Hormone replacement therapy: The right choice for your patient?

Mrs JC, a 55-year-old woman, arrives for her annual gynecologic exam. Besides wanting to update her Pap smear and mammogram, she would like to discuss estrogen replacement. She reached menopause at age 52 and began taking estrogen for hot flashes and night sweats. Her cholesterol levels have been elevated since menopause. She read that estrogen can lower cholesterol levels and therefore may possibly reduce her risk for heart disease.

She did very well with estrogen. Her hot flashes and night sweats disappeared and she felt great. However, after hearing news reports about the danger of estrogen, she discontinued the hormone pills a few months ago. She is now feeling poorly with hot flashes, night sweats, vaginal dryness, and occasional stress incontinence. She has many questions and concerns and eagerly seeks your advice about what to do.

Medical history
• Borderline hypertension
• Hyperlipidemia
• Obesity: body-mass index of 32

Family history
• Mother, age 75, has hyperlipidemia, hypertension, myocardial infarction (MI) at age 60, and osteoporosis
• Father, died at age 55 of MI; had hypertension and diabetes
• Her grandparents also had history of stroke and heart disease, but she doesn’t know all the details about their health. She believes her maternal grandmother broke her hip when she was elderly.

Social history
• Married, 2 children, works as an attorney with the local government. Her job is fairly demanding
• Does not smoke, occasional alcohol consumption
• Does not exercise on a regular basis

Review of systems
Negative except for hot flashes, night sweats, vaginal dryness, and occasional stress incontinence.

Physical examination
• Alert female in no distress. Blood pressure, 145/90 mm Hg; weight, 165 lbs; pulse, 82; respiration, 18; temperature, 98.1°F
• HEENT exam, normal
• Neck, heart, lung, abdomen, breast, and pelvic exams are all normal except for mild atrophic changes of the vaginal and genital tracts.

You perform the gynecologic exam and order a mammogram. Mrs JC has not been seen for 2 years. Her lipid profile done 2 years ago was elevated, but Mrs JC did not repeat the tests as requested. You explain that you would like to further define her risk factors and would like to order a few tests. Making a well-informed decision on hormone replacement therapy...
(HRT) is complex and requires more information and adequate time for a full discussion. You would like to see her after her laboratory tests and will reserve time to address her concerns and questions.

**Laboratory tests**

Complete blood count, normal  
Cholesterol, 250 mg/dL (LDL, 130 mg/dL; HDL, 45 mg/dL)  
Triglyceride, 220 mg/dL  
Electrolytes, blood urea nitrogen/creatinine (BUN/Cr) ratio, normal; glucose, 85 mg/dL  

Mrs JC has many symptoms of menopause:  
• Vasomotor instability  
• Urogenital symptoms  
She also has risk factors:  
• Cardiac: hypertension, hyperlipidemia, obesity  
• Osteoporosis: family history, sedentary lifestyle  

Before addressing Mrs JC’s specific concerns, you review the findings of the Women’s Health Initiative (WHI) study, which probably prompted her concerns. You also have been asked to lead an upcoming geriatric grand round presentation on HRT, and you further prepare for both encounters by meeting with colleagues Dr Richard Pees, a gynecologist, and Dr Deborah Erickson, a urologist, to discuss practical applications of the WHI findings.

### Findings of the WHI

WHI, sponsored by the National Institute of Health, comprised 2 multicentered clinical trials to determine if conjugated equine estrogen (CEE) given alone for women who had a hysterectomy or in combination with progestin (MPA, medroxyprogesterone acetate) would reduce the risk of cardiovascular events. The study also assessed the long-term risks and benefits of postmenopausal hormone therapy in other chronic disease prevention.

Exclusion criteria for the study included competing risks with survival <3 years, prior breast cancer, low hematocrit or platelets, severe menopausal symptoms, alcoholism, mental illness, and dementia. In this study, 27,000 women aged 50 to 79 years (mean age, 63) were randomized to take hormone or placebo.

The combined CEE/MPA (Prempro) trial, with 16,000 women enrolled, was discontinued at 5.2 years, on July 2002. The unopposed CEE (Premarin) trial, with 11,000 women, was discontinued at 6.8 years, on February 2004. The study was stopped earlier than planned (2005) because of increased adverse events in the group taking hormone.

**TABLE 1** summarizes the absolute risks—number of events per 10,000 as compared with the control group—for both arms of the study. In the CEE/MPA arm, there were more cases per 10,000 of coronary heart disease (+7), breast cancer (+8), stroke (+8), and venous thromboembolic disease (VTE) including deep vein thrombosis/pulmonary embolism (DVT/PE) (+18). However, there were fewer cases per 10,000 of colorectal cancer (–6) and hip fracture (–5).

