Chapter 9
Sex Hormones and Environmental Factors Affecting Exercise

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Introduction

Reproductive hormones and environmental conditions can influence physiological systems such as fluid regulation and thermoregulation, which in turn can impact exercise. There are numerous challenges with performing physiological studies on women due to the changing hormonal profiles that occur across the menstrual cycle, in addition to the various types of exogenous hormonal contraceptives used by women. Over the last 20 years, our laboratory has performed a number of research studies to examine sex and sex hormone effects on fluid regulation and temperature regulation in humans. In addition, our laboratory has developed a novel way to control reproductive hormone exposure in young women and to isolate the effects of individual sex hormones on physiological systems (discussed herein).

This chapter begins by addressing challenges in testing young, regularly menstruating, healthy women, who are not pregnant, have no chronic or acute disease, and are not medicated, much like the women (and men) recruited for physiological studies. Our purpose in beginning the chapter in this way is to emphasize that investigators need to take the same care in considering hormone milieu in both women and men as they do with any variable that can impact their findings.

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Controlling Hormonal Effects During Human Physiological Studies

The primary roles of estrogens and progestogens are to create an environment hospitable for conception and the developing fetus. Research has also told us that gonadal hormones have important influences on organs and systems outside of reproduction. Moreover, physiological systems function differently within women, and sometimes these sex differences are due to their different hormonal milieu. A major research challenge, therefore, is to control female reproductive steroid hormone exposure to examine a physiological system of interest.

Estradiol is the predominant biologically active estrogen in young, healthy women so can exert a strong influence in physiological studies. While a number of estrogens are present in young, healthy women, 17 β-estradiol (referred to as just estradiol) is the most abundant and has the greatest activity on estrogen receptors. Both estradiol and estrone vary widely across the menstrual cycle in young women (Fig. 9.1; also, see Chap. 1). The most common method to minimize the hormone effects that confound research findings is to study women in the same phase of the menstrual cycle, usually in the early follicular phase (between days 1 and 7 following the onset of menses) when both estrogen and progesterone levels in the plasma are at their lowest levels (Fig. 9.1). This is a convenient method, but considering that women exist in this part of their cycle for only about 25 % of their reproductive lives, it may not be the most clinically or physiologically relevant. Another aspect to consider is that focusing on plasma hormone levels to define hormonal impact does not take into account the potency of their associated receptors. Finally, even though estradiol and progesterone exposures are low relative to other phases of the cycle, these hormones are still considerably higher compared with those in men so their impact when drawing conclusions on sex differences, or when collapsing men and women into one experimental group, should not be ignored. Indeed, collapsing men and women into one group should be avoided when possible.

Hormonal contraceptives (usually combinations of different types of estrogens and progestins [see Chap. 1]) are also used to study hormonal effects in physiological studies. It has even become common to include women who are taking hormonal contraceptives within studies, and grouping them with men, or with other women who are not taking these hormones. A large proportion of European and US women take hormonal contraceptives, indicating high clinical applicability of findings. Hormonal contraceptives increase blood levels above endogenous estrogens and progesterone and provide a steady-state environment with which to compare with women not taking hormones. However, the hormones found in these contraceptives are simply not the same as endogenous hormones. Progestins in hormonal contraceptives differ in some of their basic hormonal actions compared with endogenous progesterone, including effects on peripheral circulation (Wenner et al. 2011a) and aldosterone function (Boschitsch et al. 2010) and differ in important ways with regard to synthesis, actions and androgenic properties (Speroff et al. 1999) and temperature regulation (Stachenfeld et al. 2000). Moreover, the types of progestogens or progestins in hormonal contraceptives are different from one contraceptive formula to another (Hapgood et al. 2014), but are often not distinguished

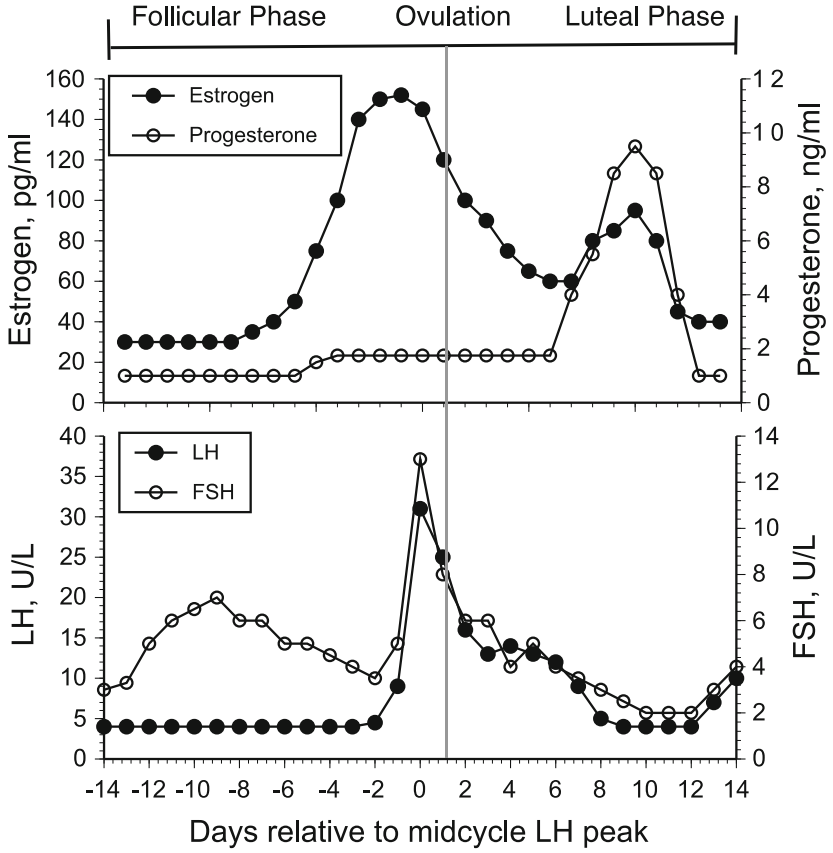


Fig. 9.1 Changes in 17β-estradiol (*top*) and progesterone (*bottom*) across the menstrual cycle. (Stachenfeld NS, Taylor HS. Sex hormone effects on body fluid and sodium regulation in women with and without exercise-associated hyponatremia. *J Appl Physiol.* 2008;107(3):864–72. Copyright 2008 The American Physiological Society. *Used with permission*)

