Navigating perimenopausal hot flashes: Pathophysiology, risk factors and management

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Abstract

Perimenopausal hot flashes exhibit vasomotor symptoms that are driven by neuroendocrine changes, particularly fluctuations in estrogen levels, which disrupt hypothalamic thermoregulation. Treatment strategies range from lifestyle modifications and behavioral interventions to pharmacologic therapies, including hormone replacement therapy (HRT) and non-hormonal alternatives such as selective serotonin reuptake inhibitors (SSRIs), gabapentinoids, and newer neurokinin receptor antagonists. Complementary therapies, including acupuncture, cognitive-behavioral therapy, and phytoestrogens, also show promise in symptom relief. This article explores the symptoms, pathophysiology underlying perimenopausal hot flashes, identifying key risk factors, helping researchers and patients navigate this transitional phase effectively.

Keywords: Estrogen, SSRI, SNRI, vasodilation, lifestyle

1. Introduction

Menopause is the complete termination of a woman's menstrual cycle. It reflects gonadal steroid reduction and oocyte depletion. It is typically found in women aged 45 to 55 and is a natural biological process. Perimenopause is the menopausal transition period that begins a few years before menopause. It causes slow loss of oocytes, abnormal menstrual cycle, hormonal changes, and impaired gonadal steroid feedback reactivity. It is typically encountered by women in their forties. The prevalence of HFs varies somewhat by race and ethnicity, with Japanese and Chinese women reporting the lowest prevalence and Caucasian women reporting the highest (1). The menopausal transition is a key factor in the development of numerous symptoms. It may also cause osteoporosis and cardiovascular issues (2).

2. Symptoms of perimenopause

Menopause and perimenopause both have similar symptoms but vary in intensity. The common symptoms observed are:

2.1. **Irregular menstrual cycle:** Before menopause, the menstrual cycle can be irregular in frequency and flow. During perimenopause, periods can be heavier, longer, or lighter than usual.

2.2. **Hot flashes (HFs):** Hot flashes are the most prevalent menopausal symptom. They include abrupt feelings of heat and sweating, which are frequently accompanied by anxiety.

2.3. **Mood changes:** Due to hormone level fluctuations, mood swings result in emotional ups and downs, depression, memory and concentration issues or "brain fog" and increased irritability.

2.4. **Weight gain:** Due to changes in metabolism, women experiencing menopause tend to gain weight and increased abdominal fat.

2.5. **Sleep disturbances:** Night sweats due to hot flashes lead to disturbed sleep and insomnia (2).

3. Hot flashes

Hot flashes (HFs) are seen in more than 80% of women and are thus considered the most prevalent symptom of menopause and perimenopause. It can be defined as the sensation of heat which causes sweating, flushing, and anxiety for a short period. Despite causing a great deal of discomfort, they are frequently overlooked because they are innocuous. The intensity and severity of HFs are seen as high during the early perimenopausal phase with maximum severity during the late menopause transition and decreases gradually (3).

3.1. Pathophysiology of HFs

HFs cause excessive peripheral vasodilation to dissipate heat, resulting in an aberrant hypothalamic thermoneutral zone. Unlike women not suffering from HFs who activate heat loss mechanisms when their core body temperature rises by 0.4°C, women with HFs start vasodilatory responses at significantly lesser increase in their core body temperature. Peripheral vasodilation causes excessive sweating and the sense of acute heat (4).

Major areas of the body experience hyperthermia and an increase in blood flow during HFs. Although the sensations of hot flashes are most severe in the upper body (head, neck, and upper chest), the greatest temperature increase is in the fingers and toes, where the temperature can rise from the typical range of 20°C to 33°C. Peripheral vasodilation causes heat loss, which lowers body temperature and eliminates flushing. The chills that follow HFs are the body's attempt to bring the lowered core body temperature back to normal (2).

HFs are frequently associated with oestrogen withdrawal during menopause; however, oestrogen alone is not responsible for HFs because the oestrogen levels are not seen to change significantly between symptomatic and asymptomatic women. Furthermore, HFs terminate during menopause, when oestrogen levels drop even further. The rate of drop in oestrogen level, rather than the actual fall, may be more important in the development of HF. Anomalies in hypothalamus thermoregulatory mechanisms are thought to be the primary cause of HF.

