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Hormone Replacement Therapy in Postmenopausal Women, do the benefits outweigh the risks?

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ABSTRACT:

Hormone therapy has been a hotly debated topic for decades. There have been countless studies celebrating and vilifying the use of hormone replacement in postmenopausal women. Initially, the research focused on the prevention of hot flashes, and mood dysphoria. As time has passed, there are new indications, such as the prevention of cognitive decline, improving bone density, and preserving a more youthful appearance. However, the risks must not be underestimated. These include a higher incidence of blood clots and breast cancer. The results suggest a more balanced view. One that focuses on the individual woman seeking care, and her very unique needs and circumstances. Age, health, and expectations all factor into the decision to treat. This article summarizes the benefits and risks of hormone replacement therapy, to help you and your patient decide whether or not hormones will benefit them, based on the most current research.

INTRODUCTION:

As a woman ages, her reproductive system slows the production of estrogen and progesterone. This physiologic change marks the end of fertility for a woman, and the transition to menopause begins. Menopause, or amenorrhea for 12 months, occurs for most women between 45 and 52 years of age. Along with the cessation of menses, come other physiologic changes. Menopause is known to cause hot flashes, insomnia, memory loss, weight gain, irritability, changes in skin and hair, and even loss of libido and vaginal atrophy.[1] Vasomotor symptoms are extremely common, occurring in 80% of women, and the reason most women seek treatment. Replacing estrogen and progesterone in these women will be the focus of this article, but it is worth noting that there are other therapies, hypnosis, herbs, and acupuncture, to name a few, that have been studied and used to mitigate symptoms as well.

Hormone replacement therapy, HRT, in postmenopausal women has only been available since 1960 and wasn't evaluated in a clinical trial until the 1990s. The Women's health initiative, WHI, made strong recommendations against hormone therapy due to the risks outweighing the benefits.[2] Prior to the WHI, 40% of postmenopausal women were receiving HRT and as a result of the study, millions of women stopped. It is estimated that approximately half of the women on HRT stopped after the WHI data was released. There were concerns that HRT was increasing risks for breast cancer and cardiovascular disease in the study participants. However, as time has passed, observational studies haven't shown any decrease in breast cancer or reduction in cardiovascular disease in the women that stopped treatment. In fact, newer data is questioning the methods the WHI used while conducting its research.[3] Evaluation of this data suggests the timing of HRT, may have the biggest impact on the risks associated with hormone therapy. The women in the WHI study were on average over 10 years past menopause when they started treatment, which is not how therapy is initiated in clinical practice, and this may have been the biggest problem with the study. It is now generally agreed upon, that the initiation of hormones, should start at menopause, as risks of HRT go up when initiated over age 60.[4]

DISCUSSION:

Breast Cancer and HRT

Probably the greatest fear around hormone therapy is the concern about hormone use and breast cancer. However, starting HRT in healthy young women is generally considered safe, if they have no history of breast cancer.[5] Even in breast cancer survivors, local vaginal estrogen may be used safely to prevent vaginal atrophy.[6] Estrogen use alone has actually shown a reduction, though modest, in rates of breast cancers. The increased rate of breast cancer was

seen only in women who were on estrogen and progestin, and the risk dropped to baseline once the therapy was discontinued.[6]

Breast cancer is the most common malignancy in menopausal women in the developed world,[7] of those cancers 3/4 are estrogen sensitive. The baseline risk for a woman developing breast cancer in an industrialized nation is 3 women out of 50 and increases to 4 women out of 50 with estrogen and progestin therapy. While the WHI established the risk of developing breast cancer in postmenopausal women on HRT, further 18-year follow-up showed no excess risk of all-cause mortality in either group on HRT compared to placebo. So, does the increased risk actually translate to worse health outcomes?

It is important to note, that there are other factors that increase the risk of breast cancer. For example, another study argues that obesity increases the risk of breast cancer by 16%, which means 8 out of 50 obese women would develop breast cancer compared to baseline, which is higher than the risk for HRT. When viewed from this lens, a woman might find the risks of HRT more acceptable. 70% of postmenopausal women in America are obese or overweight.[8] Reduction of sex hormones may be part of the problem. Menopausal women are more likely than their premenopausal peers to be obese. Drops in estrogen lead to more visceral fat being stored, and estrogens have been shown to increase fat oxidation and reduction of leptin, the hormone that triggers appetite. More research is needed, but the argument could be made that HRT may reduce postmenopausal weight gain, mitigating its overall risk.