Recently published data on the unopposed estrogen arm showed an increase in stroke (+12) and VTE (+7). No significant increase was noted for coronary heart disease (CHD) (–5) or breast cancer (–7).
Dr Pees: The WHI data do seem to confuse the issue of when to use hormonal therapy. The answer to your question lies in knowing how the WHI risks were calculated.

The WHI authors described 2 confidence indexes (CI). The first was calculated as if looking at a single outcome variable, a nominal CI; the second, an adjusted CI, took into account multiple outcomes.

For the CEE/MPA arm, when the nominal CI is used, CHD and breast cancer risks barely reached clinical significance; colon cancer and fracture reduction reached clinical significance; DVT and strokes were also clinically significant using both CIs. When the adjusted CI is used, DVT/strokes, and to a lesser degree fracture reduction, retain clinical significance.

In the CEE-only arm (February 2004 report), DVT/strokes were the only variable that reached clinical significance. CHD/breast cancer/colorectal cancer did not reach clinical significance, and fracture reduction only a slight decrease in risk.

The WHI study introduced a new term, the Global Index, which had not been tested for validity or significance of assigning weights to various outcomes. Additionally, there were certain biases in the construct of the study. Included were 1200 individuals who had prior MI, revascularization procedures, stroke, DVT, and PE. Excluded were those with severe menopausal symptoms, prior fracture/low bone mineral density (BMD), and cognitive function deficits. Also, only 10% of the group was in the 50- to 54-year-old group; 25% were in the 70- to 79-year-old group. The dropout rate was fairly high: 42% in the CEE/MPA arm, and 38% placebo arm; only 25% of the CEE/MPA arm remained at the study termination. Unblinding occurred in 40% of the CEE/MPA arm and 5.4% in the placebo arm.

It is worth noting that CHD increased in the first year of the study but decreased in subsequent years. VTE/DVT and total fractures were the only 2 items that achieved true clinical significance. Total fracture reduction was 1.6 times greater than the increases in CHD and breast cancer; and the fact that breast cancers double every 300 days and are present for 7 to 8 years before they are detected with current diagnostic testing.

Despite the biases and limitations of the data presented by the WHI report, the study does add to our knowledge and it should be included in our discussion with patients when addressing HRT.
Dr Pees: The WHI data have altered the way in which I counsel patients. I still prescribe hormone therapy within the American College of Obstetricians and Gynecologists (ACOG) guidelines, and, after a very thorough discussion, reference the WHI data. This is to ensure that patients make informed decisions about continuing or starting hormone therapy. Following ACOG recommendations, I evaluate each patient’s risk profile. I start treatment with the lowest effective dose to relieve symptoms. I discuss the use of alternative treatments for menopausal symptoms and osteoporosis prevention, as well as evaluation and treatment for quality of life issues. Most importantly I encourage periodic re-evaluation for hormone use.

After the WHI study was terminated, the North American Menopause Society (NAMS) convened an expert Hormone Therapy Advisory Panel to examine the data and prepare a report. A position statement on the recommendations for clinical practice was released in September 2003. The expert panel reached consensus on the following areas:

- The primary indication for systemic hormone therapy is moderate and severe menopausal symptoms: Hot flashes, night sweats/insomnia, mood swings.
- When treating moderate and severe urogenital atrophy (vaginal dryness, dyspareunia, urinary frequency, and incontinence), local estrogen preparations are preferred.
- The primary indication for progestogen is endometrial protection for all women with an intact uterus using systemic estrogen therapy (ET).
- Hormone therapy should not be used for primary or secondary prevention of CHD.
- Breast cancer risk is increased with ET and, to a greater extent, with estrogen progestogen therapy (EPT) used beyond 5 years.
- There is definitive evidence for EPT efficacy in reducing the risk of fracture. However, other effective alternate forms of therapy are readily available. Because of potential risk associated with long-term use of EPT, the risks and benefits of each option should be discussed with the patient.
- EPT is not recommended for primary prevention of dementia.
- Hormone therapy should be limited to the shortest duration to achieve treatment goals, taking into consideration the impact on quality of life.
- Lower-than-standard doses of EPT and ET should be considered (including 0.3 mg conjugated estrogen, 0.25–0.5 mg oral micronized 17 β-estradiol and 0.025 mg 17 β-estradiol patches). However, the long-term risk-benefit ratio has not been demonstrated.
- Extended use of ET/EPT is acceptable if the woman feels the benefits of symptom relief outweigh the risks, an attempt to withdraw ET has failed, or to prevent osteoporotic fracture when alternative therapies are not appropriate or usable.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Possible tapering schedules for estrogen regimens</th>
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<tr>
<td>Current hormone regimen</td>
<td>CEE/MPA 0.625/2.5 mg daily</td>
</tr>
<tr>
<td>Month 1</td>
<td>CEE/MPA 0.625/2.5 mg qod (x 1 mo)</td>
</tr>
<tr>
<td>Month 2</td>
<td>CEE/MPA 0.3/1.5 mg daily (x 1 mo)</td>
</tr>
<tr>
<td>Month 3</td>
<td>CEE/MPA 0.3/1.5 mg qod (x 1 mo)</td>
</tr>
<tr>
<td>Month 4</td>
<td>CEE 0.3/1.5 mg 2/wk (x 1 mo)</td>
</tr>
<tr>
<td>Month 5</td>
<td>Estrogen patch 0.025/wk if needed</td>
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</tbody>
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CEE/MPA, conjugated equine estrogen/medroxyprogesterone acetate; qod, every other day

