8 Thermoregulation in Women

LOU A. STEPHENSON, Ph.D. MARGARET A. KOLKA, Ph.D.

INTRODUCTION

Early investigations concerning thermoregulation in women emphasized direct comparisons to men; eventually the importance of controlling for physical fitness, heat acclimation, body fat, and size before comparing men and women was recognized [2, 29, 39, 93]. More recent studies have emphasized the importance of controlling for menstrual cycle phase in thermoregulatory studies [19, 23, 55, 58, 59, 68]. Since it has become obvious that the reproductive cycle has profound thermoregulatory effects, the interactions between endocrine and thermoregulatory systems must be clarified. Future study of thermoregulation in women should focus on the complex integration of these and other regulatory systems to understand the unique thermoregulatory responses of women.

Neuroendocrine variations during the menstrual cycle modulate brain function via numerous mechanisms including changes in receptor number and sensitivity, changes in pulse frequency and amplitude, as well as by other factors [32, 60, 86, 97]. The importance of reproductive neuroendocrine variations on thermoregulation, cardiovascular regulation, metabolic regulation, and fluid volume regulation is now being appreciated through both systemic [5, 27, 38, 50, 58, 59, 94, 111, 113–116] and in vitro preparation studies [10, 12, 109, 110]. In neuronal single unit activity studies, steroidal reproductive hormones have been implicated as potential modulators of integrative neurons involved in temperature regulation. Specifically, neurons isolated from the preoptic region are responsive to more than one input; a temperature-sensitive neuron may also be estrogen sensitive [10, 110]. In fact, the degree of overlap in neuronal responses to multiple factors [10, 12] indicates that neurons are not, for the most part, functionally specific [11]. Still, a small percentage of neurons are responsive to nonthermal stimuli, but not temperature, and some neurons, when tested for many different stimuli, are sensitive only to temperature [9]. Multiple sensitivity of hypothalamic neurons may be one way to integrate function among several regulatory systems [10, 12, 109, 110]. These studies are particularly useful in interpreting interactions between the reproductive system and thermoregulation and should stimulate more in vivo studies.

It is difficult to separate thermoregulation from fluid volume or cardiovascular regulation when gauging systemic responses to a stressor, such as exercise, heat exposure, or cold exposure. The usual experimental approach when studying thermoregulation in humans is to assume that fluid volume or cardiovascular regulation is static during the experiment. Such untenable assumptions are made because it is so difficult to control more than one regulatory system during experiments in humans. In women, one solution to dealing with the complex interactions among several regulatory systems is to study thermoregulation or fluid volume regulation in a defined phase of the menstrual cycle. Thus, if menstrual cycle phase is consistent, it is assumed that the interaction of multiple regulatory systems is consistent, even though all those regulatory systems are not monitored simultaneously. It would be ideal to study whole-body responses of several regulatory systems simultaneously, especially when those regulatory systems interact with each other as do thermoregulation and cardiovascular and fluid volume regulation. That is nearly an impossible task, due to the enormous resources needed to accomplish such research. In effect, studies of whole-body responses to exercise of interdependent regulatory systems are done in a way in which the regulatory system that is not actively being studied is held as constant as possible. Because research is conducted in this genre, we will review the responses of women to exercise and thermal stresses with the focus being on each regulatory system. Perhaps, preliminary conclusions might be drawn about the interaction of the regulatory systems across the menstrual cycle, especially in regard to the impact of reproductive status on each.

To begin, a model of thermoregulation will be presented, followed by a brief description of reproductive physiology of women. The major focus of the review will be thermoregulation in women who have normal menstrual function. Imbedded in the discussion will be the impact of the menstrual cycle on fluid volume regulation during exercise, heat stress, or cold stress. Special aspects of thermoregulation in women will also be considered that may help us understand the factors that affect the integrative function of thermoregulation. In addition, the impact of menstrual dysfunction, pregnancy, and menopause on thermoregulation will be reviewed. Finally, suggestions for future research and essential considerations for research design in thermoregulatory studies of women are stated.

TEMPERATURE REGULATION

Autonomic control of thermoregulation has been reported in many regions of the central nervous system (CNS) and summarized recently by Boulant et al. [9]. The most thermosensitive of these regions are the

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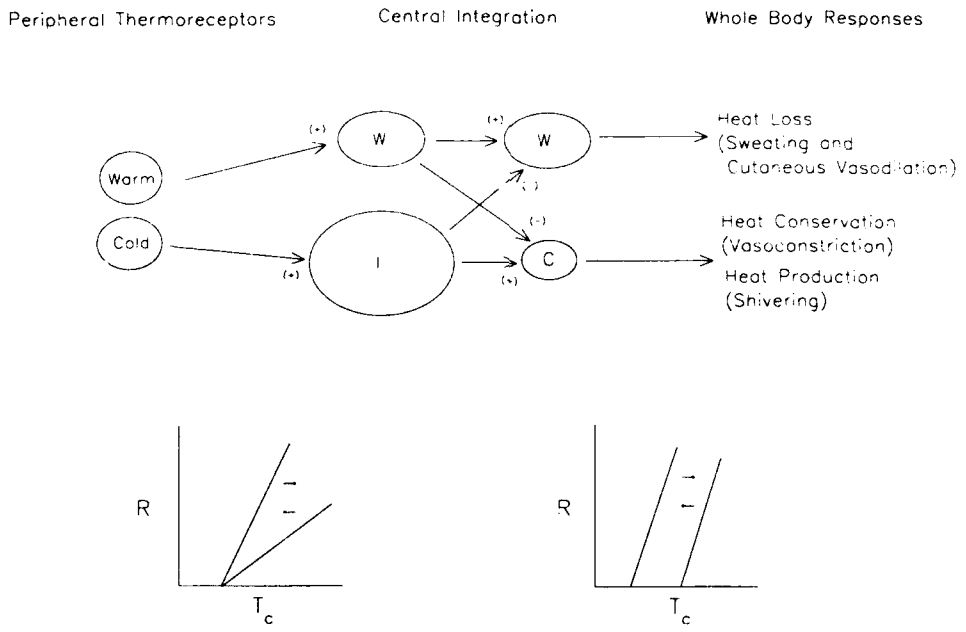
preoptic area, anterior hypothalamus, and septum (PO/AH [7]). Lesion, thermal, or electrical stimulation and neuronal preparation studies indicate the PO/AH senses changes in peripheral temperature and in its own temperature, and integrates both to modulate heat loss, heat conservation, and heat production responses as appropriate [7]. Whole-body thermoregulatory responses in humans are often interpreted in terms of a proportional control model of thermoregulation. Hammel's model [52] may also describe human thermoregulatory responses because it contains the necessary components to explain observed whole-body thermoregulatory responses. The following equation describes Hammel's model of thermoregulation [52]:

$$R - R_o = \alpha_R (T_h - T_{set})$$

R is the response of the thermoregulatory effector, R_o is the initial thermoregulatory effector response prior to the pertubation, T_h is the hypothalamic temperature, while T_{set} is the set-point temperature for initiation of thermoregulatory effector neuronal activity; α_R is a proportionality constant that is equal to the change in response per unit change in temperature and an index of hypothalamic thermosensitivity. α_R is positive for heat dissipation responses and negative for heat conservation and heat production. Factors modulating thermoregulation act by affecting T_{set} or α_R. To include the modifications of thermoregulatory effector responses due to changes in skin temperature, an additional term can be added to the right side of the equation [52]. For a detailed discussion of the impact of skin temperature on thermoregulatory effector function in humans, please see reviews by Boulant [7], Brenglemann [13], and Johnson [63].