within studies. For example, levonorgestrel, the most widely used progestin, has greater progestational, androgenic, and antiestrogen effects relative to norethindrone acetate or desogestrel, both of which minimize progestational and androgenic effects. Finally, drospirenone is derived from 17α-spirolactone and thus is an analog of spironolactone, a weak androgen *antagonist*. Thus while hormonal contraceptives can be a useful tool to control hormone exposure in women for physiological studies, care should be taken when choosing the contraceptive focusing on the hypothesis to be tested, all women should take the same contraceptive and women who are taking contraception should not be grouped with women who are not for any physiological studies.

Investigators also use the "placebo" week of the hormone contraceptive cycle, using weeks with their subjects on contraceptives as "high" hormone and weeks while taking placebo pills as "low" hormone phases (Charkoudian and Johnson 1999a). However, the placebo phase of the hormonal contraceptive pill cycle is not strictly a "low"

hormonal phase. Immediately after stopping the hormonal contraceptives, blood or tissue levels of the exogenous estrogens or progestins or their metabolites can be elevated. At the very least, by the end of the 7-day placebo period, endogenous estrogens are variable across women (Creinin et al. 2002; Schlaff et al. 2004) and there are no consistent data on the impact of progestin metabolites still present in tissue during the placebo week in the contraception cycle. Thus, the placebo week during regular hormonal contraception is not a controlled period of low hormone exposure in women. A more controlled method is testing the women prior to and during beginning hormonal contraception administration. If the women are already taking contraception, they should go off the pills for at least a full menstrual cycle before beginning studies.

The most controlled method to examine hormonal effects on physiological systems in young women is temporary suppression of the menstrual cycle with a GnRH agonist (leuprolide acetate) or antagonist (ganirelix and cetrorelix acetate). This method requires subjects to use a small needle for subcutaneous injections of the drugs. It is more invasive than measuring changes in endogenous hormones over the course of the menstrual cycle, and less clinically relevant than examining changes over the course of the menstrual cycle or responses to hormonal contraceptives. Therefore, it is a method to be used when the questions posed are very specific to the hormone being tested. This method is ideal to examine causal inferences about hormonal effects on the system targeted for study and extends study to women with irregular menstrual cycles and to women with reproductive dysfunction. Briefly, leuprolide has greater GnRH receptor binding and decreased degradation than endogenous GnRH, so it is a potent inhibitor of gonadotropin secretion. Continuous leuprolide administration downregulates the hypothalamic–pituitary–ovarian axis, causing internalization and uncoupling of the GnRH receptors in the pituitary. Leuprolide administration leads to initial FSH stimulation and related steroidogenesis, followed by low or undetectable estrogen and progesterone concentrations within 7–14 days (Heritage et al. 1980) (Fig. 9.2). Additionally, Ganirelix and cetrorelix are synthetic decapeptides that compete with GnRH for receptor binding so function as competitive receptor antagonists, inducing rapid, reversible suppression of gonadotropin secretion and suppress estrogens and progesterone production 36–48 h of administration (Oberye et al. 1999a, b) (Fig. 9.2). When hormones are suppressed, estrogens, progestogens or androgens (or combinations) can be administered in a controlled fashion to test the hypothesis of interest.

These interventional methods are ideal to examine causal inferences about hormonal effects on any system targeted for study, including body fluid regulation (Stachenfeld and Keefe 2002; Stachenfeld et al. 2001a; Stachenfeld and Taylor 2005) cardiovascular function (Wenner et al. 2011a, b, 2013; Wenner and Stachenfeld 2012), and metabolism (Day et al. 2005; D'Eon et al. 2002). Both leuprolide or ganirelix acetate lead to suppression of estrogens and progesterone to postmenopausal levels, so women can experience vasomotor symptoms ("hot flashes"), breast tenderness, headaches, and transient mood changes, or some temporary mild water retention. Because ganirelix is taken for a shorter period, these symptoms are generally less severe.

Including women in physiological research is not only required by NIH, but is essential for women's health. The changing hormonal milieu in women across the menstrual cycle and as women age creates challenges for designing controlled

