Hot Flush: A Review

Author:

Dr. Pankaj Desai MD, FICOG, FICMCH

Consultant Obstetrician and Gynecologist

Janani Maternity Hospital Baroda, India

Former Dean of Students and Chief of Unit in Obgyn

Medical College and S.S. G. Hospital

Baroda, INDIA

Call: 91-265-2437793/ 2432519

Facsimile: 91-265-2435345

Email: drpankajdesai@gmail.com

Abstract

Estrogen decline during menopause may disturb hypothalamic function, leading to hot flushes. Low estrogen alone doesn't often seem to bring on hot flushes, as children and women with low levels of estrogen due to medical conditions frequently don't experience hot flushes. The timing of the onset of hot flushes in women approaching menopause is variable. While not all women will experience hot flushes, many normally menstruating women will begin experiencing hot flushes even several years prior to the cessation of menstrual periods. Majority of women experience hot flushes at some point in the menopausal transition. Emerging research suggests links between menopausal hot flushes and cardiovascular disease risk. Lipids should be considered in links between hot flushes and cardiovascular risk. Estrogen supplementation seems to be the most effective treatment. However, the decision in regard to starting or continuing hormone therapy is a very individual one. It is currently

recommended that if hormone therapy is used, it should be used at the smallest effective dose for the shortest possible time. As regards black cohosh, there is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. As regards phytoestrogens, most studies point towards their lack of effectiveness in the prevention of hot flushes. Surgical treatment is never a treatment of choice for hot flushes.

CONTENTS:

INTRODUCTION:

Hot flush or hot flash or night sweats (If they occur at night) are distressing happenings in menopause. They appear as feeling of warmth on some part of the body usually the chest or abdomen, commencing from the back. Typically experienced as a sensation of intense heat with sweating and rapid heartbeat, hot flushes may last from thirty seconds to thirty minutes for each occurrence. Estrogen decline in the body is consistently attributed to be the main etiology of hot flushes. Vasomotor symptoms are generally recognized as one of the most common symptoms, or signs, of the menopause, together with menstrual cycle changes. However, the levels of estrogens do not appear to correlate with hot flushes. It seems more likely that the rate of change of plasma estrogen concentrations influences the thermoregulatory system via the hypothalamus (1). While hot flushes have a diverse presentation, its management has many methods. During the past few decades, remedies for the handling of hot flushes have advanced from straightforward sedatives and purgatives to the use of ovarian

extracts and, finally, to pharmacological estrogen preparations. This review aims to study the current thinkings associated with hot flush including their etiology and management.

ETIOPATHOLOGY:

While the exact cause of hot flushes is not known, declining levels of estrogens consistently precipitate them. The signs and symptoms point to factors affecting the function of the hypothalamus (2). Hot flushes are apparently episodic vasodilatation, leading to blood rising to the surface of the skin. Flushing is the attempts on the part of the body trying to get rid of that heat.

The estrogen decline during menopause may disturb hypothalamic function, leading to hot flushes. Low estrogen alone doesn't often seem to bring on hot flushes, as children and women with low levels of estrogen due to medical conditions frequently don't experience hot flushes. Instead, the pulling out of estrogen, which happens during menopause, appears to be the set off. Also, steady improvement and respite from hot flushes on supplementing estrogens have proved beyond uncertainty that estrogens

have a very significant role to play. What remains fascinating therefore is the exact link between declining estrogen and triggering of vasomotor disturbances ultimately precipitating the hot flush.

Interestingly it has also been suggested that reduction in blood flow to the brain may be precipitating this problem. One study tested two related hypotheses: (1) brain blood flow is reduced during postmenopausal hot flushes, and (2) the magnitude of this reduction in brain blood flow is greater during hot flushes when blood pressure is reduced (3). This study showed that hot flushes are often accompanied by clear reductions in brain blood flow that do not correspond with short-term reductions in mean arterial blood pressure.

