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Current issues in menopausal hormone replacement therapy

ABSTRACT: For most menopausal women, the benefits of hormone replacement therapy outweigh the risks, despite the fears aroused by the unproven link to breast cancer. If the goal is solely to relieve menopausal symptoms, the treatment duration is generally 2 to 3 years and then gradually tapered off. If the goal is to provide cardiac protection and prevent osteoporosis, long-term, possibly lifetime, treatment is needed.

KEY POINTS:

Women who have had a hysterectomy can take estrogen alone. However, if the uterus is present, an estrogen-only regimen can lead to endometrial hyperplasia (and an increased risk of uterine cancer). Therefore, most women need combined progestin-estrogen replacement therapy.

The main contraindication to hormone replacement therapy has been a history of breast cancer. However, many investigators are beginning to question this assumption.

The onset of menopause is an excellent time for the internist to assess a woman's overall health and her need for health maintenance measures.

An endometrial biopsy is indicated for women who have received estrogen but not progestin (ie, "unopposed" estrogen replacement therapy). It is also indicated for any menopausal woman not receiving hormone replacement therapy who has any bleeding more than 6 months after natural menses have ceased or who is receiving hormone replacement therapy and who has bleeding that is off schedule.

Menopause is not a disease, but it may cause "dis-ease" in some women and may also increase the risk of osteoporosis and cardiovascular disease. Like menstruation, pregnancy, and lactation, it is a time of hormonal change, when medical assessment, education, and assistance may improve the outcome.

In the next two decades, nearly 40 million American women will go through menopause. Each will experience menopause differently, and each needs to be involved in decisions regarding her own health care. By increasing a woman's awareness and knowledge of the important medical issues surrounding menopause, the physician makes it more likely that she will adhere to an individualized health maintenance program.

For many women, the program will include hormone replacement therapy (HRT). The benefits of HRT outweigh the risks for most menopausal women, but withdrawal bleeding (a nuisance) and misinformation, particularly surrounding the risk of breast cancer, prevent many women from receiving it.

THE ARGUMENT IN FAVOR OF HORMONE REPLACEMENT THERAPY

After menopause, the ovaries no longer secrete estradiol because follicular development has ceased; however, the ovarian stroma usually continues to produce some androgens. Nonovarian production of estrogen (primarily from androstenedione conversion to estrone in peripheral fat tissue) and constitutional and genetic factors account for

the differing effects of menopause in individual women.

Hormone replacement therapy relieves the vasomotor symptoms of menopause and makes patients feel better. More important in the long term, however, is that these drugs decrease the risk of cardiovascular disease and osteoporosis. The most-feared side effect — an increased risk of breast cancer — has not been convincingly substantiated.

Menopause and the cardiovascular system

The risk of a 50-year-old white woman dying of cardiovascular disease is 10 times greater than of her combined risk of dying as a result of a hip fracture or breast cancer, and African American women have at least as great a risk. Because cardiovascular disease is the leading cause of death in older women, strategies to reduce cardiovascular morbidity and mortality need to be addressed as vigorously in women as in men. Surgical menopause and premature menopause without estrogen replacement are significant risk factors for coronary artery disease, as are tobacco use, diabetes mellitus, hypertension, hyperlipidemia (including hypertriglyceridemia), family history, and advancing age. Likewise, natural menopause may be a risk factor for coronary artery disease.

Recent epidemiologic studies strongly suggest that estrogen replacement therapy significantly reduces the incidence of cardiovascular death, and that most older women, particularly those with atherosclerotic heart disease or at high risk for it, should be considered for estrogen replacement therapy on this basis alone.[1] A current multicenter randomized trial known as the HERS (Heart and Estrogen-Progestin Replacement Study) is examining whether HRT can prevent cardiovascular events in women with existing heart disease.

Favorable effect on lipids. Oral conjugated estrogens decrease total cholesterol and LDL-cholesterol and increase HDL-cholesterol levels. Transdermal estradiol decreases both total cholesterol and LDL-cholesterol and, unlike oral estrogen in some predisposed women, does not increase triglycerides. (Elevated triglyceride levels are usually inversely related with HDL-cholesterol levels, and are an established risk factor for coronary artery disease in women.)

