

Hormone Replacement Therapy

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Most women experience menopause between 40-60 years old with 51 years being the average age. Several factors can affect the time when menopause occurs. Genetics is implicated since most women mirror the age when their mothers developed menopause. Early menarche is linked with later menopause while cigarette smoking is associated with menopause occurring earlier. Women who have undergone hysterectomy leaving their ovaries intact tend to experience menopause several years earlier.

Women who develop menopause before the age of 40 years have by definition premature ovarian failure and should have an evaluation for secondary amenorrhea. Workup should include a pelvic examination and laboratory studies. Labs should include a pregnancy test, TSH, prolactin level, FSH and 17 beta-estradiol. These patients frequently require referral for additional testing to rule out an endocrine or autoimmune diagnosis.

The diagnosis is usually made clinically on the basis of amenorrhea and vasomotor symptoms. If additional testing is needed a FSH level should be checked. A value over 40 mIU/L is diagnostic. During perimenopause hormonal levels fluctuate so that checking then has limited value. Menstrual cycles tend to become shorter during the transition. Anovulation is also common which can lead to heavy irregular bleeding. Any abnormal bleeding pattern should be evaluated due to increasing risk of endometrial cancer in this age group. 50-70% experience vasomotor symptoms while this number reaches 90% if there has been surgical removal of the ovaries. Hot flashes often occur at night leading to sleep interruption. This in turn can cause mood changes partially due to sleep deprivation. These symptoms will usually resolve within four years. Vaginal atrophy is also common and symptoms include coital pain and bleeding.

There are currently two indications for the treatment of menopause--- urogenital and vasomotor symptoms due to estrogen deficiency and prevention of osteoporosis. The Women's Hope Study showed that lower doses of hormone replacement are effective in relieving symptoms, cause less vaginal bleeding and provide prevention of osteoporosis. There are several routes for estrogen replacement including oral, transdermal and intravaginal. Intravaginal estrogen treats only urogenital atrophy. The patient should be given the full dose for two weeks to restore the vaginal lining. Then she should receive half the recommended dose for two weeks. After this the dose is given once or twice a week as needed. This dose is usually low enough that the endometrium is not stimulated. Serum estradiol levels can be checked and if greater than 30pg/ml consideration should be given to adding progesterone treatment as well. Transdermal estrogen avoids the hepatic circulation and may be safer in patients who are at risk for gallbladder disease. Oral estrogen is usually given continuously to avoid vasomotor symptoms during the off week. The starting dose should be 0.625mg conjugated equine estrogen or its equivalent. The dose should be titrated down based on symptoms. Most women will have control of the vasomotor symptoms within the first month.

Side effects of estrogen therapy include vaginal bleeding, nausea, and exacerbation of migraines. Changing the type of oral estrogen or lowering the dose may help decrease the adverse side effects. Progestin is for the prevention of endometrial cancer and thus is used if the woman has an intact uterus. Side effects include irritability and breast tenderness. Progestins affect the lipid profile especially lowering HDL. Micronized progestin and medroxyprogesterone acetate (MPA) will have the least androgenic effect and affect the lipid panel the least.

Hormone replacement therapy (HRT) can be given continuously or cyclically. Women who have recently become menopausal are more likely to have heavy unpredictable bleeding so they should have cyclic HRT initially. The clinical difference between the two methods is the expected bleeding. Cyclic therapy causes monthly, predictable withdrawal bleeding beginning after day 6 if progestin is given day 1-14. If bleeding is before day 6 or if unusually heavy, biopsy may be warranted. With continuous progestin, there may be unpredictable bleeding or spotting for 6-12 months. For most women, this will stop after 12 months. Patients should have a gynecological evaluation if they bleed after six months or if the flow is heavier than expected. The duration of treatment is usually five years since most hot flashes will resolve by then. Women receiving estrogen for premature ovarian failure should be treated with HRT (if clinically appropriate) until the age 50 years for prevention of osteoporosis.

Ultrasound can be used to evaluate abnormal bleeding. If the endometrial lining is less than 5mm, biopsy is not indicated. However 25-53% of women on HRT will have a lining thickness equal to or greater than 5mm. Of these patients only 4% will have an abnormal biopsy.

