Chapter 6
Nutritional Strategies and Sex Hormone Interactions in Women

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Introduction

There are a number of nutrients, foods and supplements the manipulation of which has the potential to augment health and/or exercise performance and/or recovery. The focus of this chapter is to address those dietary manipulations that have particular relevance for women. By and large these are related to differences imposed by female sex hormone fluctuations and decreases with age, or in response to stressors, including exercise training load and energy balance. This chapter begins by addressing those elements of the diet known to have the largest effect on and be altered by exercise, beginning with energy supply and macronutrient intakes, particularly carbohydrate and protein. The varying impact of manipulation will be highlighted with respect to timing of intake relative to exercise. This is followed by a discussion of fluid and electrolyte handling and application to thermal regulation, exercise tolerance and exercise associated hyponatraemia. Hereafter, oestrogen as an antioxidant is discussed and a number of more minor nutrients are highlighted that, due to specific action of oestrogen, or lack thereof, may warrant increased consumption.

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Energy and Macronutrients

Traditionally high/er carbohydrate diets have been recommended for athletes engaging in endurance and high intensity intermittent exercise (Jeukendrup 2011; Broad and Cox 2008). This recommendation has been established on the basis that both forms of exercise, either as a result of the duration or dominance of carbohydrate as a substrate, put a drain on body carbohydrate stores. Based on research conducted primarily in males, it has been assumed that these recommendations would translate equally well for the female population performing similar activity. Evidence from metabolic studies conducted in animal and human populations indicate that both oestrogen and progesterone have varying effects on carbohydrate, lipid and protein metabolism. Specifically, the female sex hormones appear to have an influence on insulin-stimulated and contraction-stimulated glucose uptake (Hansen et al. 1996; Latour et al. 2001; Campbell and Febbraio 2002; Van Pelt et al. 2003), glycogen storage (Nicklas et al. 1989; Hackney 1990; McLay et al. 2007), plasma glucose availability during exercise (Campbell et al. 2001; Zderic et al. 2001; Devries et al. 2006), whole body glucose kinetics (D'Eon et al. 2002), lipolysis (Casazza et al. 2004), cellular capacity for fatty acid oxidation (Campbell and Febbraio 2001) and protein catabolism (Lamont et al. 1987; Lariviere et al. 1994; Kriengsinyos et al. 2004). Further, it is highly conceivable that the ingestion of specific nutrients before, during and after exercise has the potential to affect the impact of the ovarian hormones on metabolism, raising the possibility that sex-specific or even hormonal-status specific dietary guidelines for exercising females may be warranted.

The following sections are limited to describing nutritional strategies where research has been conducted using exercising females and variation in ovarian hormones (e.g., menstrual cycle phase or oral contraceptive use) has been incorporated. To date, this research is limited to manipulation of carbohydrate and protein intake and predominantly in relation to endurance exercise. Research investigating low-carbohydrate, high-fat diets (acute and chronic adaptation and fat adaptation with carbohydrate restoration) has almost exclusively been conducted using male participants (Burke 2015). As a consequence, the research in this area that incorporates fluctuations in ovarian hormones is non-existent.

Habitual Diet

Few studies have actually tested the impact of modifying the habitual diet of female athletes prior to exercise. Those that have been conducted have used a variety of protocols, performance tests and female participants in various states of hormonal influence, making it difficult to discern consistent results. Increasing the daily carbohydrate content (up to 8 g/kg body weight per day) of the habitual diet of well-trained eumenorrhoeic female cyclists in the week preceding cycling exercise to fatigue has been shown to both improve performance (O'Keeffe et al. 1989) and to also have no effect (Reznik

Dolins et al. 2003). The application of these results is limited as the research was either conducted in only one phase of the menstrual cycle (Reznik Dolins et al. 2003) or did not include any control of menstrual cycle phase (O'Keeffe et al. 1989).

Recently, an empirical estimate of the protein requirements of female endurance athletes undertaking training of moderate intensity and duration (1.5 h day^{-1}) during the midfollicular phase of the menstrual cycle was determined using nitrogen balance (Houltham and Rowlands 2014). Estimated mean protein requirement was 1.63 g kg^{-1} day^{-1}, which is similar to previous estimates for men, but somewhat higher compared to previous non-empirical estimates for endurance training women (1.2–1.4 g kg^{-1} day^{-1}). This appears to be the first study of its kind to incorporate and control for the potential effects of menstrual cycle phase.