The *top part* of Figure 8.1 shows a neuronal scheme adapted from Boulant [8] to represent a proportional control system as proposed by Hammel [51]. It shows that skin thermoreceptors stimulate warm-sensitive (W) and temperature-insensitive (I) neurons in the PO/AH. The input from these temperature-sensitive and temperature-insensitive neurons are integrated by thermoregulatory effector neurons in the PO/AH to modulate heat loss, heat conservation, and heat production, depending on the summation of the inputs. For example, if warm thermoreceptors from the skin stimulate W neurons to increase firing frequency, excitatory input from W neurons to the heat-loss effector neurons is enhanced while the inhibitory input from I neurons will remain constant. The integrated effect would be to $\downarrow T_{set}$ of the heat-loss effector neurons so that heat loss would occur at a lower hypothalamic temperature when the skin was warm. Also, W neurons would inhibit cold-sensitive (C) neurons so that the integration of I input (excitatory) and W neuron input (inhibitory) would decrease the firing

FIGURE 8.1
Schematic representation of central thermoregulation in humans. Input from peripheral and central thermoreceptors is integrated and the appropriate thermoregulatory effector response **(R)** *is initiated. This simplified diagram was adapted from Boulant, J. A. [Thermoregulation. P. Mackowiak (ed).* Fever. Basic Mechanisms and Managements. New York: Raven Press, 1991] *and Hammel* [H. T. Neurons and temperature regulation. W. S. Yamamoto, and J. R. Brobek (eds). Physiological Controls and Regulations. *Philadelphia: W. B. Saunders, 1965.*], *and represents warm-sensitive* **(W)**, *cold-sensitive* **(C)**, *and temperature-insensitive* **(I)** *neurons in the PO/AH.*



rate of C neurons. This would decrease the T_{set} of neuronal effectors for heat conservation and heat production. In other words, a lower hypothalamic temperature is needed to activate heat conservation and heat production mechanisms when skin temperature is warm.

Cold thermoreceptors in the skin provide excitatory input to I neurons. The increased firing rate of I neurons provides excitatory input C neurons to increase firing rate, thereby decreasing the T_{set} of the thermoregulatory effector neurons controlling heat conservation and heat production mechanisms. Therefore, the effect of a cold skin is to increase the hypothalamic temperature at which heat conservation, as well as heat loss, mechanisms are activated. Also, the increased firing rate of I neurons inhibits the firing rate of heat-loss effector neurons.

If the inputs of the temperature-sensitive and I neurons are equal and opposite to each other, the PO/AH is at the set-point temperature and whole-body thermoregulatory effectors are in equilibrium [7]. When the PO/AH temperature is greater than T_{set}, there is an increased firing rate of the W neurons and the effector neurons driving heat-loss responses are activated. This activation results in a proportional increase in cutaneous vasodilation and sweating as a function of the magnitude of the difference between T_h and T_{set} [51, 52]. When the PO/AH temperature is less than T_{set}, the firing rate of C neurons increases, and the effector neurons driving heat conservation and heat production mechanisms are activated in proportion to the magnitude of the difference between T_h and T_{set}.

The *bottom* of Figure 8.1 shows a simplistic scheme for whole-body thermoregulatory responses in humans. The same parameters are used in these diagrams, the only difference being that PO/AH temperature in humans is not measured, so the best approximation of the regulated temperature is used. In humans, esophageal temperature (T_{es}) has been advanced as the best index of brain temperature [14].

The *bottom* of Figure 8.1 illustrates several concepts used to explain how human thermoregulation may be adapted or modified. Whole-body effector responses (R), which are measured during exercise or during exposure to a hot environment, are plotted as a function of core temperature. If R is a heat dissipatory response as depicted here, R increases in proportion to the increase in core temperature as predicted by a proportional control model of thermoregulation. The *left bottom panel* shows a change in the slope of the $R:T_c$ relationship caused by some factor that affects thermoregulation. In Hammel's model [52], this slope is the term α_R. For a given change in core temperature, the change in the thermoregulatory effector response is less when the slope is reduced. In human thermoregulatory experiments, this change in slope is interpreted as a change in central thermosensitivity. That is, central integration or peripheral thermoregulatory effector response is modified so that the same change in core temperature causes less change in effector response. An example of altered central thermosensitivity is sleep deprivation, which decreases the central thermosensitivity of the sweating response during exercise [71, 103].

In human thermoregulation, any changes in PO/AH activity of thermoregulatory effector neurons indicative of set-point changes have to be interpreted from whole-body responses. Modulation of the core temperature threshold for onset of thermoregulatory effector response is determined as shown in the *bottom right panel* of Figure 8.1. The core temperature threshold for a thermoregulatory response during exercise or heat exposure is that temperature above which the effector response is greater than the control response in an individual resting in a thermoneutral environment. A decrease in the core temperature

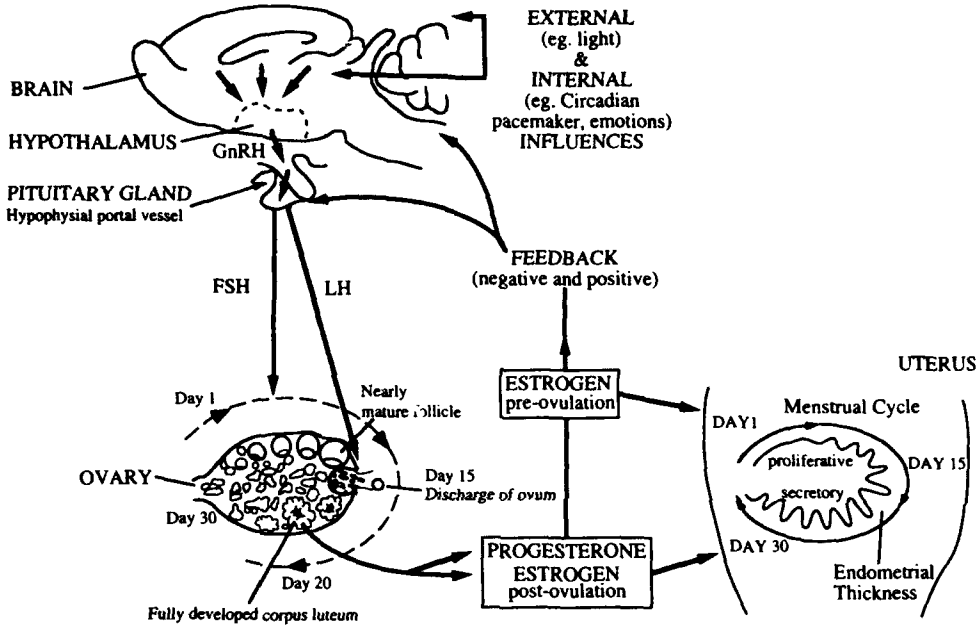
threshold for onset of a thermoregulatory effector response is interpreted as a decrease in the set-point temperature for neuronal activation of that thermoregulatory effector response. Both heat acclimation and physical training decrease the core temperature threshold for onset of cutaneous vasodilation and sweating [91, 96], while dehydration causes an increase in the core temperature threshold for onset of thermoregulatory effectors acting to dissipate heat [90]. Depending on the time of day used as the reference, the core temperature thresholds for onset of cutaneous vasodilation and sweating are either increased or decreased [117]. These threshold modifications may be the most useful indicator in human thermoregulation that there has been a change in the set-point temperature.

MENSTRUAL CYCLE

The reproductive system has an important role in modulating thermoregulation in women, at least in that core temperature is regulated at a higher temperature during the luteal phase compared with the follicular phase of the menstrual cycle. This regulated elevation in basal body temperature during the luteal phase may be necessary to provide the proper environment for implantation of the zygote in the uterus or it may be a vestigial event resulting from cyclic neuroendocrine changes in the brain. No matter how the luteal phase elevation in basal body temperature evolved, it is an interesting feature of thermoregulation in humans. Before reviewing how the menstrual cycle affects thermoregulation, a brief and simplified description of female reproductive physiology is presented. The detailed diagram of the reproductive system of women, modified from Fink [32], depicts the complex neuroendocrine interactions that occur throughout the reproductive cycle in the brain, including the hypothalamus, the anterior pituitary gland, and in the ovary and uterus (Fig. 8.2). Other factors that influence reproductive integration, such as light and circadian pacemakers, are also indicated. Figure 8.3 (modified from Fink [32] and McLachlan et al. [86]) shows the variation in circulating hormones from the pituitary and ovary, and core temperature changes.

