CHAPTER 33

BENEFITS AND RISKS OF HORMONE REPLACEMENT THERAPY IN POST-MENOPAUSAL WOMEN

Stephanie Comer, D.P.M.

One of the major outcomes of this century in terms of medical advancements is the increase in the average human lifespan. Two hundred years ago, only 30% of women survived long enough to experience menopause, versus >90% of women today.[1] Women now live approximately one-third of their lives after menopause.[2] Thus, much is being discovered in recent years in regard to the effect of estrogen, or lack of estrogen, on women's health.

Menopause is the period of time in a woman's life when estrogen levels fall, ovulation and menstrual cycles cease, and reproductive ability ends. The onset of natural (i.e. non-surgical) menopause occurs typically between the ages of 44 and 56 years, with a mean age of 48. Menopause is not a sudden event, but occurs gradually, usually over a 3 to 5 year span. As estrogen levels slowly begin to fall, the menstrual cycle becomes irregular and the production of estradiol and progesterone by the ovaries declines, and adipose tissue becomes the primary site of estrogen production. Adipose-derived estrogen is much weaker than estradiol and unfortunately does not prevent the consequences of estrogen deficiency.[2] Common systemic symptoms of falling estrogen levels are vasomotor in origin such as flushing and sweating ("hot flashes"). Vaginal atrophy is another common complaint. These are considered acute symptoms of menopause and typically only last a few years. Chronic estrogen deficiency is thought to play a role in the increased incidence of osteoporosis and heart disease in postmenopausal women. By taking exogenous estrogen, these acute and chronic symptoms can be alleviated or decreased. Since a majority of podiatric patients are over the age of 50, a discussion on the benefits and risks associated with hormone replacement therapy (HRT) is warranted, as many female patients may be taking exogenous hormones or have questions in regard to it.

BENEFITS OF HRT

What are the benefits and risks of HRT? Unfortunately, many reports in the past have produced contradictory results and legitimate, large, double-blind, placebo-controlled prospective trials are few in number. However, in recent years, more and more studies are supporting the theory that HRT reduces the risk of fractures secondary to osteoporosis and is cardio-protective in nature.

Osteoporosis and HRT

In the United States, 1.5 million fractures and more than 50,000 deaths are attributable to osteoporosis.[3-5] Osteoporosis is a disease characterized by degeneration of bone mass and strength such that fractures may occur without any preceding traumatic event. Radiographically, bones appear osteopenic (thin cortices with decreased mineral content causing a decrease in radiodensity). Type I osteoporosis is bone loss secondary to estrogen deficiency, and is the leading cause of osteoporosis in females. Especially affected is trabecular bone due to its higher turnover rate compared to cortical bone. Patients with type I osteoporosis may lose up to 50% of their trabecular bone.[6] Type II osteoporosis (senile osteoporosis) affects men and women as they advance in age and is characterized by slow cortical bone loss. It is estimated that 50% of women have an osteoporotic fracture by the age of 70, with treatment costs estimated between $7 billion and $10 billion annually in the U.S.[7] Understandably, treatments that could prevent, slow, or reverse the occurrence of osteoporosis are needed.

The effects of HRT on osteoporosis are extensive. And most research has shown that estrogen replacement is beneficial in preventing the disease. In fact, the prevailing consensus is that HRT is the most effective treatment of osteoporosis in women.[8] Other treatments of osteoporosis are calcium supplementation, weight-bearing exercise, and the new class of biphosphonate drugs such as Fosamax (Merck, Westpoint, PA).

Maximum bone density peaks in both men and women around age 35, then slowly declines about 0.3% annually. In women, this annual rate of decline of bone mass sharply increases after menopause, especially in the first 3 to 6 years post-menopause. During this time, the rate of decline of bone mass is about 2% to 3% per year. In highly trabecular bones such as vertebrae, the rate is as high as 6% to 8% per year. By replacing the body's own estrogen with exogenous hormones, this rate of decline can be slowed dramatically and may actually reverse.[9,10] Research had shown this positive effect of HRT on osteoporosis is most dramatic when initiated soon after the onset of menopause. The greatest benefit is obtained in the first 3 to 7 years post menopause. Unfortunately, the increase in bone mass is reversible if HRT is not continued. Studies have shown that any protection from osteoporosis that was gained while taking estrogen is lost within 10 years after discontinuation. This fact is probably the most convincing reason to maintain HRT long term (for the rest of one's life) if prevention of osteoporosis is the primary goal.

Estrogen acts directly on the osteoclasts, decreasing bone resorption and allowing normal mineralization.[2] Exogenous estrogen, together with other preventive modalities (calcium and exercise) has been shown to reduce the risk of fractures by up to 50%.[11] As podiatrists, we frequently encounter radiographs indicative of osteoporotic disease. Knowing that bone loss due to osteoporosis can be reduced by HRT, the initiation of treatment may be a topic we should discuss with our patients, especially those experiencing pathology secondary to the weakened bones, or in those patients who likely may require a surgical procedure utilizing internal fixation. As we know, osteoporotic bone presents a challenge to fixate in the surgical setting. HRT can be a powerful tool to assist us in caring for these patients.

