FERTILITY AND STERILITY
Vol. 47, No. 2, February 1987
Printed in U.S.A.

Objective measurement of hot flushes associated with the premenstrual syndrome*

Robert F. Casper, M.D.†‡
Gillian R. Graves, M.D.†
Robert L. Reid, M.D.§

University of Western Ontario, London, Ontario, and Queens University, Kingston, Ontario, Canada

Many theories have been advanced to explain the pathophysiology of premenstrual syndrome (PMS). One of the most popular, that of estrogen (E) excess and progesterone (P) deficiency, has persisted since 1931,[1] and vaginal P therapy for PMS has been widely promoted[2] although controlled studies do not support its efficacy.[3] The occurrence of PMS for 1 or 2 days at midcycle is a characteristic pattern of PMS that was once thought to support the concept of E excess. In fact, PMS symptoms coincide with the time of E withdrawal after ovulation.[4] Similarly, relative E withdrawal occurs with luteolysis immediately premenstrually, at a time when PMS symptoms are often maximal. Our recent observation of the presence of sweats and chills resembling postmenopausal flushes coincident with PMS symptoms in 72% of 120 patients may also support relative E withdrawal (unpublished). The purpose of the current study was to document objectively whether the thermoregulatory and neuroendocrine changes consistent with menopausal flushes occurred in a typical patient with PMS.

Received July 28, 1986; revised and accepted October 28, 1986.

*Supported by grants from the Medical Research Council of Canada, and the Efamol Research Institute, Kentville, Nova Scotia, Canada.

†Department of Obstetrics and Gynecology, University of Western Ontario.

‡Reprint requests: Robert F. Casper, MD., University Hospital, 339 Windermere Road, London, Ontario, Canada N6A 5A5.

§Department of Obstetrics and Gynecology, Queens University.

MATERIALS AND METHODS

SUBJECT

The patient was a 26-year-old, single nulligravid woman referred with a 6-month history of PMS. Her periods were regular every 26 to 28 days and lasted 5 days. About 1 week before menses and occasionally for 2 days at midcycle, she complained of classical symptoms of PMS including irritability, depression, fatigue, marked emotional lability, and abdominal bloating. With the onset of menses or shortly thereafter, her symptoms disappeared. The patient also described episodes of an intense feeling of heat centered on her upper body, lasting from 2 to 10 minutes and followed by chills. The episodes occurred 2 to 3 times a day just before and during menses and always occurred in conjunction with her premenstrual symptoms. She took no medications except acetylsalicylic acid for headaches and tetracycline for acne. General and pelvic examinations were within normal limits. Baseline luteinizing hormone (LH) and follicle-stimulating hormone levels were 14 mIU/ml and 8 mIU/ml, respectively.

DOCUMENTATION

To document the presence of PMS, the patient completed three prospective scales daily for two consecutive cycles. We used the Self-Rating Scale of Premenstrual Symptomatology (SRS), the Prospective Record of the Impact and Severity of Menstrual Symptomatology (PRISM), and a 6-

item visual linear analog scale (LAS) composed of three mood-related symptoms (irritability, depression, and anger) and three somatic symptoms (headache, bloating, and breast tenderness.

OBJECTIVE MONITORING OF FLUSHES

On day 26 of the first cycle, the patient was admitted to our clinical investigation unit. She wore only a bathing suit in order to keep skin temperature slightly above ambient temperature (23°C). At 9:30 A.M., an intravenous catheter was inserted in a left forearm vein for blood sampling (6 ml) every 15 minutes for 6 hours. Serum was separated and stored at −20°C until assayed for LH by radioimmunoassay (RIA). Skin resistance was measured with the use of gold-plated silver electrodes and electrode paste (Grass Instruments, Quincy, MA) attached to the skin over the sternum 4 cm apart. With a Grass polygraph 7P1 preamplifier, a constant current of 10 μA was passed through the electrodes, and changes in skin resistance were determined by measuring the resulting voltage. Finger temperature was monitored continuously with a banjo thermister (Yellow Springs Instruments, Yellow Springs, OH). The patient verbally indicated the start and end of each subjective flush episode.

LH RIA

Serum LH was measured by double-antibody RIA with a kit purchased from Amersham (Oakville, Ontario, Canada). Interassay and intraassay coefficients of variation were 5% and 4.7%, respectively. Because of low serum levels of LH in the late luteal phase, we defined an LH pulse as a 30% increase in LH over a preceding nadir (a sixfold increase over the intraassay coefficient of variation).

RESULTS

On clinical review, our patient fulfilled the criteria for primary recurrent PMS. In addition, her scores on SRS in both study cycles (Fig. 1A and B) were compatible with significant PMS. LAS and PRISM scores also revealed a clear cyclic pattern of symptoms. Flush episodes occurred in the premenstrual phase in both cycles in association with elevated PMS symptom scores.