The term "menstrual cycle" describes the approximately monthly rhythm in the function of the uterine endometrium, while the term "ovarian cycle" describes the cyclic change in ovarian function over the same time. The terminology of the ovarian and menstrual cycles is often interchanged so that the terms "follicular" and "luteal" phases of the menstrual cycle connote changes in ovarian hormone status. Because the ovarian and uterine cycles are the same length, the generic term "menstrual cycle" is used to include both of these cycles, as well as the neuroendocrine cycle of the brain. The reproductive cycle varies in

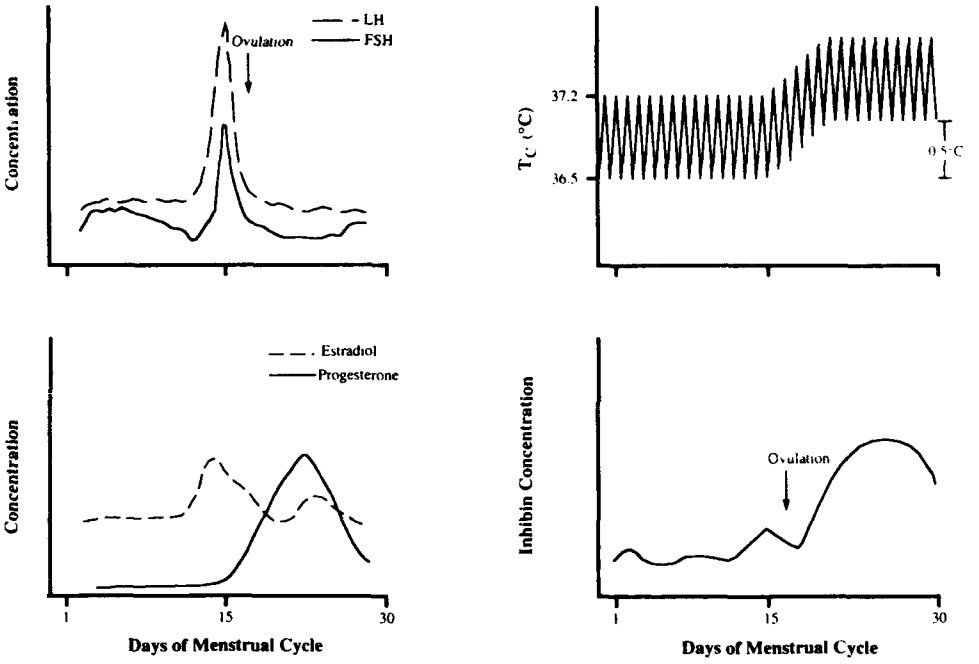
FIGURE 8.2
Schematic diagram of the female reproductive system including the hormonal interactions among the **brain, hypothalamus, pituitary, ovary** and **uterus** *during a 30-day menstrual cycle. This figure was modified from Fink, G. Gonadotropin secretion and its control. E. Knobil and J. D. O'Neill (eds).* The Physiology of Reproduction. *Vol. 1. New York: Raven Press, 1988.*



women from 27–35 days [122], but for this review, a reproductive cycle length of 30 days will be used.

The onset of menses is designated as the first day of the menstrual cycle in Figures 8.2 and 8.3. This presentation of time of the menstrual cycle is fine for a review, but it is more useful to depict changes in ovarian and pituitary hormones during the reproductive cycle as a function of time from the luteinizing hormone (LH) surge. The LH surge can then be used as a biological marker for each individual to standardize menstrual cycles of varying length. The time during which the follicle grows and matures is called the follicular phase of the ovarian cycle (days 1–14). Menses occurs from day 1 through approximately day 7, during which time the process of follicle recruitment occurs in the ovary [49, 60]. Several follicles (cohort) grow when follicle-stimulating hormone (FSH) is at a fairly high concentration from days 2–5 [86]. By approximately day 7, a dominant follicle is evident (Fig. 8.2), FSH decreases, and the rest of the cohort become atretic. As the dominant

FIGURE 8.3
*Schematic representation of pituitary (***LH** *and* **FSH***) and ovarian (***estradiol, progesterone,** *and* **inhibin***) hormonal and daily core temperature (*$\mathbf{T_C}$*) fluctuations during a 30-day menstrual cycle. This figure was modified from Fink, G., Gonadotropin secretion and its control. E. Knobil and J. D. O'Neill (eds).* The Physiology of Reproduction. *Vol. 1. New York: Raven Press, 1988, and McLachlan, R. I., D. M. Robertson, D. L. Healey, H. G. Burger, and D. M. deKrester. Circulating immunoreactive inhibin levels during the normal menstrual cycle.* J. Clin. Endocrinol. Method. *65:954–961, 1987.*



follicle increases in size (days 7–14), it produces greater quantities of estradiol and some progesterone (Fig. 8.3 [43]). The theca cells of the follicle become more vascularized [82]. Circulating estradiol secreted from the dominant follicle is necessary for the proper pulsatile frequency and amplitude in the secretion of gonadotropin-releasing hormone (GnRH) by the anterior hypothalamus [32, 60] in response to a neural pulse-generating signal [32, 134]. The combination of estradiol and GnRH increases the sensitivity of the gonadotropes in the anterior pituitary gland so that both FSH and LH secretion are increased [32]. In addition, increased circulating estradiol stimulates the endometrium of the uterus [21] during the proliferative phase of the menstrual cycle

(days 7–14). By day 13–14, estradiol secretion from the dominant follicle is at its peak [43, 60, 86], and progesterone is slightly elevated.

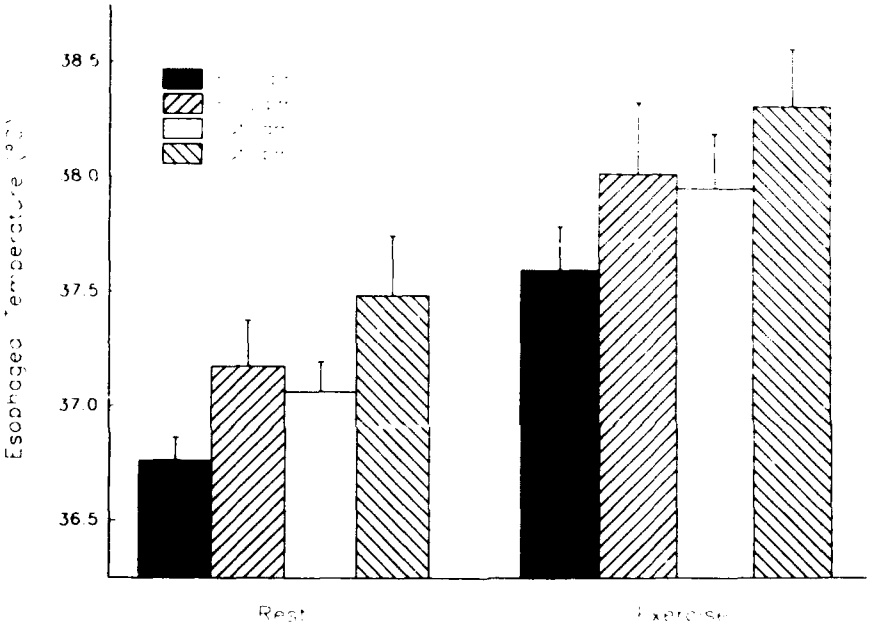
In response to a neural signal [32], a GnRH surge is generated approximately 12 hr after the estradiol peak [60] causing both the FSH and LH surge on day 14–15 (Fig. 8.3). LH stimulation of the dominant follicle causes increased follicular blood flow and edema as well as increased prostaglandin synthesis. About 9 hr after the LH surge [60], *ovulation occurs* (Fig. 8.2) by follicle rupture [82].

After the LH surge and ovulation, the follicle involutes to become the corpus luteum. The gonadotropin surges and prolactin (PRL) secretion trigger changes in the enzymes of the granulosa (FSH, LH, PRL) and theca (LH, PRL) cells of the follicle so that they change from producing mainly estrogen to secretion of large amounts of progesterone [43]. The luteal phase of the ovarian cycle lasts 14 days, and the ovarian and pituitary hormones fluctuate during that time (Fig. 8.3). LH maintains the corpus luteum and enables progesterone secretion to become maximal during the midluteal phase [43]. During the luteal phase, estrogen and progesterone stimulate secretory activity in the uterine endometrium to support implantation (Fig. 8.2). Inhibin, another hormone secreted by the corpus luteum (Fig. 8.3 [112]), has approximately the same pattern of release during the luteal phase as does progesterone [86]. McLachlan et al. [86] have proposed that inhibin acts to decrease FSH release from the anterior pituitary during the luteal phase to arrest follicle stimulation. The LH pulse interval is greatly increased in the late luteal phase [49], probably because of changes in the GnRH pulse generator [97, 121]. When inhibin decreases in late luteal phase, FSH secretion increases, which begins the process of recruitment of the next cohort of follicles [49, 86, 112]. Progesterone and estradiol secretion also decrease dramatically in the late luteal phase, which is associated with curtailment of endometrial secretion and triggers endometrial necrosis and sloughing. Initiation of menses occurs and the reproductive cycle is repeated.