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>HRT dosing options</th>
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<tr>
<td>MEDICATION</td>
<td>DOSAGE</td>
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<tr>
<td>Conjugated estrogens (Premarin)</td>
<td>0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg</td>
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<tr>
<td>Estradiol (Estrace)</td>
<td>0.5 mg, 1 mg, 2 mg (scored tablets)</td>
</tr>
<tr>
<td>Estradiol patches (Climara/Vivelle)</td>
<td>0.025 mg/d, 0.0375, 0.05 mg/d</td>
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**Menopausal symptoms**

**Q:** If Mrs JC does not wish to take hormone, what advice can you give to minimize menopausal symptoms? Are herbal products safe?

**A:**

Dr. Leong: Because estrogen is the most effective treatment for menopausal symptoms, Mrs JC may yet consider taking it on a short-term basis, if her symptoms are debilitating. We should use the lowest dose required to control symptoms. She has already stopped her therapy, of course. But had she still been taking ET and told you she wished to discontinue it, you could have advised her that, often times, tapering estrogen over several months results in fewer symptoms than when quitting “cold turkey” (TABLES 2 AND 3).

If Mrs JC is absolutely against taking estrogen, several other drugs have been shown to reduce hot flashes. The selective serotonin reuptake inhibitors (SSRIs) were effective in several randomized trials using venlafaxine (Effexor), paroxetine (Paxil), and, less effectively, fluoxetine (Prozac). Clonidine (Catapres) was effective at reducing hot flushes in some, but not all, clinical trials. Gabapentin (Neurontin) and megestrol acetate (Megace) are other possible choices.

Complementary and alternative therapies have been very popular among some postmenopausal women as they look for symptom relief. There are mixed data on soy compounds (phytoestrogen and isoflavone), with only 3 of 8 trials demonstrating a beneficial effect. Black cohosh showed modest benefits, but ginseng, dong quai, red clover, evening primrose oil, vitamin E, acupuncture, wild yam, and progesterone cream were ineffective. The main cautions with these products are that safety and efficacy are not well established and quality control of the products is often lacking.

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**Urinary tract symptoms**

**Q:** If the patient does not wish to go back on estrogen, what can be done about her urinary symptoms?

**A:**

Dr Erickson: Urinary problems most commonly associated with menopause are incontinence and recurrent urinary tract infections. Fortunately, both of these problems can be reduced with topical estrogen, which has minimal systemic absorption (TABLE 4). For example, a recent study of intravaginal estradiol (25 µg) vs placebo showed that the estrogen-treated group had significant reduction in symptoms (including dysuria, frequent voiding, and incontinence) and urodynamic findings, but no increase in serum estradiol levels or endometrial growth. Thus, a topical estrogen could provide the urologic benefits without the risks of systemic treatment. If she wants to avoid estrogen altogether, she has other options.

**Stress incontinence.** For stress incontinence, pelvic floor muscle exercises are helpful. These can be done without any assistance if the patient is able to do the exercises and is motivated. For patients with marginal ability or motivation, options include biofeedback training, vaginal weights, electric stimulation, or...
magnetic stimulation.

Alpha-adrenergic agonists have also been used,\(^1\) although treatment of stress incontinence is an off-label use for these drugs and they have risks including hypertension and tachycardia. Phenylpropanolamine (eg, Entex LA) is the alpha-adrenergic agent with the most reported studies for stress incontinence, but it was withdrawn from the market due to increased risk of cerebrovascular accident.\(^1\) The alternative now contains pseudoephedrine (eg, Entex PSE) but there are no published trials of pseudoephedrine for stress incontinence.

