier P, et al. Clinical and biologic prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. *Obstet Gynecol* 1995; 85:11-17.
23. Grady D, et al. Hormone replacement therapy and endometrial cancer risk: A meta-analysis. *Obstet Gynecol* 1995;85:304-313.
24. The Writing Group for the PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996;275:370-375.
25. Daly E, et al. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-980.
26. Davis SR, et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227-236.
27. Watts NB, et al. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol* 1995;85:529-537.
28. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999; 130:431-439.
29. Delmas PD, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-1647.
30. Ettinger B, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. *JAMA* 1999;282:637-645.
31. Cummings SR, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the

MORE randomized trial. *JAMA* 1999;281:2189-2197.
32. Albertazzi P, et al. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol* 1998;91:6-11.
33. Anderson JW, et al. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333: 276-282.
34. Cauley JA, et al. Prevalence and determinants of estrogen replacement therapy in elderly women. *Am J Obstet Gynecol* 1990;163:1438-1444.
35. Grodstein F, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769-1775.
36. Col NF, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA* 1997;277:1140-1147.

Physician CME Questions

29. Which of the following serum values is increased by estrogen therapy?
    a. Total homocysteine
    b. LDL cholesterol
    c. Triglycerides
    d. Lipoprotein (a)
    e. None of the above

30. Which of the following is *not* true of premature ovarian failure (POF)?
    a. Most women do not require HRT, as symptoms tend to be mild.
    b. Causes of POF include chemotherapy and radiation therapy.
    c. POF is more common than many physicians realize.
    d. Women with POF tend to have more severe vasomotor symptomatology.
    e. Decrease in sexual functioning is a frequent complication of POF.

31. Which of the following is a potential disadvantage of estrogen therapy in the postmenopausal woman?
    a. Breast cancer protection
    b. Increased risk of cardiovascular disease
    c. Decreased risk of gallbladder disease
    d. Breast tenderness
    e. Accelerated bone loss

32. Which of the following is correct regarding clinical effects of raloxifene?
    a. Raloxifene has been shown to decrease HDL cholesterol.
    b. Raloxifene has no effect on LDL cholesterol.
    c. Raloxifene results in significant endometrial hyperplasia.
    d. Raloxifene is effective in relieving vasomotor symptoms.
    e. Raloxifene is effective in prevention of postmenopausal bone loss.

Attention *Primary Care Reports* Subscribers

No one knows the clinical information and analysis that primary care physicians want and need as much as readers of *Primary Care Reports*. To tap into that expertise, we are happy to announce that we are opening up our monograph selection process to our readers.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Associate Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@medec.com.

In Future Issues:

The Recognition and Management of Sleep Disorders—David N. Neubauer, MD