THE NEUROCIRCUITS:

Hot flushes are also experienced by men and women treated with tamoxifen for breast cancer, men undergoing androgen-ablation therapy for prostate cancer, young oophorectomized women, and hypogonadal men (4, 5). Hot flushes are closely timed with luteinizing hormone (LH) pulses, providing a clue that the generation of flushes is

linked to the hypothalamic neural-circuitry controlling pulsatile Gonadotropin-Releasing Hormone (GnRH) secretion. Current evidence suggests that pulsatile GnRH secretion is modulated by a subpopulation of neurons in the arcuate (infundibular) nucleus that express estrogen receptor-α (ERα), neurokinin 3 receptor (NK3R), kisspeptin, neurokinin B (NKB), and dynorphin (6, 7, 8).

It has been found that ERα-expressing neurons are markedly altered in the hypothalamus of postmenopausal women. It is hypothesized that these neurons could be involved in the generation of hot flushes (9). These neurons have now been identified as KNDy neurons.

Hot flushes represent a disorder of central thermoregulation characterized by the episodic activation of heat loss mechanisms. It has been proposed that hormone withdrawal increases the sensitivity of hypothalamic neural pathways that control heat dissipation effectors. Presuming this to be so, it was predicted by Dacks and Rance recently that ovariectomized rats without estradiol treatment would activate tail skin vasodilatation (a major heat loss effector) at lower ambient temperatures and thereby

lower the thermoneutral zone. It was found that rats without estradiol exhibited increased skin vasodilatation and a shift in the thermoneutral zone to lower ambient temperatures. Moreover, the ambient temperature threshold for skin vasodilatation was significantly lower in rats without estradiol treatment. These findings support the hypothesis that estrogen withdrawal increases the sensitivity of thermoregulatory neural pathways and modifies the activation of heat loss mechanisms (10).

CLINICAL FEATURES:

Hot flushes are classically experienced as a feeling of intense heat with sweating and speedy heartbeat. It may characteristically last from thirty seconds to thirty minutes for each episode. The feeling of heat frequently begins in the face or chest, even though it may appear somewhere else such as the nape of the neck. It can extend all through the body. Some women feel as if they will collapse. In addition to being an inner sensation, the surface of skin, particularly the face, becomes warm to feel. This is the derivation of the term "hot flush." The sensation of heat is often accompanied by visible reddening of the face. Excessive perspiration can also occur; when hot flushes occur

during sleep they may be accompanied by night sweats. In some women there can be nocturnal awakening and headache (11).

The timing of the onset of hot flushes in women approaching menopause is variable. While not all women will experience hot flushes, many normally menstruating women will begin experiencing hot flushes even several years prior to the cessation of menstrual periods. It is impossible to predict if a woman will experience hot flushes, and if she does, when they will begin. Majority of women experience hot flushes at some point in the menopausal transition.

CONTROVERSY SURROUNDING CARDIOVASCULAR DISEASE RISKS AND HOT-FLUSHES:

It has long been hypothesized that increased adiposity would be associated with decreased vasomotor symptoms during menopause because of conversion of androgens to estrogens in body fat. However, recent thermoregulatory models have postulated that increased adipose tissue would infact be associated with a greater likelihood of vasomotor symptoms. Thus the pitch for a controversy on this aspect has

been queered. Emerging research suggests links between menopausal hot flushes and cardiovascular disease risk. The mechanisms underlying these associations are unclear, due to the incomplete understanding of the physiology of hot flushes. Interestingly one study has shown that hot flushes, but not night sweats, were associated with lower cardiovascular risk factors in these healthy postmenopausal women (12). On the other hand another study that examined associations between vasomotor symptoms and lipids, controlling for other cardiovascular risk factors, estradiol, and follicle-stimulating hormone found that vasomotor symptoms were associated with higher LDL, HDL, apolipoprotein A1, apolipoprotein B, and triglycerides. Lipids should be considered in links between hot flushes and cardiovascular risk (13).