The Postmenopausal Estrogen/Progestin Intervention Trial (PEPI) demonstrated that HRT significantly lowered LDL-cholesterol levels even with the addition of medroxyprogesterone acetate (MPA) or micronized progesterone.[2] The estrogen-only regimen had the most favorable effect on HDL-cholesterol; however, a high rate of endometrial hyperplasia (10% per year) makes this regimen unacceptable for women with a uterus. All four regimens lowered LDL-cholesterol and fibrinogen levels, and none of them increased blood pressure or had detectable effects on insulin levels after challenge.

These favorable lipid changes are only a small part of the cardiovascular benefit of HRT. Estradiol relaxes smooth muscle and has a direct beneficial effect on vessel-wall physiology and endothelial function. Low doses of conjugated estrogens do not increase coagulation, although oral contraceptive doses of synthetic estrogen do. Transdermal estrogen preparations do not increase renin substrate, and HRT does not increase blood pressure.

Estrogen replacement and the breast

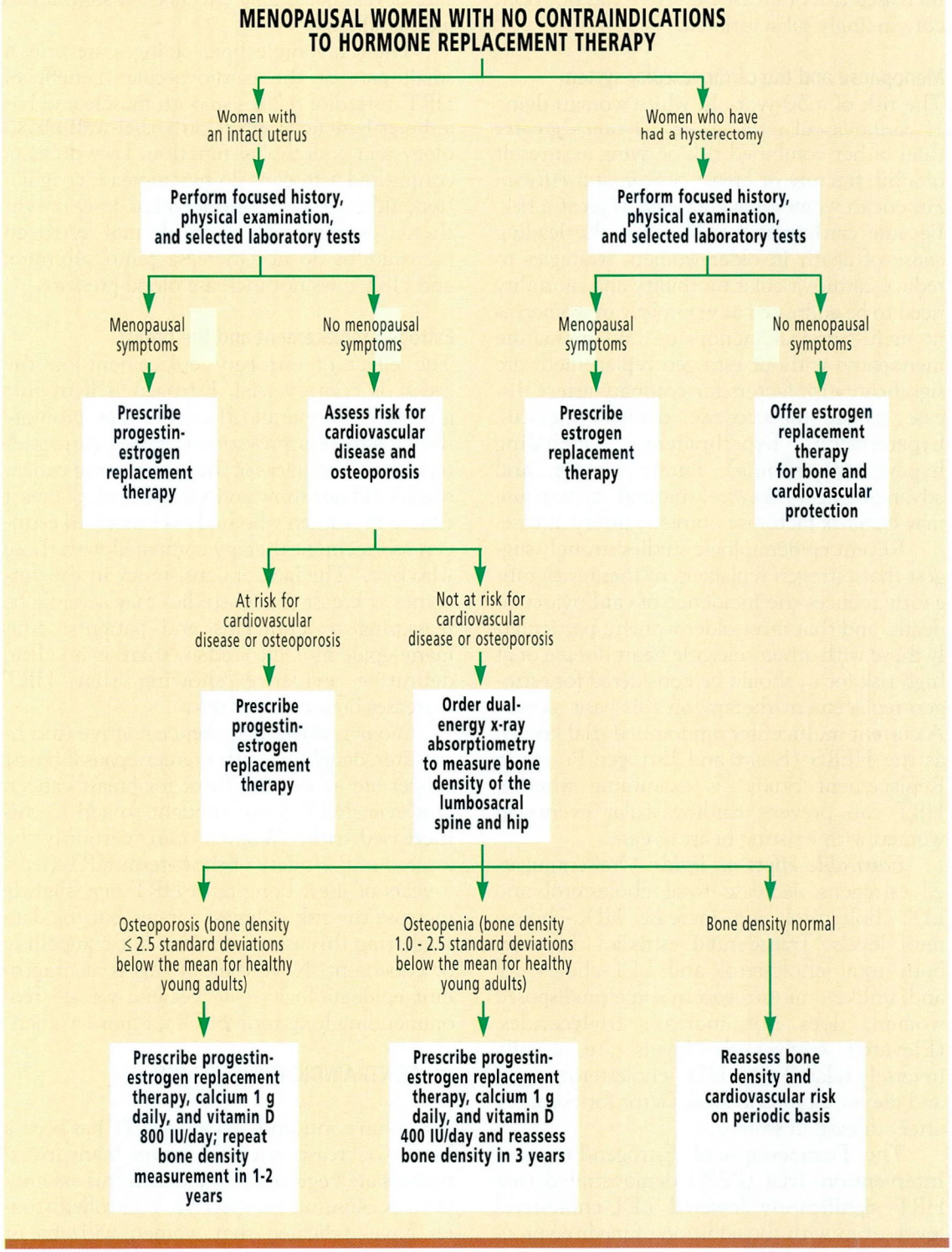
The effect of estrogen replacement on the breast is controversial. Estrogen is a trophic growth hormone and therefore may promote the growth of a pre-existing breast cancer. A recent meta-analysis of the major breast cancer studies did not show an increased risk of breast cancer in women who had ever received estrogen replacement therapy compared with those who had.[3] The lack of consistency in the outcomes of breast cancer studies may actually be reassuring to clinicians and patients: after many epidemiologic studies, there is no clear, definitive evidence showing that HRT increases breast cancer risk.[4]