Nutrient Intake in the Days Before Exercise

Results of early research suggested menstrual cycle phase might influence muscle glycogen concentration (Nicklas et al. 1989), which in turn, has the potential to affect subsequent exercise capacity or performance of eumenorrhoeic female athletes (Nicklas et al. 1989). Carbohydrate loading is a performance-enhancement strategy often used by endurance athletes before competition to increase muscle glycogen stores in an effort to improve performance in events lasting longer than 90 min (Sedlock 2008). Recent 'modified' versions of the approach involve combining a high dietary carbohydrate intake and exercise taper for several days prior to competition (Sedlock 2008). Only a small number of studies have attempted to elucidate this relationship by investigating the impact of a modified carbohydrate loading regime prior to exercise in females under a variety of hormonal influences. Carbohydrate loading (8.4–9 g kg body $weight^{-1}$ day^{-1}) has been shown to increase muscle glycogen concentration in the midfollicular phase of the menstrual cycle (Paul et al. 2001; Tarnopolsky et al. 2001; McLay et al. 2007). In contrast, following carbohydrate loading during the midluteal phase, muscle glycogen concentration has remained unchanged (McLay et al. 2007) or shown only a modest increase (13 %) (Walker et al. 2000) compared to what is generally reported for male athletes (18–47 %) (Sherman et al. 1981; Rauch et al. 1995; Hawley et al. 1997; Burke et al. 2000; Tarnopolsky et al. 2001; Rauch et al. 2005) or female athletes during the follicular phase (17–31 %) (Paul et al. 2001; McLay et al. 2007; Tarnopolsky et al. 2001).

The impact of carbohydrate loading on the muscle glycogen content of oral contraceptive users is even less clear. Endurance trained female athletes taking a triphasic oral contraceptive (ethinyl oestradiol/levonorgestrel) showed increased muscle glycogen concentration following carbohydrate loading in both the midfollicular and midluteal phases (James et al. 2001). However, unlike a normal natural menstrual cycle where resting levels of both oestradiol and progesterone are higher during the midluteal than midfollicular phase, James et al. (2001) reported no difference in the levels of ovarian hormones between phases at the time muscle glycogen content was measured. This lack of difference in hormone profiles between phases raises the possibility that the midluteal

phase could actually be interpreted in the same way as the midfollicular phase results from this study, potentially adding to the evidence that carbohydrate loading in the midfollicular phase increases resting muscle glycogen content (Hackney 1990; Paul et al. 2001; McLay et al. 2007; Tarnopolsky et al. 2001). At this time it is unknown what effect carbohydrate loading may have on muscle glycogen concentration in female athletes taking an oral contraceptive with a different chemical composition.

Although the lower level of muscle glycogen storage in the midfollicular phase of the menstrual cycle appears to be overcome by carbohydrate loading, this has not necessarily always translated into improved time trial performance (Paul et al. 2001; McLay et al. 2007). In contrast, cycle time to exhaustion at 80 % VO_2max, measured during the midluteal phase of the menstrual cycle, increased (approximately 9 min) in response to the small CHO loading induced improvement in muscle glycogen concentration (Walker et al. 2000), whereas time trial performance was not improved following carbohydrate loading in the midluteal phase (McLay et al. 2007).

As with research conducted using male participants, there are a number of factors that can influence performance outcomes in studies investigating carbohydrate loading. These include the training status of the participants; the, often, small sample sizes used; the pre-loading glycogen depletion; the type of exercise performance test that is employed (e.g., time trial versus exercise to exhaustion); and the duration and intensity of the exercise undertaken prior to or as part of the performance assessment (Sedlock 2008; Correia-Oliveira et al. 2013). An additional factor to consider in research investigating the effect of menstrual cycle phase on performance outcomes is the magnitude and relative proportions of the fluctuations of the ovarian hormones. It has been proposed that a metabolic response to changes in the ovarian hormones (and the associated potential performance effects) occur only when the oestrogen to progesterone ratio (E/P) is elevated sufficiently in the luteal compared to follicular phase and the magnitude of the increase in oestrogen between the follicular and luteal phases is in the order of at least twofold or more (D'Eon et al. 2002; Oosthuyse and Bosch 2010). It is likely the effect of carbohydrate loading on performance in female athletes is also impacted by this particular hormone milieu.

Achieving the high intakes of CHO ($\geq$8 g kg body weight^{-1} day^{-1}) needed for carbohydrate loading can be difficult for women whose habitual energy intakes are <2000 kcal day^{-1} (8400 kJ day^{-1}) (Tarnopolsky et al. 1995; Wismann and Willoughby 2006; Sedlock 2008), as this dose amounts to ingesting more than 90 % of total energy intake as carbohydrate for a 60 kg woman. Therefore, women who attempt to carbohydrate load should pay particular attention to consuming sufficient total energy to achieve the necessary relative carbohydrate intake, especially during the follicular phase of the menstrual cycle.