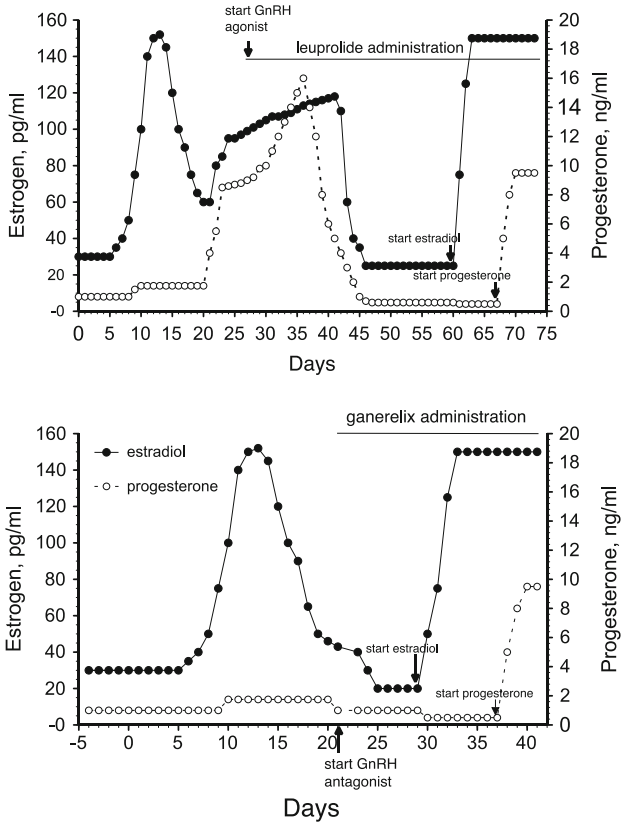


Fig. 9.2 Changes in 17β-estradiol and progesterone during treatment with a gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate) beginning on day 25 of a normal menstrual cycle, followed by treatment with two 17β-estradiol patches (0.1 mg) and oral progesterone (200 mg/day) (*left*). Changes in 17β-estradiol and progesterone during treatment with a GnRH antagonist (ganirelix acetate) beginning on day 25 of a normal menstrual cycle, followed by treatment with two 17β-estradiol patches (0.1 mg) and oral progesterone (200 mg/day) (*right*)

studies, can also provide an interesting environment to compare both sex hormone and sex differences. Investigators should consider hormone milieu in both women and men as they do with any variable that can impact their findings.

Water Regulation

Water is the largest component of the human body, representing from 60 % to 70 % of body weight. In a healthy, 60 kg woman, about 34 L of her body is composed of water. Athletes who generally have high lean muscle mass have a greater percentage of body water compared to sedentary individuals. Approximately 65 % of the body's

water is contained in the cells (intracellular water), and approximately 5 % of the remaining extracellular water is in the blood stream (blood/plasma volume). Fluid within cells and outside of the vascular compartment cannot be immediately accessed during exercise, so only plasma volume is available for sweating and thermoregulation during exercise. Thus, it is this very small percentage of water (about 3.5 L in a normal woman) in the plasma that is used by the body's fluid regulatory and cardiovascular systems to control temperature, as well as stimulate thirst and modulate cardiac output and blood pressure.

Mechanisms that control fluid balance are complex and are influenced by reproductive hormones (Fig. 9.3). Both estradiol and progesterone can influence the complex and integrated neural and hormonal systems that have evolved to control thirst, fluid intake, sodium appetite, and renal fluid and sodium regulation (Fig. 9.3). In addition, sophisticated regulatory mechanisms have evolved to maintain body fluid volume and composition during challenges, including exercise, increases in water intake or deprivation. These regulatory mechanisms use receptors within the vasculature, brain, and gut that are sensitive to mechanical and chemical changes in water and electrolyte content, and whose effector systems act to modify rates of fluid intake and fluid output. For example, dehydration (hyperosmotic hypovolemia) leads to the sensory and behavioral responses of thirst and fluid intake and the phys-

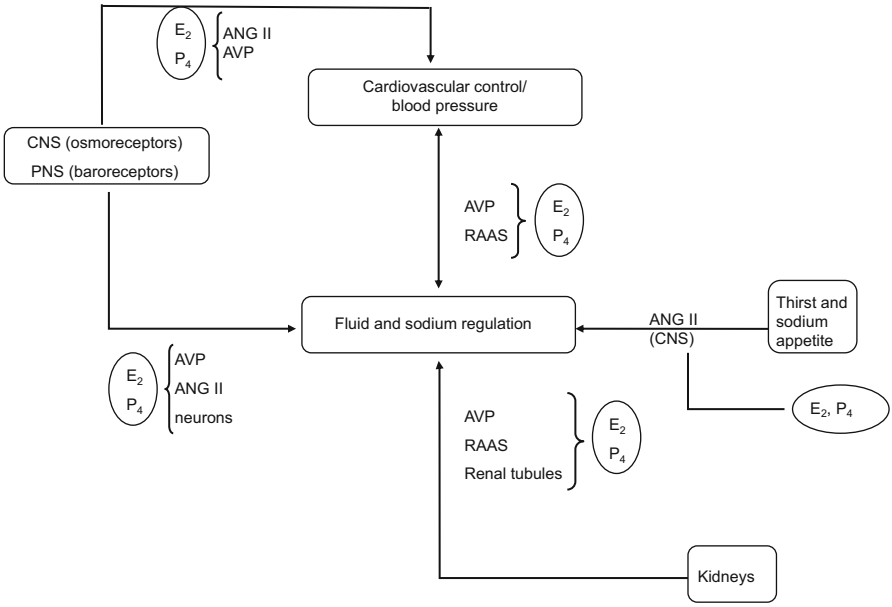
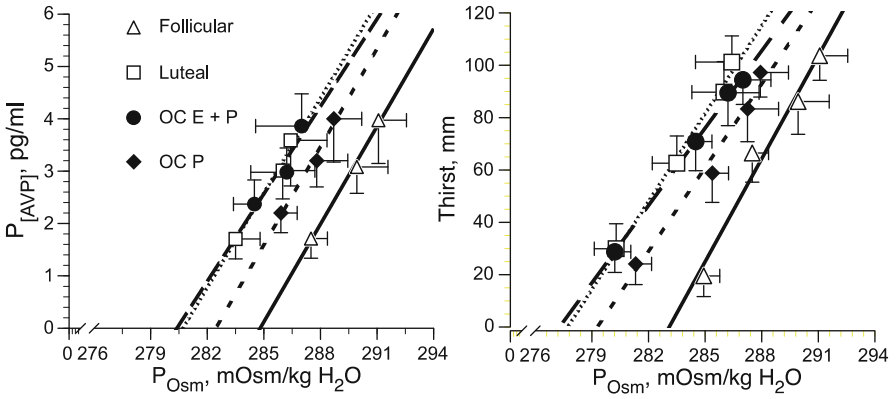