HRT and cardiovascular risk

Estrogen generally improves lipid profiles overall and improves insulin sensitivity. There was a time when HRT was recommended for the prevention of heart disease, but studies have not supported this theory and at present time, there is no evidence to support the use of HRT for the

prevention of cardiovascular disease.[9] If a woman has had a thromboembolic event, it is contraindicated to initiate HRT. There are prothrombotic effects primarily with oral estrogen, that can lead to an increase in clot formation. The risks again seem to correspond with timing, suggesting the closer hormones are started in relation to menopause, the less the risk. It is also important to note that transdermal estrogen is safer than oral estrogen.[10] HRT may be protective against cardiovascular disease when initiated at menopause and not exceeding ten years of use. Therefore timing is critical, and therapy should be evaluated annually for safety.

Benefits of HRT

When considering the benefits of HRT, there is one indication that is clear, and that is the prevention and treatment of osteoporosis in postmenopausal women.[11] The research suggests HRT is both an affordable and effective treatment to prevent fractures in postmenopausal women, and the results are long-standing. There does not seem to be a difference between estrogen alone and a combination of estrogen and progesterone therapy. The most significant benefits were seen in women who initiated treatment at the beginning of menopause and continued for ten years.

We know that the risk for coronary vascular disease, CVD, increases after menopause, but there is a lot of debate on prevention and cause. There is some very interesting research exploring whether or not the timing of the hormone therapy in the WHI may have influenced the results and current guidelines as numerous studies before the WHI suggested hormone therapy reduced CVD. Cardiovascular disease is the leading cause of death in women, causing 4 xs as many deaths as breast cancer. Researchers like Howard Hodis are working hard to determine safe and effective guidelines for using HRT to prevent CVD.[12] If his research is successful, he will prove that the cardiovascular risks with HRT are related to the timing. He believes that if

started at menopause, HRT will prevent the development of CVD in women, but for now, this is only speculation.

HRT in menopausal women is only medically indicated for symptom management. Improving bone density is a benefit of use, but not a clinical indication. Symptoms of menopause range from hot flashes to irritability to depression. Replacement of hormones in this population can dramatically improve quality of life, translating to better sleep, more productive time working, and better relationships with family and friends. The most common reason a woman seeks treatment from a provider is to find relief from hot flashes or vasomotor symptoms. Another common problem that women experience is the development of vaginal atrophy, which can be painful and result in frequent bladder infections.

Treatment

Another challenge in treatment for the postmenopausal female is what route and dosage to choose. Most symptoms will resolve with estrogen use alone and since progesterone has been found to increase the risk of breast cancer, it is recommended that you only use combination therapy in women with an intact uterus. If a woman has had a hysterectomy, use only estrogen therapy to minimize risk. It has been found that transdermal estrogen will achieve the same effects and has a lower incidence of blood clots. This is due to a liver metabolite that occurs when estrogen is taken orally and passes through the liver. So, it is recommended that if possible use transdermal estrogen for therapy. The most common of these would be a topical patch, but could also be a cream. The lowest dose is always recommended and used for the shortest amount of time. To maximize benefits and minimize risk, a good rule of thumb is to initiate treatment at menopause and consider discontinuing use when the female approaches 60 years of age. Starting with a transdermal patch of 0.025mg twice weekly or oral estradiol 0.5mg daily, if

