

Prescribing Hormone Replacement Therapy for Menopausal Symptoms

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This paper addresses the clinical presentation of menopause, pretreatment assessment for hormone replacement therapy, benefits and risks of this treatment, common hormone replacement regimens and their side effects, and patient management. The case-based discussion focuses on the clinical management of a patient who is considering hormone replacement therapy for menopausal symptoms.

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Editors' Note: Readers may notice that this Clinical Review, organized around a clinical case and specific case-related questions, differs from the usual format for Annals Reviews. It represents our first publication in a planned series of carefully documented, case-based reviews of topics relevant to primary care practice. We are especially interested in readers' comments on this format. Please send your comments to us by regular mail or by e-mail to claine@mail.acponline.org.

Clinical Presentation of Menopause

A 52-year-old woman comes to see you because she is having hot flashes that annoy her during the day and disturb her sleep. Her menses stopped naturally approximately 10 months ago after several months of light or skipped periods. She wonders whether this is menopause and whether hormones could help.

Is This Patient Menopausal?

Menopause, the permanent cessation of menstruation after loss of ovarian follicular function, is clinically defined as the absence of menses for 12 months (1, 2). Natural menopause occurs at an average age of 51 years; this age has remained constant since it was first recorded in 600 A.D. (3–5). Approximately 1% of women become postmenopausal before 40 years of age, and 5% become postmenopausal after 55 years of age (6). During the several years before menopause, a period known as *menopause transition*, serum levels of follicle-stimulating hormone (FSH) increase and ovarian follicles abnormally mature; as a result, estrogen and progesterone levels become erratic (7). Women

may experience menstrual irregularities, hot flashes, sleep disturbances, and vaginal dryness (8, 9). Sleep disruption from hot flashes may cause some irritability, and fluctuating levels of hormones are associated with an increase in emotional lability. However, menopause transition is not considered a cause of depression (9). Later signs and symptoms of estrogen loss include breast atrophy and dyspareunia caused by severe vaginal dryness (9).

Do Clinicians Need To Confirm Cessation of Ovarian Function before Prescribing Hormone Replacement Therapy?

To document with certainty that ovarian function has ceased, clinicians would confirm that the serum level of FSH is greater than 40 IU/L (9–11). Several clinical situations warrant this investigation (11). For example, if a clinician were considering prescribing hormone replacement therapy (HRT) for an asymptomatic 48-year-old woman who had had a hysterectomy and was at high risk for osteoporosis, the FSH level should be measured. The FSH level would also help to rule out pregnancy and confirm menopause in a woman experiencing hot flashes after a few months of amenorrhea. Finally, clinicians should confirm ovarian failure in all women who experience early menopause (before 40 years of age) by obtaining two elevated levels of FSH and performing an appropriate work-up for secondary amenorrhea (1).

In the case described here, the patient's age, history of hot flashes, and menstrual irregularities are consistent with estrogen deficiency (9–11). It is therefore not necessary to confirm the cessation of ovarian function by determining FSH level. However, clinicians must always rule out pregnancy in sexually active women who have been amenorrheic for only a short period.

Contraindications and Pretreatment Assessment in Prescribing Hormone Replacement Therapy

The patient's medical history is remarkable only for hypertension, which is well controlled with β -blocker

Table 1. Contraindications and Pretreatment Assessment in Prescribing Hormone Replacement Therapy

Contraindications*
Pregnancy
Unexplained vaginal bleeding
Active or chronic liver disease
History of breast or endometrial cancer†
Recent vascular thrombosis
Informed patient refusal
Relative contraindications‡
Hypertriglyceridemia
History of thromboembolic disease
Family history of breast cancer
Gallbladder disease
Migraine headaches
Uterine leiomyoma
Seizure disorder
Pretreatment assessment and medical record documentation before initiation of hormone replacement therapy*
Medical history consistent with the diagnosis of menopause
Assessment of contraindications and relative contraindications
Discussion of the risks and benefits of hormone replacement therapy
Physical examination, including blood pressure and breast and pelvic examinations
Results of cervical cytologic examination and screening mammography negative for malignancy
Baseline endometrial aspirate is not necessary

* Reference 11.

† Reference 21.