Fig. 9.3 Schematic to illustrate the complex control of fluid and sodium balance and the multiple ways in which estradiol (E2) and progesterone (P4) may influence these processes. AVP indicates arginine vasopressin; ANG II, angiotensin II; CNS, central nervous system; PNS, peripheral nervous system; RAAS, renin-angiotensin-aldosterone system (Stachenfeld NS. Sex hormone effects on body fluid regulation. *Exerc Sport Sci Rev.* 2008;36(3):152–9. Used *with permission*)

iological responses of sodium and water retention by the kidney (Fig. 9.3). During long-term exercise, a small percentage of athletes (1–13 %) retain water leading to a fall in plasma sodium concentration, or hyponatremia. Hyponatremia is the result of excess ingestion of hypotonic fluids (fluids with lower sodium concentration than is in the blood) combined with fluid retention (hypervolemic hyponatremia). Hyponatremia can also occur when excessive sodium is lost in sweating (hypovolemic hyponatremia).

Arginine vasopressin (AVP) is the primary hormone in the body involved in the retention of free water. Arginine vasopressin is synthesized in cell bodies of nuclei located in the anterior hypothalamus (AH), and axons from the AH project into the posterior pituitary where AVP is stored and released in response to central osmoreceptor stimulation. Osmotic regulation of AVP and thirst are linear, and a steeper slope indicates a greater sensitivity of the central osmoreceptors controlling thirst sensation and AVP synthesis and release from the AH and posterior pituitary (Fig. 9.4). A leftward shift in the intercept for this curve indicates an earlier threshold for the onset of thirst and AVP release, while a rightward shift in the intercept for this curve indicates a later threshold for the onset of thirst and AVP release. Likewise, changes in the steepness of this curve detect sensitivity. Arginine vasopressin and thirst are also sensitive to changes in intravascular fluid as sensed by peripheral baroreceptors, so are sensitive to changes in plasma volume during exercise, drinking or dehydration (Fig. 9.3).



Osmotic regulation of arginine vasopressin and thirst during dehydration.

Fig. 9.4 Plasma arginine vasopressin (AVP) concentration and thirst sensation as a function of plasma osmolality (P_{Osm}) during 120 min of hypertonic (3.0 % NaCl) saline infusion the early follicular and mid luteal phases of the menstrual cycle, and during combined (ethinyl estradiol + progestin, OC E+P) and progestin-only (OC P) hormonal contraceptive administration. Note the high progesterone/progestin conditions (luteal phase, OC E+P, OC P) shifted the $P_{[AVP]}$-P_{Osm} curves to the left relative to the follicular phase (From Stachenfeld NS, Silva CS, Keefe DL, Kokoszka CA, Nadel ER. Effects of oral contraceptives on body fluid regulation. *J Appl Physiol.* 1999;87:1016–25. Copyright 1999 The American Physiological Society. Used with permission)

Sex Hormone Effects on Fluid Regulation

Both hypertonic saline infusion (3 % NaCl) and dehydration are used to increase plasma osmolality (P_{Osm}) under different sex hormone conditions to determine the effects of these hormones on the sensitivity and threshold on the linear relationship of $P_{[AVP]}$- P_{Osm} and thirst- P_{Osm} (Stachenfeld et al. 1998, 1999; Calzone et al. 2001). With these methods, the impact of estrogens and progesterone on osmotic control of AVP and thirst are examined by observing changes in the slope (sensitivity) and intercept (threshold) of the $P_{[AVP]} - P_{Osm}$ and thirst-P_{Osm} relationships (Stachenfeld et al. 1998, 1999; Calzone et al. 2001). The plasma hypertonicity associated with a 3 % NaCl infusion induces powerful and linear thirst responses and increases in $P_{[AVP]}$ and thirst. Moreover, hypertonic saline infusion increases P_{Osm} by as much as ~20 mOsmol/kg H_2O during a 2-h infusion so is a power AVP stimulus (Calzone et al. 2001). However, hypertonic saline infusion is not at all a dehydrated state, despite the large increases in P_{Osm}, thirst and $P_{[AVP]}$ because a large intravascular fluid expansion (~10–20 %) develops as water is drawn from cells in response to the increased osmotic pressure in the surrounding intracellular fluid in addition to the fluid infused (Stachenfeld and Keefe 2002; Calzone et al. 2001; Stachenfeld et al. 2001b). Under these conditions, the osmotic stimulus overwhelms the inhibitory input by the plasma volume expansion with regard to thirst and $P_{[AVP]}$ (Fig. 9.4) as well as renal fluid retention (Stachenfeld and Keefe 2002; Calzone et al. 2001; Stachenfeld et al. 2001b).