Several authors have proposed role of serotonin in HFs. Oestrogens increase the formation of serotonin and endorphins. After menopause, there is a 50% fall in serotonin levels due to decreasing oestrogen levels. A decrease in serotonin causes a rise in norepinephrine, which disrupts the hypothalamic thermostat. Several indirect data indicate that serotonin and norepinephrine play a role in the development of HFs which includes favourable reaction of hot flashes to (i) selective serotonin reuptake inhibitors (SSRIs); (ii) elevated plasma levels of norepinephrine, a key brain chemical during HFs and (iii) Clonidine which is an α2 adrenergic antagonist that lowers brain norepinephrine levels. An α2 adrenergic agonist, Yohimbine, that raises brain norepinephrine levels, may also provoke HFs (5).

Calcitonin gene-related peptide (CGRP) may also play a role in HFs. It is the most effective vasodilator in the human body, localised to sensory fibres. Animal studies imply that CGRP plays a function in HFs. CGRP's vasodilatory function is not dependent on histamine, prostaglandin, bradykinin, and epinephrine. HFs do not respond to their antagonist compounds. The distribution of CGRP in the skin corresponds to the distribution of sensory nerves, which is why flashes are seen to mostly affect the head, neck, and upper chest. CGRP, present in cholinergic sympathetic neurons of sweat glands, can augment methacholine-induced sweating in a dose dependent manner (2).

3.2. Treatment and management of HFs

Table 1. Various treatment regimens adopted for HFs in literature

S.No.	Treatment Regimes	Benefits	Current status	Side Effects/ Contraindications	Ref.
1	Oral oestrogen combined with micronized progestin or transdermal oestrogen. Marketed transdermal oestrogen products: **Climara, Menostar, Minivelle**	Effective for moderate to severe hot flashes	First choice for treatment	Stroke or breast cancer, active liver disease, coronary artery disease, unexplained vaginal bleeding, venous thromboembolic event, active gallbladder disease	(6)

2	SSRIs (Paroxetine and Escitalopram). Marketed products: **Lexapro, Cipralex, Nexito**	Effective for moderate to severe level hot flashes	For women unable to tolerate hormone therapy, this is the first line of treatment.	Paroxetine contraindicates tamoxifen	(6)
3	SNRIs (Venlafaxine)	Effective for moderate to severe level hot flashes and in women who cannot tolerate SSRIs	Definite option for nonhormonal treatment	-	(6)
4	Gabapentin **Brand name: Neurontin**	Effective for hot flashes occurring at night	Option for non-hormonal treatment	Can cause sedation	(6)
5	Depomedroxyprogestr oneacetate 500mg i.m **Brand name: Depo-Provera**	Comparatively more effective than venlafaxine	Option for non-hormonal treatment	Suitable for women with contraindications to estrogen therapy.	(2)
6	Tibolone **Brand names: Livial, Tibofem, Ladybon**	Synthetic drug used in Europe for hot flashes, also improves bone metabolism	Option for non-hormonal treatment	High chances of stroke	(2)
7	Conjugated Estrogen + Bazedoxifene	In theory, this combination exerts an antagonistic effect on the endometrium and an agonistic effect on bones.	Requires further studies	-	(2)
8	Oral contraceptive pills	Effective for perimenopausal women with heavy bleeding and desire for contraception	Definite option for non-hormonal treatment	Same as oral oestrogen combination therapy	(2)
9	Clonidine	Recommended for treating hot flashes	meta-analysis of 10 trials involving clonidine found that 50% of the trials showed a benefit with the use of clonidine, when compared with placebo	Dry mouth, constipation and drowsiness	(7)

In addition to the above-mentioned treatments some other traditional methods are use of cognitive behavioural therapy, progesterone creams, weight loss, evening primrose oil, plant-based therapies, flaxseed, ginseng, wild yam, black cohosh, and medicinal Chinese herbs. Acupuncture has long been used to treat menopausal HFs, but there is little data to support its effectiveness (2,3).

