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A Hot Flash about Menopause Hormone Therapy

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ABSTRACT

Hormone therapy (HT) for vasomotor and genitourinary symptoms associated with menopause has been an effective treatment for relief of these symptoms and the prevention of bone loss and fracture, but does entail potential risks for which our understanding continually evolves with additional studies. Risks of HT are likely to be minimized if started within 10 years of menopause onset. HT, types of HT, dose, route of application, and duration of use should be individualized taking into account age, personal health risks, time since menopause, and individual preferences and quality of life issues to minimize risks and maximize benefits.

Keywords

Menopause, Hormone therapy, Health outcomes.

Introduction

As a woman ages, her reproductive system undergoes many changes. A woman in her early to mid-20s has a 25 to 30% chance of getting pregnant every month. By age 40, the chance of getting pregnant in any monthly cycle is around 5% [1]. This decline is a result of both the decrease in quality and quantity of a woman's eggs. At birth, females have approximately 1 million eggs. By puberty, roughly, 300,000 eggs remain and of these, only 300 to 400 will be ovulated during a woman's reproductive lifetime [2]. When a woman's eggs are depleted, the ovaries cease to make estrogen and menstruation stops permanently, marking the end of her reproductive years. This stage is known as menopause.

Menopause occurs on average in women around 51-52 years of age. Perimenopause occurs during the 8 to 10 years prior to menopause. At this stage, women still have periods and can still become pregnant. In the last year or two of perimenopause, many women begin to experience symptoms of menopause as a result of both the decline in progesterone and estradiol, the main form of estrogen. In premenopausal women, normal estrogen levels range from 30-400 pg/ml. During menopause, when the menstrual cycle ceases, estrogen levels fall below 30 pg/ml [3].

The female sex hormones progesterone and estrogen are two hormones that decline with age. Progesterone is a hormone responsible for preparing the womb for pregnancy. Estrogen has many effects throughout the body. Estrogen's primary role is developing and maintaining the female reproductive system. Additionally, estrogen helps maintain bone density, skin thickness, protects against arterial disease, and promotes cognitive health [4,5]. Estrogen can also protect against diseases, including SARS-CoV-2 (COVID-19). Studies have found the host entry cell receptors for COVID-19 are modulated by estrogen [6,7]. Experts predict this might explain why men of all ages are at a higher risk of severe infection and have a 70% greater risk of death from COVID-19 than women [8].

It is estimated that as many as 90% of women have experienced a menopause-related symptom in their lifetime [9]. Commonly reported symptoms include vaginal discomfort (48%), vaginal dryness (85%) and pain during intercourse (52%). Of these women, 80% considered vaginal discomfort to negatively impact their lives including sexual intimacy (75%), ability to have a loving relationship (33%), and overall quality of life (25%) [10]. Other symptoms of menopause include hot flashes (75%), sleep disturbances (60%) and the development of osteoporosis [11,12]. It is estimated half of a women's lifetime bone loss occurs during the first 10 years after menopause [13]. Most women report night

sweats and sleep disturbances as the most bothersome of all the menopause symptoms. Therefore, many women are searching for solutions to relieve menopausal symptoms.

Currently, there is no "cure" for menopause, but there are treatment options to alleviate symptoms of menopause. One treatment option is Hormone Therapy (HT). HT was first commercially available in 1942, launching the first orally active estrogen form of HT, to help alleviate symptoms of menopause. It was not until the 1960s HT grew in popularity because of the feminist movement. HT is the most effective treatment designed to replace this deficiency in estrogen to help alleviate menopausal symptoms. HT comes in several different forms. Which option a woman receives depends on the menopausal symptoms the treatment is meant to address. Systemic HT is usually prescribed to treat hot flashes and to prevent osteoporosis. Systemic HT can be taken orally, through a skin patch, an implant, or a gel applied to the skin. More local forms of HT include pessaries inserted into the vagina, a vaginal ring, or vaginal cream. Local HT is prescribed to treat genitourinary symptoms such as vaginal dryness [14]. Premarin is a commonly used vaginal cream for HT. Premarin contains hormones derived from a pregnant horse's urine as the source of estrogen [15]. In fact, the drug's name is short for pregnant mare's urine.

In the 1990s two of the largest studies of HT were conducted: one a randomized trial in the United States, the Women's Health Initiative (WHI) and one observational questionnaire study in the United Kingdom, the Million Women Study (MWS) [16,17]. The WHI study involved over 16,000 postmenopausal women age 50-79 who received a combined pill of progesterone and conjugated equine estrogen, conjugated equine estrogen alone, or placebo for a planned 8.5 years. The study ended 3 years earlier than planned as older women (age 60-79) receiving HT had an elevated risk of developing breast cancer, heart disease, stroke, and a pulmonary embolism compared to the placebo group [16].

In the MWS, women age 50–64 provided information about their use of HT. Several different types of HT use were queried including estrogen only and an estrogen-progestogen combination. The study found users of HT had significantly increased mortality from breast cancer comparing current users and never users. Use of HT in the past decade has resulted in an estimated 20,000 extra breast cancers (15,000 from estrogen-progesterone) [17].