Cardiovascular Disease and HRT

After menopause, the protective effects of estrogen on the heart are lost, and a female's risk for myocardial infarction approaches that of a male. Over 30 published clinical studies have shown that estrogen replacement therapy is beneficial in reducing mortality, morbidity, and risk factors associated with cardiovascular disease.[12] Estrogen is thought to accomplish this by favorably affecting the lipid profile. Studies have shown that exogenous estrogen increases the level of circulating HDL cholesterol (good cholesterol) and lowers LDL cholesterol (bad cholesterol).[13] There also is data from animal research that suggests that estrogen reduces the formation of atherosclerotic plaques in monkeys fed high fat diets.[14] It is thought that this is due to the hormone's effect on vascular connective tissue.[12] Some studies have shown up to a 50% reduction in the risk of coronary heart disease in post-menopausal women taking exogenous estrogen.

RISKS OF HRT

As with most things in medicine, no drug is without risk. The most discussed risks of HRT are an increase in the incidence of breast and endometrial cancer. Recent studies have shown an increased risk of idiopathic venous thrombosis in women currently using HRT, especially in the first few years of therapy (approximately 30:100,000 compared to 10:100,000 in non-users).[15-17] Also, since estrogen has a first pass hepatic effect, orally administered estrogens should be avoided in patients with active, chronic liver conditions. Women with pre-existing hypertryglyceridemea are at increased risk of pancreatitis while taking HRT, and should be monitored for this condition.[18] Annual lab testing for triglyceride level is also recommended.

Unlike women on oral contraceptives, smoking is not a contraindication for HRT. There is no evidence that suggests smokers on HRT are at greater risk for venous thrombosis than are non-smokers. Lastly, HRT has an unpredictable effect on patients with migraines and may or may not worsen their headaches. If they do, often modification in the dose or preparation may help.[18]

Breast Cancer

Although in the public mind, HRT is associated with breast cancer, this relationship is still unclear. Most of the studies on this issue have provided conflicting results, some showing an increase risk of breast cancer and others showing a decreased risk. Most of the studies have been observational, with a limited number of subjects.[1] Only 1 of 3 major meta-analysis performed on HRT effects on breast cancer in 1991 and 1992 has shown an increased risk, and this was only after 14 years of use.[19] Another study which spanned 22 years

showed no increased risk.[20] As you can see, this is a medical dilemma. The current opinion is that unless a woman has a personal history of breast cancer, or has a first-degree relative with the disease (mother, sister, or daughter), the benefits of HRT outweigh the risk of developing breast disease.

Endometrial Cancer

There is undisputed evidence linking the use of estrogen with the development of endometrial cancer. In women who have undergone a hysterectomy, this is not of concern because they no longer have a uterus in which to develop endometrial disease. However, in women with an intact uterus, this is something to consider. Fortunately it has been shown that by adding progesterone to estrogen, a woman's endometrium is protected from the hyperplastic changes associated with estrogen-only therapy.[21] It is important that women who have not had a hysterectomy be placed on combination therapy (estrogen plus progesterone derivative) and not on estrogen therapy alone.

TYPES OF HORMONE REPLACEMENT THERAPY

Exogenous estrogen is available in oral, transdermal, and vaginal preparations. Intravaginal preparations are used only for localized symptoms and do not provide adequate serum levels to prevent osteoporosis or heart disease. Transdermal estrogens are effective in ameliorating the vasomotor symptoms of early menopause (i.e. hot flashes) and also provide high enough serum levels to positively affect bone mineral density and circulating lipid levels, but to a lesser extent than oral estrogens. Transdermal patches are good alternatives for patients with liver disease, since it avoids the hepatic first pass effect. These patches may cause localized skin irritation in some women. Oral estrogens are by far the most commonly used form. Conjugated equine estrogen (CEE), isolated from mare's urine, is the most commonly prescribed type, however plant and chemically-synthesized derivatives are now available.[22] Dosages vary according to the type of estrogen, but 0.625 mg daily is the optimal dose of CEE to be cardio-protective and anti-osteoporotic.

Women who have undergone a hysterectomy need only estrogen for replacement therapy, but all other women need progestin added to their regimen to protect them from endometrial disease. Unfortunately, studies have shown that the addition of progestin somewhat diminishes the favorable effect estrogen has on the lipid profile, specifically, combination therapy does not raise HDL levels as high as does estrogen alone.[13,23] However, progestin does not attenuate estrogen's beneficial effect on bone mineral density. The most commonly used progestin in the U.S. is medroxyprogesterone acetate (MPA) and it can be given either cyclically (10 mg daily for 10 straight days of a 30 day cycle) or continuously (2.5 mg daily). Women seem to prefer the continuous dosing of progestin because it causes amenorrhea within 6 to 12 months of initiation. Women on cyclic progestin dosing regimens will continue to have monthly menstrual cycles, and many find this undesirable. In fact, the most often cited reason for non-compliance with HRT is the occurrence of break-through bleeding.

SUMMARY

As members of the health care profession, it is important to be aware of the impact commonly-prescribed drugs have on patient's health. This article has provided a general overview of the major benefits of HRT such as reduction in menopausal symptoms, increased risk of osteoporosis and fractures, and decreased risk of heart disease. The risks (breast cancer, endometrial cancer, venous thrombosis) of HRT were also presented, along with a description of the main types of replacement therapy available to female patients. Ultimately it is up to women themselves to make the decision whether HRT is effective for them, but as health care providers, we should be able to provide information and give recommendations to patients in the process of making this decision.

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