Women with a first-degree relative (mother, sister, daughter) with premenopausal breast cancer are at increased risk for breast cancer. However, HRT is not thought to add to this increased risk. Women can certainly be assured of the safety of short-term HRT (ie, < 5 years of use). Long-term HRT may slightly increase the risk of breast cancer, but the data suggesting this association are not compelling or consistent. Nevertheless, this is an important epidemiologic issue because we are recommending long-term HRT for more women.

CONTRAINDICATIONS TO HRT

The main contraindication to HRT has been a history of breast cancer. However, many investigators are beginning to question this assumption, because no prospective, controlled studies have indicated that women with breast

FIGURE 1



An algorithm can help guide how to institute hormone replacement therapy, but treatment plans must be tailored for the individual woman.

cancer do any worse (or better) while receiving postmenopausal HRT. Other contraindications include undiagnosed genital bleeding, pregnancy, uterine cancer that has not been cured with surgical treatment, and the very rare conditions of benign metastasizing leiomyomata and lymphangioleiomatosis. Because HRT appears to increase the risk of cholelithiasis and subsequent cholecystectomy, conditions such as liver disease and cholelithiasis call for closer monitoring during HRT, as do seizures, uterine fibroids, and migraine headaches.

Women who could not use oral contraceptives because of diabetes, hypertension, hyperlipidemia, or myocardial infarction are excellent candidates for HRT, because the doses are lower and different types of estrogen are used.

HORMONE REPLACEMENT THERAPY: GOALS AND REGIMENS

An algorithm (**FIGURE 1**) can help guide how to institute HRT, but treatment plans must be tailored for the individual woman. The goal of HRT is not to normalize the folocle stimulating hormone value, but rather to use the minimum effective dosage to suppress vasomotor reactions, treat urogenital atrophy, prevent trabecular and cortical bone loss, and reduce cardiac risk.

Women who have had a hysterectomy can take estrogen alone. However, if the uterus is present, an estrogen-only regimen can lead to endometrial hyperplasia (and an increased risk of uterine cancer). Therefore, most women need combined progestin-estrogen replacement therapy.

Women practicing contraception before menopause should continue to do so for 1 year, as HRT does not provide enough hormones to prevent an occasional ovulation that may occur during the year after menses cease.

Estrogens

Conjugated equine estrogens. Of the oral estrogen preparations (**TABLE 1**), the conjugated-estrogen preparation (Premarin), a complex blend of multiple estrogens, has been available the longest and consequently has been studied most, primarily with regard to cardiac protection. It is therefore the preferred estrogen preparation for this indication.

Esterified estrogen preparations (Estratab, Menest) principally contain estrone and equilin sulfate and may be cost-effective alternatives for treating vasomotor symptoms, although they are not biochemical equivalents to the conjugated-estrogen preparation. Their dosage is the same as for conjugated estrogen.