3.3. Herbal remedies for management of HFs

Black cohosh and foods rich in phytoestrogens show promising results in treating menopausal symptoms. These foods are not seen to have major side effects however mild nausea, upset stomach and skin rashes have been reported (8). Homeopathic remedies made of malagueta peppers (fruits of *Capsicum frutescens L., Solanaceae*) are effective in relieving menopausal hot flashes (9). Studies also show promising results with the administration of liquorice roots in decreasing the severity of hot flashes (10). Evening primrose oil is another herbal remedy that is seen to decrease the severity of night sweats. Minor side effects like nausea and stomach pain have been reported. Soybeans are a rich source of isoflavones. They are structurally similar to the hormone oestrogen and may thus exert weak oestrogenic effect in perimenopausal women. Several typical menopausal symptoms are linked to a decrease in the oestrogen formation and thus soy is said to ease menopausal symptoms because of its oestrogen like characteristics (11). Another structurally similar compound to oestrogen are flax seeds. They are a naturally rich source of lignans. They help alleviate menopausal symptoms including HFs and bone loss due to their structural similarity to oestrogen (12).

3.4. Risk factors associated with HFs

Cigarette smoking and consumption of alcohol can worsen hot flashes (13). A significant amount of evidence indicates that nicotine affects oestrogen metabolism and vascular function, increasing the risk of hot flashes. Alcohol can trigger vasodilation, exacerbating hot flashes (14).

Certain meals and beverages, such as hot and spicy foods, caffeine, and high sugar diets can lead to HFs. A few studies have also found certain medications like Niacin and history of oral contraceptives as a trigger for HFs (15).

Studies have also shown a correlation between sedentary lifestyle and HFs. According to research, women who exercise were found to have lesser HF incidents as exercise can help regulate thermoregulation (16).

Single nucleotide polymorphisms (SNPs) in the intronic sections of the tachykinin receptor 3 gene, which encodes the neurokinin B neuropeptide receptor (NK3R), were found to be strongly linked with vasomotor symptoms during menopause (2).

Hyperthyroidism or other endocrine imbalances can contribute to thermoregulatory instability. Metabolic dysfunction can influence vasomotor symptoms by affecting blood sugar regulation and vascular health.

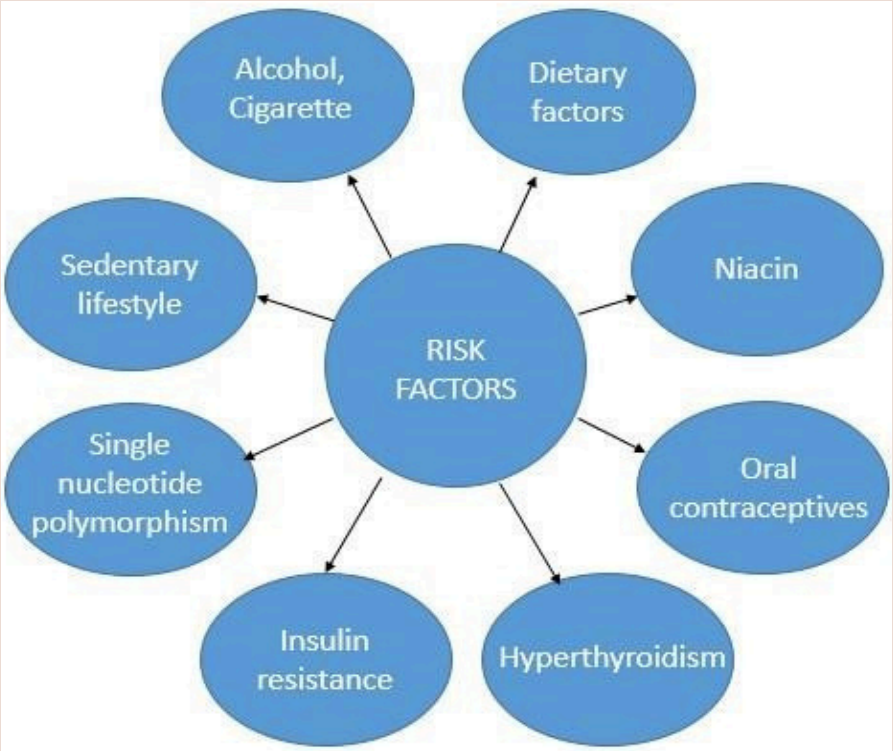

Figure 1. Risk factors associated with HFs

4. Conclusion

HFs are a common and often distressing symptom, particularly among menopausal women, with a complex pathophysiology involving thermoregulatory dysfunction, estrogen decline, and neurochemical changes. Various risk factors, including genetics, lifestyle, and comorbid conditions, influence their severity and frequency. Effective management strategies range from lifestyle modifications and non-hormonal therapies to hormone replacement therapy (HRT). As research continues to refine our understanding, a personalized approach to treatment remains essential in improving quality of life for those affected by hot flashes.

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