Estrogen receptors are present in the hypothalamic nuclei that produce AVP (Heritage et al. 1980; Sar and Stumpf 1980) and there are sex differences in the AVP neuron activity and size in these nuclei (Ishunina et al. 2000). Resting $P_{[AVP]}$ is greater in men than in women (in the early follicular phase) (Stachenfeld et al. 2001b; Claybaugh et al. 2000), although men have greater AVP sensitivity and blood pressure responses to hypertonic saline infusion (Stachenfeld et al. 2001b). With regard to sex hormone effects *within* women, the osmotic threshold for AVP release and thirst stimulation during both hypertonic saline infusion and exercise-induced dehydration is lower when using hormonal contraceptives containing estradiol compared to either the follicular phase or to hormonal contraceptives that contained only progestins. These findings are similar to those in postmenopausal women when compared to women taking estradiol (Stachenfeld et al. 1998) and support a role for estrogens in the osmotic regulation of AVP. Interestingly, free water clearance was unaffected during hypertonic saline infusion, dehydration, or rehydration in our younger subjects. This unchanged water and sodium balance in the face of estrogen-related shifts in osmotic AVP, thirst and drinking suggested *a shift in body water regulation to a lower plasma osmolality operating point* during estradiol exposure in young women. This shift in water regulation is in contrast to our earlier findings in postmenopausal women in whom estradiol administration increased osmotic production of AVP, but also resulted in greater water retention (Stachenfeld et al. 1998).

Exercise Effects on Fluid Balance

Environmental conditions (i.e., heat and humidity) and exercise type and intensity impact fluid and electrolyte loss that occurs with activity. During exercise, there is an increase in cardiac output as exercise intensity increases in order to meet the metabolic demands of the exercising skeletal muscle. The increase in cardiac output is due to increases in heart rate and stroke volume. However, in a hot environment, a large portion of cardiac output (up to 60 %) is shifted from the core to the periphery (Rowell 1974), primarily to the skin for thermoregulation via sweating and cooling the body through evaporation.

Plasma volume expansion not only improves cardiovascular responses to exercise, but also increases internal water available for sweating thereby improving thermoregulation during exercise (Nadel et al. 1980; Fortney et al. 1983). These thermoregulatory improvements are due to the increase in cardiac output, as there is a greater ability for cutaneous vasodilation and heat dissipation in the periphery. In contrast, plasma or blood volume contraction (such as with hypovolemia or dehydration) limits the ability to effectively increase skin blood flow to dissipate heat (Fortney et al. 1983), as evident by a reduction in skin vascular conductance for a given core temperature (Tripathi et al. 1990). With exercise in the heat during hypovolemic or dehydrated states, without fluid and electrolytes replacement, sweating to dissipate heat is compromised, which can lead to heat illness (Sawka et al. 1992, 2007; Armstrong et al. 2007; Byrne et al. 2006).

Research laboratory studies have been conducted to examine thermoregulatory mechanisms, as highlighted in a number of review articles (Shibasaki et al. 2006; Gagnon and Kenny 2012a, b; Charkoudian and Stachenfeld 2014; Charkoudian 2015). In order to compare thermoregulatory function, cutaneous vasodilation or sweating is plotted as a function of core temperature. Both the threshold (core temperature at which either skin blood flow or sweating begins to increase) and/or the sensitivity (slope) are analyzed to determine effectiveness of heat dissipation (Fig. 9.5). The leftward shift in the threshold or set point for sweating indicates an earlier onset of sweating, or that sweating began at a lower core temperature. This commonly occurs with exercise training in the heat (acclimatization), and is an important adaptation because earlier sweating onset results in more effective core temperature maintenance (Roberts et al. 1977). While this is an important thermoregulatory advantage, this adaptation also requires greater attention to fluid and electrolyte intake, an important caveat for long training bouts. Thus, with adequate hydration and plasma volume, body water is available for sweating, there is less cardiovascular strain, and exercise performance is maintained. In contrast, with dehydration and the correlate reduction in plasma volume and cardiac output, there is typically a delayed core temperature set point for cutaneous vasodilation (Nadel et al. 1980) seen as a rightward shift in the threshold for vasodilation in the skin (Fig. 9.5) or sweating threshold. Further, for a given core temperature, both skin vasodilation and sweating rate are lower in dehydrated persons (Nadel et al. 1980; Sawka et al. 1992; Sawka and Wenger 1988). Thus, dehydration, or plasma volume

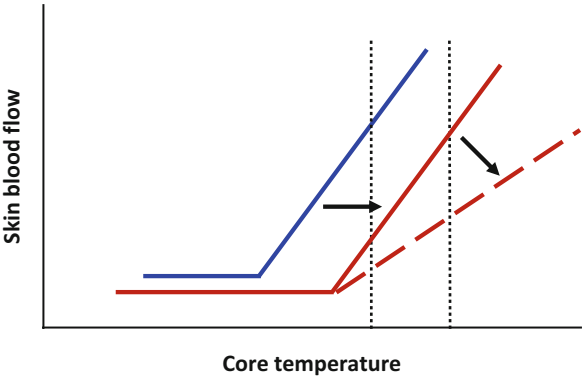


Fig. 9.5 Schematic example of graphs used in analysis of thermoregulatory effector mechanisms (primarily sweating and cutaneous vasodilation), showing the relevant effector as a function of core body temperature. As core temperature increases, a point is reached (the threshold) at which the heat dissipation mechanism begins to increase. The slope of the relationship after this threshold is referred to as the sensitivity of the response. A "rightward" shift in threshold and/or a decrease in sensitivity will decrease the amount of heat dissipation for a given core temperature, resulting in less efficient heat loss. *Vertical lines* show the change in the amount of a given effector response (at a given core temperature) caused by a shift in threshold or sensitivity. (From Charkoudian N, Stachenfeld N. Reproductive hormone influences on thermoregulation in women. *Compr Physiol.* 2014;4(2):793–804. Copyright 2014 The American Physiological Society. *Used with permission*)

contraction, results in less effective thermoregulation (i.e., high core temperature), increased cardiovascular strain, fatigue, limits exercise performance, and increases the risk for heat illness (Sawka et al. 1992, 2007; Armstrong et al. 2007; Byrne et al. 2006; Sawka and Wenger 1988).