TABLE 1

ORAL ESTROGEN PREPARATIONS

DRUG	BRAND NAME	TABLET STRENGTHS, mg
Conjugated equine estrogen	Premarin	0.3, 0.625, 0.9, 1.25, 2.5
Esterified estrogen	Estratab	0.625, 1.25, 2.5
	Menest	0.3, 0.625, 1.25, 2.5
Micronized estradiol	Estrace	0.5, 1.0, 2.0
Estrone	Ogen	6.25, 1.25, 2.5
	Ortho-Est	6.25, 1.25

Estradiol is the principal estrogen secreted by the premenopausal ovary. Given orally, micronized 17ß-estradiol (Estrace) is conjugated and metabolized by the liver to estrone. It increases sex-binding globulin protein levels and may be advantageous for women with skin and hair problems related to androgen excess. Oral estradiol is rapidly absorbed and has a short half-life. Therefore, the total daily dose may need to be split in a twice-a-day regimen.

Estropipate (estrone). Two formulations (Ogen, Ortho-Est) contain purified estropipate without any equine estrogen. Physiologically, these formulations are slightly weaker than conjugated or esterified estrogens at comparable doses because they contain only estropipate. These weaker formulations may be advantageous in women prone to mastalgia. However, for adequate osteoporosis prophylaxis, calcium supplements or higher doses of estropipate or both may be needed.

Estradiol patch. In theory, a low-dose transdermal estradiol patch mimics ovarian estradiol secretion and may be preferable to an oral preparation for women who have nausea, worsening migraine headaches, or hypertension (a rare occurrence) while taking an oral formulation or who have a history of deep venous thrombosis or thromboembolism. By avoiding enterohepatic metabolism, transdermal estradiol does not increase hepatic coagulation proteins. A remote history of a deep venous threinbesis is not a contraindication to estrogen replacement therapy; however, one should avoid high oral doses of estrogen.

The 0.05-mg transdermal 17ß-estradiol patch (Estraderm) is comparable in strength to

TABLE 2

TRANSDERMAL ESTRADIOL PATCHES

BRAND NAME	PATCH STRENGTHS, mg/day	PATCH CHANGE INTERVAL
Estraderm (reservoir system)	0.05, 0.1	Every $3^1/_2$ days
Climara (newer matrix system)	0.05, 0.1	Weekly
Vivelle (newer matrix system)	0.0375, 0.05, 0.075, 0.1	Every $3^1/_2$ days

TABLE 3

SIDE EFFECTS OF HORMONE REPLACEMENT

ESTROGEN	
Side effects	Comments
Induction of breast cancer	Not conclusively proved
Induction of endometrial cancer	When used without progestin
Gallbladder disease	
Cardiovascular disease	In high doses, in men
Hypercalcemia	In patients with breast cancer and bone metastases
Fluid retention	
Abnormal uterine bleeding, mastodynia	
Uterine fibroids	In preexisting uterine leiomyomata
Breast tenderness, enlargement	
Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice	
Chloasma or melasma	
Steepening of corneal curvature, intolerance of contact lenses	
Headache, migraine, dizziness, mental depression	
Increase or decrease in weight	With oral contraceptives
Reduced carbohydrate tolerance	With oral contraceptives
Aggravation of porphyria	With oral contraceptives
Change in libido	
PROGESTIN	
Side effects	Comments
Symptoms of premenstrual syndrome	
Withdrawal bleeding	Expected during cycled therapy
Thromboembolism	In conjuntion with estrogens
Decreased glucose tolerance	
Patchy alopecia, skin rash, galactorrhea	

conjugated estrogen 0.625 mg or oral estradiol 1 mg daily. This patch, which needs to be applied to the abdomen or buttocks every $3^1/_2$ days (**TABLE 2**), contains only an adhesive and 17ß-estradiol and may cause skin irritation in some patients.

Climara, a newer estradiol patch available in two strengths (0.05 and 0.10 mg), has the advantage of being changed only once weekly. Vivelle, the newest formulation, has the advantage of four dosage strengths (0.0375, 0.05, 0.075, and 0.1 mg); the patch must be changed twice a week.