More recent studies have shown duloxetine (Cymbalta) to be effective,\(^1\) although incontinence is currently an off-label use for it.

Fem-Soft urethral inserts are used by some patients and are covered by Medicare. These soft inserts are held in place by a unique balloon, which expands automatically after insertion and compresses when the patient pulls on the insert to remove it (ie, the balloon does not need to be inflated or deflated in the office). They are similar in width to Foley catheters (16 or 18 Fr) but are shorter, extending only about 1 cm out from the urethral meatus.

Surgical options for stress incontinence include periurethral injections and sling operations. The former involves injecting a bulking material (such as collagen paste) around the urethra to increase its coaptation (urethral closure). It is a simple, almost painless, outpatient procedure with minimal risks, but results vary. Several procedures may be required to achieve continence, and most patients have recurrent incontinence within 5 years.

In contrast, sling operations have a better success rate. Slings can be made from various materials including the patient’s own fascia, cadaveric fascia, animal materials such as porcine intestinal submucosa, or synthetic mesh. Most materials have good short-term results, with stress incontinence cured or significantly improved for over 90% of patients.\(^\text{15}\)

Long-term success depends on the sling material used. The risks and duration of hospitalization depend on the specific materials and techniques, but most slings are inserted either as outpatient surgery or with overnight hospitalization.

**Urg e incontinence.** For urge incontinence, pelvic floor muscle exercises are beneficial because contraction of the pelvic floor inhibits the detrusor by a reflex. This is well described in a book for lay people.\(^\text{16}\)

Anticholinergic drugs are commonly used and are more effective than placebo.\(^\text{1,17}\) Side effects include dry mouth, constipation, and mental status changes. Ways to reduce side effects:

1. Sustained-release formulations of oxybutynin (Ditropan XL) or tolterodine (Detrol LA)
2. Anticholinergics that are more selective for the bladder, such as tolterodine (Detrol)
3. Transdermal oxybutynin (Oxytrol), which decreases the first-pass liver metabolism and minimizes production of metabolites that have side effects of their own
4. Trospium chloride (Sanctura), which does not cross the blood-brain barrier and therefore has less effect on the central nervous system.\(^\text{18}\)

Interestingly, magnesium supplementation (MgOH, 350 mg twice daily) was effective for urge incontinence in a placebo-
controlled trial. If conservative treatments fail, the surgical options include sacral nerve stimulation or augmentation cystoplasty. The latter has high morbidity and should be considered only as a last resort for a person with incapacitating incontinence.

Recurrent UTI. For recurrent urinary tract infections, several options are available. Cranberries contain polymeric proanthocyanidins, which inhibit the binding of *Escherichia coli* to uroepithelial cells. Cranberry juice or cranberry extract tablets were more effective than placebo in the few studies available, but the optimum preparation and dose are unknown. Also, since the P fimbriae on *E coli* bind to mannose residues on uroepithelial cells, it is expected that free mannose in the urine might competitively inhibit this binding.

Mannose is sold over the counter as a preventative for urinary tract infections. No published literature supports its use, but it appears harmless.

Another option is methenamine hippurate, which is a urinary tract antiseptic. Controlled trials to date have not proven its efficacy, but adverse events are infrequent.

Antibiotics can also be used as chronic low-dose prophylaxis or intermittent self-start therapy when infection symptoms occur. Best for low-dose prophylaxis are antibiotics with minimal adverse effects on the fecal and vaginal flora, such as trimethoprim alone, trimethoprim/sulfamethoxazole, nitrofurantoin, cephalexin (in minimal doses), and fluoroquinolones.

■ Cardiac risk factors

**Q:** What should be done about Mrs JC’s cardiac risk factors? Osteoporosis prevention?

**A:**

**Dr Leong:** Mrs JC’s risk factors for heart disease include hypertension, hyperlipidemia, obesity, and family history of CHD. While hormone therapy should not be used to prevent heart disease, there are well-established treatments for hyperlipidemia including diet, exercise, and lipid lowering medications, such as the statins. She should be advised to lose weight. If healthy lifestyle changes do not control her blood pressure, antihypertensive medication would be indicated.

For prevention of osteoporosis, Mrs JC should be advised to start weight-bearing exercise and to include adequate calcium and vitamin D in her diet. Besides estrogen, bisphosphonates, raloxifene, and calcitonin are effective medication for osteoporosis treatment and prevention.