Cardiovascular risks are associated with atherosclerosis and its antecedent events. It is therefore understandable to study the association between atherosclerosis or its associated marker changes and hot flushes to reach some conclusions about the association between hot flushes and cardiovascular changes. One study has evaluated the effect of menopausal transition on vascular inflammation indices and investigated

the association of hot flush severity with these indices in early menopausal women. It found that increased severity of hot flushes was associated with adverse changes in vascular inflammation, supporting the emerging role of hot flushes in cardiovascular prognosis in these women (14).

Another study tried to go into further depth of the matter. In this study, it was tested whether, beyond hot flushes, menopausal symptoms were associated with biochemical and biophysical risk factors for cardiovascular disease. It was found that menopausal symptoms evaluated by a validated climacteric scale are associated with a worsening of biochemical risk factors for atherosclerosis and cardiovascular disease (15).

So as to get a more clarity on the matter some studies have examined the association between hot flushes and insulin resistance, one of the most powerful markers of cardiovascular health. One study has examined hot flushes/night sweats in relation to glucose and the Homeostasis Model Assessment (HOMA). It found that compared to no flushes, hot flushes were associated with a higher HOMA index - an

estimate of insulin resistance, and to a lesser extent higher glucose (16). However this also gets confusing by conflicting results emerging from another study. In this study the impact of hot flushes on insulin resistance in recently postmenopausal women was studied. It found that Insulin resistance may not be involved in hot flush-related changes in cardiovascular health (17). However, this study is handicapped with a small sample size.

It therefore seems that though there is conflicting evidence, by and large there are indications that there is an increased risk for cardiovascular disease in postmenopausal women suffering from hot flushes.

BLOOD PRESSURE AND HOT FLUSHES:

As blood pressure tends to be higher in menopausal women than their peers it would be of interest to know if there is any association between hot flushes and blood pressure changes. One study was conducted to examine the 24-hour changes of blood pressure in menopausal women experiencing hot flushes. It was found that systolic blood pressure of the symptomatic group (experiencing hot flushes) was significantly

higher than the asymptomatic group during waking hours (18). It therefore seems that similar to hot flushes, the increase in systolic blood pressure may arise from central sympathetic activity. Peripheral vasoconstriction and increased cardiac output, both caused by baroreflex dysfunction, might also have been responsible for increments in systolic blood pressure.

1. DIAGNOSIS

Hot flushes can be essentially diagnosed on basis of the symptoms and the comprehensive clinical picture. However in some subjects it may be necessary to get the reproductive hormonal profile (especially FSH) done to confirm that the subject is approaching menopause. In some subjects thyroid dysfunction is known to worsen hot flushes. In such an event it would be worthwhile getting a thyroid profile done. Elderly women with severe or resistant menopausal symptoms can be offered TSH, T3 and T4 assays to rule out the thyroid disturbances (19).

TREATMENT:

The issue of treatment of hot flush was settled with estrogens alone or estrogen-progesterone combination being the mainstay. However this got unsettled with some disturbing research that showed increased risk of some potentially fatal conditions in women taking long term Hormone Replacement Therapy (HRT). This led to introduction of other modalities of treatment like non-hormonal treatment, psychological treatment and others. Their current status is being reviewed below:

TREATMENT: HORMONAL

Traditionally, hot flushes have been treated with either oral or transdermal (patch) forms of estrogen. Hormone Replacement Therapy (HRT) consists of estrogens or a combination of estrogens and progesterone (progestin). Both oral and transdermal, estrogens are available either as estrogen alone or estrogen combined with progesterone. Generally, these medications decrease the frequency of hot flushes by about 80% to 90%.

In one study recently published bazedoxifene/conjugated estrogens were tried in treatment of hot flushes. The aim of this study was to examine the number of hot flush

symptom-free days in symptomatic postmenopausal women treated with bazedoxifene/conjugated estrogens (BZA/CE). In this 12-week, randomized, double-blind, placebo-controlled, phase-3 study, 322 postmenopausal women aged 40-65 years with an intact uterus who had ≥ seven moderate-to-severe daily hot flushes (or ≥ 50 per week) were randomized to BZA 20 mg/CE 0.45 or 0.625 mg or placebo. Subjects recorded the incidence and severity of hot flushes on daily diary cards. In this secondary analysis, the number of days per week without hot flushes from baseline to week 12 was determined. It was found that BZA/CE increased the number of hot flush symptom-free days and the proportion of women without hot flushes over 12 weeks of therapy (20).