Sex Differences in Thermoregulation

Sex differences in thermoregulation can influence fluid and electrolyte losses during exercise (Gagnon and Kenny 2012a, b; Charkoudian and Stachenfeld 2014; Charkoudian 2015). Most sex differences in thermoregulation are attributed to differences in body size, body composition, and fitness level (Gagnon and Kenny 2012a, b). Because of their smaller body size and lower lean mass, the amount of heat generated during exercise is typically lower in women compared to men. Women also generally have lower sweating rates compared to men due to their lower body size, although this is difficult to detect at lower exercise intensities (Gagnon and Kenny 2012b). Although sweating rates may differ between men and women, core temperature and cutaneous vasodilation during exercise in the heat are generally similar between the sexes. Thus, sex differences in thermoregulation are minimal, and likely not to influence exercise capacity for most young healthy people. However, because women lose less fluid and electrolytes from sweat during

intense exercise in the heat, overconsumption of fluids can contribute to the higher incidence and more severe outcome of exercise associated hyponatremia in women compared to men (Almond et al. 2005).

There are important caveats to these statements regarding sex differences, however. The environment in which humans exercise also affects sex differences in thermoregulation (Shapiro et al. 1980). Heat production is mainly weight dependent, so women produce less heat during exercise due to their smaller body weight compared to men. In contrast, evaporation or cooling is mostly related to body surface area (BSA, i.e., *skin surface*) dependent, and thus, the sex with the higher BSA has the advantage (men). However, their greater body size and muscle mass induce greater heat production, so it is variable as to whether or not there are sex differences in dry heat. In contrast, in hot wet environments, evaporation is suppressed, so the greater BSA in men does not convey as great an advantage for sweating, while heat production remains the same. Because body weight is generally lower in women, core temperature increases less relative to men, so under hot wet conditions, women may fair better (Shapiro et al. 1980). In addition, of course, the slower sweating rates in women in the hot wet environment may convey an advantage to women who maintain better hydration.

Sex Hormone Effects Within Women During Exercise

As described above, sex hormones (specifically estrogens and progesterone) can impact fluid and electrolyte regulation. These hormones can also alter thermoregulatory mechanisms. Early studies conducted in women during the menstrual cycle demonstrated that sex hormones shift the core temperature threshold for sweating (Stephenson and Kolka 1999). During the luteal phase, there is a rightward shift in core temperature for the onset of sweating, such that for a given core temperature, sweating rates are lower in the luteal compared to follicular phase (Stephenson and Kolka 1999; Kolka and Stephenson 1989). The threshold for the onset of sweating during exercise in the preovulatory phase of the menstrual cycle, when estrogen is elevated independent of progesterone (Stephenson and Kolka 1999), is shifted leftward compared to the follicular phase, suggesting that estrogen lowers the threshold for the onset of sweating. Taken together with other studies, estrogen is likely associated with greater sweating rates for a given core temperature (Stachenfeld et al. 2000; Brooks-Asplund et al. 2000). Similar findings of a shift in core temperature due to changes in estrogen and progesterone exposure have also been reported in women using oral contraceptive pills (Rogers and Baker 1997; Charkoudian and Johnson 1999b). The sensitivity or slope of the sweating response does not appear to be influenced by changes in reproductive hormones. These data indicate that estrogen and progesterone have opposing effects on thermoregulatory mechanisms, and can alter the core temperature threshold for sweating to occur during exercise in the heat.

In order to directly determine whether estrogen opposes the progesterone-induced increase in core temperature threshold for sweating, women were tested during four different hormone conditions: the early follicular phase of menstrual cycle, the mid luteal phase of menstrual cycle, after 4 weeks of combined estradiol and progestin (OC-E+P) oral contraceptive pills, and after 4 weeks of progestin-only contraceptive pills (OC-P) (Stachenfeld et al. 2000). In this manner, changes in the onset of sweating during the menstrual cycle were assessed, and progestin effects on thermoregulation during exercise in the heat in the same women were isolated. Women were tested at rest, in response to passive heat stress, and during exercise (60 % of VO_{2peak} for 40 min) under each hormonal condition. Consistent with previous studies (Kolka and Stephenson 1989), core temperature was higher during the mid luteal compared to the early follicular phase of the menstrual cycle (Fig. 9.6). This change in resting core temperature is primarily due to the increase in progesterone, and consistent with increases in core temperature with progestin during OC-P compared to OC-E+P, follicular, and luteal phases (Stachenfeld et al. 2000). However, the addition of estrogen to progestin only pills *prevented* the rightward shift in core temperature. Furthermore, the onset of sweating occurred at a lower core temperature with the addition of estrogen to progestin pills (Fig. 9.6). As a result, for a given