Side effects (**TABLE 3**) occur much less frequently during HRT than during oral contraceptive use, because the doses are lower. Nevertheless, the physician should be aware of them.

Dosage and monitoring. The lowest effective estrogen dosage for most menopausal women is 0.625 mg daily of conjugated equine estrogens or an equivalent. The estrogen dose can be increased if needed to control vasomotor symptoms, but should generally not be decreased to less than the recommended starting dose if preventing osteoporosis and heart disease is the treatment goal. However, women without vasomotor symptoms who cannot tolerate higher dosages of estrogen because of breast tenderness or fluid retention can receive a lower dose (eg, conjugated estrogens 0.3 mg or micronized estradiol 0.5 mg).

The oral and transdermal routes of administration are preferred. Estrogen injections and pellets provide too high an estradiol level which then drops below therapeutic levels before the next dose. Vaginal preparations such as Estrace vaginal cream (2 g daily for 2 weeks, then 1 g, one to three times per week) are excellent options for women who still have mild residual genitourinary atrophy while taking standard doses of systemic estrogens. There may be some initial systemic absorption of vaginal estrogen through the thin, atrophic mucosa; however, once mucosal integrity is restored with local therapy, systemic absorption of estradiol is generally not a concern. Therefore, vaginal estrogen alone is an option for women who only need treatment of urogenital atrophy.

Younger women and women who have undergone surgical menopause may need at least twice the minimum estrogen dose to suppress vasomotor symptoms (eg, conjugated

Menopause: an opportunity for health assessment and intervention

The onset of menopause is an excellent time for a woman's principal physician — her internist — to reassess her overall health and her need for health maintenance measures. On the basis of a focused history and physical examination and selected diagnostic tests, one can perform an individualized risk assessment.

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination should focus on the five target areas affected by menopause: the cardiovascular system, the skeleton, the genitourinary system, the neuroendocrine system, and the integument.[1] In particular, one should ask about symptoms of estrogen deficiency and about factors related to personal risk (TABLE).

In the physical examination one should record the height, weight, and blood pressure to establish baseline values, and examine the skin, thyroid, breasts, cardiovascular system, abdomen, pelvis, and rectum. During the pelvic examination the physician should:

Obtain Papanicolaou smears of the exocervix and endocervix, using a spatula and cytobrush, to screen for cervical cancer.

Look for signs of pelvic relaxation (cystourethrocele, rectocele).

Palpate for pelvic masses. In general, a palpable postmenopausal ovary is abnormal.

Note any signs of genitourinary atrophy, including a thin, pale atrophic vaginal mucosa (diffuse or in patches), a stenotic introitus in severe cases, a urethral caruncle, and a small cervix with a stenotic cervical os. In severe cases the cervix may be flush with the vaginal wall.

LABORATORY EVALUATION

Total and high-density lipoprotein (HDL) cholesterol. If the total cholesterol concentration is elevated or the HDL-cholesterol concentration is low, a 12-hour fasting lipid profile (including triglycerides) is needed. Marked hypertriglyceridemia is an independent risk factor for coronary artery disease in women.

Follicle-stimulating hormone (FSH) and estradiol (E2) levels are usually not needed to diagnose the menopausal state, but can occasionally be helpful, such as when deciding whether to institute estrogen replacement therapy in a woman who has had a hysterectomy without oophorectomy.

Another situation in which measuring these hormone levels may be helpful is in a healthy, nonsmoking woman who continues to take oral contraceptives up through menopause, in whom it may be difficult to determine when menopause has occurred. In such women, the FSH level is usually measured on day 5 of the pill-free week (which would be Thursday if the pill pack is started on Sunday).

An assay-specific, second-generation FSH level greater than 20 IU/L and particularly 100 IU/L with an estradiol (E2) level less than 20 to 40 pg/mL usually confirms primary gonadal failure. Perimenopausal women may have similar values; therefore, the diagnosis of menopause is always retrospective.