‡ Currently under debate. Some physicians prescribe hormone replacement therapy for survivors of breast cancer (12, 22–24). For survivors of endometrial cancer, most gynecologists prescribe estrogen in those who had stage I, grade I disease (11, 12).

therapy, and rare migraine headaches. She has never had deep venous thrombosis or pulmonary embolism. Her only daily medications are atenolol and a multivitamin. She uses no herbal therapies, smokes 10 cigarettes per day, drinks alcohol occasionally, and does not exercise. Her mother had hypertension and Alzheimer disease, but she has no family history of heart disease, breast cancer, or other gynecologic cancer. On examination, the patient is moderately overweight and her blood pressure is 138/80 mm Hg; her heart rate is 62 beats/min. Results of the remainder of the examination, including breast and pelvic examinations, are normal. Test results include normal mammography and Papanicolaou smear; fasting glucose level of 5.99 mmol/L (108 mg/dL); and fasting lipid panel of total cholesterol of 0.63 mmol/L (244 mg/dL), low-density lipoprotein (LDL) cholesterol level of 4.0 mmol/L (155 mg/dL), high-density lipoprotein (HDL) cholesterol level of 1.16 mmol/L (45 mg/dL), and triglyceride level of 1.73 mmol/L (153 mg/dL).

Does This Patient Have Relative Contraindications to Hormone Replacement Therapy?

Hypertension (12–15) and cigarette smoking (12, 13) are not considered contraindications for HRT (12–15). The Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial, a randomized trial of more than 800 women, confirmed that HRT does not increase blood pressure (16). Despite the well-documented increased risk for venous thromboembolic events in smokers who use oral contraceptives, smoking status does not seem to affect the associa-

tion between HRT and venous thromboembolic events (17, 18).

The patient's migraine headaches are not an absolute contraindication to HRT, but the patient should be cautioned that interruption of her estrogen regimen for more than a few days may exacerbate her headaches (19). Migraine frequency may increase during menopause transition, when estrogen levels are in flux (20).

The American College of Obstetricians and Gynecologists (ACOG) has established absolute and relative contraindications to HRT (Table 1). In addition to reviewing the contraindications with patients, physicians are encouraged to follow the pretreatment assessment in Table 1 and to consult the ACOG recommendations for medical record documentation (11).

Benefits and Risks of Hormone Replacement Therapy

At the patient's follow-up visit, you discuss her laboratory and mammography results. The patient's hot flashes persist, and you recommend that she consider HRT.

What Benefits and Risks Should You Discuss with the Patient To Allow Her To Make a Well-Informed Decision about Hormone Replacement Therapy?

Hormone replacement therapy is the best treatment for the patient's hot flashes (9, 10, 12, 25, 26). This therapy will also help prevent osteoporosis, will improve LDL and HDL cholesterol levels, and may decrease her risk for heart disease and Alzheimer disease (12, 13, 16, 27–37). Hot flashes usually subside naturally within 5 years, so she will not need to use HRT indefinitely (38). If she discontinues HRT after 5 years, she should not be concerned about increased risk for breast cancer. Breast cancer risk is not elevated with short-term use of HRT, and annual breast cancer screening is appropriate (13, 39–42). With adequate progestin, HRT will not increase the patient's risk for uterine cancer (12, 13, 16). Finally, although HRT does increase her risk for blood clots and gallbladder disease, both are uncommon in her age group (17, 18, 43, 44).

This patient has a straightforward presentation; however, the discussion of the benefits and risks of HRT can be complex in other patients (10, 13, 45–51). In addition, there is considerable confusion between established benefits and risks that are based on strong evidence and those that have been suggested by some evidence but have not been confirmed. Results from large randomized, controlled trials are considered strong evidence of effect,

whereas results from observational, cross-sectional, or case-control studies are considered to offer some evidence of effect (Table 2).

It has been suggested that HRT protects cardiovascular and cognitive function; these are the most important potential benefits to consider among postmenopausal women in the United States. If HRT reduces the likelihood of developing coronary heart disease or Alzheimer disease, then its benefits would greatly outweigh its risks in most cases (13, 46, 54, 66). Until these benefits are confirmed by results from large randomized trials, however, physicians must inform patients that the available evidence is inconclusive.

Benefits of Hormone Replacement Therapy

Hormone replacement therapy is by far the most effective therapy for treating estrogen-deficient hot flashes and vaginal atrophy (9, 10, 12, 25, 26). Most women require no more than 5 years of HRT; hot flashes usually subside naturally within this period (38). An increased incidence of hot flashes is associated with using tobacco and having a mother with a history of hot flashes (67). For women who have absolute contraindications to HRT, hot flashes can be modestly reduced with transdermal clonidine, megestrol, or soy protein (68–72).

Hormone replacement therapy is approved by the Food and Drug Administration (FDA) for the

prevention and management of osteoporosis (73), and it is established that this therapy helps to preserve bone mineral density (74). Of note, the improvement in bone mineral density caused by HRT is not maintained after cessation of this therapy; this suggests that lifelong estrogen replacement therapy is necessary for prevention of osteoporosis (60). Information about the effect of HRT on rates of fracture is limited to one randomized study of 75 women (27), but observational studies of women receiving HRT suggest a 50% to 80% decrease in vertebral fractures and a 25% decrease in nonvertebral fractures after at least 5 years of use (75).