Nutrient Intake in the Hours Before Exercise

Menstrual cycle phase appears to influence glucose kinetics during exercise due to the ability of oestrogen to impede gluconeogenesis (Matute and Kalkhoff 1973; Lavoie et al. 1987). Glucose rate of appearance in the luteal phase is reduced

compared to the follicular phase when the energy demands of exercise are high enough to exert pressure on endogenous glucose production (>50% VO_2max) (Campbell et al. 2001; Zderic et al. 2001). The influence of menstrual cycle phase on glucose kinetics is evident in females who exercise in a fasted state but is negated by feeding in the pre-exercise period, as this reduces the demand on endogenous glucose production (Suh et al. 2002; Oosthuyse and Bosch 2010). Eumenorrhoeic female athletes should, therefore, follow the recommendation to consume a pre-exercise meal or snack containing carbohydrate 3–4 h before beginning endurance exercise, especially during the luteal phase of the menstrual cycle.

Exogenous ovarian hormones appear to exert greater effects on glucose flux during exercise than endogenous hormones, as decreases in glucose rate of appearance and disappearance can be observed in recently fed women taking a triphasic oral contraceptive compared to before oral contraceptive use (Suh et al. 2003). Findings from studies investigating oral contraceptive use and substrate utilisation may vary due to the use of different types of oral contraceptive agents, monophasic vs. triphasic and different oral contraceptive formulations, and varied definitions of oral contraceptive phase (Rechichi et al. 2009). As well as the acute effects, oral contraceptive use may have effects on glucose kinetics that persist into the inactive phase (Suh et al. 2003). Female athletes using a triphasic oral contraceptive should, therefore, ensure carbohydrate is consumed prior to exercise during both the active and inactive phases.

Nutrient Intake During Exercise

Carbohydrate ingestion has a positive influence during endurance exercise (Temesi et al. 2011; Cermak and van Loon 2013). However, the majority of research has been conducted using trained male participants and the findings generalised and applied to female athletes. The performance of moderately trained females can be improved with carbohydrate supplementation during endurance exercise compared to a placebo (Sun et al. 2015; Campbell et al. 2001; Bailey et al. 2000). When exogenous glucose is provided during exercise to ovulatory females, the influence of the menstrual cycle phase on glucose kinetics is minimised as the demand for endogenous glucose production is reduced (Campbell et al. 2001). Further, menstrual cycle phase appears to have little impact on performance under these conditions (Campbell et al. 2001; Bailey et al. 2000), although amino acid catabolism was reduced when carbohydrate supplementation was provided during exercise (Bailey et al. 2000). Also of interest is the finding that provision of a carbohydrate-electrolyte beverage during endurance exercise in the heat attenuates immune disturbances compared to a placebo beverage, especially in the luteal phase of the menstrual cycle (Hashimoto et al. 2014). During the follicular phase in endurance-trained women the highest rates of exogenous carbohydrate oxidation and greatest endogenous carbohydrate sparing were observed when carbohydrate was ingested at a rate of 1.0 g min^{-1} (60 g h^{-1}) with no further increases when the rate was increased to 1.5 g min^{-1} (90 g h^{-1}) (Wallis et al. 2007). In

light of the limited data available it would seem prudent to recommend eumenorrhoeic female endurance athletes ingest carbohydrate at a rate of 60 g h^{-1} during exercise to offset menstrual cycle effects on glucose kinetics/exercise metabolism, and to limit potential immune disturbances in the heat and protein catabolism.

Nutrient Intake and Recovery from Exercise

Little is known on how extensively fluctuations in ovarian hormones may actually impact on post-exercise needs for recovery of energy stores or structural repair in exercising females. As with the influence of ovarian hormones on exercise metabolism, the impact on recovery may also be secondary to factors such as nutritional status/energy availability, exercise intensity and overall energy demand of exercise (Hausswirth and Le Meur 2011).

