HORMONE REPLACEMENT THERAPY

Hormone Replacement Therapy (HRT) is an effective treatment for menopausal symptoms. For many years, clinicians used systemic HRT to treat women in menopause, believing that HRT could benefit cardiovascular health, prevent osteoporosis, and help women live longer and healthier lives. In 2002, however, the Women's Health Initiative (WHI) changed this practice. The trial was stopped early because the results showed that the risks of hormone replacement with estrogen and progesterone in women with a uterus outweighed the potential health benefits. Subsequent research has further clarified the risks associated with HRT, as critics felt that the results of the WHI trial could not be generalized because the participants were older (primarily 60s and 70s) and used only oral preparations of estrogen and progesterone.

The following information summarizes the benefits and risks for women using HRT for menopausal symptoms. Ultimately, HRT is an individual decision that must be made by a patient, considering her specific situation and health history, in consultation with her provider.

BENEFITS OF HORMONE REPLACEMENT THERAPY

Hormone replacement therapy is the most effective treatment for the vasomotor and vaginal symptoms associated with menopause.[1] Research shows that estrogen-only therapy decreases coronary heart disease and reduces risk of breast cancer in women younger than 60 years when started within 10 years of menopause onset. Both estrogen-only and estrogen plus progesterone therapy decrease the risk of hip fracture.[2,3]

RISKS OF HORMONE REPLACEMENT THERAPY

The risks of HRT vary with the type, dose, route of administration, duration of use, and age of initiation. Results from the WHI, with treatment consisting of oral estrogen and medroxyprogesterone acetate, demonstrated an increased risk of invasive breast cancer and cardiovascular events including heart attacks, cerebrovascular events, and blood clots.[4]. Further analysis and research has shown that oral HRT (both estrogen-only and combined estrogen and progesterone) increases the risk of thromboembolic events, with risk of stroke increasing with age and with initiation of therapy >10 years from onset of menopause. Estrogen plus progesterone therapy is associated with a small increased risk of breast cancer, which is greater with use of synthetic progestins (ie, medroxyprogesterone acetate). HRT is also associated with an increased risk of gallbladder disease, although overall risk is low.[2,5,6]

TYPES OF HORMONE REPLACEMENT THERAPY

ESTROGEN

The body produces three types of estrogen that can be supplemented. Estrone (E1), made primarily in fat tissue, is the main type of estrogen present in the body after menopause. Estradiol (E2) is the strongest estrogen, present in the body before menopause. Estradiol is made by the ovaries, and its level decreases significantly after menopause. Estriol (E3) is the weakest estrogen, present in the body primarily during pregnancy.

Conjugated equine estrogen (CEE) is the most commonly prescribed oral estrogen replacement. It includes mainly estrone (E1) and is derived from pregnant horse urine. Estradiol (E2) is also available as oral, topical, and vaginal preparations. Some clinicians recommend combinations of the various types of estrogen, made at compounding pharmacies, as they may better represent the ratios of estrogen found naturally in the body. Some clinicians believe that the higher levels of estriol (E3), or the weakest estrogen, may protect women against estrogen-driven cancers like breast and uterine cancers, although the research has not yet been done.

Common starting doses include:

- Conjugated equine estrogen 0.45 to 0.625 mg orally daily
- Micronized 17β-estradiol 0.5 to 1 mg orally daily
- 17β-estradiol 0.0375 to 0.075 mg per day transdermal patch
- Estradiol 10 mcg intravaginally

PROGESTERONE

Any woman with a uterus taking oral or transdermal estrogen must also take progesterone to prevent endometrial cancer. Recent advancements to improve the absorption and duration of action for progesterone have resulted in the development of micronized progesterone (MP). Compared to medroxyprogesterone acetate (MPA), micronized progesterone is better tolerated with fewer side effects (bloating, irritability) and has a decreased risk of invasive breast cancer.[5]

Common starting doses include:

- medroxyprogesterone acetate 1.5 to 5 mg daily
- norethindrone acetate 0.1 to 0.5 mg daily
- drospirenone 0.25 to 0.5 mg daily
- micronized progesterone 100 to 200 mg daily

PRINCIPLES OF PRESCRIBING HORMONE REPLACEMENT THERAPY

HRT is contraindicated in women with unexplained vaginal bleeding, estrogen-sensitive breast and endometrial cancers, a history of blood clots, coronary artery disease, and elevated triglyceride levels, or chronic liver disease. HRT should be an individual decision

that each woman makes with help from her clinician based on her quality of life and attitude toward menopause, time since menopause and menopausal symptoms, medical history, and risk factors.

Use the lowest effective dose of HRT to treat symptoms and minimize risks.

Initiate HRT early and treat for the shortest duration of time, regularly evaluating for ongoing need and effectiveness.

According to the Global Consensus Statement on Menopausal Hormone Therapy,[1] "Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause." For combined estrogen and progesterone therapy, re-evaluate continued use at 3-5 years due to small increased risk of breast cancer. For estrogen-only therapy, duration of use can be longer.[2]

Use the safest preparation of hormones that is associated with the lowest risks.

Consider vaginal administration of HRT if symptoms are limited to vaginal dryness. Consider transdermal or topical estrogen, which bypasses the first-pass liver effect resulting in a lower risk of venous thromboembolism compared to oral preparations.[2]. Consider oral micronized progesterone rather than synthetic progestins to minimize breast cancer risk. [2].

Prescribe a progestin along with estrogen if a uterus is still present to reduce the risk of endometrial cancer.

According to the North American Menopause Society,[2] progestin should be given along with systemic or transdermal estrogen. Progestin is unnecessary if only intravaginal estrogen is prescribed at appropriate doses.[2,7] The levonorgestrel IUD is sufficient to protect against this risk although it is not FDA approved for this indication.[8]

Consider using *MenoPro,* a free app provided by the North American Menopause Society that helps providers and women develop a personalized treatment plan based on patient preferences and risk factors.

BIOIDENTICAL HORMONE THERAPY

Since the publication of the WHI trial, alternatives for the treatment of menopausal symptoms have become popular, including bioidentical hormone therapy (BHT). Bioidentical hormones, by definition, are identical in chemical structure to those hormones made by the body. Often the media refers to these hormones as "natural"; however, "natural" can have many meanings. Some use "natural" to suggest that the hormones come from nonsynthetic or nonartificial sources (such as wild yams or soybeans). Others use "natural" to describe the process of supplementing hormone levels and types that are similar to those levels and types in the human body. By definition, BHT only communicates that the hormone structure is identical to that of the body.

Compounded bioidentical hormones are custom-made formulations of multiple bioidentical hormones. Many women seek out compounded BHT, believing it to be safer than standard HRT. Many of these formulations are not approved by the FDA. In reviewing the evidence on compounded BHT, Cirigliano[9] concluded, "Many advocates of compounded BHTs customize prescriptions based on saliva tests or blood sera levels in direct contradiction to evidence-based guidelines, which support tailoring hormone therapy individually according to symptoms. Currently, scientific uncertainties associated with compounded BHTs make their use less preferable to that of conventional hormone therapy." Organizations including the American College of Obstetricians and Gynecologists and the North American Menopause Society discourage the use of compounded bioidentical hormone therapy because of the lack of research regarding its safety and efficacy.[2,10]

The FDA has approved bioidentical formulations of both estrogen and progesterone. Products include (FDA) oral, transdermal, and vaginal 17β-estradiol and oral progesterone. These products are carefully controlled and regulated, allowing for improved safety and known risks. If women are interested in using bioidentical hormone therapy, consider these products.[11]

In conclusion, starting hormone replacement is an individual decision and treatment goals should be reviewed before starting therapy. Remember, menopause is a powerful time of transition for women. When addressing menopausal symptoms, clinicians have an opportunity to allow for reflection, encourage commitment to an overall healthy lifestyle, and support women in celebrating their strength and vitality.

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