Unopposed oral conjugated equine estrogen, 17 β -estradiol, esterified estrogen, estropipate, and ethinyl estradiol have all been shown to decrease LDL cholesterol levels and increase HDL cholesterol and triglyceride levels in the first year of treatment (76–79). The long-term effect of estrogen on the lipid profile has been studied only with conjugated equine estrogen (16). After 3 years, average changes from baseline measurements LDL cholesterol, HDL cholesterol, and triglyceride levels in women randomly assigned to receive conjugated equine estrogen without a progestin were -0.37 mmol/L (-14.5 mg/dL), -0.14 mmol/L (-5.6 mg/dL), and 0.15 mmol/L (13.7 mg/dL), respectively (16). Therefore, although oral conjugated equine estrogens improve HDL and LDL cholesterol levels,

Table 2. Estimated Effects of Current Use of Hormone Replacement Therapy on Disease Outcome*

Condition (Reference)	Significant Outcome†	Comment
Strong evidence of effect in randomized, controlled trials		
Hot flashes (25, 26, 56–59)	>70% reduction	Most effective treatment‡
Osteoporosis		Long-term use required§
Vertebral fracture (61)	61% reduction	After 1 year of transdermal estrogen
LDL cholesterol level (16)	10% reduction	After 3 years of CEE alone
HDL cholesterol level (16)	9% increase	After 3 years of CEE alone
Triglyceride level (16)	14% increase	No increase with transdermal estrogen
Coronary heart disease, secondary prevention (44)	No effect	With CEE and MPA
Deep venous thrombosis or pulmonary embolism (44)	Threefold increase	With CEE and MPA
Cholecystitis (44)	40% increase	With CEE and MPA
Endometrial cancer (16)	No effect¶	Increased risk with estrogen alone¶
High blood pressure (16)	No effect	
Weight (16)	No increase	Useful in counseling women
Some evidence of effect in meta-analyses of epidemiologic studies**		
Hip fracture (13)	25% reduction	11 studies
Coronary heart disease, primary prevention		
Estrogen alone (29)	50% reduction	16 studies
Estrogen and progestin (54)	34% reduction	7 studies
Risk for dementia (37)	29% reduction	10 studies
Colon cancer (65)	31% reduction	6 studies
Breast cancer (39)		
<5 years of use	No effect	51 studies
≥ 5 years of use	35% increase	51 studies

* Outcomes are reported as changes in relative risk for disease. Absolute risk reduction is not reported because of its high variability among persons. For example, the 10-year absolute risk for coronary heart disease for a 55-year-old woman ranges from 3% to greater than 42%, depending on her cardiac risk profile (52). CEE = conjugated equine estrogen; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MPA = medroxyprogesterone acetate.

† $P < 0.05$.

‡ Reference 9.

§ Reference 60.

|| References 62–64.

¶ Risk for endometrial hyperplasia or cancer compared with placebo did not increase when both estrogen and progestin were prescribed. Estrogen alone significantly increased the risk for adenomatous or atypical hyperplasia when compared with placebo (34% compared with 1%) (16).

** Epidemiologic studies include the following designs: prospective and retrospective, observational cohort, cross-sectional, and case-control; in these studies, all apparent beneficial or detrimental effects of hormone replacement therapy may be a result of bias (53–55).

Table 3. Progestins Commonly Prescribed in the United States

Progestins (Trade Name, Manufacturer)	Cyclic Regimen (10–14 Days per Month)	Continuous Regimen (Daily)
		mg
Medroxyprogesterone acetate (Provera, Pharmacia & Upjohn; Cytrin, Wyeth-Ayerst; Amen, Carnrick)*	5 or 10†	2.5
Micronized progesterone (Prometrium, Schering-Plough)	200‡	100–200§
Intravaginal progesterone (Crinone 4%, Wyeth-Ayerst)§¶	45–90**	
Norethindrone (Micronor, Ortho; Nor-QD, Syntex)§††	0.7–1.0	0.35

* References 16, 107, and 108.

† The American College of Obstetricians and Gynecologists considers the 5-mg, 14-day dosage (rather than the 10-mg, 10- to 12-day dosage, to be the optimal dosage for cyclic therapy (106).

‡ 12-day dosage (16).

§ Not approved by the Food and Drug Administration for hormone replacement therapy.

|| References 111–113.

¶ References 114 and 115.

** Each applicator contains 45 mg of progesterone; recommended dosage, 45 mg to 90 mg every other day for 12 days each month.

†† References 82, 109, and 110.

these improvements are modest with long-term treatment.