Considerations for Timing of Experiments

Core temperature exhibits a rhythm during the menstrual cycle in which body temperature is approximately 0.4°C higher in the luteal phase (after ovulation) than during the follicular phase [69, 98]. In addition, there is also a circadian rhythm in body temperature as shown in Figures 8.3 and 8.4 [113]. The impact of these distinct rhythms on resting esophageal (core) temperature for four women at two different times of day during the follicular and luteal phases of the menstrual cycle is shown on the *left side* of Figure 8.4. These resting body temperatures range from 36.76°C during early morning in the follicular phase to 37.48°C during the afternoon of the luteal phase, a 0.72°C (1.30°F)

FIGURE 8.4
Mean [illegible]D equilibrated esophageal temperatures measured at rest and during exercise (60% peak $\dot{V}O_2$) for experiments conducted in the early mornings and midafternoons during the follicular and luteal phases of the menstrual cycle. Environmental conditions were 35°C, 30% relative humidity (rh). Adapted from Stephenson, L. A., and M. A. Kolka. Menstrual cycle phase and time of day after reference signal controlling arm blood flow and sweating. Am. J. Physiol. *249:R186–R191, 1985.*



difference in resting core temperature! Statistical analysis of the individual data on the *left side* (resting) of Figure 8.4 indicates that core temperature is significantly different at all measured times ($P<0.01$).

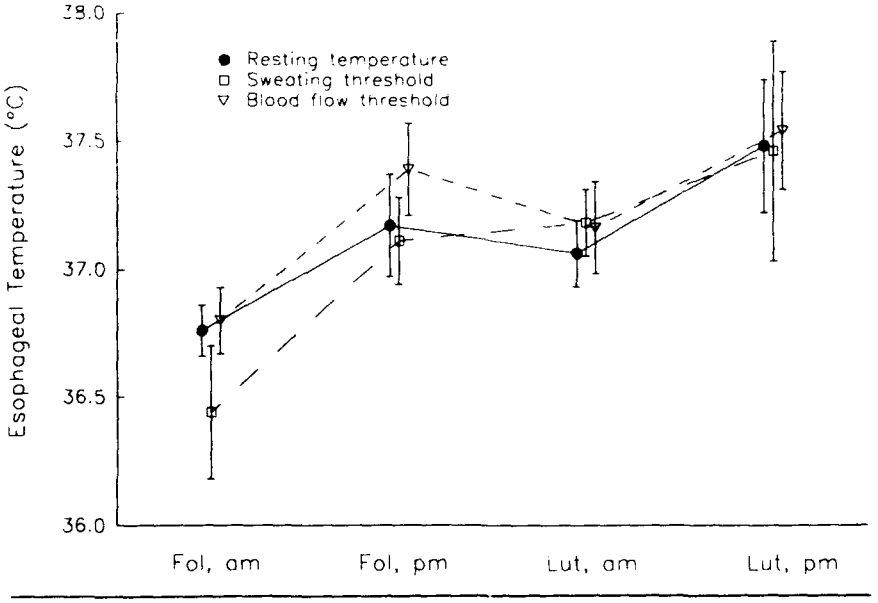
Furthermore, the exercise data presented on the *right side* of Figure 8.4 indicate that resting core temperature recorded in the afternoon of the luteal phase is very similar to the core temperature measured during 30 minutes of moderate exercise in the early morning of the follicular phase experiments. If either the time of day, or menstrual cycle phase are mixed in the individual data that comprise the mean data shown in Figure 8.4 (for example, two subjects in each of morning, afternoon, follicular phase, or luteal phase), statistical differences in core temperature disappear ($P=0.48$). This example shows the effect about which Cunningham et al. [24] warned when they stated: "Such an experimental

design tends to maximize variability within each phase, and to minimize the difference between the follicular and luteal phases."

Both experimental design and timing of experiments can influence the findings of a particular investigation. Many published papers indicate no clear difference in measured thermoregulatory parameters between menstrual cycle phases or between genders [2, 36, 129]. Generally, a closer examination indicates that the starting point in core temperature for the women used in those studies was mixed by time of day or menstrual cycle phase, thus there was an a priori bias toward finding insignificant differences. Not only can the timing of steady-state exercise or equilibrated resting temperatures affect statistical comparisons and the significance of research findings, but in addition, the core temperature thresholds for thermoregulatory effectors (sudomotor, vasomotor, shivering) are affected by time of day and menstrual cycle phase. This point is illustrated (Fig. 8.5) for the same core temperature data shown in Figure 8.4. In this example, the pattern of variability in resting core temperature is similar to that of both sudomotor and

FIGURE 8.5

*Mean ± SD esophageal temperatures at rest during the morning and afternoons of both follicular and luteal phase experiments (***closed circles***). The core temperature for the onset of sweating (***squares***) and skin blood flow (***triangles***) during exercise are superimposed on the resting core temperature data for circadian and menstrual cycle variability.*



vasomotor core temperature thresholds. Clearly, menstrual cycle phase, as well as time of day, must be controlled when evaluating thermoregulatory function in women [113].

PHYSIOLOGICAL RESPONSES

The tolerated core temperature in humans is relatively narrow, ranging from 36–40°C [131]. Outside of this temperature range, thermoregulation is impaired or even lost. Humans routinely change their behavior to offset possible changes in body temperature, and have exquisite physiological mechanisms to regulate body temperature closely.

Cold Stress

At rest in a neutral environment, blood flow to the skin can be 0.2–0.3 liters·min^{-1} and, under severe cold stress, skin blood flow approaches zero [64]. During mild cooling of the skin and core, venoconstriction of cutaneous vessels increases the volume of the deeper veins. If cooling of the skin and core is more severe, additional heat-conserving vasoconstriction of surface vessels occurs, further increasing the volume of deeper veins [99]. Increased central venous blood volume inhibits antidiuretic hormone (ADH) release, which then causes diuresis and water loss. Elevated cardiac output, cardiac stroke volume, arterial pressure, and total peripheral resistance can accompany severe cold stress [99]. At rest in the cold, heat production increases secondarily to the initial venoconstriction and vasoconstriction [80] by increased metabolic rate and shivering. Since heat is lost from the body proportionally to surface area/mass, and smaller individuals have a smaller thermal mass and larger surface area to mass, smaller individuals (i.e., women) are less resistant to cold stress than larger individuals.

Exercise is associated with cutaneous vasoconstriction [64], which when combined with cold stress increases vasoconstrictor outflow to cutaneous arterioles to increase insulation and decrease heat loss from the body surface. During exercise in moderately cold environments, heat production dramatically increases and heat retention can be controlled behaviorally by varying the layers of clothing worn [41].

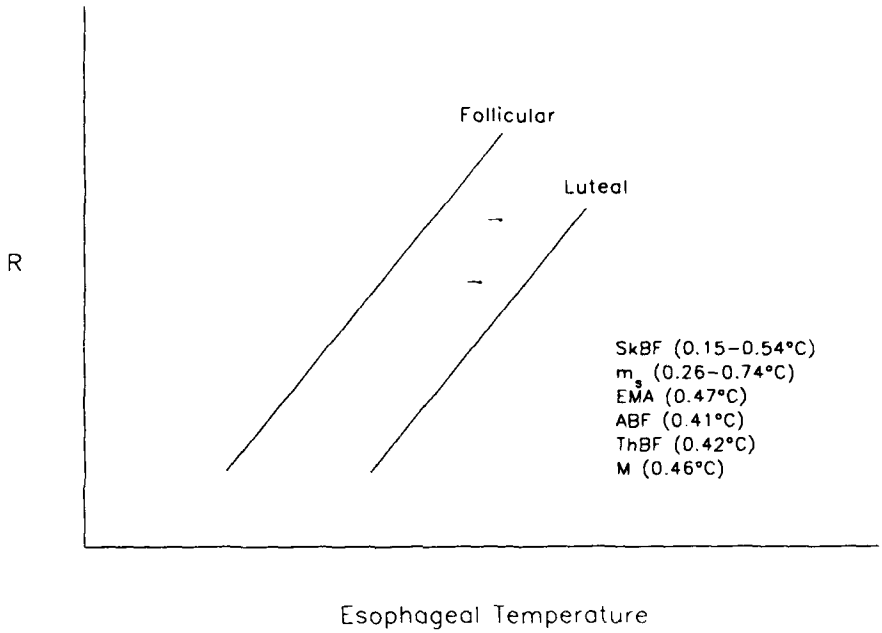
Differences in thermal mass, body surface area, surface area to mass, limb proportions, and distribution and amount of body fat all influence heat exchange in a cold environment by affecting heat production (lower muscle mass = lower heat production), insulation, or effective area for heat loss. Over 50 years ago, it was recognized that little was known about responses of women upon exposure to environmental cold stress [53]. Since that time, many descriptive studies comparing gender responses to cold stress have been done, but little effort has been spent to examine possible physiological mechanisms for differences between the genders, or the possible influence of menstrual cycle phase [44]. Nunneley [93]

and, more recently, Graham [45], have summarized gender differences in the responses to cold stress (in both air and water) at rest and during exercise. In general, women resting in a cold environment have lower skin temperatures and, therefore, lower core to skin thermal conductance than men [24, 30, 45, 53, 133]. In cold-water immersion, women cool at faster rates than men [56, 76, 84].