However, long-term studies (the NIH-sponsored Women's Health Initiative, or WHI) of women receiving oral preparations of combined hormone therapy with both estrogen and progesterone were halted when it was discovered that these women had an increased risk for heart attack, stroke, and breast cancer when compared with women who did not receive HT. Later studies of women taking estrogen therapy alone

showed that estrogen was associated with an increased risk for stroke, but not for heart attack or breast cancer. Estrogen therapy alone, however, is associated with an increased risk of developing endometrial cancer in postmenopausal women who have not had their uterus surgically removed.

In a recent Cochrane Review interesting results have emerged. This review analyzed the role of HRT in post-menopausal women. It was undertaken with a specific objective of assessing the effects of long term HRT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition and quality of life in perimenopausal and postmenopausal women, both during HRT use and after cessation of HRT use. Twenty-three studies involving 42,830 women were included. It was found that HRT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HRT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable. There are insufficient data to

assess the risk of long term HRT use in perimenopausal women or postmenopausal women younger than 50 years of age (21).

The decision in regard to starting or continuing hormone therapy, therefore, is a very individual one in which the patient and doctor must take into account the inherent risks and benefits of the treatment along with each woman's own medical history. It is currently recommended that if hormone therapy is used, it should be used at the smallest effective dose for the shortest possible time.

TREATMENT: PHYTOESTROGENS

Women have always looked for non-hormonal options to alleviate menopausal vasomotor symptoms and prevent menopausal bone loss. Phytoestrogens are plant-derived estrogens that, although less potent than estradiol, bind to the estrogen receptor and can function as estrogen agonists or antagonists. Soy isoflavones extracted from soy are the phytoestrogens most commonly used by menopausal women. Because typical western diets are low in phytoestrogens and taking into account the general difficulty in changing dietary habits, most clinical trials in western

women have used isoflavone-fortified foods or isoflavone tablets. Although some women might experience a reduction in the frequency or severity of hot flushes, most studies point towards the lack of effectiveness of isoflavones derived from soy or red clover, even in large doses, in the prevention of hot flushes and menopausal bone loss.

Recently a meta-analysis was undertaken to study the efficacy of phytoestrogens for menopausal bone loss and climacteric symptoms by Geriatric Research, Education, and Clinical Center and Endocrinology Section, University of Miami Miller School of Medicine. It was found that although some women might experience a reduction in the frequency or severity of hot flushes, most studies point towards the lack of effectiveness of isoflavones derived from soy or red clover, even in large doses, in the prevention of hot flushes and menopausal bone loss (22).

TREATMENT: HERBS

Black cohosh seems to be the most popular herb that has been used in treatment of hot flushes. It is a species of flowering plant of the family Ranunculaceae. It is native to eastern North America. The roots and rhizomes have long been used

medicinally by Native Americans. Extracts from these plant materials are thought to possess analgesic, sedative, and anti-inflammatory properties. Black cohosh preparations (tinctures or tablets of dried materials) are used mainly to treat symptoms associated with menopause. Another study also found that no consistent monotonic relations were observed between any dietary phytoestrogen or fiber and incident vasomotor symptoms (23).

Cochrane Database undertook a review study to evaluate the clinical effectiveness and safety of black cohosh for treating menopausal symptoms in perimenopausal and postmenopausal women. All randomized controlled trials comparing orally administered monopreparations of black cohosh to placebo or active medication in perimenopausal and postmenopausal women were included in this study. Sixteen randomized controlled trials, recruiting a total of 2027 perimenopausal or postmenopausal women, were identified. All studies used oral monopreparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks. Comparator interventions included placebo, hormone therapy, red clover and fluoxetine.

It was found that there is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area and the effect of black cohosh on other important outcomes, such as health-related quality of life, sexuality, bone health, night sweats and cost-effectiveness also warrants further investigation (24).