Progestins decrease some of estrogen's beneficial effects on lipoproteins, particularly on HDL cholesterol levels (16, 34, 59, 77–82); this is directly related to the dose and degree of androgenicity of the progestin. Androgenicity of progestins increases in the following order: natural micronized progesterone, medroxyprogesterone acetate (MPA), and norethindrone (16, 34, 59, 77–82). In women taking conjugated equine estrogen without a progestin, HDL cholesterol level increased an average of 0.14 mmol/L (5.6 mg/dL), compared with smaller increases of 0.11 mmol/L (4.2 mg/dL) when micronized progesterone was added and 0.03 mmol/L (1.2 mg/dL) when MPA was added (16). When norethindrone was added to estrogen, HDL cholesterol levels did not improve significantly from baseline (78, 82). The addition of methyltestosterone led to a significant decrease of 0.41 mmol/L (16 mg/dL) in HDL cholesterol levels (79). Thus, to maximize the beneficial effect of estrogens on lipid levels, micronized progesterone or MPA is preferred.

In one randomized, placebo-controlled trial of 93 postmenopausal women with recurrent urinary tract infections, intravaginal estriol cream significantly reduced urinary tract infections to 0.5 episode per person-year (compared with 5.9 episodes per person-year in the placebo group) (83). It is not known whether oral or transdermal estrogen would have the same beneficial effect.

Hormone replacement therapy may help prevent coronary heart disease (12, 13, 28–36). Although more than 30 observational and cross-sectional stud-

ies have reported a significant risk reduction for coronary heart disease (35% to 55%) (13, 29, 36), no large randomized trials assessing the effect of HRT in the primary prevention of coronary heart disease have been completed. However, the Heart and Estrogen-Progestin Replacement Study (HERS) was the first randomized trial to examine the effect of HRT in secondary prevention of coronary heart disease. After 4 years of follow-up, HRT had no effect on rates of nonfatal myocardial infarction and sudden cardiac death in more than 2700 women with established coronary heart disease (44). Of interest, the HERS investigators reported a significant 52% increase in nonfatal myocardial infarction and cardiac death during the first year of HRT compared with placebo. They concluded that women with established coronary heart disease should not begin receiving HRT (44). This study did not address the use of unopposed estrogen, HRT in younger women with no preexisting coronary heart disease, or other forms or doses of estrogen or progestins. The apparent cardioprotection reported in observational and case-control studies may not be caused by HRT but may instead be a result of fundamental differences between women who choose to take HRT and those who do not (54, 55, 84–88). For example, women who choose to take HRT, when compared with women who choose not to use HRT, have better metabolic risk factors before menopause, have healthier lifestyles, are more educated, and are more likely to adhere to medication. These are all factors associated with overall disease risk reduction (54, 55, 84–88). Therefore, until findings from randomized trials confirm that HRT helps to prevent coronary heart disease, this treatment should not be routinely recommended solely for this purpose (54).

It has also been suggested that HRT has a beneficial effect on cognitive function and prevention of dementia (37). Although there are plausible biological mechanisms through which estrogen could improve cognition, every review of the subject emphasizes the fact that current information is incomplete, uncontrolled, and conflicting (37, 66, 89–92). Women who are prescribed estrogen replacement therapy may report improved cognitive function as a result of relief of vasomotor symptoms and insomnia rather than as an actual direct effect of estrogen on the brain (37). Of note, results of cognitive tests did not improve with estrogen replacement therapy in asymptomatic postmenopausal women (93). Therefore, it is premature to suggest that estrogen has any established beneficial effect on brain function.

Accumulating epidemiologic evidence seems to support the theory that HRT may decrease the risk for colorectal cancer (65, 94–96), but this evidence is inconsistent. Of the 21 epidemiologic studies pub-

lished to date, 9 reported a significant reduction in colorectal cancer (range, 20% to 60%), 9 reported no significant protective effect, and 3 found a small but nonsignificant increased risk for colorectal cancer (65, 94–97). Other unconfirmed benefits of HRT include prevention of stroke (98–100), treatment of incontinence (101), and improvement in appearance of facial wrinkles (102).

Risks of Hormone Replacement Therapy

When estrogen is used without a progestin, risk for endometrial adenomatous hyperplasia, a precursor of endometrial cancer, increases significantly (13, 16, 103). Conversely, risk for endometrial adenomatous hyperplasia does not increase significantly over an average follow-up of 3 years in women who are prescribed the appropriate dose of progestin (**Table 3**) compared with those who receive placebo (12, 13, 16). Therefore, all patients with a uterus require both estrogen and progestin for HRT.

Other risks that have been confirmed in randomized, controlled trials include a threefold increase in venous thromboembolic events. In healthy women, the absolute numbers of extra cases of deep venous thrombosis and pulmonary embolism attributed to HRT seem to be only about 1 in 5000 users per year and 1 in 20 000 users per year, respectively (17, 18, 43); therefore, the absolute increase in risk is small. However, in the HERS population of older women with established coronary heart disease, the group using HRT had 1 extra venous thromboembolic event per 250 users per year compared with those taking placebo; the cumulative risk over 4 years was therefore 1 extra venous thromboembolic event per 62 women (44). Although the absolute effect of HRT on risk for venous thromboembolic events is extremely small in healthy women, the excess incidence of such events in older women with coronary heart disease is approximately two orders of magnitude greater.