In the mid-1980s, Hessemer and Brück characterized the effect of varying menstrual cycle phase on thermoregulation in women exposed to cold air [58, 59]. Heat production (metabolic rate) and electrical muscular activity were measured during cold exposure to ascertain the onset of shivering in the midfollicular and midluteal phases of the menstrual cycle. As earlier noted, body temperature is regulated at a higher level in the luteal phase in women with normal ovulatory menstrual cycles. This higher body temperature at rest, 0.6°C in this study, was associated with a higher core temperature threshold for heat production, measured by both increased muscular activity and increased oxygen consumption. These core temperature thresholds averaged 0.47°C higher in luteal phase experiments than in follicular phase experiments (see Fig. 8.6). So, the core temperature thresholds for the onset of thermoregulatory effectors to prevent body cooling occurred at higher core temperatures in the luteal phase compared with the follicular phase. Over 20 yr ago, two different laboratories demonstrated behavioral thermoregulatory changes to cooling [23, 68]. These behavioral changes were: *(a)* women sensed skin cooling more quickly in the luteal phase [68], and *(b)* women had a higher skin temperature preference in the luteal phase [23]. Both behavioral [23, 68] and autonomic thermoregulatory function [58, 59] were altered during the luteal phase so that the higher core temperature was maintained. Both of these modifications are consistent with an $\uparrow T_{set}$ in the luteal phase of the menstrual cycle.

During exposure to cold water, skin temperature is held constant or "clamped" so gender differences observed in skin temperature during cold air stress disappear. In general, women cool faster in cold water than men do [56, 76, 84]. In fact, in men and women matched for body fat percentage, McArdle et al. [84] observed faster cooling rates in both 20°C and 24°C water in women. Kollias et al. observed that women (22% fat) cooled at the same rate as men (15% fat) in 20°C water [76]. Increased body fat in women does provide insulation during water immersion [45], but the larger surface area to mass ratio and lower mass contributing to heat production in women certainly contribute to faster cooling during water immersion in women compared with men. At warmer water temperatures, Rennie et al. reported that women required a warmer water temperature than men did during water immersion that could be tolerated for 3 hr [95]. Women have a similar heat production effector response (increased metabolism to decreased core temperature)

FIGURE 8.6
*Summary of changes in thermoregulatory effector (***R***) function, during* **follicular** *and* **luteal** *phase experiments, showing the higher core temperature thresholds for both heat loss and heat production mechanisms.* **SkBF,** *skin blood flow [113];* $\mathbf{m_s}$, *local sweating [73, 113];* **EMA,** *electrical muscular activity [58];* **ABF,** *arm blood flow [58, 59];* **ThBF,** *thumb blood flow [58];* **M**, *metabolic rate [58].*



as men have during cold water exposure even though women cool at a faster rate than men do [56, 84].

In studies combining cold-water immersion with exercise, there are no differences in cooling if men and women exercise at the same absolute work intensity [76, 85]. However, the women are exercising at a higher percentage of their maximal aerobic power, which directly relates to the rate and amount of heat storage [101]. Yet, if men and women exercise at the same percentage of their maximal aerobic power, women cool faster than men do [44], illustrating the imbalance between heat loss and heat production.

Women have lower skin temperatures than men during cold air exposure [24, 53, 118, 124, 133], perhaps because of their greater body fat. The lower temperature of the general body surface reduces the gradient for sensible heat flux between the skin and the environment and helps prevent a decrease in core temperature during cold exposure [53]. Hardy et al. [53] and Wyndham and colleagues [133] reported

similar core temperatures in men and women exposed to cold air at rest, while Cunningham et al. [24] and Wagner and Horvath [125] reported slightly higher core temperatures in women than men resting in the cold. There were no differences between genders in the skin temperature of acral areas, so women are probably not at a greater risk for peripheral cold injuries than men [124, 133].

The lower skin temperature seen in women at rest in cold environments is also observed during exercise [44, 46, 118, 126]. At similar absolute exercise intensities [46], men increase heat production whereas women decrease skin temperature (lower thermal conductance from core to skin) to maintain core temperature. However, during exercise at similar relative exercise intensities, core temperature in women decreases after 2 hr while men maintain their core temperature during that time [44]. This is another indication that heat loss exceeds heat production and heat conservation faster during exercise in a cold environment in women than in men.

Although $\uparrow T_{set}$ was described by the higher core temperature threshold for the onset of heat production during the luteal phase of the menstrual cycle [58, 59], additional studies of thermoregulatory effector function during cold exposure throughout the menstrual cycle are necessary. Graham [44] was unable to detect differences in rectal and skin temperature responses during exercise in cold air between the follicular and luteal phases. Mittleman and Mekjavic [88] have recently described a method for characterizing heat production effector responses as a function of decreasing esophageal temperature during cold-water immersion. Using their techniques, effector changes in heat conservatory and heat-producing thermoregulatory function associated with reproductive status may be characterized during water immersion.

Heat Stress

Exposure to the heat, even in a resting individual, requires active thermoregulatory effector mechanisms to maintain core temperature. During exercise, muscular contraction results in increased heat production, whereas at rest, when the ambient temperature is higher than the skin surface temperature, heat will be transferred from the environment to the body. Skin temperature is set by the environmental temperature and will reach a level imposed by the ambient conditions [42]. The same conductive and convective heat exchange avenues that remove heat from the body core to the skin surface transport heat from the body surface to the core. When core or skin temperatures are elevated, heat loss mechanisms are activated (via proportional control, Fig. 8.1), and sweat secretion and blood flow to the skin surface increase. Heat can then be eliminated by evaporative heat loss and by dry heat loss (if skin temperature exceeds ambient temperature). Evaporative heat loss is determined by the water vapor pressure gradient between the skin and

the environment. High sweating rates increase body water loss, initially from extracellular compartments. In addition, a greater proportion of the blood volume is directed to the skin vascular beds for heat dissipation from the core to the skin and from skin to the environment. In fact, skin blood flow can reach 8 liters $\cdot min^{-1}$ or up to 60% of the cardiac output during heat stress [64], which will increase cardiovascular strain.

During exercise, if the heat of muscular contraction is not dissipated, core temperature would increase to an intolerable level within minutes. However, after a short time lag, increasing core temperature is sensed by the PO/AH, and neurons activating sweat secretion are stimulated. Subsequently, heat loss occurs by evaporation at the skin surface. If the water vapor pressure in the ambient air is high, evaporation of secreted sweat will not occur, and heat will not be dissipated. In the same way, increasing core temperature results in increased blood flow to the skin surface. At the skin, heat can be transferred to the environment by radiative and convective (R + C, dry) heat flux when the skin temperature is higher than the ambient temperature. If the ambient temperature is warmer than the skin surface temperature, heat is gained by the body.

Haslag and Hertzman [55] demonstrated that the onset of thermoregulatory sweating during whole body heating occurred at a higher core temperature in women during their luteal phase compared with their follicular phase. In addition, as mentioned earlier, women preferred a higher skin temperature in the luteal phase than during the follicular phase [23]. These observations suggested that the higher core temperature observed in the luteal phase was regulated. Changes in both behavioral and physiological thermoregulation [23, 55] were attributed to an elevation in the thermoregulatory set-point during the luteal phase of the human menstrual cycle. Thus, in a warm environment, the threshold for onset of sweating is at a higher temperature during the luteal phase in resting women, which serves to regulate core temperature at the higher temperature [55]. Central thermosensitivity is apparently not affected by the menstrual cycle, at least in the follicular and ovulatory phases, as indicated by thermal latency and sensitivity of sweat glands to acetyl-β-methylcholine stimulation [102].

