HORMONE REPLACEMENT THERAPY

In the historical period it was commonly held that estrogen had two principal benefits to postmenopausal women: 1) To alleviate the constitutional symptoms related to the climacteric such as vasomotor symptoms (hot flushes), night sweats, somnolence, and vaginal dryness; and, 2.) To work in concert with weight-bearing exercise and diet replete with calcium to decrease or minimize their role in bone mineral density loss. Biphosphonates have been available for over a decade and are now used to slow or reverse bone mineral density depletion. It is currently well established that estrogen has little or no value in maintaining bone density—its sole value is treatment of menopausal symptoms. This discussion covers various alternative treatments for hot flushes associated with menopause.

Menopausal Symptoms--

Hormone replacement therapy (HRT) involves use of estrogen for treatment of menopausal symptoms. Progesterone is added in women with uterus intact to avoid development of abnormal changes in the endometrium including endometrial hyperplasia and cancer. Hormone replacement has been studied extensively but no single study has had a greater impact on its use than the Federal Women's Health Initiative, a large collaborative study in healthy postmenopausal women ages 50 to 79, designed to primarily assess cardiovascular implications of HRT use.

WHI Estrogen--Progestin vs. Placebo (Women with intact uterus)—

The arm of the study involving use of estrogen and progestin was halted after 5.2 years because of increased negative outcomes[1]:

Coronary heart disease — the rate of coronary events was increased with combined therapy (39 versus 33 per 10,000 person-years for postmenopausal hormone therapy and placebo, respectively).
Stroke — a 31 percent increase in stroke risk was seen with combined therapy compared with placebo.
Venous thromboembolism — the rate of venous thromboembolism (VTE) in the WHI increased with combined CEE-MPA therapy (34 versus 16 per 10,000 person-years, respectively).
Breast cancer — the risk of invasive breast cancer was significantly increased with combined hormone therapy at an average follow-up of 5.6 years (HR 1.24, unadjusted 95% CI 1.01-1.54).
Osteoporotic fracture — the risk of osteoporotic fracture with combined hormone therapy versus placebo was reduced at the hip (HR 0.67, unadjusted 95% CI 0.47-0.96) and at the vertebrae and wrist (HR 0.65, unadjusted 95% CI 0.46-0.92; and HR 0.71, 95% CI 0.59-0.85, respectively).
Colorectal cancer — the risk of colorectal cancer was reduced with combined CEE-MPA use (43 cases versus 72 in the hormone and placebo groups, respectively).

Later evaluation of the same data on use of both Estrogen and progestin revealed additional findings[2]. The Coronary Heart Disease risk appeared to be age dependent; women who were <10 years since menopause or between the ages of 50 to 59 years did not have excess risk. In addition, mortality rates appear to be lower in young postmenopausal hormone users compared to nonusers.

WHI Estrogen vs. Placebo (Women status post hysterectomy)—

The arm of the study involving use of estrogen and progestin was halted after 7 years because of increased negative outcomes[3]:

Stroke — the stroke risk was significantly increased with CEE versus placebo.

Venous thromboembolism — risk was also increased with unopposed CEE when compared with placebo (HR 1.33, 95% CI 0.99-1.79).

Osteoporotic fracture — risk reductions were seen with unopposed CEE for hip fracture (HR 0.61, 95% CI 0.41-0.91) and vertebral fracture (HR 0.62, 95% CI 0.42-0.93).

Breast cancer — a trend towards a slightly lower rate of breast cancer risk was seen in the unopposed estrogen trial (HR 0.77 for unopposed estrogen versus placebo, 95% CI 0.59-1.01).

Colorectal cancer — no significant differences were found in rates of colorectal cancer for unopposed CEE versus placebo use (HR 1.08, 95% CI 0.75-1.55).

Coronary heart disease — use of CEE did not appear to affect the incidence of CHD events over an average follow-up of 6.8 years (HR for CEE versus placebo 0.91, 95% CI 0.75-1.12).

The WHI study's data has continued to be analyzed and significant differences in assessment of the data are now commonly accepted. First, it is well accepted that estrogen use early on (i.e., in the first decade after either surgical castration or natural onset of menopause) likely decreases the incidence of endovascular disease (marked by calcifications in large vessel walls) and cardiac disease. Other conclusions have also been reached: 1.) starting HRT over a decade following onset of menopause likely increases risks of endovascular disease and stroke and, thus, must be discouraged; 2.) women 65 years and older taking HRT for many years may increase their risk of Alzheimer's disease slightly; 3.) women taking HRT prior to 65 years of age substantially decrease their risk for dementia.