Symptomatic gallbladder disease also increased by approximately 40% in the HERS population of older women with coronary heart disease who were using HRT (oral conjugated equine estrogen and MPA); of this 40%, 89% required gallbladder surgery (44). The 40% increase in risk translates to 1 extra case of cholecystitis per 250 users of HRT per year or 1 extra case per 62 women over 4 years (44). Although surgery was required for most women with cholecystitis, none of the events were fatal (44).

More than 50 studies, none of them randomized, have explored the relation between HRT and breast cancer (39). Despite continued uncertainty, three meta-analyses show and several consensus panels agree that no evidence suggests an increase in risk

for breast cancer when HRT is used for 5 years or less (13, 39–42). However, an increased risk for breast cancer of approximately 30% may be seen in women who have used HRT for more than 5 years (13, 39–42). The relation of HRT to histologic types of breast cancer is also uncertain. Although the results are not yet confirmed in randomized trials, one observational study of more than 37 000 women reported that HRT was associated most strongly with an increased risk for invasive breast cancer that had favorable histologic characteristics and, therefore, a more favorable prognosis (116).

Other risks of HRT that are supported by some evidence include significant increases in benign breast disease (117–120) and endometrial cancer (despite appropriate doses of progestin when women take HRT for more than 5 years) (121) and a possible decrease in sensitivity and specificity of screening mammography (122, 123). Confirmation of these risks awaits results from large randomized trials, such as the Women's Health Initiative Hormone Trial, a randomized, placebo-controlled trial designed to assess the risks and benefits of HRT in more than 27 000 women (124).

Alternative Therapies, Testosterone, and "Designer Estrogens"

The patient mentions that a coworker is taking "natural therapy" for menopause. She says she doesn't think "herbs are for her" but asks what you know about alternative medicine for relief of hot flashes. She also mentions that something she read in a magazine mentioned testosterone and "designer estrogens" as options for managing menopause.

What Alternative Therapies Do Women Use To Manage the Symptoms of Menopause?

The patient may wish to try soy protein products but should understand that her hot flashes will probably decrease by only about 45%, compared with the 80% to 90% reduction seen with standard estrogen replacement therapy (72). In addition, she may experience constipation, bloating, and nausea (72). To obtain an effective dose of soy protein, she would have to consume at least 40 g daily of a preparation that contained approximately 75 mg of phytoestrogens, usually labeled "total isoflavone content." For comparison, the typical western diet contains almost no soy protein, whereas in Japan, the average daily consumption of soy protein is approximately 56 g (125, 126). Genistein and daidzein are the isoflavones in soy protein, and the concentration of isoflavones per gram of soy protein varies among different preparations (127). The patient should be advised that pills containing concen-

Table 4. Estrogens Commonly Prescribed in the United States

Estrogens (Trade Name, Manufacturer)	Daily Dose*	Available Doses
		mg
Oral conjugated equine estrogen (Premarin, Wyeth-Ayerst)	0.625	0.3, 0.625,† 0.9, 1.25, 2.5
Oral micronized estradiol (Estrace, Mead Johnson; estradiol, Watson Laboratories)	1	0.5,† 1.0, 2.0
Transdermal 17 β -estradiol (Estraderm, Ciba-Geigy; Climara, Berlex)	0.05	0.05,† 0.1
Oral esterified estrogen (Estratab, Solvay; Menest, SmithKline Beecham)	0.625	0.3,† 0.625, 1.25, 2.5
Oral estropipate (Ogen, Abbott)	0.625	0.625,† 1.25, 2.5, 5.0
Oral synthetic conjugated estrogens (Cenestin, Duramed)	0.625	0.625, 0.9

* Usual starting dose for relief of menopausal symptoms (10, 21, 73, 104).

† Recommended dose for prevention of bone loss (76, 105).

trated isoflavones are not an equivalent substitute for soy protein. Another health benefit of soy protein is that an average daily intake of 47 g decreases LDL cholesterol levels by 12.9%, decreases triglyceride levels by 10.5%, and does not significantly change HDL cholesterol levels (128).

Alternative remedies for hot flashes are plentiful (129, 130), but only nutritional supplements that contain soy protein with phytoestrogens have been shown to diminish hot flashes when compared with placebo (72). Common food sources of phytoestrogens include soybeans, lentils, whole-grain cereals, flaxseed, and dried seaweed (127, 131). No randomized, placebo-controlled trials have established any efficacy of herbal remedies, homeopathic treatments, or acupuncture in the treatment of hot flashes (129, 130).