The higher core temperature for sweating onset in women resting in a hot environment in their luteal phase compared with their follicular phase was confirmed by Bittel and Henane [6]. More recently, the effect of the menstrual cycle on effector function in women was investigated at rest and during exercise by two laboratories (Fig. 8.6 [58, 59, 73, 113]). Stephenson and Kolka reported higher core temperature thresholds for onset of both thermoregulatory sweating [73, 113] and cutaneous vasodilation [113] during exercise in a hot environment for women in the luteal phase of the menstrual cycle when compared with the follicular phase. Threshold changes in the onset of sweating and skin blood flow demonstrate that the thermoregulatory set-point was increased in the

luteal phase, and fulfill the criterion [40] that a change in the thermoregulatory set-point must be observed by parallel changes in all involved thermoregulatory effectors (see Fig. 8.6).

Gender differences in autonomic thermoregulatory effector function during exercise have been reported [24, 92, 96]. The core temperature thresholds for both sweating and vasodilation were higher in women than in men. Menstrual cycle phase was not standardized in these studies [24, 92, 96], although it had been previously reported that preovulatory women respond to body heating similarly to men, but different than their own postovulatory responses [55]. The observations of these investigators [24, 92, 96] are similar to those reported by Fox et al. [34] and Morimoto et al. [89] and suggest that at a given core temperature, sweating and skin blood flow are lower in women compared with men. Men and women were compared while working at the same absolute exercise intensity, which required women to exercise closer to their maximal aerobic power than did the men [92, 96].

If the data of untrained men and trained women are compared [92], the differences between the men and the women narrow, even when the menstrual cycle phase of the women is not standardized. Also, if there was a disparity in training history between the men and the women, autonomic effector function may not be all that different between women in the follicular phase and men. In support of this, training appears to $\downarrow T_{set}$ as indicated by a lower core temperature threshold for the onset of cutaneous vasodilation and sweating during exercise [96]. In fact, the thermoregulatory responses of men and women were shown to be similar during exercise and moderate heat stress [74, 75] when the women were studied in only the follicular phase of the menstrual cycle, and the women had trained as many years as the men did. There were no differences in either the core temperature thresholds or the slopes of skin blood flow and sweating to core temperature between men and women (follicular phase) during the same environmental and exercise stress [74, 75]. If thermoregulatory effector responses are to be compared between genders, or if both men and women comprise the study population, it is essential that women be studied in the early follicular phase.

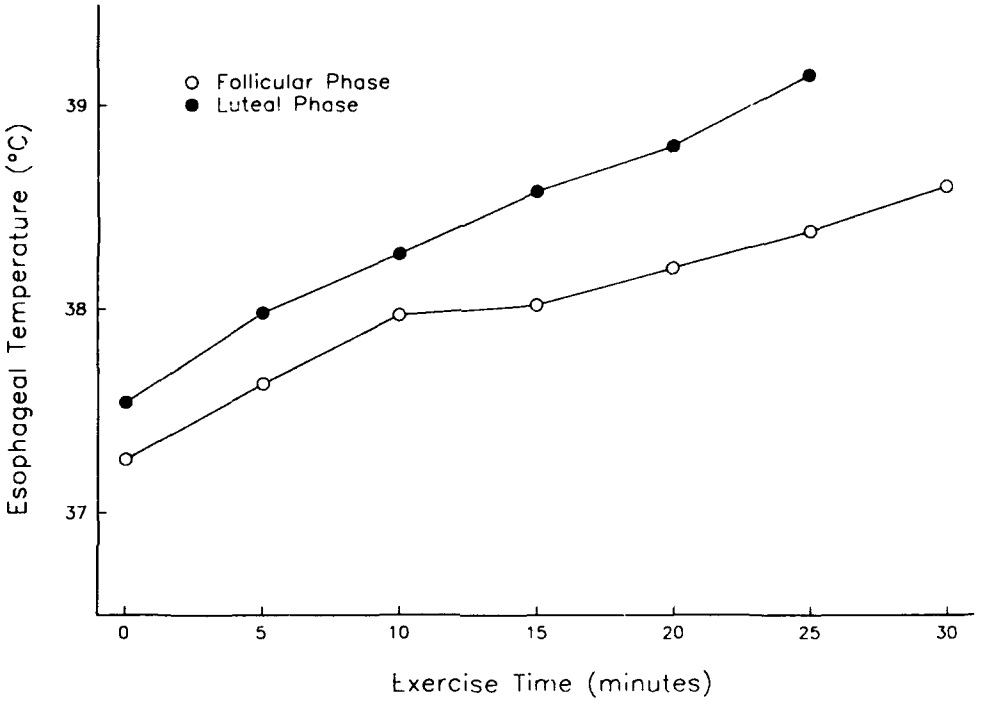
There were a number of other investigations between 1940 and 1978 that described how women respond to heat exposure [15, 30, 34, 40, 53, 55, 68, 89, 102, 127, 152]. Nunneley [93], in her review of 1978, interpreted these data as being qualitatively similar between men and women. Yet, for the most part, women had higher core and skin temperatures, higher heart rates, lower sweating rates, and later onset of sweating (determined by time and core temperature) than men had when both groups were exposed to the same environment. In 1969 Fox et al. [34] and in 1975 Bittel and Henane [6] reported that women began to sweat at higher core temperatures than did men, suggesting a delay in

thermoregulatory heat loss that could lead to decreased heat tolerance. Wyndham et al. [132] and Morimoto et al. [89] reported lower sweating rates during heat exposure in women compared to men. However, Haslag and Hertzman [55] reported that the women studied before ovulation had similar sweating onset during passive heating to men. In these early studies, the men were more fit than were the women. Since tolerance to heat is related to aerobic fitness [16, 29, 39], some of the reported differences in heat tolerance between men and women might be, again, accounted for by differences in aerobic fitness. Anthropometric differences between genders can also affect heat loss to the environment, since women generally have a larger surface area to mass, heat gain is greater in severely hot environments [93]. Therefore, women may be at a disadvantage in severely hot environments.

Many studies were done comparing the responses of men and women to heat stress in the late 1970s and early 1980s [2, 3, 22, 25, 29, 31, 33, 35–37, 61, 62, 106–108, 128–130]. These papers compared men and women exercising at low intensities in a wide range of hot and humid environments. Some studies considered individual characteristics such as maximal aerobic power, body fat, or body surface area in an attempt to eliminate differences between men and women associated with any of these factors [2, 29, 35, 36, 107, 128]. In all cases, men had higher sweating rates than women did during light exercise in hot, dry conditions. Otherwise, the responses of men and women were similar during light exercise in warm to hot environments. Unfortunately, few of these investigators controlled experiments for menstrual cycle phase [2, 36, 62, 130], and only Horvath and Drinkwater [62] showed differences in resting core temperature between menstrual cycle phase. The general findings suggest that during light to moderate exercise in dry heat, women sweat less and have higher heart rates and core temperatures than do men [2, 35–37, 107]. If men and women exercise at the same percentage of their maximal aerobic power, and are matched for cardiovascular fitness, these differences narrow, especially during light exercise [2, 35–37, 107, 128]. Men still have higher sweating rates in dry environments. However, it was also reported that women may be more efficient "sweaters" during exercise in humid environments, as more of their secreted sweat was evaporated and less sweat drippage occurred [2, 35].