Additional interpretation of the WHI data shows combined estrogen / progesterone supplementation has some significant negative impact on the three big female cancers. Combined

HRT doubles a woman's likelihood of death from breast cancer, nearly doubles the risk of death from non-small cell lung cancer and increases the chance of death from colorectal cancer by 54%. These data must be weighed in considering long-term use of combined HRT.

Treatments for Vasomotor Symptoms—

Various management alternatives are available for vasomotor symptoms. Progesterone (usually medroxyprogesterone acetate- Provera) is used only when a uterus is still present in concert with estrogen. Use of Progestin has a clear dose-response relationship for efficacy in reduction of hot flushes[5]. In addition to pills, delivery systems include patches, creams, gels and rings.

Selective estrogen receptor modulators can be used in combination with estrogen. Raloxifene 60 mg/day (no benefit alone) used with estrogen shows statistically significant benefit in reducing frequency of vasomotor symptoms. Increased thickness of the endometrium can result and surveillance is recommended. Bazedoxifene, also a SERM, used with conjugated estrogen (and progesterone where indicated) resulted in statistically significant decrease in vasomotor symptoms without demonstrable impact on the endometrium.

Women with contraindications to use of Estrogens, such as breast cancer survivors, women with history of deep vein thrombosis and stroke, may benefit from use of some antidepressant medications.

Many anti-depressants have been tested with favorable results. The first category with the most promise are Selective Seratonin Reuptake Inhibitors (SSRI's)[6-10]. The principal drug in this class is Escitalopram[11]. Used in doses of either 10 or 20 mg per day, Escitalopram often leads to a fifty percent decrease in frequency of hot flushes. This reduction is comparable to commencement of estrogen[11]. Paroxetine (SSRI) in two large studies involving breast cancer survivors at a dose of $\geq$ 12.5 mg / day showed decrease in incidence of vasomotor symptoms. In women actively using tamoxifene showed significant reduction at a dose of > 10 mg / day. Fluoxetine (SSRI) was only shown to reduce incidence of vasomotor symptoms in breast cancer survivors but was of no benefit in unaffected women.

Another category are Seratonin Norepinephrine Reuptake Inhibitors (SNRI's). Venlafaxine (SNRI) at doses of either 75 or 150 mg / day showed significant reduction in incidence of vasomotor symptoms over control groups in two large studies.

Gabapentin at a dose of 900 mg / day showed reduction in vasomotor symptoms in breast cancer survivors and previously unaffected women[12].

Clonidine is a centrally active alpha-2 adrenergic agonist, effectively relieved hot flashes[13]. It is usually given transdermally, starting with a patch that delivers 0.1 mg/day that is left in place for one week. Clonidine also may be given orally in doses of 0.1 to 0.4 mg three times daily.

Numerous studies involving "complimentary" and "alternative" treatments including black cohosh, soy and isoflavones have not sown statistically demonstrable benefits when compared with placebo.

Vaginal Dryness—

Alternatives to estrogen are available to treat vaginal dryness and related insertional pain (dyspareunia). Replens or similar products are synthetic copies of natural human lubricants and their use on an every other night basis (not related to vaginal coitus) can markedly decrease the incidence of insertional dyspareunia without use of estrogen locally on the vaginal mucosa. Use of Replens for improvement of coital satisfaction is strongly recommended independent of the use of HRT.

A new product, Osphena (ospemifene) tablets, are FDA approved to treat vulvar and vaginal atrophy associated with menopause. A single daily dose of 60 mg has been shown to relieve dryness successfully over two to three months.

Other organ systems—

Because HRT probably minimally increases risk of breast cancer, women should remain vigilant for breast health. Women should be doing monthly self breast exams, having annual physician exams and availing themselves to mammography on the following screening schedule: baseline study at 35 years of age, screening every two years from forty through fifty years of age, and annual screening after fifty years old. It is through this methodology that the greatest number of breast lesions are located early.

Evaluation for osteoporosis is necessary in menopause. Recommendation to evaluate bone mineral density (e.g., Dexa scanning) and decide whether biphosphonate therapy is indicated based on test results is the current standard of care.

Recommendation for exercise to promote cardiovascular health and muscle fitness is also essential to long term, healthy survival.

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