HORMONE REPLACEMENT THERAPY

For many years, clinicians used systemic hormone replacement therapy (HRT) to treat women with menopausal symptoms, 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. These women had an increased risk of invasive breast cancer and cardiovascular events including heart attacks, strokes, and blood clots.[1]

RISKS OF HORMONE REPLACEMENT THERAPY

According to the WHI, for every 10,000 women treated per year with conjugated equine estrogen and medroxyprogesterone acetate, there would be:

- 7 more heart attacks or cardiac deaths
- 8 more strokes
- 8 more pulmonary emboli
- 8 more invasive breast cancers
- 6 fewer colorectal cancers
- 5 fewer hip fractures

Overall, the results showed an increased risk of invasive breast cancer and of heart attack if HRT was started later rather than earlier in menopause.

When discussing these risks with patients, some find this information easier to understand according to the number needed to harm (NNH). The number needed to harm is the number of people taking HRT for a certain period of time for one person to have a bad outcome (refer to Table 1).

However, the results of the WHI trial cannot be generalized to all women using hormone replacement therapy. Women in the trial were primarily in their 60s and 70s and took only oral preparations of one particular type of estrogen and progesterone. Although the potential risks associated with HRT must be reviewed before initiating therapy, each woman’s specific situation and health history must be considered.
TABLE 1. RISK OF HRT.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Number Needed to Harm (NNH) with HRT [1]</th>
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</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>1,000-1,250 after 1 year&lt;br&gt;200-250 after 5 years</td>
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<tr>
<td>Blood clot</td>
<td>555 after 1 year</td>
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<tr>
<td>Stroke</td>
<td>1,250 at 1 year</td>
</tr>
<tr>
<td>Heart attack</td>
<td>1,429 after 1 year</td>
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BENEFITS OF HORMONE REPLACEMENT THERAPY

Despite the associated risks, HRT is the most effective treatment for the vasomotor and vaginal symptoms associated with menopause.[2] Research shows that estrogen-only therapy may decrease coronary heart disease and all-cause mortality in women younger than 60 years when started within 10 years of menopause; estrogen plus progesterone therapy shows a similar trend for mortality but no change in coronary heart disease.[3] Since the publication of the WHI trial, additional research has led to more recommendations on the safest, most efficacious use of HRT to treat menopausal symptoms as described below.

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 0.3 milligram to 0.45 milligram oral
  - micronized 17β-estradiol 0.5 milligram oral
  - 17β-estradiol 0.014 milligram to 0.0375 milligram patch
  - estradiol 10 micrograms intravaginally
PROGESTERONE

Any woman with a uterus taking 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), improves cholesterol levels, and has a decreased risk of invasive breast cancer.[4] It can worsen blood glucose levels and should be used with caution in those with diabetes. MP can also cause drowsiness and should be taken before bed. Topical progesterone may decrease hot flashes but is likely not enough to protect against endometrial cancer.[5]

Common starting doses include:

- medroxyprogesterone acetate 1.5 milligrams
- norethindrone acetate 0.1 milligrams
- drospirenone 0.5 milligrams
- micronized progesterone 100 milligrams

PRINCIPLES OF PRESCRIBING HORMONE REPLACEMENT THERAPY

HRT is contraindicated in women with unexplained vaginal bleeding, breast or uterine cancer, a history of blood clots, 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.

According to the Global Consensus Statement on Menopausal Hormone Therapy,[2] “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, duration should be limited to three to five years due to increased risk of breast cancer and breast cancer mortality. For estrogen-only therapy, duration of use can be longer.[3]

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

Consider local 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.[3]

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,[3] progestin should be given along with systemic or transdermal estrogen. Progestin is unnecessary if only intravaginal estrogen is prescribed at appropriate doses.[6] The levonorgestrel IUD is sufficient to protect against this risk.[7] Topical progesterone is likely insufficient.[5]

**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.

Many people claim that bioidentical hormones are a safer, effective treatment for menopausal symptoms and, furthermore, prevent the natural changes associated with aging when compared to traditional HRT. Unfortunately, little research has been done to evaluate the efficacy and safety profile of bioidentical hormones.

In reviewing the evidence on BHT, Cirigliano[8] 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.” Both Maskowitz[9] and Holtorf,[10] however, reported the benefits of progesterone include a decreased risk of breast cancer and improved cardiovascular effects compared to nonbioidentical progestins. Additionally, Maskowitz reports, “studies of both bioidentical estrogens and progesterone suggest a reduced risk of blood clots compared to non-bioidentical preparations.” Organizations including the American College of Obstetricians and Gynecologists, the Endocrine Society, and the North American Menopause Society all discourage use of BHT because of the lack of research regarding its safety and efficacy.[2,3,11]

Additionally, the Food and Drug Administration has not approved the use of BHT, stating they cannot ensure its safety or effectiveness.[12] All agree that more research is needed.

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.
AUTHOR(S)

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REFERENCES