It has been suggested that during long duration exercise or heat exposure, differences observed in resting core temperature during the follicular and luteal phases of the menstrual cycle will be eliminated, and may be one reason for the lack of significant findings in some studies [58, 59]. Esophageal temperature data for a single exercising subject (80% peak $\dot{V}O_2$, 35°C) are shown in Figure 8.7 for both the follicular and luteal phases (Stephenson and Kolka, unpublished observations). At no time during the first 30 minutes of heavy exercise was the difference in core

FIGURE 8.7
Esophageal temperature *during exercise (80% peak* $\dot{V}O_2$*) in both the* **follicular** *and* **luteal** *phases of the subject's menstrual cycle. Environmental conditions of the experiments were 35°C, 20% rh (Stephenson and Kolka, unpublished observations).*



temperature less than that observed at rest between menstrual cycle phases. In fact, it appears that the difference in core temperature may be increasing. During 2 hr of low-intensity exercise in a hot environment, core temperature differences observed at rest among the follicular, ovulatory, and luteal phases were increased by approximately the same magnitude [19]. Further, it was recently reported by Pivarnik and colleagues [94] that, during exercise (65% peak $\dot{V}O_2$) in a cool environment (22°C), rectal temperature continued to increase throughout a 1-hr experiment during the luteal phase, whereas during the follicular phase, rectal temperature reached a steady-state after approximately 30 min. Also, the heart rate was significantly increased during exercise in the luteal phase when compared with the follicular phase. It was suggested that the inability of women to reach thermal equilibrium during exercise in the luteal phase was mediated by progesterone [94].

Skin blood flow responses are different during the follicular and luteal

phases of the menstrual cycle [1, 58, 59, 67, 68, 113, 116]. In general, limb blood flow is higher during the luteal phase compared with the follicular phase [4, 58, 59, 67, 68], which indicates that vascular responses vary with the changes in hormonal status during the menstrual cycle. Stephenson and Kolka have shown that the onset of vasoconstrictor activity during sustained heavy exercise is at both a higher skin blood flow and core temperature during the luteal phase than the follicular phase [116]. These observations suggest that heat transfer to and from the skin surface can be modified by menstrual cycle phase.

Postmenopausal women have similar thermoregulatory responses to 2 hr of heat exposure as do younger women [28]. The time and core temperature at which sweating was initiated, heat storage, skin blood flow, evaporative heat loss, and plasma volume changes were not different between the two groups of women, although phase of the menstrual cycle was not controlled in the premenopausal group. Drinkwater et al. [28] concluded that the function of the sweating mechanism of active postmenopausal women was not different from premenopausal women.

Fluid Volume Issues

Changes in vascular and extravascular fluid volumes impact significantly on thermoregulatory function, as sweating and skin blood flow responses to heating or exercise are attenuated when these fluid volumes are decreased (see [54] for review). Plasma volume decreases in euhydrated women at rest in hot environments [105, 114]. However, Wells and Horvath reported higher plasma volumes in women resting in a hot environment [129]. In most cases, during treadmill [29] and cycle exercise [33, 38, 72, 114, 115] in hot environments, plasma volume decreases. An expansion of the plasma volume after treadmill exercise was reported [130]; however, these data were complicated by positional changes in the subjects between blood samples [54]. Also, in one study [104], hemodilution occurred in both men and women during light exercise on a treadmill in a hot environment, but the resting blood sample was drawn in a cool environment. Increased skin temperature upon moving from a cool to a hot environment would be expected to cause a hemodilution [54].

Differences in plasma volume during the follicular and luteal phases of the menstrual cycle at rest or during exercise have been reported [38, 72, 114, 115]. Other investigators [33, 129, 130] indicated equivocal results. Those studies reporting differences show that resting plasma volume is lower during the luteal phase than the follicular phase [72, 114, 115], and a greater volume of vascular fluid is shifted during exercise and/or heat stress during the follicular phase than the luteal phase [38, 72, 114, 115]. There is some evidence [114] that a lower limit for plasma volume reduction during exercise or heat stress exists during

the luteal phase. The variations in plasma volume at rest and during exercise that are observed during different menstrual cycle phases are similar in magnitude to the reported effects of posture, skin temperature, or perhaps even exercise intensity [54].

Aldosterone [27, 48, 66], plasma renin activity (PRA) [115], renin [66], and angiotensin [66] are higher in the luteal phase compared with the follicular phase of the menstrual cycle. The higher concentrations of these fluid regulatory hormones persist during both moderate [115] and heavy exercise [27] as aldosterone [115], PRA [27, 115], and vasopressin PVP [27] are higher during, and following, exercise in the luteal phase than the follicular phase. The increased aldosterone, PRA, and PVP during the luteal phase are consistent responses to the stimulus of decreased plasma volume. Each of these hormones will act to maintain fluid intravascularly and each participates in blood pressure regulation.

MENOPAUSE, PREGNANCY AND MENSTRUAL DYSFUNCTION

It is sometimes discouraging to study the physiology of women because our understanding of how the reproductive cycle impacts on other regulatory systems is far from complete. However, changes in reproductive status such as menopause, pregnancy, or menstrual dysfunction might provide an excellent opportunity to study how the reproductive system interacts with other regulatory systems, in particular, thermoregulation.

Amenorrhea/Menstrual Dysfunction

Amenorrhea is the term used to describe the absence of menses and is associated with infertility. Reduced follicular phase length and luteal phase insufficiency are other types of menstrual dysfunction associated with abnormal menstrual cycle length and anovulation [123]. In 1940, Hardy and DuBois observed that an amenorrheic female did not increase her metabolism during exposure to cold air like eumenorrheic women did [53]. These authors were not convinced that this observation was significant. It was shown 50 years later that amenorrheic women have lower core temperatures than eumenorrheic women when both groups rested in a cool (22°C) environment [47]. Core and skin temperature responses to cooling (22°C and 5°C) at rest and during exercise were similar between amenorrheic and eumenorrheic women. However, the amenorrheic women had lower finger temperatures than the eumenorrheic women while resting at 22°C [47]. In addition, increased heat production in response to body cooling was delayed in amenorrheic compared with eumenorrheic women. Conversely, there were no reported differences in core temperature, skin temperature, or sweating rate between amenorrheic and eumenorrheic women during light treadmill exercise in a hot environment [37].

In another report [94], a woman was studied during an hour of moderate exercise during both the follicular and luteal phases of her menstrual cycle. Low progesterone concentration measured during the luteal phase indicated luteal insufficiency and it was presumed that she did not ovulate. The resting core temperature of this woman was lower in the luteal than in the follicular phase, which likely indicates that T_{set} was not increased in her "luteal" phase. This woman also did not exhibit the uncompensated increase in rectal temperature during the last 20 min of exercise as the other women did [94]. One reason that her core temperature was maintained during prolonged exercise in the luteal phase was that her skin temperature was about 1°C higher than the mean skin temperature of the normally ovulating women. Increased skin temperature would increase dry heat loss, thereby decreasing heat storage. Also, the anovulatory woman did not have an increased heart rate during exercise in the luteal phase as the normally ovulating women did, which reflects her lower cardiovascular strain in conjunction with lower heat storage. Pivarnik et al. [94] attributed the better thermoregulatory capability of the anovulatory woman to her low progesterone concentration in the luteal phase.

Pregnancy

Physiological changes associated with pregnancy can impact on thermoregulatory function in women. McMurray and Katz [87] have recently reviewed critical issues associated with thermoregulation during pregnancy. Possible teratogenic effects of increased body temperature during exercise and/or heat stress early in pregnancy, and the maintenance of uterine blood flow as pregnancy continues, are of primary concern. Two studies reported thermoregulatory function during aerobic exercise through 32 weeks of gestation [20, 65]. The intensity of the exercise decreased with time of pregnancy. However, these women were able to regulate core temperature effectively in temperate environments into the third trimester [20, 65, 87]. In general, exercise at either high intensity or long duration is probably not appropriate during pregnancy due to the risks of hyperthermia and dehydration [87]. There is no evidence that temperature regulation is impaired, but blood pressure regulation can be adversely affected by pregnancy. Therefore, thermoregulation might also be influenced because the two systems closely interact [99].

Menopause

The process of menopause begins when normal cyclic ovarian function is intermittently disrupted, and is manifested by either reduced follicular phase length or luteal phase dysfunction [123]. Both conditions are associated with anovulatory cycles. Steroidogenesis by the follicle and the corpus luteum are impaired so that the neuroendocrine balance of the

menstrual cycle is upset [123], which causes further disruption of follicle growth (Fig. 8.2). The process of menopause is complete when the follicles within the ovary are depleted. Estrogen, progesterone, and probably inhibin concentrations are markedly reduced while FSH and LH concentrations are greatly increased [123]. It is thought that GnRH is secreted in high concentration during the process of menopause and is the stimulus for the elevated LH concentrations. Hot flashes are experienced by 75% of women undergoing menopause [77]. Estrogen and progesterone replacement therapy is effective in reducing hot flashes.