Following depleting exercise undertaken 4 days prior, muscle glycogen repletion has been shown to be reduced in the follicular phase compared to the luteal phase in moderately trained eumenorrhoeic women consuming a diet containing 56% of energy intake from carbohydrate (Nicklas et al. 1989), suggesting a potential impairment in muscle glycogen resynthesis in the follicular phase. However, muscle glycogen repletion during the follicular phase of the menstrual cycle has been shown to occur in similar proportions to males following carbohydrate consumed in the hours after depleting exercise using both untrained (Kuipers et al. 1989) and endurance-trained (Tarnopolsky et al. 1997) participants. Further, post-exercise supplementation (1.2 g kg^{-1} of carbohydrate, 0.1 g kg^{-1} of protein and 0.02 g kg^{-1} of fat), following four training sessions across a week during the follicular phase, improved time to exhaustion during a subsequent bout of endurance exercise (Roy et al. 2002). These effects have not been tested during different phases of the menstrual cycle or in women taking oral contraceptives.

Eumenorrhoeic women should aim to consume carbohydrate as soon as possible following glycogen-depleting exercise, particularly during the follicular phase of the menstrual cycle, in order to maximise glycogen replenishment. This may be especially important if the next training session or event is likely to occur in <8 h.

Protein catabolism appears to be increased in the luteal phase compared with the follicular phase at rest (Lariviere et al. 1994; Kriengsinyos et al. 2004) and compared to the early follicular phase during prolonged exercise (Lamont et al. 1987; Bailey et al. 2000). It appears progesterone is responsible for the increased catabolism of protein in the luteal phase (Kriengsinyos et al. 2004). Oestrogen may have a role to play in reducing protein oxidation; however, this has only been observed in oestrogen supplemented men (Hamadeh et al. 2005a) and has not been examined across the menstrual cycle. It is possible the energy–protein ratio in the luteal phase of the menstrual cycle may also be an important determinant of the extent of protein catabolism in this phase (Oosthuyse and Bosch 2010).

The protein requirements for female endurance training women were recently estimated to be 1.63 g kg^{-1} day^{-1} (Houltham and Rowlands 2014). However, as this research was conducted in the follicular phase where the hormonal environment is

potentially less catabolic, this may represent the minimal protein requirement across the menstrual cycle for women engaged in endurance training.

Research into the role of dietary protein ingested after exercise on recovery processes and subsequent performance in females is lacking. There is some evidence from research conducted in males that the consumption of protein, and the simultaneous ingestion of carbohydrate and protein, offer protection against exercise-induced muscle damage (Howatson and van Someren 2008). In contrast to research in males, high protein feeding immediately after and for 2 days following a 2.5 h high-intensity ride did not improve subsequent exercise performance in trained female cyclists (Rowlands and Wadsworth 2011). This research was undertaken in the follicular phase, and as noted previously, during this phase protein catabolism may be less than encountered in the luteal phase and this may have influenced the results of this study. Although not systematically tested across different phases of the menstrual cycle, exercise-induced muscle damage has been shown to negatively affect functional performance for several days in female athletes tested in the luteal phase (Keane et al. 2015). The pattern and magnitude of exercise-induced muscle damage showed differences compared to previous research in male athletes and is in contrast to animal research in which females have been shown to experience less damage than males.

In order to offset the potential increased protein catabolism and to protect against exercise-induced muscle damage, eumenorrhoeic women should focus on consuming protein, possibly coupled with carbohydrate, during the post-exercise recovery period in the luteal phase of the menstrual cycle. Endurance training women should endeavour to consume a diet containing around 1.6 g kg^{-1} day^{-1}, and possibly more, during the luteal phase.

Summary

Although speculative and open to adjustment and revision as more information becomes available, some broad recommendations regarding the manipulation of energy and macronutrient intake in relation to sex hormone interactions can be garnered from the currently available research. These recommendations are summarised in Table 6.1.

The research knowledge necessary to support potential gender-specific or hormone-status specific dietary guidelines is vast and as yet the field is barely in its infancy. Small steps have been taken with regard to endurance exercise but this is by no means complete. Additional avenues that may warrant exploration include the effect of a carbohydrate mouth rinse and fat adaptation with carbohydrate restoration. A broader scope beyond endurance exercise is needed and future research directions should include the impact of fluctuations in ovarian hormones on macronutrient-based nutritional strategies associated with ultra-endurance exercise, strength-based activities and high-intensity intermittent (team sport) exercise. For future studies investigating menstrual cycle phase variation, consideration should

Table 6.1 Potential macronutrient manipulations recommended for female athletes in relation to fluctuations in ovarian hormones