A thyroid-stimulating hormone (TSH) measurement can help detect possible overreplacement in women receiving thyroxine, who may be at increased risk for bone loss. Such women can be clinically euthyroid but biochemically hyper-thyroid, as evidenced by a suppressed TSH level. In addition, any perimenopausal woman with nonspecific symptoms or a menstrual disorder or both should also have thyroid function tests, as symptoms of the perimenopause may overlap with symptoms of thyroid dysfunction.

A screening mammogram should be obtained yearly in women older than 50 years.

Bone densitometry with dual-energy x-ray absorptiometry (DXA) of the hip and spine, in healthy menopausal women, should generally be reserved for those in whom its results would affect the decision to institute HRT (FIGURE 1). Estrogen replacement is still the only approved drug therapy for preventing osteoporosis.[2]

OTHER HEALTH MAINTENANCE MEASURES

Counseling regarding seat belt use, immunizations, smoking cessation, diet, and exercise is recommended. Screening for colorectal cancer should also be done.

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TABLE

ASPECTS OF HEALTH ASSESSMENT AT ONSET OF MENOPAUSE

TARGET SYSTEMS:
- Cardiovascular
- Skeletal
- Genitourinary
- Neuroendocrine
- Integument

SYMPTOMS RELATED TO ESTROGEN DEFICIENCY:
- Hot flashes
- Sleep disturbance
- Mood and memory changes
- Skin and hair changes
- Urinary frequency or urgency
- Exacerbation of stress urinary incontinence
- Dyspareunia
- Pruritus of the vulva
- Sexual dysfunction

FACTORS RELATED TO PERSONAL RISK:
- Gynecologic and sexual history (including HIV risk factors)
- Tobacco, alcohol, drug use
- Exercise habits
- Diet
  - Percentage of calories from fat
  - Calcium intake
  - Caffeine intake
  - Total servings of fruit and vegetables

TABLE 4

MEDROXYPROGESTERONE ACETATE (MPA) REGIMENS

BRAND NAME	DOSAGE
Provera	MPA 5-10 mg on days 1-12, or 2.5 mg daily
Cycrin	MPA 5-10 mg on days 1-12, or 2.5 mg daily
Amen	MPA 5 or 10 mg on days 1-12 (one half or one scored 10-mg tablet)
Prempro	MPA 2.5 mg daily; conjugated equine estrogens 0.625 mg daily
Premphase	MPA 5 mg/day for 14 days; conjugated equine estrogens 0.625 mg daily (28-day pill pack)

estrogen 1.25 mg daily, transdermal estradiol 0.10 mg, or oral estradiol 1 mg twice a day). Estratest (esterified estrogen 0.625 mg and methyltestosterone 2.5 mg or 1.25 mg) is particularly indicated for selected young, surgically menopausal women, as bilateral oophorectomy removes almost half of the circulating testosterone, potentially decreasing their sense of well-being and libido. Oral androgens are associated with abnormal liver enzyme tests and, in higher doses, liver damage; therefore, periodic monitoring of liver function is recommended for women who take them. Rarely, a woman taking the estrogen-methyltestosterone preparation may experience acne, hirsutism, or other virilizing effects.

It can be clinically helpful to measure blood estradiol levels during treatment with any of the oral or transdermal preparations. The minimum target level is approximately 60 pg/mL. Measuring the estradiol level is particularly helpful in women who continue to experience vasomotor symptoms or mastalgia, or who are receiving estrogen replacement because of established osteoporosis. Follow-up intervals should be individualized, but at least every year.

Progestins

A woman taking estrogen who has a uterus (and therefore an endometrial lining) also needs progestin to prevent endometrial hyperplasia associated with estrogen therapy.[5] In general, progestins are not recommended after hysterectomy unless residual endometriosis is a concern. Progestins may have androgenic effects, depending on the agent, dose, and route of administration. In combination with estrogen, progestins can cause premenstrual syndrome-like symptoms, the most common limiting side effect. Current epidemiologic studies do not support adding progestins to estrogen to protect the bones or breasts.

The progestin can either be taken for the first 12 days of every calendar month (ie, "cycled") or every day (ie, "continuously").