The changes in thermoregulatory effector function that occur during menopause present an interesting topic for students of temperature regulation [79]. The hot flush or hot flash is associated with physical and emotional discomfort [77, 78]. During a hot flash, a woman will have increased blood flow (higher skin temperature) and sweating at various areas of the skin surface [123]. These events occur more often when the skin is hot (high environmental temperature) than when the skin is cool [78]. Lomax et al. [83] have suggested that the hot flash is triggered by a downward setting of the regulated core temperature or $\downarrow T_{set}$, which immediately gives rise to a "feeling of hotness." A $\downarrow T_{set}$ is then followed by $\uparrow$ thermoregulatory heat dissipation effector activity, that is, sweating and increased blood flow to the skin surface to dissipate body heat so that core temperature decreases to the transiently $\downarrow T_{set}$. It has been suggested that vasomotor changes associated with a hot flash are related to the pulsatile LH release, or perhaps to GnRH activity in the PO/AH [120].

Menopausal hot flashes are of short duration [78] and may be initiated by a transient decrease in T_{set}. Such a short duration shift in T_{set} is a somewhat unique observation in thermoregulatory integrative function. In contrast, the circadian alteration in T_{set} develops over several hours. Another quickly developing modulation in T_{set} may be associated with transitions between arousal states [57, 81, 100]. The postulated $\downarrow T_{set}$ of the hot flash is temporally consistent with changes in GnRH, FSH, and/or LH pulses, but could just as easily be associated with neurotransmitter oscillator(s) or pulse generators because the hot flash appears to precede increased LH [120, 123]. Withdrawal of the cyclic feedback action of estrogen and progesterone during menopause would be expected to alter the pulse frequency and/or pulse amplitude of neuromodulators controlling hypothalamic release of GnRH because that normally happens during the menstrual cycle [97, 134]. Studies that show that individual temperature-sensitive and I neurons are multisensory [10, 12] suggest that menopausal neuroendocrine modulations could impact on either or both of these PO/AH neuronal populations to $\downarrow T_{set}$. For example, a transient change in neuroendocrine pulse frequency or amplitude might increase the firing rate of W neurons. The

equilibrium with input from I neurons is upset, which increases the firing rate of those neurons driving heat-loss effectors (Fig. 8.1). The same effect could occur by neuroendocrine modulation, which reduces inhibitory input of I neurons. The summation of inputs would increase the firing rate of those neurons initiating sweating and cutaneous vasodilation. The observation that warm skin is associated with more frequent hot flashes [78] is consistent with the proportional control of thermoregulation. In a warm environment, afferent input from warm skin would increase the firing rate of W neurons such that the inhibitory input to the neurons affecting heat loss mechanisms is exceeded. This also would have the effect of $\downarrow T_{set}$ and would initiate sweating and cutaneous vasodilation.

Estrogen Replacement Therapy

Estrogen replacement therapy (ERT) is commonly prescribed at or around menopause to decrease physiological symptoms of estrogen withdrawal, such as the occurrence of hot flashes [77]. Kronenberg et al. [77] and Lomax [83] have suggested the estrogen withdrawal at menopause $\downarrow T_{set}$. However, estradiol increases the firing of W neurons and decreases core temperature [10, 11, 110]. Menopause is a condition of very low estrogen concentration and it does not seem likely that there would be episodic pulses of estrogen reaching the PO/AH. Apparently, the effect of estrogen withdrawal is to change other neuroendocrine factors, perhaps the neurotransmitter mediating GnRH pulse generation, which, in turn, has an effect on the thermoregulatory neurons. Estrogen replacement therapy (Premarin or Estraderm) in postmenopausal women decreased core temperature at rest and during exercise, decreased heart rate and arm blood flow during exercise, and decreased the esophageal temperature for the onset of arm blood flow and sweating [119]. These observations [119], combined with the observations of increased firing rate for W PO/AH neurons by Silva and Boulant [110], suggest that estrogens may $\downarrow T_{set}$.

SUMMARY AND FUTURE CONSIDERATIONS

Reproductive physiology is an important modulator of thermoregulatory function in women. The mechanism causing the increase in the thermoregulatory set-point in the luteal phase of the ovarian cycle is not known, but integration among higher brain centers and the hypothalamic-hypophyseal-ovarian axis are involved. One of these integrative events, or a combination of events, apparently causes heat-loss effector neurons to be activated at a higher core temperature compared with the follicular phase. Heat retention and production effectors are also activated at a higher temperature during the luteal phase than in the

follicular phase as evidenced by whole-body thermoregulatory responses of women.

To stimulate future research on thermoregulatory function in women and to provoke modification of current neuronal models of thermoregulation, a few speculative thoughts about how T_{set} is increased during the luteal phase are presented. If Hammel's model of thermoregulation [51, 52] is used, the luteal T_{set} elevation could be modified through a mechanism similar to the elevation in T_{set}, which occurs during fever. Boulant [8] has reviewed how a pyrogen caused an elevation in T_{set} and has presented evidence that this response was consistent with Hammel's model of thermoregulation. In short, the pyrogen decreases the firing rate of W neurons. This causes the equilibrium temperature, at which the excitatory input from W neurons is equal to the inhibitory input from I neurons, to increase, thereby effecting an increase in T_{set}. An elevated T_{set}, in turn, causes heat-loss effector neurons to be activated at a higher temperature, and causes activation of neurons effecting heat retention and heat production mechanisms. Therefore, the body temperature is increased to the new set-point temperature [8]. Thermoregulatory modifications may be as subtle as a behavioral change or vasoconstriction of cutaneous blood vessels when there is a small increase in T_{set} or as obvious as intense shivering to produce heat, which increases core temperature when T_{set} is elevated substantially.

In fever, several pyrogens have been identified [70], among them interleukin-1 (IL-1) and interleukin-6 (IL-6). In the luteal phase, basal body temperature is elevated for days and the 0.4°C-elevation in T_{set} is comparable with a low-grade fever. Cannon and Dinarello [17] have shown that there is increased IL-1 circulating during the luteal phase, which could explain this T_{set} elevation if the increased IL-1 identified is acting to decrease firing rate of W neurons in the hypothalamus. T_{set} may be elevated during the luteal phase by increased inhibitory input of I neurons to heat-loss effector neurons and/or by increased excitatory input to C neurons. This will increase the firing rate of heat retention effector neurons and will increase heat production. This possibility, without evidence from neuronal studies, is attractive because estradiol and progesterone feedback to the brain modulates hypothalamic GnRH release. Hypothalamic modulation of GnRH is just one of many complex neuroendocrine interactions that occur during the luteal phase. It is not hard to imagine that any one of many neuroendocrine events occurring during the time of ovulation and the luteal phase may be increasing the firing rate of I neurons to cause an increased T_{set}. Progesterone injected intramuscularly in amenorrheic or ovariectomized women caused body temperature to increase [26]. Also, when there is little or limited increase in progesterone concentration in the luteal phase, basal body temperature does not increase despite surges in LH and FSH [18]. Although increased progesterone is the most often proposed mechanism for

mediating the ↑ T_{set} [23, 58, 59, 68, 113] and other thermoregulatory modifications in the luteal phase [94], there are many other possibilities. If an ovarian factor is responsible for ↑ T_{set} during the luteal phase, inhibin might be just as likely a candidate as progesterone is, because both fit the same temporal pattern of secretion (Fig. 8.3). Other potential stimuli for mediating the ↑ T_{set} in the luteal phase are interactions between fluid volume regulation and thermoregulation, including multisensory neurons [10 12, 109] and whole-body responses.

To summarize, thermoregulation in women of reproductive age is characterized by increased core temperature thresholds for onset of all thermoregulatory effectors during exercise, heat, and cold exposure during the luteal phase of the menstrual cycle [23, 55, 58, 59, 73, 113]. Higher core temperature thresholds for onset of thermoregulatory effector function are consistent with ↑ T_{set} in the luteal phase. Thermoregulation may be somewhat compromised during prolonged exercise or heat exposure in the luteal phase [94, 114], perhaps due to the smaller plasma volume [38, 114]. Postmenopausal women have the same thermoregulatory effector response (sweating) to increased core temperature during heat exposure as have premenopausal women [28]. Perimenopausal and postmenopausal women have a lower resting core temperature and lower core temperature thresholds for onset of sweating and cutaneous vasodilation during exercise (↓ T_{set}) after estrogen replacement therapy than they did before therapy [119].

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