	Nutritional strategy	Target	Recommendation	Rationale
Habitual diet	Protein Requirement	Eumenorrhoeic, endurance training	Protein intake: ≥1.6 g kg^{-1} day^{-1}	Only assessed in the FP. A higher intake may be required in the LP due to increased protein catabolism at rest and during exercise.
Days before exercise	Modified CHO Loading	Eumenorrhoeic—FP[a], endurance	Increase energy intake by up to 30 % to achieve CHO intake >8 g kg^{-1} day^{-1} on CHO loading days.	To overcome lower muscle glycogen storage in FP.
Hours before exercise	Pre-Exercise Feeding	Eumenorrhoeic—LP[a], endurance Triphasic OC—active and inactive phases	High CHO meal or snack 3–4 h before exercise	To reduce demand on endogenous glucose production which can be suppressed in the luteal phase and under OC influence
During exercise	Exogenous source of CHO	Eumenorrhoeic, endurance	CHO intake: 60 g h^{-1} during prolonged exercise	To reduce demand on endogenous glucose production. Limit potential immune disturbance and protein catabolism.
Recovery after exercise	CHO Protein + CHO	Eumenorrhoeic—FP[a], endurance Eumenorrhoeic—LP[a], endurance, activities that induce muscle damage	Ingestion of CHO as soon as practical following prolonged glycogen-depleting exercise Co-ingestion of protein and CHO during the recovery period	To overcome potential reduced muscle glycogen resynthesis in FP. To offset increase in protein catabolism and protect against EIMD in the LP.

CHO carbohydrate, *EIMD* exercise-induced muscle damage, *FP* follicular phase, *LP* luteal phase, *OC* oral contraceptive

[a]Particular attention needed to adhere to the recommendation in this phase though benefits are likely in other phases too

be given to the increase in oestrogen relative to progesterone in the luteal phase and the absolute magnitude of increase in oestrogen between any two menstrual phases. Oral contraceptive use is prevalent in athletes (Rechichi et al. 2009) but data evaluating macronutrient manipulation and the effects of oral contraceptives is virtually non-existent and this needs to be addressed. What is becoming evident is that many researchers are now at least acknowledging the potential for menstrual cycle driven effects on metabolism and subsequent performance with numerous studies testing female participants during the mid-follicular phase. Unfortunately, by choosing this more subdued hormonal environment relative to the late follicular or luteal phases, interesting and informative interactions may be missed.

Fluids and Electrolytes

Thermoregulation and Body Fluids

It has been established that women and men differ in their thermoregulatory responses to exercise heat stress largely due to females having a reduced sudomotor function (Gagnon and Kenny 2012; 2011), thus decreasing evaporative heat loss capacity with the resultant increase in physiological strain (Moran et al. 1999; Kawahata 1960; Mack and Nadel 2010). Women and men display similar rates of heat dissipation at low requirements for heat loss; however, sex differences in sudomotor function have been demonstrated beyond a certain requirement for heat loss (Gagnon and Kenny 2012). On the other hand, when males and females display similar heat loss for a given heat production, females may display a higher change in body temperature due to physical characteristics (Mee et al. 2015; Gagnon et al. 2008). These results suggest that women may become hyperthermic in a shorter time period than men, consequently, women have been more frequently diagnosed as heat intolerant compared with males (Druyan et al. 2012; Charkoudian and Stachenfeld 2011), potentially putting them at greater risk of experiencing a heat-related illness.

Due to central and peripheral effects of female sex hormones and oral contraceptives on fluid balance and thermoregulation, women may be at a further disadvantage when exercising in warm conditions. Plasma volume (PV) is highest during the preovulatory phase of the menstrual cycle, when oestrogen levels are increasing. However, PV falls by as much as 8 % during the midluteal phase when both oestrogen and progesterone levels are elevated. Progesterone and oestrogen function in body fluid regulation by modifying sodium and water distribution rather than retention (Oian et al. 1987; Stachenfeld and Keefe 2002; Stachenfeld et al. 1999, 2001a; Bisson et al. 1992; Kang et al. 2001). Increased progesterone is associated with increased resting core and skin temperatures as well as changes in the threshold temperatures for sweating and active cutaneous vasodilation (Charkoudian and Johnson 1999; Charkoudian et al. 1999; Kolka and Stephenson 1997a, b; Stephens et al. 2002; Stephenson and Kolka 1999) These effects appear to result from a central thermoregu-

latory effect of progesterone (Kolka and Stephenson 1997a, b), which may also account for core temperature being elevated throughout the 28-day OC cycle relative to that in the natural menstrual cycle (Stachenfeld et al. 2000). Oestrogen also functions in vasodilation via modulation of prostacyclin and nitric oxide release (Charkoudian and Johnson 1997; Charkoudian et al. 1999; Hiroshoren 2002; Houghton et al. 2005). Moreover, plasma volume has been found to differ significantly in the two phases at higher ambient temperatures, as oestrogen enhances aldosterone-mediated sodium absorption in the renal tubules and increases nitric oxide-mediated vasodilation (Houghton et al. 2005; Kang et al. 2001; Salazar and Llinas 1996).