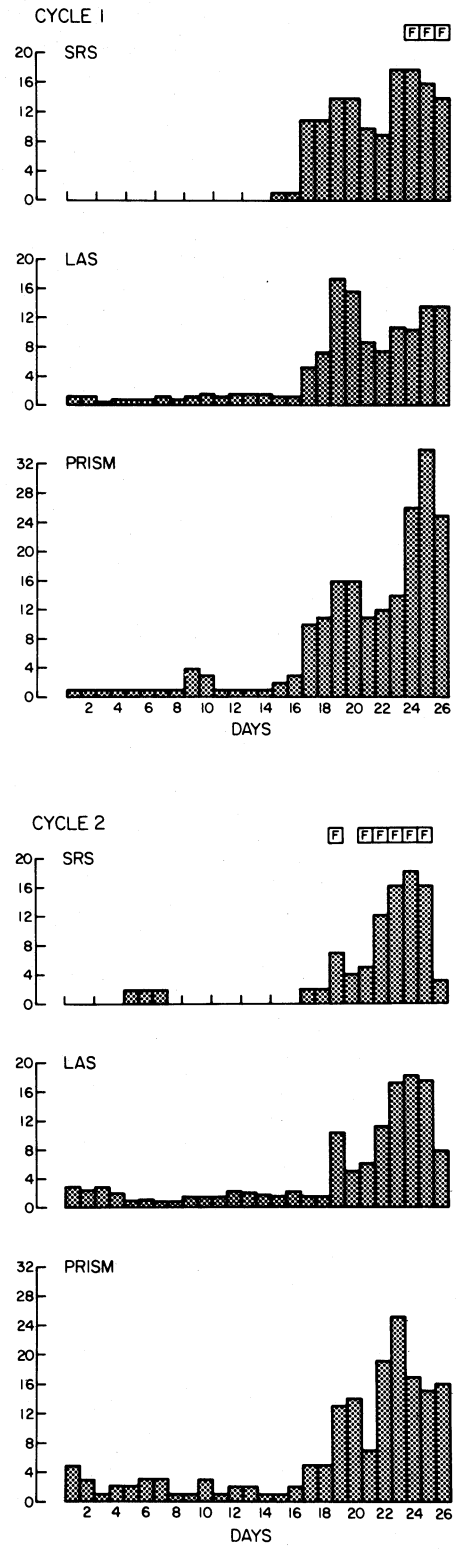

Figure 1
Daily symptoms calculated from three prospective self-rating scales during two consecutive cycles. The occurrence of hot flush-like episodes in the premenstrual phase is indicated by the *F*.

Data from skin resistance and finger temperature recordings during flushes are shown in Figure 2A. The first recorded flush began at 10:00 A.M. with an intense feeling of heat on the face and neck. The patient described the sensation of heat as coming in four successive waves of varying duration over the course of 13 minutes. Skin resistance decreased 4000 Ω coincident with the onset of the flush, and finger temperature rose 10°C from 26°C to 36°C. The next subjective flush occurred at 10:47 A.M. with a feeling of heat beginning on the face and neck, spreading to the shoulders and back, and lasting for 2.5 minutes. This flush was associated with a drop in skin resistance of 2000 Ω. Finger temperature was 36°C at the time of the onset of this flush and presumably could not rise further. The third episode of heat occurred at 1:05 P.M. in two waves lasting a total of 7 minutes. There was a drop in skin resistance of 1400 Ω and a rise in finger temperature of 3°C. The next subjective flush at 1:58 P.M. was perceived as a short period of heat lasting 2.5 minutes. There was an associated fall in skin resistance of 800 Ω but no rise in finger temperature. The final recorded flush was reported as a mild feeling of warmth mainly on the back in three waves lasting 7 minutes with a small drop in skin resistance (600 Ω) and a 2°C rise in finger temperature.

Serum LH concentrations during the objective monitoring of flush episodes are shown in Figure 2B. Seven LH pulses occurred during the period of observation, and all flush episodes occurred just before an LH pulse.