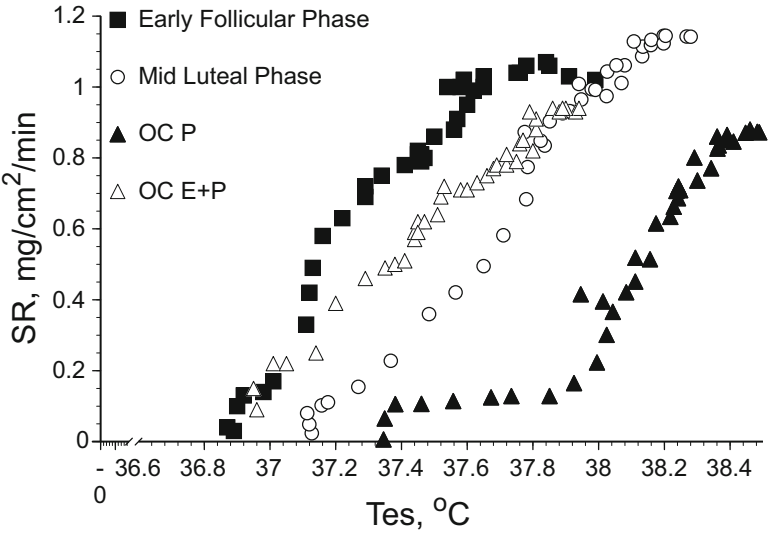


Fig. 9.6 Sweating rate (SR) as a function of core (esophageal) temperature during 40 min of exercise in the heat in young, healthy women during the early follicular and mid luteal phases of the menstrual cycle, and during combined (ethinyl estradiol + progestin, OC E+P) and progestin-only (OC P) hormonal contraceptive administration. Note the progestin alone condition (OC P) shifted the SR-°C curves to the right relative to the other conditions, and consistent with earlier data, mid luteal phase SR-°C curves were also shifted to the left relative to the early follicular phase (Kolka and Stephenson 1989; Stephenson et al. 1989) (Data are based on Stachenfeld NS, Silva C, Keefe DL. Estrogen modifies the temperature effects of progesterone. *J Appl Physiol.* 2000;88:1643–9. Copyright 2000. The American Physiological Society. Used with permission)

core temperature, sweating rates were greater in the presence of estrogen compared to the progestin only pills. This greater sweating rate with the addition of estrogen was also associated with a small plasma volume expansion that occurred with estrogen administration (Stachenfeld 2004). Conversely, the lower sweating rates during OC-P were associated with a significant plasma volume contraction (~3 %) that occurred with OC-P (Stachenfeld 2004). Throughout exercise, sweating sensitivity as represented by slopes of the relationship between sweat rate and core temperature were unaffected by hormone condition.

In summary, estrogens and progesterone/progestins have opposing effects on core temperature and the threshold for sweating onset, whereas the slope or sensitivity does not appear to be effected by fluctuations in sex hormones. Estrogen lowers the core temperature threshold for sweating promoting heat dissipation, whereas progesterone/progestins have the opposite effect. Although core temperature is higher and sweating onset is later in these circumstances, phase of the menstrual cycle or hormonal contraceptive use do not predict heat illness during exercise in women. Lastly, although sex hormones influence thermoregulation and sweating responses to exercise, it does not appear that these changes significantly impact exercise performance.

Training and Fitness Effects on Fluid and Electrolyte Requirements

Aerobic fitness may also influence fluid and electrolyte requirements during exercise. Exercise training can impact the sensitivity (or slope) and threshold of the relationships between core temperature, peripheral vasodilation, and sweating. For example, Roberts et al. demonstrated that 10 days of aerobic exercise training reduced the internal threshold for sweating and peripheral vasodilation in men and women, permitting greater heat dissipation (Roberts et al. 1977). Moreover, the sweating and blood flow are augmented if the exercise training is performed in the heat (acclimatization). While the responses to exercise training and acclimatization are similar between the sexes, women have lower sweating rates and a higher internal threshold for both sweating and peripheral vasodilation compared to men for a given core temperature (Hertig and Sargent 1963; Wyndham et al. 1965). Although these classic studies demonstrated important sex differences in sweating responses, they did not take into account the fluctuations in reproductive hormones that occur across the menstrual cycle.

As discussed earlier in this chapter, estrogen and progesterone also alter thermoregulatory sweating responses during exercise, so thermoregulation will change across the menstrual cycle. In order to determine fitness effects in women while minimizing the influence of hormonal fluctuations, Araki et al. (Araki et al. 1981) measured sweating responses to exercise in a hot environment in trained and untrained women during the same time period of phase menstrual cycle (within 7 days after menstruation, or when both estrogens and progesterone are low). The trained women demonstrated an

earlier sweating onset compared to the untrained women. Furthermore, the untrained women underwent 60 days of exercise training and demonstrated improved thermoregulatory sweating responses. Therefore, exercise training can improve sweating responses in women so that they can more efficiently dissipate heat during exercise. The differences in sweating responses between trained and untrained women have been reproduced in subsequent studies (Kuwahara et al. 2005a, b), which also tested trained and untrained women during different phases of the menstrual cycle. In untrained women, sweating rate and skin blood flow responses to exercise in a thermoneutral environment were lower during the mid luteal compared to the mid follicular phase of the menstrual cycle (Kuwahara et al. 2005a). Furthermore, the internal temperature threshold at which sweating occurred was greater during the mid luteal phase of the menstrual cycle in untrained women (Kuwahara et al. 2005a). Interestingly, these menstrual cycle differences in sweating were not observed in trained women. Therefore, it seems possible that exercise training attenuates the impact of sex hormones on thermoregulation (Kuwahara et al. 2005a, b).

The greater sweating responses in trained women also indicate greater body fluid losses, so women need to be cognizant that as they improve their fitness or acclimatize to heat that their fluid and electrolyte requirements may change. Another important consideration is the lower tonicity of the sweat that can occur with training. The lower concentration of sodium in sweating is an important training adaptation because this lower electrolyte loss will balance the greater sweating rates achieved with training. It is also important to note that even though sweat sodium concentration is reduced with training, it remains highly variable across individuals, varying as much as 10–70 mEq/L (Sawka et al. 2007). Sims et al. (2007) showed that consumption of a high sodium beverage prior to exercise in the heat increased performance during the mid luteal phase of the menstrual cycle. Therefore, women should not only pay attention to fluid intake but also sodium intake, especially during exercise in the heat.