Charkoudian and Johnson (1999) reported that oral contraceptive use shifts baseline core temperature and the threshold for the active vasodilator system to higher internal temperatures via effects on the central thermoregulatory function. Further, it was reported that this shift in active vasodilation results in 43 % lower skin blood flow for a given level of internal temperature during passive heating in the high hormone vs. low hormone phases of the oral contraceptive cycle; consistent with the theory that it is the progestational activity which dominates the effects of oestrogen on the central thermoregulatory mechanisms (Charkoudian and Johnson 1997). Further, Houghton and colleagues found that the nitric-oxide dependent portion of active vasodilation was greater in women taking an oral contraceptive with a lower vs. higher level of progestational bioactivity, with the higher level of progestation bioactivity associated with less relative nitric oxide contribution to reflex cutaneous vasodilation. Furthermore, it is suggested that the synthetic oestrogen and progestins found in oral contraceptive pills have similar influences on the cutaneous vascular response to heat stress. Charkoudian and Johnson (1999) investigated the effect of oral contraceptives on cutaneous vascular control during heat stress, expecting to find an inhibition of the active cutaneous vasodilator system. They determined that oral contraceptives inhibit skin blood flow in response to body heating and that they cause the function of the cutaneous active vasodilator system to be shifted to higher internal temperatures, similar to that observed in the midluteal phase of the menstrual cycle. Moreover, central influences of oestrogen and progesterone on hypothalamic thermoregulatory centres have been reported (Stephenson and Kolka 1988; Stephenson et al. 1989; Stephenson and Kolka 1999; Stachenfeld et al. 2000). Increases in the threshold for cutaneous vasodilation and sweating during heat stress in the luteal phase have been attributed to an increase in the hypothalamic thermoregulatory set-point temperature, thus, the heat dissipation effector functions are not initiated until this higher set-point temperature is reached.

Plasma volume maintenance can be important for exercise performance, especially in the heat (Berger et al. 2006). Fluid balance is often not achieved as a result of an inability to take on sufficient fluids or limits to gastric emptying, preventing the rate of ingestion and absorption from matching sweat rate (Maughan et al. 1997, 2007). In these situations plasma volume can decrease considerably. Therefore, an increased plasma volume can have positive implications for those exercising in thermally challenging environments in which large sweat losses occur. One method of inducing hyperhydration and hypervolaemia—originally developed to help offset effects of plasma volume loss in microgravity (Greenleaf et al. 1997; Fortney et al. 1984)—is

'sodium loading'. A sodium concentrated beverage composed of sodium citrate and sodium chloride (164 mmol $Na^{+} \cdot L^{-1}$), with moderate osmolality (253 mOsm kg^{-1}), has been shown to be effective in inducing hyperhydration and hypervolaemia at rest in both phases of the menstrual cycle, although attenuated in the high hormonal state, irrespective of pill usage (Sims et al. 2007a). This sodium-loading strategy has also been found to be effective in aerobically trained men in warm conditions (Greenleaf et al. 1997, 1998a, b; Sims et al. 2007b). Moreover, earlier studies (Frey et al. 1991) demonstrated that ingested saline solutions between 0.9 and 1.07 % expanded plasma volume over a 4-h post ingestion time period. Frey and colleagues (Frey et al. 1991) determined that the 1.07 % saline solution elicited the greatest plasma volume expansion and urine concentration over the 4-h post-ingestion period; however, the addition of 1 % glucose did not improve the effectiveness of plasma volume expansion, but did increase diuresis. Thus, the authors concluded that a slightly hypertonic saline-only solution provided the most effective means of plasma volume expansion.

Electrolyte Handling and Imbalances

Menstrual cycle hormones affect fluid dynamics by altering capillary permeability, vasomotor function, the central set-point control of renal hormones and plasma osmolality (Charkoudian and Stachenfeld 2011). The elevation in plasma progesterone concentration during the luteal phase inhibits aldosterone-dependent sodium reabsorption in the kidneys due to progesterone competing with aldosterone for the mineralocorticoid receptor. Moreover, Eijsvogels and colleagues (2013) determined that women demonstrate a post-exercise increase in plasma volume concomitant with a decreased plasma sodium concentration as compared to age-and fitness-matched men; suggesting that the control of fluid balance is regulated differently between the sexes during prolonged exercise.