■ Should the patient be treated with HRT?

**Q:** With the patient’s family history of CHD and her personal risk factors, is HRT contraindicated?

**A:**

**Dr Pees:** Mrs JC’s family history of CHD does not contraindicate hormonal therapy. But neither is hormonal therapy indicated to prevent CHD. Mrs JC should be strongly urged to begin an exercise program, diet modifications, and possibly the use of statins. Studies support exercise as a significant factor in reducing the risk...
Hormone replacement therapy (HRT) has generated fear and confusion among many women. While the absolute risk for diseases associated with hormone use is low, the diseases are devastating. Breast cancer and stroke are 2 of the most feared illnesses, yet research studies often provided conflicting results on the risk of hormone replacement associated with these conditions.

Individualize every decision
The calculation of risks/benefits ratio has changed with the WHI data. All patients on HRT must be counseled on the new data, ideally in a face-to-face visit. Phone calls for medication refill, annual exam, and regular office visits are opportunities to revisit the subject of hormone therapy (HT). Given the mixed benefits and risks associated with HT, every decision should be individualized. A patient-centered counseling approach would allow a shared decision: the patient expresses her needs, goals, and preferences, and the physician applies medical knowledge to his and her values. In this dynamic approach, the physician can shift from a directive to a nondirective posture, taking the lead vs giving the patient full autonomy. The point in the continuum where the physician chooses to participate is determined by the patient, the physician, and the medical evidence.

The patient’s personal and family histories (breast/colon cancer, stroke, MI, osteoporosis) and risk factors (lipid profile, diet, exercise, body-mass index) play major roles in the decision. However, the patient’s philosophical approach to health often is the determining factor. The physician must provide the facts and ensure a patient is not taking HRT for reasons no longer valid. Questions such as, “What benefits do you hope to gain from HRT?” and “What are your major fears of HRT?” can help facilitate the discussion.

The patient’s philosophy
Patients often will select treatments most consistent with their philosophical approach to health. Patients with a holistic view of healthcare and an uneasiness with HRT are unlikely to have many questions. The patients who could benefit from your counsel are those who stopped HRT due to the findings of the WHI studies and those still on HRT who would like to continue. A recalculation of their individual risk/benefit ratio will help determine if HRT is still the right decision for them.

Considering symptoms
Menopausal symptoms are common and bothersome, often adversely impacting patients’ quality of life. Symptoms should be considered in calculating the risks/benefits ratio, but unfortunately, they are seldom included in research studies. In a UK qualitative study using a “time trade-off” method, participants were asked to make trade-offs between a shorter life span in “perfect health” compared with a longer life span with the condition under study. Women reported they might give up 3 months of their life to live the rest of the year without menopausal symptoms, underscoring the importance of menopausal symptoms.

Unanswered questions remain
Though national organizations such as ACOG, NAMS (The North American Menopause Society), and USPSTF (US Preventive Services Task Force) generally agree that estrogen and progestin should not be used routinely to prevent chronic conditions of menopause, such as CHD, there remain many unanswered questions. What are the risks associated with progestin? Is topical estrogen truly safe? Does the type of estrogen and delivery system have an impact on the safety profile? A recent systematic review and meta-analysis of the commonly used estrogen preparations showed that CEE and oral and transdermal 17 B-estradiol have consistent and comparable efficacy in the treatment of hot flashes and may have similar short-term adverse effects. But current clinical trials have many limitations, and further testing is needed to answer many remaining questions. Until clear strategies become available for HRT, the role of the physician continues to be that of a medical advisor helping patients make well-informed, personal, and thoughtful decisions.

—Shou Ling Leong, MD
of CHD and, to a lesser degree, the risk of breast cancer. If, after thorough counseling with reference to WHI risk findings, Mrs JC wishes to remain on or start hormone therapy, she should start on the lowest effective dosage to relieve her vasomotor symptoms. She should also be reevaluated periodically and be kept apprised of new data as they become available.

REFERENCES


DRUG BRAND NAMES

Calcitonin • Calcimar, Cibacalcin, Micacalcin
Cephalexin • Biocef, Keflex, Keftab
Clonidine • Catapres
Duloxetine • Cymbalta
Fluoxetine • Prozac
Gabapentin • Neurontin
Megestrol acetate • Megace
Nitrofurantoin • Furadantin, Macrobid, Macrodantin
Oxybutynin • Ditropan, Oxytrol
Paroxetine • Paxil
Raloxifene • Evista
Tolterodine • Detrol
Troxipil chloride • Sanctura
Venlafaxine • Effexor