Hot flushes and Hormone Therapy (HT)

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Question 1: "Will hot flushes go away if I do not take HT?"
The menopausal transition stage, which marks the beginning of the peri-menopause, the phase in a female's life associated with clinical changes that signal the end of reproductive capabilities, is divided into early and late phases. Women in the early phase often have shortened menstrual cycles, typically defined as a variation of more than 7 days in cycle length compared with their regular pattern. During the late phase, skipping of periods occurs and intervals of 60 days or more occur between periods. It is during the late phase of the peri-menopause that the hot flushes occur, although there are studies that report up to 40% of women beginning to have episodes of hot flushing and night sweating at least 10 years prior to their menopause. The post-menopausal stage is also divided into early and late phases. The early phase includes the first five years after the last menstrual period. The late phase extends for the remainder of the woman's life. Onset of peri-menopause occurs between 45 and 47 years of age, typically lasts 4 to 6 years, with the post-menopause generally beginning at 51 years of age. Some women may begin their transition in their early 40's, but the decade between 45 and 55 years typically encompasses the transition from peri-menopause to post-menopause.

As the hormonal levels shift, with estrogens decreasing, FSH and LH increasing, 85-90% of women begin to experience vasomotor instability described as hot flushes and night sweats, attributable to the effect of decreasing estrogen levels on brain activity. Although the exact mechanism responsible for hot flushes remains unclear, numerous neuroregulators are involved: LH levels surge before the flush, hypothalamic norepinephrine activity increases, adrenocorticotrophin hormone and growth hormone levels rise after the flush, and beta endorphin levels decrease at the onset of a flush and rise significantly after it subsides. It is during this time that susceptible women begin to have problems related to insomnia, irritability and mood disturbances. Vasomotor symptoms tend to occur with the onset of rapid-eye-movement sleep thus disrupting normal sleep architecture. The resulting day time fatigue, poor concentration and dysphasia may be difficult to differentiate from the somatic symptoms associated with depression.

Approximately 60% of patients will experience profound physiological changes with significant discomfort. With the flushes there is a peripheral skin temperature change of between 5 and 9°C, and there can be a change in basal heart rate of up to 12-20 beats/min. Women can experience up to ten flushes per day and chronic sleep disturbance results if intense night sweats wake the patient four to five times each night. The resultant sleep deprivation may be associated with psychological changes, namely difficulty in making decisions, anxiety, irritability and loss of confidence. The psychological problems tend to be self-limiting for most women, but 25% of symptomatic women still experience hot flushes and night sweats 5 years after the menopause. Generally, the average duration of the vasomotor symptoms is 12-24 months, even though FSH and LH levels remain high until 65 years of age, after which they slowly decrease.

Question 2: "Will low dose HT relieve hot flushes?"
Currently, systemic estrogen or HT is the only therapy that effectively treats vasomotor and genito-urinary symptoms while also preserving bone. Concerns initially raised by the WHI study about the long-term side effects of HT have resulted in much confusion about how to reduce risks while relieving menopausal symptoms and preserving bone health. The most recent recommendations have been to advocate the individualisation of treatment plans, taking into account the patient's specific risk factors. This includes using the lowest effective doses and reviewing duration of therapy according to treatment goals and patient risk factors. As with conventional doses of HT, effective low-dose estrogen regimens should decrease vasomotor symptoms, relieve genito-urinary symptoms, prevent osteoporosis and protect the endometrium. The HOPE study, amongst others, which compares 0.625 mg, 0.45 mg and 0.3 mg respectively of conjugated equine estrogen, has clearly shown that all estrogen and combination regimens decrease hot flushes, with low-dose estrogen plus progestogen providing results similar to standard combination therapy with 0.625 mg of estrogen. Adding progestogens to low/lower doses of estrogen enhances the beneficial effects of estrogen in relieving frequent and severe flushes in women **with an intact uterus**. Low dose estrogen alone is as effective as standard dose estrogens in suppressing hot flushes and night sweats in women **without a uterus**. Similar control of vasomotor symptoms has been reported with transdermal estrogen i.e. doses as low as 0.02 mg/d effectively controlling hot flushes as early as 2 weeks after the patch is applied. Symptoms have shown a reduction of 84% after 12 weeks of therapy.

Question 3: **"Are alternative medicines safe and effective for hot flushes?"**
Many women use herbal medicines, soy and phytoestrogens for treatment of menopausal symptoms. Interest in soy and isoflavones derived from soy has been stimulated by epidemiological data from Asian countries. Women in several Asian countries have less frequent and less severe menopausal symptoms and a lower incidence of breast cancer, compared with women in western countries. The diet in Asian countries is rich in soy and other sources of phytoestrogens.