Cycled regimens. The standard progestin dosage is medroxyprogesterone acetate (MPA — Provera, Cycrin, Amen) 5 to 10 mg on days 1 through 12 of every calendar month (**TABLE 4**). Other regimens of cycling the progestin for 14 days every third month (four times per year total) are being investigated and look promising, but are not yet standard.[6] Only Provera and Cycrin are available in 2.5- and 5-mg tablets; however, Amen is a scored 10-mg tablet that can be broken in two and may be a cost-effective alternative. A combination preparation is now available (Premphase; conjugated estrogens 0.625 mg in a 28-day pill pack with 14 days of added MPA 5 mg) and may be slightly less expensive than both drugs ordered separately.

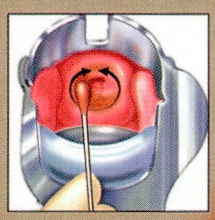
During cycled treatment, mild to moderate uterine bleeding usually occurs midmonth, usually between days 10 and 15. Some women object to the resumption of monthly uterine bleeding during cycled therapy; others accept the inconvenience.[7]

If the cervical os is not occluded or stenosed, the absence of withdrawal bleeding indicates there is no endometrial lining to be shed. Any abnormal bleeding needs to be investigated. Bleeding is generally considered to be normal if it occurs on or after the 10th of the calendar month, but a recent study challenged this assumption.[8]

Cycling the estrogen alone, previously a common practice, does not protect against endometrial hyperplasia and is not routinely advocated when cardiovascular and osteoporosis prevention are the treatment goals, but it might decrease the incidence of mastalgia in some women.

Continuous regimens. A continuous

FIGURE 2



HOW TO PERFORM AN OUTPATIENT ENDOMETRIAL BIOPSY

1. Perform a bimanual examination to determine uterine size and position. Note any signs of pelvic inflammatory disease, a contraindication to biopsy. Using a bivalve vaginal speculum, examine the cervix and evaluate for an open cervical os. Using a povidone/iodine solution, cleanse the cervix and surrounding tissue.

2. Insert a 3.1 mm-flexible Pipelle until it reaches the tip of the fundus, usually a depth of about 6 to 7 cm.

3. While leaving the tip of the Pipelle in position, withdraw the plunger to its extended position, creating negative pressure to suction endometrial tissue into the Pipelle through the curet hole.

4. Leaving the plunger fully extended, gently rotate the Pipelle, which moves the curet from side to side, suctioning tissue samples from various locations. Do not allow the curet hole to emerge from the uterus, or the negative pressure will be lost. Continue the rotating maneuver while gradually pulling the Pipelle back along the uterine cavity.

Withdraw the Pipelle completely and insert the tip into a specimen bottle containing preservative solution; push the plunger to the return position to fully expel the biopsy tissue. The specimen is now ready for the pathologist.

If a copious amount of tissue is obtained, it is necessary to use another Pipelle and continue to curet the endometrium, as it is difficult to determine how much of the sample is blood and how much is endometrial tissue. For women with thick endometrium, two or three Pipelles may be required.

If a minimal amount of tissue is obtained, it usually means there is little endometrium. However, because technical difficulties may be the reason, it is necessary to pass another Pipelle to complete the procedure adequately.

regimen of estrogen and MPA 2.5 mg daily can be offered to women who object to monthly menses; however, there is much less published information regarding it. This may be a good option for older women who have not had a menstrual period in several years and who want to avoid regular, cyclic withdrawal bleeding. The advantage of the continuous, combined regimen is that it can produce amenorrhea within 6 to 9 months, but only in 50% to 70% of women.

Because this is not a cycled program, it is impossible to tell whether uterine bleeding after the first 6 months is normal or not. Therefore, one of the disadvantages of this regimen is the potential for irregular bleeding, which may lead to the need for outpatient endometrial biopsy. The American College of Physicians recommends an endometrial biopsy be done if there is any bleeding that is prolonged (more than 10 days) or heavy (heavier than the woman's previous menses) during this continuous, combined HRT or any bleeding that persists beyond 6 months of instituting such a regimen.[1]

The vast majority of postmenopausal women receiving HRT can be successfully cared for by their primary care physicians.