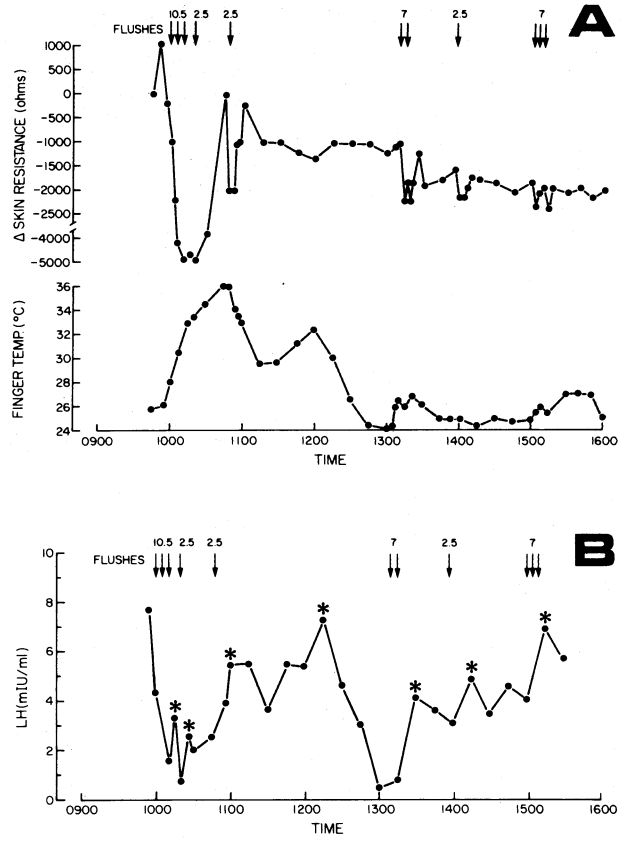

Figure 2
(**A**), The change in skin resistance (ohms) and finger temperature (°C) during flush episodes on day 26 of cycle 1. The *arrows* indicate the occurrence of a flush episode, and the numerical value indicates the total duration in minutes of the episode of heat. *Grouping of arrows* indicates the number of waves of heat that make up each episode. (**B**), Serum LH values in milli-international units per milliliter during 6 hours on day 26 in cycle 1. Each LH pulse is indicated by a *star*, and flush-like episodes are indicated by the *arrows*.

DISCUSSION

To our knowledge, this case report represents the first description of a phenomenon resembling the thermoregulatory dysfunction of menopausal flushes associated with PMS in a young woman. This report does not represent an isolated case, however. Over the past year, we have observed similar flush episodes in the majority of women with moderate to severe PMS. These episodes of an awareness of a feeling of heat resemble menopausal flushes in their sudden onset, in their origin of the face and neck with subsequent spread to the upper body, and in their association with chills after the flush has passed. The duration of a menopausal flush is typically from 2 to 4 minutes.[5] In the current report, the patient experienced "waves" of heat, which together lasted 2.5 to 13 minutes. Objectively, a decrease in skin resistance is the most consistent physiologic change observed during menopausal flushes. Other physiologic parameters that are altered during flush episodes include an elevation of finger temperature, a decrease in core temperature, and an increase in LH pulses and adrenocorticotropic hormone and cortisol release.[5] In the case reported here, all flush episodes were associated with a drop in skin resistance, and three of the five were accompanied by an increase in finger temperature. All flush episodes were associated with an LH pulse. Therefore, all subjective and objective descriptions of these phenomena are consistent with the thermoregulatory and neuroendocrine changes seen with menopausal flushes.

The significance of these findings in terms of our understanding of PMS remains to be determined. We[5] have suggested the possibility that menopausal flushes are mediated by the central withdrawal of endogenous opioid peptide activity secondary to E withdrawal. Relative E withdrawal does occur immediately premenstrually and during menses as a result of degeneration of the corpus luteum. Also, the effects of P to decrease the number of E receptors[6] and to increase the activity of 17β-dehydrogenase[7] may result in a decrease in central E activity in the luteal phase of the cycle. It is possible that the concomitance of hot flush-like episodes with PMS symptoms may serve as a marker of central E withdrawal, which results in the symptoms of PMS. Alternatively, PMS may result in the sensitization of the area/areas of the hypothalamus responsible for thermoregulation and GnRH release, resulting in the occurrence of hot flushes during times of E withdrawal, which would normally be too brief or of insufficient magnitude to trigger flushing. Further study is needed to determine if the presence of flush-like episodes in premenopausal women is invariably linked with the presence of PMS. If so, we believe that our findings may provide an important clue to the pathophysiology of premenstrual syndrome.

SUMMARY

Because the majority of women with PMS complain of sweats and chills resembling menopausal flushes, we attempted to document the physiologic changes during these episodes. A 26-year-old, nulliparous woman with PMS described the occurrence of hot flush-like episodes coincident with PMS symptoms. The patient completed prospective self-rating scales for two consecutive cycles to establish the pattern and severity of PMS. On day 26 of the first cycle when PMS symptom scores were elevated, continuous monitoring of skin resistance and finger temperature and frequent blood sampling for LH were performed for 8 hours. The patient experienced five flush episodes, each of which was associated with a drop in skin resistance of up to 4000 ohms and was coincident with an LH pulse. Three of the flushes were associated with a rise in finger temperature of up to 10°C. These physiologic changes are identical to those seen during menopausal flushes and suggest that PMS may be associated with neuroendocrine events typical of E withdrawal.

REFERENCES

1. Frank RT: The hormonal causes of premenstrual tension. Arch Neurol Psychiatry 26:1053, 1931
2. Dalton K: The premenstrual syndrome and progesterone therapy. Chicago, Year Book Medical Publishers, 1983
3. Maddocks S, Hahn P, Moller F and Reid RL: A double-blind placebo controlled trial of progesterone vaginal suppositories in the treatment of premenstrual syndrome. Am J Obstet Gynecol 154:573, 1986
4. Reid RL: Endogenous opioid activity in premenstrual syndrome. Lancet 2:786, 1983
5. Casper RF, Yen SSC: Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. Clin Endocrinol 22:293, 1985
6. Hsueh AJW, Peck EJ and Clark JH: Progesterone antagonism of the estrogen receptor and estrogen-induced uterine growth. Nature 254:337, 1975
7. Gurpide E, Ginsberg S, Tsang L: Estradiol binding and metabolism in human endometrial hyperplasia and adenocarcinoma. J Steroid Biochem 7:891, 1976