Do Testosterone or "Designer Estrogens" Have Any Role in the Treatment of This Patient?

Estrogen-androgen combinations do not reduce hot flash frequency more than estrogen alone (132); in addition, these combinations detrimentally decrease serum levels of HDL cholesterol (79). Therefore, the patient should not be prescribed an estrogen-androgen combination solely for treatment of hot flashes. Some evidence suggests that the estrogen-androgen combination of oral methyltestosterone and esterified estrogen may improve sexual sensation and desire, but such results must be confirmed in large randomized trials (133–136).

Selective estrogen-receptor modulators (SERMs), also known as "designer estrogens," are compounds that bind with high affinity to estrogen receptors and activate them, eliciting mixed agonist/antagonist activity depending on the tissues involved (137, 138). The ideal SERM would protect against coronary heart disease, osteoporosis, and cognitive decline and would decrease the incidence of breast,

endometrial, and colorectal cancer without increasing the risk for venous thromboembolic events and gallbladder disease or exacerbating menopausal symptoms. To date, no SERM is ideal; those that are currently available would actually increase the patient's hot flashes (137, 138).

Types of SERMs include the triphenylethylenes (tamoxifen, clomifene, toremifene, idoxifene, droloxifene), the benzothiophenes (raloxifene), and the pure antiestrogens (ICI 182 780 and ICI 164 384) (137, 138). The two most clinically tested SERMs in postmenopausal women are tamoxifen and raloxifene. In a large randomized trial, tamoxifen has been shown to significantly decrease the risk for breast cancer in high-risk women by 45% (139); in addition, it is well established that tamoxifen is effective in secondary prevention of breast cancer (140, 141). However, tamoxifen significantly increases the risk for venous thromboembolic disease and uterine cancer and has not been definitively shown to decrease osteoporosis or heart disease (139–141). In a randomized trial of more than 7000 white women with osteoporosis, raloxifene significantly decreased the incidence of breast cancer by 75% and the incidence of fractures by 50% without increasing endometrial cancer (142). Raloxifene significantly improved LDL cholesterol levels without increasing triglyceride levels; randomized trials are in progress to determine the effect of raloxifene on coronary heart disease (143, 144). It is not known whether tamoxifen or raloxifene has beneficial or deleterious effects on cognition. The FDA has approved the use of tamoxifen for primary prevention of breast cancer in high-risk women and for secondary prevention of breast cancer for up to 5 years. Raloxifene has been approved by the FDA for prevention of osteoporosis.

Prescribing Hormone Replacement Therapy

The patient calls you 1 week later and asks for a prescription for HRT.

Which Hormone Replacement Regimen Should You Prescribe?

Any of the estrogen medications in **Table 4** will effectively treat hot flashes (25, 26, 57, 59, 73). Estrogen must be taken every day; if it is taken only 25 days each month, hot flashes sometimes return in the estrogen-free days (9). Most women report that hot flashes decrease within days of beginning HRT; full effect of treatment is seen after 1 month (9). Intravaginal estrogen preparations are not relevant for the treatment of hot flashes and will not be reviewed for this case.

The patient will also require progestin because

she has a uterus (16, 106). Clinicians may prescribe cyclic regimens—10 to 14 days each month—or daily regimens (12, 106). The doses listed in **Table 3** offer adequate endometrial protection (16, 73, 82, 106, 107, 145). When choosing between cyclic and continuous progestin therapy, clinicians should consider the amount of time that has passed since menopause and patient preference concerning the bleeding-related side effects that may result. For instance, some women would rather have predictable withdrawal bleeding than wear daily pads for unpredictable spotting. Women who have recently experienced menopause have a higher risk for excessive, unpredictable bleeding while receiving continuous therapy and are therefore often offered cyclic therapy to start. Our patient should be encouraged to use a cyclic regimen that includes an estrogen and a progestin for at least the first 6 months of treatment. The patient should also use a diary to record occurrence of withdrawal bleeding. To facilitate adherence, she should begin therapy with the estrogen and progestin together on the first day of every month.

Most U.S. women are prescribed conjugated equine estrogen and MPA for HRT (**Table 5**) (146, 147), although no evidence shows that this regimen treats hot flashes more effectively than other regimens. To improve compliance, physicians may prefer to prescribe preparations that combine estrogen and progestin in one pill or patch. Combination preparations may also offer added safety by ensuring that adequate amounts of progestin are taken with the estrogen. The cost of the medication may be another consideration.

In general, compliance with HRT is poor, especially when therapy is prescribed for prevention of osteoporosis in older women rather than for treatment of hot flashes (148–152). Compliance may be improved by thorough patient counseling, use of continuous rather than cyclic therapy, use of therapy tailored to patient preferences, and careful management of side effects (152).