TREATMENT: SURGICAL

Surgical treatment is never a treatment of choice for hot flushes. It is reserved for a few refractory subjects who do not respond to non-surgical methods. A limited amount of uncontrolled data suggests that stellate-ganglion block (SGB) may be useful for the treatment of hot flushes. In a recently published study it was found that SGB may be a useful therapy for a subset of women with severe postmenopausal flushing. But the authors do suggest that controlled, single-blinded study is warranted to improve the evidence of efficacy (25).

TREATMENT: OTHERS

A myriad of treatment modalities have been suggested and tried in hot flushes which are neither drug-based nor surgical. These include applied relaxation (26), clinical hypnosis (27) paced breathing (28), dietary interventions and weight change (29). All of these have shown promising results in the papers published to study their efficacy. However claims of their efficacy are not corroborated consistently but good quality studies. Therefore they are mentioned to complete the list.

PROGNOSIS:

In most subjects, the use of low-dose estrogen medication is effective in treating hot flushes. However, it may take two to four weeks of treatment before improvement is noticeable. With or without using estrogen, hot flushes gradually diminish and disappear completely with time.

CONCLUSION:

Hot flush or hot flash or night sweats (If they occur at night) are distressing happenings in menopause. Estrogen decline in the body is consistently attributed to be the main etiology of hot flushes. Hot flushes are classically experienced as a feeling of

intense heat with sweating and speedy heartbeat. Emerging research suggests links between menopausal hot flushes and cardiovascular disease risk. Lipids should be considered in links between hot flushes and cardiovascular risk. Most studies point towards the lack of effectiveness of phytoestrogens in the prevention of hot flushes. There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. In most subjects, the use of low-dose estrogen medication is effective in treating hot flushes. However, it may take two to four weeks of treatment before improvement is noticeable. With or without using estrogen, hot flushes gradually diminish and disappear completely with time.

REFERENCES:

1. Andrikoula M, Prelevic G. Menopausal hot flushes revisited. Climacteric. 2009 Feb; 12(1):3-15.

2. Joffe H, Deckersbach T, Lin NU, Makris N, Skaar TC, Rauch SL, Dougherty DD, Hall JE. Metabolic activity in the insular cortex and hypothalamus predicts hot flushes: an FDG-PET study. J Clin Endocrinol Metab. 2012 Sep; 97(9):3207-15.

3. Lucas RA, Ganio MS, Pearson J, Crandall CG, Brain blood flow and cardiovascular responses to hot flushes in postmenopausal women, Menopause: 2012 Oct 29. [Epub ahead of print]

4. Stearns V, Ullmer L, López JF, Smith Y, Isaacs C, Hayes D. Hot flushes. Lancet. 2002 Dec 7; 360(9348):1851-61.

5. Freedman RR. Physiology of hot flushes, Am J Hum Biol. 2001 Jul-Aug; 13(4):453-64

6. Rance NE, Krajewski SJ, Smith MA, Cholanian M, Dacks PA. Neurokinin B and the hypothalamic regulation of reproduction. Brain Res. 2010 Dec 10; 1364:116-28.

7. Kinsey-Jones JS, Grachev P, Li XF, Lin YS, Milligan SR, Lightman SL, O'Byrne KT, The inhibitory effects of neurokinin B on GnRH pulse generator frequency in the female rat. Endocrinology. 2012 Jan; 153(1):307-15.

8. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, Lai J, Ciofi P, McMullen NT, Rance NE. Arcuate kisspeptin/neurokinin B/dynorphin (KNDy) neurons mediate the estrogen suppression of gonadotropin secretion and body weight. Endocrinology. 2012 Jun; 153(6):2800-12.

9. Rance NE, Young WS., 3rd Hypertrophy and increased gene expression of neurons containing neurokinin-B and substance-P messenger ribonucleic acids in the hypothalami of postmenopausal women. Endocrinology. 1991; 128(5):2239–2247

10. Dacks PA, Rance NE. Effects of estradiol on the thermoneutral zone and core temperature in ovariectomized rats. Endocrinology. 2010 Mar; 151(3):1187-93.