The progestin dose in the continuous, combined daily regimen is generally half of a cycled dose, ie, 2.5 mg of MPA daily (Prempro, a new combination menopausal pill, contains this amount of MPA and conjugated estrogen 0.625 mg). Giving 5 mg of MPA daily for the first few months and then lowering the dose to 2.5 mg may induce amenorrhea sooner.

Alternatives to MPA are norethindrone (available as a low-dose progestin-only birth control pill called Micronor or Nor QD) and micronized progesterone. The micronized progesterone used in the PEPI trial is generally not commercially available but can be prepared by a few pharmacies across the country. However, such preparations, not being standardized, may differ in bioavailability and subsequent endometrial protection. Transdermal norethindrone is currently under investigation (in combination with transdermal estrogen) and may hold promise as a combination sequential menopause patch causing fewer undesirable metabolic and psychological side effects.

■ ENDOMETRIAL BIOPSY

Indications for biopsy

An endometrial biopsy is indicated for women who have received estrogen but not progestin (ie, unopposed estrogen replacement therapy). It is also indicated for any menopausal woman not receiving HRT who has any bleeding more than 6 months after natural menses have ceased, or who is receiving HRT and has bleeding that is off schedule. Abnormal fluid collections in the endometrial canal need to be investigated with biopsy regardless of the menstrual bleeding history. A normal bleeding pattern that occurs at the expected time, ie, after the 10th of the calendar month, does not need to be routinely investigated with endometrial biopsy.

Contraindications to outpatient endometrial biopsies include pregnancy and any cervical, uterine, or pelvic infections. Stenosis of the internal or external cervical os is a relative contraindication, because dilating a stenotic os is usually too painful without anesthesia.

Biopsy techniques

Most women, particularly parous women without cervical stenosis or atrophy, tolerate the outpatient plastic cannula endometrial biopsy without much discomfort or need for analgesia (**FIGURE 2**). The cervix is first swabbed with povidone iodine; then a 3.1-mm flexible plastic Pipelle (or a 3.0-mm Z-sampler or Gyno-sampler catheter) is inserted into the endometrial cavity under aseptic technique. The catheter serves to both curet and aspirate the endometrial tissue. This method is much easier than the Vabra technique, and much better tolerated by patients. Primary care physicians caring for menopausal women should consider becoming proficient with this outpatient technique.

When to refer

Women should be referred to a gynecologist for surgical dilation and curettage and possible hysteroscopy if abnormal endometrial tissue is detected by the endometrial sampling. In addition, women who continue to have abnormal

bleeding in the face of normal Pipelle biopsy findings or in whom a Pipelle biopsy was unsuccessful should also be referred to a gynecologist. However, the vast majority of postmenopausal women receiving HRT can be successfully cared for by their primary care physicians.

Postmenopausal sonographic endometrial thicknesses of 5 mm or less suggest the endometrium is normal.[9] Although sonographic assessment of the endometrium alone is currently investigational and cannot be recommended as the only means to evaluate abnormal bleeding, it can provide some additional information.

THE PERIMENOPAUSAL WOMAN

Some women begin to have menopausal vasomotor symptoms while they are still regularly menstruating. If these symptoms cannot be controlled with environmental changes, avoidance of caffeine, and vitamin E 400 IU daily, one can prescribe estrogen in very low doses (ie, Premarin 0.3 mg every day or Vivelle 0.0375-mg patch twice a week). Alternatively, a nonsmoking, healthy perimenopausal woman who takes oral contraceptives can continue taking them, which will suppress vasomotor symptoms. Oral contraceptives are a good option for the symptomatic perimenopausal woman with oligomenorrhea, as they control the menstrual cycle, conception, and vasomotor symptoms. However, even the newer low-dose oral contraceptives contain four times the amount of hormone needed for postmenopausal replacement purposes.

HOW LONG TO TREAT?

If the goal of HRT is solely to relieve menopausal symptoms, the treatment duration is generally 2 to 3 years and then gradually tapered off. If the goal is to provide cardiac protection and prevent osteoporosis, long-term, possibly lifetime, treatment is needed. ■

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