Both oestrogens and progestogens can influence neural and hormonal control of thirst, fluid intake, sodium appetite and sodium regulation. Moreover, there are sex differences in the activity and stimulus of the cell bodies of the periventricular nuclei and the supra-optic nuclei (located in the anterior hypothalamus), where arginine vasopressin is synthesised (Ishunina and Swaab 1999; Sar and Stumpf 1980). Stachenfeld and colleagues demonstrated an oestrogen associated shift to an earlier threshold in the osmotic sensitivity of thirst and release of arginine vasopressin, indicating a smaller increase in plasma osmolality is required to trigger arginine vasopressin release and thirst in the brain. This shift persists during OC use (Stachenfeld and Keefe 2002; Stachenfeld et al. 2001b; Verney 1947)).

Exercise-associated hyponatraemia (EAH) refers to a clinically relevant reduction in the serum, plasma or blood sodium concentration during or up to 24 h after physical activity [99]. This can be a result of solute (primarily sodium) loss and/or excess fluid load (Hew-Butler et al. 2015). Women are at greater risk for EAH and this risk has been primarily attributed to their lower body weight and size, excess water ingestion and longer racing times relative to men (Almond et al. 2005). While these factors

may contribute to the greater incidence of hyponatraemia in women, it is likely that the differential effects of female sex hormones on sodium handling play a role.

Menopause, Ageing and Hydration

Independent of menopause, ageing in itself has important effects on fluid balance. Ageing is associated with a higher baseline plasma osmolality, coupled with an age-related blunting of thirst sensation during exercise (and water deprivation); the usual thirst mechanism that occurs with a drop in fluid volume (dehydration) is impaired (Stachenfeld et al. 1998). Older women are slower to excrete water (as compared to younger, premenopausal women) increasing the risk of hyponatraemia (Rosner et al. 2013; Stachenfeld 2014). Moreover, rehydration is a slower process with ageing, primarily due to slower kidney function and hormonal responses to sodium and water flux. Oestrogen-based hormone replacement therapy results in an increased basal plasma osmolality, plasma volume expansion, and an earlier osmotic threshold for arginine vasopressin release (e.g., 280 vs. 285 mOsmol kg^{-1} H_2O), but a reduction in urine output, resulting in greater overall fluid retention. This overall fluid retention is, however, not due to increased free-water retention, but rather increased sodium retention—the synthetic oestrogens inducing a reduction in sodium excretion (Stachenfeld et al. 1998, 2001b), eliciting a slight reduction in the hyponatraemic risk.

Summary

Drinking fluids with a higher sodium concentration than in regular sports drinks, before exercise, can elicit a transient hypervolaemic response that is partly preserved (relative to a low-sodium beverage) in exercise and is associated with improved physiological status and exercise capacity in warm conditions in female athletes. In women susceptible to EAH, more fluid is retained and more sodium lost when both oestradiol and progesterone are elevated. As women are at greater risk of EAH, knowledge of the hormonal status of women who develop it may prove helpful in the prevention of EAH. Moreover, during long-lasting exercise special care should be taken to monitor fluid and electrolytes in women susceptible to hyponatraemia when both oestrogen and progesterone are elevated, such as during pregnancy, while taking oral contraceptives, during the luteal phase of the menstrual cycle, and in perimenopausal athletes.

Oestrogen and Antioxidants

Oestrogen has wide-ranging metabolic effects impacting on immune and tissue integrity, energy stores and repair. Most recently its role as a potent antioxidant has been touted with evidence provided from research with numerous animal models and in

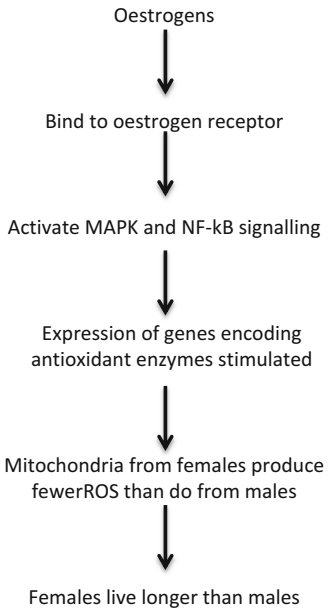

Fig. 6.1 Theoretical relationship between oestrogen ROS and longevity of females (Adapted from Vina et al. (2005))

humans. Differences between men and women in inflammatory disease states, coronary heart and cardiovascular disease, and quite possibly longevity, have been suggested to be attributed to differences in antioxidant capacity (Vina et al. 2005) (see Fig. 6.1).