Temperature Regulation and Fluid Balance: Special Populations

Aging and Menopause

The menopausal transition is a period where significant physiological changes occur due to dramatic fluctuations in reproductive hormones, and can occur at different ages among women (Harlow et al. 2012). After menopause, estradiol and progesterone levels are significantly reduced compared to premenopausal women. This loss of estradiol can have significant implications on numerous physiological systems, such as bone, cardiovascular, and thermoregulatory (see Chap. 16). During the menopausal transition, women often experience symptoms such as vaginal dryness, hot flashes, and night sweats. Thus, fluctuations in reproductive hormones during this time period can also have important implications for thermoregulation and fluid balance.

Aging is associated with impairments in thermoregulation and thirst sensation during exercise in both sexes (Kenney and Anderson 1988; Stachenfeld et al. 1997). In perimenopausal (Tankersley et al. 1992) and postmenopausal (Brooks et al. 1997) women, estrogen therapy reduces core temperature at rest and during exercise. Furthermore, the core temperature threshold for sweating onset occurs lower with estrogen therapy in older women (Tankersley et al. 1992; Brooks et al. 1997). These improvements in thermoregulation may be one mechanism whereby estrogen therapy reduces the frequency and intensity of hot flashes. However, these thermoregulatory effects on core temperature and sweating were not apparent in postmenopausal women taking combined estrogen and progesterone hormone therapy (Brooks et al. 1997), suggesting that the effects of progesterone predominate over that of estrogen, similarly to what is observed in young women.

Although the mechanisms controlling skin blood flow and sweating during postmenopausal vasomotor symptoms (VMS) has not been established, a series of elegant studies has demonstrated that these physiological responses are controlled by similar autonomic mechanisms that contribute to peripheral changes in the thermoregulatory response during peripheral and core temperature heat challenges (Hubing et al. 2010; Low et al. 2008). Interestingly, while these mechanisms include a nitric oxide component, they are independent of prostaglandins (Hubing et al. 2010). These studies have also demonstrated a sympathetic cholinergic neural mechanism for skin blood flow increases during VMS (Low et al. 2011). Importantly, it appears that exercise training may improve subjective ratings of frequency and intensity of VMS events in postmenopausal women (Luoto et al. 2012).

With regard to fluid balance, the typical expansion in plasma volume that occurs with exercise training is impaired in postmenopausal women (Stachenfeld et al. 1998). However, estrogen administration induces basal transient fluid retention and plasma volume expansion, increases $P_{[AVP]}$, and reduces the osmotic set-point for AVP release in postmenopausal women (Stachenfeld et al. 1998). These changes are associated with water and sodium retention, which are likely due to a reduction in urine output because thirst and drinking patterns are not altered with estrogen administration. Lastly, although progesterone effects on fluid balance have been examined in young women, to our knowledge there are no data in postmenopausal women. Progestins and progesterone are commonly prescribed as part of hormone therapy regimens, so it is important to determine these effects on sodium and water balance.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy (Barontini et al. 2001), affecting between 5 and 10 % women of reproductive age (Tsilchorozidou et al. 2004), and is the most common cause of menstrual irregularity in young women. Approximately 75 % of women with PCOS have the more severe reproductive and metabolic PCOS phenotype that is dominated by features

of hyperandrogenism. This androgen excess (AE)-PCOS phenotype is typically associated with insulin resistance (IR), compensatory hyperinsulinemia, obesity, subcutaneous and visceral adiposity, dyslipidemia, enlarged adipocytes, hypoadiponectinemia, and oligoovulation or anovulation. AE-PCOS is also associated with obesity and metabolic syndrome (Rojas et al. 2014; Ehrmann et al. 2006; Legro et al. 2001). A sedentary lifestyle is a primary environmental risk factor for PCOS (Diamanti-Kandarakis et al. 2012; Diamanti-Kandarakis and Dunaif 2012). Physical activity independent of weight loss improves insulin sensitivity (Harrison et al. 2011; Hutchison et al. 2011) and improves reproductive function in PCOS (Harrison et al. 2011). Therefore, exercise is routinely prescribed for women with PCOS (Moran et al. 2006), although there are few data on exercise effects on women with PCOS. Obese women with PCOS appear to regulate temperature adequately during exercise in the heat, maintaining similar core temperature to obese women without PCOS, although with higher sweating rates even at mild exercise intensity, relative to control obese subjects (Stachenfeld et al. 2010). Women with PCOS sweat at a lower core temperature and more profusely relative to women without PCOS and this greater water loss was independent of obesity (Stachenfeld et al. 2010). These data suggest that women with PCOS should pay special attention to hydration during longer exercise periods. Finally, similar to lean women, estradiol administration lowered the sweating threshold in the control obese women, but had no effect on women with PCOS, who were insensitive to estradiol administration, with or without testosterone suppression (Stachenfeld et al. 2010). Despite the importance of physical activity in treating PCOS, there are no exercise guidelines for women with PCOS based on clinical or physiological data.

Conclusions

Including women in physiological research is essential for women's health, but creates challenges for designing controlled studies. Researchers cannot simply pool men and women into one group when they are included in physiological studies and cannot simply test women in one phase of the menstrual cycle. Regardless of methodology, the same attention to detail used to control the rest of the environment of our physiological studies should be paid to the hormonal environment when including women, female animals, cells or cell lines in research studies.

The primary female reproductive hormones—estrogens and progesterone—have physiological effects on fluid and electrolyte regulation and thermoregulation. These effects are most profound in lowering the set point for the regulation of thirst and the fluid/sodium regulation hormones, but do not typically induce fluid or sodium retention. Moreover, these hormones play an important role in reducing the core temperature sweating. Regardless of these physiological effects, there is not yet strong evidence that estrogens and progesterone/progestins impact performance significantly in younger or older women, or that they significantly increase the risk of heat illness.

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