11. Lucchesi LM, Hachul H, Yagihara F, Santos-Silva R, Tufik S, Bittencourt L. Does menopause influence nocturnal awakening with headache? Climacteric. 2012 Nov 1. [Epub ahead of print]

12. Hitchcock CL, Elliott TG, Norman EG, Stajic V, Teede H, Prior JC. Hot flushes and night sweats differ in associations with cardiovascular markers in healthy early postmenopausal women. Menopause. 2012 Nov;19(11):1208-14.

13. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Gold EB, Sternfeld B, Joffe H, Selzer F, Matthews KA. Vasomotor symptoms and lipid profiles in women transitioning through menopause. Obstet Gynecol. 2012 Apr; 119(4):753-61.

14. Bechlioulis A, Naka KK, Kalantaridou SN, Kaponis A, Papanikolaou O, Vezyraki P, Kolettis TM, Vlahos AP, Gartzonika K, Mavridis A, Michalis LK. Increased vascular inflammation in early menopausal women is associated with hot flush severity. J Clin Endocrinol Metab. 2012 May; 97(5):E760-4.

15. Cagnacci A, Cannoletta M, Palma F, Zanin R, Xholli A, Volpe A. Menopausal symptoms and risk factors for cardiovascular disease in postmenopause. Climacteric. 2012 Apr; 15(2):157-62.

16. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Sternfeld B, Joffe H, Gold EB, Selzer F, Matthews KA. Vasomotor symptoms and insulin resistance in the study of women's health across the nation. J Clin Endocrinol Metab. 2012 Oct; 97(10):3487-94.

17. Tuomikoski P, Ylikorkala O, Mikkola T. Menopausal hot flushes and insulin resistance. Menopause. 2012 Oct; 19(10):1116-20.

18. Sadeghi M, Khalili M, Pourmoghaddas M, Talaei M. The correlation between blood pressure and hot flushes in menopausal women. ARYA Atherosclerosis. 2012 Spring; 8(1):32-5.

19. Badawy A, State O, Sherief S. Can thyroid dysfunction explicate severe menopausal symptoms? J Obstet Gynaecol. 2007 Jul;27(5):503-5.

20. Yu H, Racketa J, Chines A, Mirkin S. Hot flush symptom-free days with bazedoxifene/conjugated estrogens in postmenopausal women. Climacteric. 2012 Oct 4. [Epub ahead of print]

21. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012 Jul 11; 7:CD004143.

22. Lagari VS, Levis S. Phytoestrogens for menopausal bone loss and climacteric symptoms. J Steroid Biochem Mol Biol. 2012 Dec 13

23. Gold EB, Leung K, Crawford SL, Huang MH, Waetjen LE, Greendale GA. Phytoestrogen and fiber intakes in relation to incident vasomotor symptoms: results from the Study of Women's Health Across the Nation. Menopause. 2012 Oct 29. [Epub ahead of print]

24. Leach MJ, Moore V. Black cohosh for menopausal symptoms. Cochrane Database Syst Rev. 2012 Sep 12; 9:CD007244.

25. van Gastel P, Kallewaard JW, van der Zanden M, de Boer H. Stellate-ganglion block as a treatment for severe postmenopausal flushing, Climacteric. 2012 Sep 27. [Epub ahead of print]

26. Lindh-Åstrand L, Nedstrand E. Effects of applied relaxation on vasomotor symptoms in postmenopausal women: a randomized controlled trial. Menopause. 2012 Nov 12. [Epub ahead of print]

27. Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flushes: a randomized controlled trial. Menopause, 2012 Oct 22.

28. Sood R, Sood A, Wolf SL, Linquist BM, Liu H, Sloan JA, Satele DV, Loprinzi CL, Barton DL. Paced breathing compared with usual breathing for hot flushes. Menopause. 2012 Sep 17. [Epub ahead of print]

29. Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, LeBlanc E, Lee C, La Croix AZ, Park HL, Sims ST, Vitolins M, Wallace R. Effects

of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. Menopause. 2012 Sep; 19(9):980-8.