Do Any Hormone Replacement Regimens Have a More Favorable Effect on Lipid Levels?

As described earlier, long-term use of oral conjugated equine estrogen modestly improves HDL and LDL cholesterol levels but increases triglyceride levels (16). Although transdermal estrogens slightly improve or do not affect HDL and LDL cholesterol levels, they do not increase serum triglyceride levels (58, 62, 64). Therefore, if our patient's triglyceride level were greater than 3.39 mmol/L (300 mg/dL), transdermal estrogen plus a progestin would be recommended.

Progestins are added to HRT only to protect the uterus; they actually reduce some of estrogen's ben-

Table 5. Combination Therapies Commonly Prescribed in the United States

Combination Therapy (Trade Name, Manufacturer)	Daily Estrogen Dose, mg	Progestin Dosage
Oral conjugated equine estrogen and medroxyprogesterone acetate (Premphase, Wyeth-Ayerst; Prempro, Wyeth-Ayerst)	0.625	5 mg for 14 days/ 28-day cycle
	0.625	2.5 mg daily or 5.0 mg daily
Transdermal estradiol and norethin- drone acetate (Combipatch, Rhône-Poulenc Rorer)	0.05	0.14 mg or 0.25 mg daily

eficial effects on lipid levels (16, 34, 59, 77–82). Oral estrogen plus micronized progesterone (200 mg for 12 days per cycle) would have the best effect on serum levels of HDL and LDL cholesterol (16, 34, 59, 77–80, 82).

Management of Common Side Effects of Hormone Replacement Therapy

You call the patient's pharmacy with prescriptions for oral estrogen (to be taken daily) and progestin (to be taken on the first 14 days of each month). Your office nurse calls the patient 6 weeks later to ask about side effects. The patient reports that her hot flashes have greatly decreased, but she notices some breast tenderness. Her uterine bleeding occurred about 10 days after she began the progestin pill, and the amount of blood was less than in her past menses.

Are Any Side Effects More Common with Certain Hormone Replacement Regimens?

When addressing side effects of HRT, it is helpful to first determine whether the estrogen or the progestin is responsible. Common side effects of estrogen include nausea, headaches, and heavy bleeding (73, 153–155). Women differ greatly in their response to standard doses and varied estrogen formulations. Although breast tenderness is considered a side effect of estrogen replacement therapy, one recently published randomized trial of more than 800 women reported that conjugated equine estrogen without a progestin was not associated with breast tenderness when compared with placebo (156). In women who have been postmenopausal for several years and require both estrogen and progestin, prescribing half the estrogen dose for the first month can minimize breast tenderness. Transdermal estrogen is less likely than oral estrogen to cause headache and nausea and may improve compliance; in theory, transdermal estrogen may also confer a decreased risk for gallbladder disease

because it does not alter the composition of bile (150, 157–160). Changing from one oral estrogen to another is sometimes enough to decrease side effects of estrogen.

Common side effects of progestin include breast tenderness, irritability, depression, and headaches; if severe, these side effects will require changing regimens from cyclic to continuous dosing, decreasing the interval of progestin administration, or switching to a different progestin (73, 153–155, 161). If the patient feels fine until she begins taking cyclic MPA therapy, she may benefit by switching to continuous MPA therapy or by using MPA every 3 months at a dose of 10 mg for 14 days (162). Alternatively, she could be prescribed one of the oral or vaginal micronized progesterone formulations listed in **Table 3**. The vaginal preparation may be inconvenient but has the advantage of offering endometrial protection with minimal increase in progesterone blood levels (114, 115). Some physicians prefer to prescribe micronized progesterone instead of MPA because it is the natural progestin produced by the human ovary, does not affect the estrogenic increase of HDL cholesterol level, and reportedly causes less depression and irritability (16, 113). Women who are unable to tolerate a progestin may be given unopposed estrogen if they are informed of the significant increased risk for endometrial cancer and have endometrial biopsy annually or whenever uterine bleeding is present (10, 21).

To Minimize Side Effects, When Is Low-Dose Estrogen with and without Progestin an Option?

This patient's hot flashes are more effectively treated with the usual starting dose of estrogen (**Table 4**) rather than with low-dose estrogen regimens (163). However, for women who cannot tolerate the usual starting dose of estrogen, low doses (equivalent to 0.3 mg of conjugated equine estrogen), which decrease hot flashes more than placebo, may be used (163).

The use of low-dose estrogen is more relevant when estrogen is prescribed for the prevention of osteoporosis in older, asymptomatic postmenopausal women (163, 164). When given with adequate calcium supplementation, equine estrogen (0.3 mg/d) and esterified estrogen (0.3 mg/d) significantly prevented bone loss with minimal side effects when compared with placebo but were not as effective as estrogen doses equivalent to or greater than 0.625 mg of equine estrogen (76, 165, 166). Therefore, when women cannot tolerate the usual starting estrogen doses, low-dose estrogen is an alternative for prevention of osteoporosis.