HRT can usually be stopped in 2-5 years as the vasomotor symptoms wane. It is best to try to taper over six months to avoid exacerbation of hot flashes. No one knows what percent of women will become symptomatic after stopping long term HRT. Most women have mild symptoms that resolve over a few months. A subgroup of women have difficulty stopping due to rebound of their vasomotor symptoms. There are two methods of weaning; dose taper and day taper. With the dose taper one lowers the estrogen dose one day a week in a progressive fashion. If the lower dose is associated with symptoms, maintain at this dose until the symptoms are tolerated. It may take up to six months to wean the patient. With the day taper the patient starts by skipping one dose a week. If this is tolerated the patient adds a second day off HRT, etc. Practitioners can combine the two methods as well.

There are absolute and relative contraindications to HRT. Absolute contraindications include pregnancy, unexplained vaginal bleeding, liver disease, CAD, and recent venous thrombosis. Relative contraindications include hypertriglyceridemia (avoid if triglycerides are over 300), history of thromboembolic disease, family history of breast cancer, gallbladder disease, migraines, uterine leiomyoma, and seizure disorder. Women with migraine history may find a

worsening of their headaches if not compliant with the estrogen schedule. It is controversial if HRT can be given with a history of breast cancer.

There are definite risks associated with HRT, including coronary artery disease, thrombosis, and cancer. These have been examined in several large randomized clinical trials.

- 1.) The Heart and Estrogen/Progestin Study (HERS) trial looked at secondary prevention of CAD. During the first year of HRT there was a 52% increase in CAD primary events. After a mean follow-up of 4.1 years there was no significant difference between hormone and control in CAD events. The Women's Health Initiative (WHI) is the first randomized trial to look at primary prevention. This study showed increased risk in CAD, CVA and pulmonary embolus. These were found in patients on both estrogen and progestin and that arm of the study was stopped at 5.2 years, three years early. The estrogen-only arm of the WHI trial is continuing.
- 2.) Several studies have shown increased risk of venous thromboembolus with older patients having the greatest risk. If a patient has a CAD event or is immobilized it would be prudent to stop her HRT due to the above studies.
- 3.) The WHI study also showed an increased risk of invasive breast cancer. The Breast Cancer Detection Demonstration Project showed estrogen alone had a significant increased risk of ovarian cancer associated with longer duration of treatment. The million woman study investigated the specific types of HRT and breast cancer. Current users were all at increased risk of breast cancer. Combined estrogen-progestin therapy raised the risk four times than other forms of HRT. Gall bladder disease is significantly higher in women on HRT. Lipid panels will show increase in triglycerides by 14%.

There are benefits associated with HRT besides the relief of vasomotor symptoms. These include prevention of osteoporosis, and the WHI study showed a decrease in hip fracture. Estrogen therapy causes significant improvement in bone mineral density but this benefit stops after discontinuing the hormone replacement. Unopposed estrogen will cause a decrease in the low density lipoprotein (LDL) and elevate the high density lipoprotein (HDL). An unexpected finding in the WHI study was a decrease in colon cancer in the treated group.

Alternatives to HRT include selective estrogen receptor modulators (SERMS, which bind to estrogen receptors. Raloxifene (Evista) is FDA approved for the prevention and treatment of osteoporosis. HRT is only approved for prevention of osteoporosis. Raloxifene increases BMD and decreases vertebral fractures. There is also a significant decrease in invasive breast cancer. Raloxifene treatment is associated with a three-fold increase in venous thromboembolic events. Raloxifene does not treat hot flashes.

Other alternatives to traditional hormone therapy include phytoestrogens. These are sources from plants that have weak estrogen activity. Phytoestrogens are found in grains, flaxseed, rye, fruits and vegetables. Isoflavones, a subset of phytoestrogens, are found in soybeans. One trial found soy protein at 60grams per day decreased hot flashes in 45% but had associated GI symptoms. When used as a tablet it was not as effective as using in food sources. Native Americans have used black cohosh for gynecological purposes for years. It is the active ingredient found in Remifemin. This may also help hot flashes. Side effects include gastrointestinal upset and headaches.

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