The role of these alternative therapies is confusing, controversial and unsubstantiated. Each of these therapies has a "placebo beneficial effective" of

approximately 40% whilst patients generally take multiple agents. There is currently no scientifically derived database, with widespread promotion of the products being misleading and commonly not evaluated by the FDA. The following is a very brief synopsis of some products:

Wild yam: Despite promotional claims, the content of the plant does not convert to progesterone when ingested or applied topically as a cream. Even though diosgenin is found in the plant, it needs to be extracted in the laboratory, and will not be absorbed otherwise. Significant symptomatic improvement of hot flushes has not been shown to occur.
Phytoestrogens: These are plant-derived compounds that have estrogenic activity found in legumes, soy beans, vegetables and cereals. The most abundant soy isoflavones, genistein and daidzein, have received the most attention as alternative treatments for hot flushes. Initial studies of the effect of soy or isoflavone supplementation on hot flushes produced conflicting results. Most studies have been of short duration (<12 weeks) and comparisons are difficult because of variations in product dosage and scoring systems for symptoms of hot flushes. Some studies reported a slight benefit (10-15%) compared to placebo, whereas others showed no significant benefit over placebo. The reduction in hot flushes reported in the positive studies was modest (40-54%) in comparison with the 80-90% reduction achieved with hormone therapy, and not much more than placebo effects in many trials.
Black cohosh: This is not a phytoestrogen, nor does it contain phytoestrogens. Its use has been approved by the German Commission E for the treatment of hot flushes for up to 6 months. Whereas early studies did suggest that it had estrogenic activity, more recent studies have shown that it has no effect on serum levels of LH, FSH, prolactin, SHBG or estradiol. A 6 month study of the agent accompanied by an extensive literature search shows the plant to have a good safety profile. Different extraction processes are used in its production, with the result that there are wide variations in the product ingredients and it is often packaged in combination with other plant products. Most studies of its efficacy are of limited methodological quality and there is little solid evidence from high-quality trials that it works.
Red clover: It contains phytoestrogens i.e. isoflavoid and coumestan, and has estrogen-like activity in animal models. The limited available data on its effect on hot flushes is not impressive.
Dong quai: It has no significant effect on menopausal symptoms, endometrial thickness or vaginal maturation. Seldom given on its own, it is generally prescribed as part of a combination specifically tailored to the individual patient i.e. with wild yam, chaste tree, black cohosh, milk thistle, cobelia etc.
Ginseng: Although considered to have "tonic" effects, it also has the reputation of being one of the most adulterated products on the world market. Its use has been shown to improve fatigue, insomnia, mood and depression. No significant improvement of menopausal symptoms has been described. Its use is contraindicated in the presence of breast cancer.
St John's wort: It is widely used in Germany and often combined with black cohosh to treat menopausal hot flushes, irritability, minor depression and insomnia. There are, to date, no clinical trials evaluating its activity in menopause.
Kava: It has been shown to improve irritability and insomnia but has been banned in Germany, Switzerland, the United Kingdom, Ireland, Australia and Canada because of purported hepatotoxicity. It is unwise to recommend it as part of a treatment regimen.
Chastetree: Frequently used for early menopausal menstrual irregularity and commonly a component of combination formulations. It is approved in Germany for treating premenstrual syndrome, mastalgia and irregularities of the menstrual cycle. There are currently no studies to assess its effect on menopause. Safety data derived from studies are reassuring.

Question 4: "I get blood clots. which other products can I take to relieve hot flushes?"

All patients presenting with a history of thrombotic episodes and associated menopausal systems for which treatment is requested should be investigated. The aim of the investigation is to exclude underlying thrombophilia. Investigations include activated protein C, protein S, Leiden Factor V (activated protein C resistance), anti-thrombin 3, homocysteine levels, prothrombin gene 220101 and exclusion of the anti-phospholipid syndrome. The issue of hormonal supplementation and the risk of thromboembolic disease should be discussed if there is no evidence to support an underlying thrombophilia, and particularly if the thrombotic episode was associated with a predisposing event such as surgery, a period of immobilisation, or air travel. The patient should be given aspirin and low dose HT, primarily as transdermal administration. If there is evidence of thrombophilia, the current recommendation would be to consider venlafaxine, life-style modifications or clonidine. If all fails, and the meno-pausal symptoms are particularly debilitating, full oral anticoagulation and conventional HT administered via transdermal application could be considered. Patients should be carefully selected for the latter option and it would be prudent to consult with the hematologist.

Question 5: "How long should I take HT to relieve my hot flushes?"

It takes approximately one week for a woman to detect some difference, and 3 weeks to 3 months to have a significantly noticeable difference. Patients should be seen 6 months after commencing HT and then annually. Serological estradiol levels need not be monitored routinely and the patient's response to the HT treatment is probably the best guide to its efficacy. However, in the case of subcutaneous estradiol implants, further administration of implants should be considered once the serological level of the estradiol is <400pg/h. These patients require assessment of serological estradiol levels whenever they become "symptomatic" and request further implants. A serological level of >400pg/l excludes further implants and the patient's symptoms are likely to be due to other conditions i.e. hypothyroidism or depression. In the latter group of patients the author has used SSRIs as additional treatment with significant improvements of symptoms. Only once the estradiol levels are <400pg/l should the implants be re-inserted.

Therapy may be continued for at least 5 years before re-assessing whether continuance is necessary. The author does not recommend stopping HT intermittently for "a rest" or during winter "to see whether further HT is still necessary".

References available from the author.