Prescription of low-dose estrogen without a progestin for women with a uterus is problematic. Although unopposed low-dose estrogen (esterified es-

trogen, 0.3 mg/d, or conjugated equine estrogen, 0.3 mg/d) did not significantly increase endometrial hyperplasia more than placebo in several randomized trials (76, 165, 166), participants were followed for only 2 years (167). In a case-control study, women who reported using low-dose estrogen without a progestin for more than 8 years were nine times more likely to have endometrial cancer than non-users (167). Additional studies are necessary to confirm the long-term safety of unopposed low-dose estrogen.

How Long Should the Patient Try a Specific Regimen before Switching to Another Regimen because of Minor Adverse Effects?

For breast tenderness, a switch to another oral estrogen or transdermal estrogen is usually not recommended unless symptoms persist longer than 3 months. If the patient's hot flashes do not improve substantially after 3 months of therapy, the estrogen dose can be doubled, with gradual titration downward to the lowest estrogen dose necessary to treat the hot flashes adequately.

When and How Should You Evaluate Vaginal Bleeding in a Patient Receiving Hormone Replacement Therapy?

When taking HRT with a cyclic progestin, more than 95% of women will have monthly withdrawal bleeding (168). Normal withdrawal bleeding begins after day 6 when the progestin is given on days 1 to 14 of the month (21). If the withdrawal bleeding occurs before day 6 or is unusually heavy and prolonged, outpatient endometrial biopsy should be considered (21, 169). One of the most important elements in both the initial and follow-up visits is stressing that the patient call the physician when abnormal uterine bleeding occurs.

When continuous MPA therapy, oral micronized progesterone, or norethindrone is prescribed, more than 75% of women will have uterine bleeding during the first year; approximately 10% to 15% of women continue to have some bleeding after 12 months (112, 168, 170, 171). Increasing the progestin dose usually decreases or stops the spotting. Guidelines recommend endometrial evaluation if bleeding continues for more than 6 months (21, 172); however, some physicians wait to perform a biopsy until spotting has continued for more than 9 months because benign spotting is common in the first year of therapy. In one review of the medical records of women who used cyclic or continuous HRT for more than 2 years, 14% of women receiving the cyclic regimen had endometrial biopsy for unexpected bleeding per year, compared with 10% of women receiving continuous progestin (173).

Therefore, more than 10% of women receiving HRT may require endometrial biopsy each year.

Endovaginal ultrasonography is also used in the evaluation of abnormal uterine bleeding after HRT (174–181). When the endometrial thickness is less than 5 mm, endometrial disease is highly unlikely and endometrial biopsy is not necessary (176, 180). The drawback of endovaginal ultrasonography is that the endometrial thickness will be at least 5 mm in 23% to 53% of women receiving HRT; of this percentage, less than 4% will actually have abnormal findings on biopsy (176, 180). Therefore, endovaginal ultrasonography is not a practical screening procedure because up to 50% of the women screened would still have to undergo endometrial biopsy (176).

Patient Follow-up

The patient plans to stay on HRT for the short term but remains uncertain about whether she wishes to take it indefinitely. She wants to learn more to help her decide how long she should continue. She asks when she should see you next.

When Should You Next See the Patient for a Routine Visit?

It can be useful to schedule a brief follow-up visit about 2 to 3 months after the patient begins HRT to discuss symptom relief, side effects, and patterns of withdrawal bleeding. Some physicians may prefer to handle patient questions and medication adjustments over the telephone. Medication compliance has been shown to improve when a nurse telephones at 6 weeks and inquires about patient concerns (12). Medication adjustment and management of side effects do not usually require referral to a gynecologist. The most common reason for gynecologic referral is abnormal uterine bleeding that requires endometrial evaluation.

For routine follow-up, the patient should schedule annual visits that include a medical history, blood pressure measurement, breast and pelvic examination, and screening mammography (11). If the initial Papanicolaou smear, which is done before initiation of HRT, is negative for malignancy, screening for cervical cancer with Papanicolaou smears should be continued as indicated for the individual patient (11).

Should You Encourage Long-Term Use of Hormone Replacement Therapy?

The one accepted benefit of long-term use of HRT is prevention and management of osteoporosis (75). If physicians prescribe HRT to achieve unproved benefits, they are encouraged to document

in the medical record that the patient has been informed of the established and unproved benefits and risks of the treatment.

Where Can Physicians Refer Patients for Educational Materials on Menopause and Osteoporosis?

Lists of organizations offering educational materials on menopause and osteoporosis for health professionals and patients can be obtained from the National Women's Health Information Center through their Web site (<http://www.4woman.org>) or by telephone (800-994-9662).

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