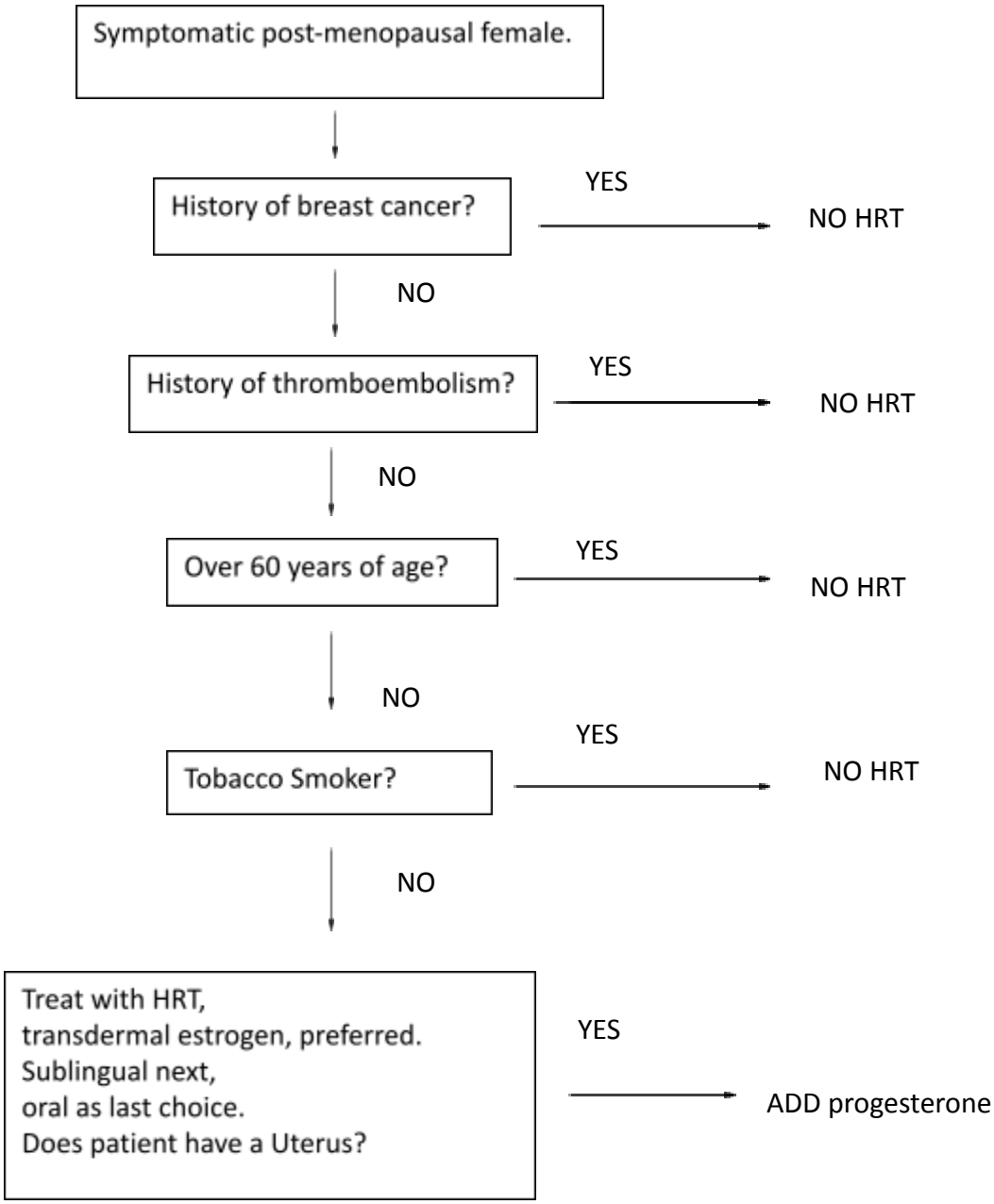
the patch isn't tolerated, is a good starting point, and can be titrated up as needed for symptom management. In a woman with an intact uterus, concurrent micronized progesterone is recommended in an oral capsule at a dose of 100mg daily, preferably taken at bedtime, as it has a side effect of somnolence. There could be an entire article written about the formulations of compounded hormones, but at this time, compounds are not recommended unless a patient has an allergy to a commercial formulation.

For vulvar and vaginal atrophy, topical estrogen is recommended. Estradiol creams and tablets at the dose of 0.1mg daily or several times a week, can be used safely without the need for concurrent progesterone therapy, even in women with an intact uterus, due to the small systemic absorption.

CONCLUSION

Hormone therapy for postmenopausal women once postulated as a way for all women to stay young, may not be the panacea it was hoped to be. Clinicians get very little training on HRT, and the research seems to conflict, adding more confusion to the choice of whether or not to treat postmenopausal women with hormones. While there are certain risks, it appears the WHI may have overstated the risks of hormone therapy. Re-analysis of the data, when looking at the bigger picture revealed the statistical risk is quite small and may not be relevant for all women when looking at all-cause mortality. As in all medicine, the patient needs to be taken into consideration, when determining if the benefits of therapy outweigh the risk of harm. The patient's medical history and timing of initiation of therapy are critical in determining risk and benefit. It is complicated to prescribe HRT, as there is no single way to replace hormones in women, with decisions on the type of hormone, route of administration, and length of treatment. The many nuances and complicated risk profile make hormone therapy replacement a challenge

for the primary care provider. It is hoped that this guide will help patients and clinicians understand the risks and benefits of hormone therapy in postmenopausal women, providing a roadmap to navigate the decision as a team.



- Re-evaluate therapy annually.
- Women receiving annual mammograms.

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