Given the results of both the WHI and MWS on HT, many providers stopped prescribing HT for many of their patients and use of HT dropped by 46% in the United States [18]. The clear message from the media was that HT had more risks than benefits.

In the following years, a reanalysis of the WHI trial was performed and found HT started in younger women or in early postmenopausal women had a beneficial effect on reducing coronary artery disease and all-cause mortality compared to those not using HT [18]. Additionally, the WHI trial found a significant reduction in breast cancer diagnosis and mortality in women using estrogen only HT. However, women using combined estrogen and progestogen HT had an increased risk of breast cancer diagnosis, but no significant increase in mortality [19].

A Danish study further analyzed whether HT can be beneficial for younger women. The study consisted of over 1,000 women age 45-58 demonstrating recent postmenopausal and perimenopausal symptoms. After 10 years of treatment, women receiving HT early after menopause had a significantly reduced risk of mortality and heart disease without any apparent increase in the risk of cancer, venous thromboembolism, or stroke [20].

Overall, hormone therapy is currently the most effective treatment for menopausal symptoms. HT can help maintain or restore sex drive, prevent or delay vaginal dryness, osteoporosis, hot flashes and pain with intercourse. Studies show HT seems to be most beneficial for healthy women up to age 59 or women within 10 years of menopause [21]. Doctors typically prescribe transdermal forms of HT, patches or gels, versus oral HT. One of the reasons providers prescribe transdermal HT is because transdermal HT maintains physiological blood estrogen levels without exposing the liver to a high concentration of conjugated estrogens in portal blood to lessen the likelihood of liver disease [22]. There are also several studies suggesting increased safety of transdermal estrogen vs oral estrogen, but large randomized trial data are lacking [23-26]. The FDA currently recommends short-term use of transdermal or oral HT at the lowest effective estrogen dose to control menopausal symptoms. Low levels of transdermal estrogen (0.0375mg) can help alleviate symptoms such as hot flashes. Higher levels of transdermal estrogen HT (0.05mg) are required to alleviate symptoms such as vaginal dryness. Many women have requested bioidentical options for HT, such as the use of estradiol or micronized progesterone rather than synthetic hormones. There are many FDA approved bioidentical HT options, however, insurance coverage may vary. Estradiol patches may cost over $100 a month out of pocket. The lack of adequate insurance coverage may hinder access to treatment of menopausal symptoms and reduce quality of life.

All women wishing to start HT should discuss the benefits and risks of HT with their provider. In the WHI study of women 50-79 years old randomized to HT (n=8506) or placebo (n=8102), HT appeared to increase the risk of the following after follow-up of 8.2 years: invasive breast cancer (206 cases on HT vs. 155 on placebo, $p=0.04$), stroke (159 cases on HT vs. 109 on placebo, $p=0.01$), and pulmonary embolism (87 cases on HT vs. 41 on placebo, $p<0.001$); HT appeared to decrease or not increase risk of the following: coronary heart disease (196 cases on HT vs. 159 cases on placebo, $p=0.13$), colorectal cancer (50 cases on HT vs 75 on placebo, $p=0.009$), endometrial cancer (27 cases on HT vs 30 on placebo, $p=0.49$), hip fracture (53 on HT vs 75, $p=0.03$). All-cause mortality was not significantly different between the two groups: 250 deaths on HT vs 238 on placebo, $p=0.97$. The increased risks related to HT appear to increase especially when HT is started at a later age. Absolute risks of adverse events per 10,000 women annually taking HT age 50-59 had 19 fewer cases of absolute risks and 51 excess cases for ages 70-79 years. Additionally, HT is not

recommended for women who have been diagnosed with hormone dependent cancers, since hormones may promote further tumor growth and cancer recurrence [27]. Interestingly, studies of HT use in breast cancer survivors have produced conflicting results, with some studies showing an increased risk of breast cancer recurrence and others showing no increased risk of recurrence. Especially of note is the use of low-dose topical vaginal estrogen therapy in breast cancer survivors, which has been shown to be safe in numerous studies [28].

Other alternatives to HT include dietary changes. Some soy-based foods contain phytoestrogens, which are estrogen-like compounds believed to possibly minimize the number of hot flashes. Soy food products include tofu, tempeh, soymilk, and soy nuts. Additionally, consuming foods rich in calcium and vitamin D can reduce the risk of bone weakening. Lastly, certain foods may trigger hot flashes. Common triggers include caffeine, alcohol, and spicy foods [29].

In summary, the North American Menopause Society concludes that HT is very effective in relieving vasomotor and genitourinary symptoms of menopause, and has been shown to prevent bone loss and fracture. Risks of HT are likely to be minimized if started within 10 years of menopause onset. HT, types of HT, dose, route of application, and duration of use should be individualized taking into account age, personal health risks, time since menopause, and individual preferences and quality of life issues to minimize risks and maximize benefits [23].

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