Reactive oxygen species (ROS), although integral in the immune response and signalling pathways, can result in lipid peroxidation, cellular and mitochondrial membrane and DNA damage as well as protein and low-density lipoprotein (LDL) oxidation (Kehrer 1993). Exercise with a high rate of flux through the electron transport chain and/or increased hypoxanthine production and catabolism increases ROS production (Sjödin et al. 1990). Females have higher immune responses and lower oxidation and inflammation than male mammals, but this is reduced in ovariectomised females (Baeza et al. 2011), and reinstated with oestradiol supplementation (Stupka and Tiidus 2001) as in menopausal women reinstated with oestrogens and progestins (Tranquilli et al. 1995). Most human studies have been done in postmenopausal women, with and without hormone replacement therapy or in amenorrhoeic in contrast to eumenorrhoeic (Ayres et al. 1998) (Massafra et al. 1996). With the increase in lipid peroxidation and associated potential membrane damage with lack of oestrogen in females a case might be made for increased vitamin E supplementation in postmenopausal or amenorrhoeic women engaged in strenuous exercise regimens. However, Akova et al. (2001) observed a greater effect of endogenous oestrogen level on post exercise damage than vitamin E, with no synergistic effect.

Differences across the menstrual cycle are less well studied and findings not all consistent especially regarding the responses of varying measures of oxidative stress and antioxidant systems (See Fig. 6.2 for an overview of major endogenous antioxidant systems.).

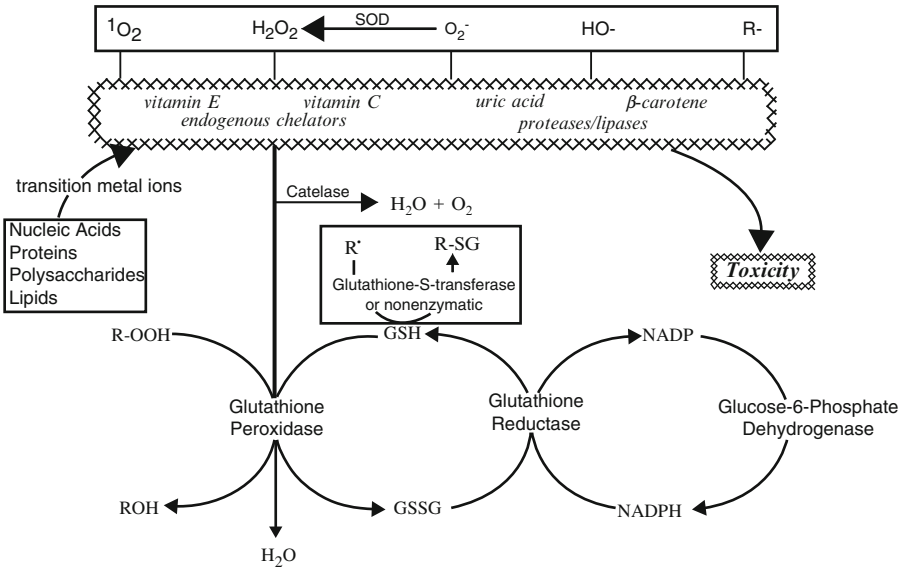

Fig. 6.2 Overview of endogenous antioxidant systems [from (Kehrer 1993)]

Chung et al. (1999) observed subtle differences in total glutathione and oxidation thereof in response to exercise between the luteal and follicular phases of the menstrual cycle and concluded that there was a nominal menstrual cycle effect on this endogenous antioxidant system. Joo et al. (2004) also noted an inverse correlation between superoxide dismutase activity and oestrogen concentration but reduced thiobarbituric acid reactive substances (Tbars) (indicating lipid peroxidation) in response to exercise in the late follicular compared to midluteal phases, and total superoxide dismutase activity greatest after exercise in the luteal phase.

More recently, however, Cornelli et al. (2013) monitored oxidative stress (hydroperoxides) every 3 days over the menstrual cycle and found that the greatest oxidative stress was at the oestrogen peak, decreasing through the progestin (luteal) phase until the end of the cycle. They concluded that oestrogen itself was not an antioxidant, but rather prooxidant, like exercise, such that, in response, antioxidant systems were upregulated. There is, however, considerable conflicting evidence, supporting oestrogen's role as an antioxidant. The varying models, species, methodologies and timing of measurement may explain some of the contradiction in findings and interpretation thereof.

If Cornelli et al.'s (2013) findings and conclusions are upheld, it may be that supplementing premenopausal women with antioxidants may not only be ineffective, but counterproductive.

Research conducted analysing vitamin C (ascorbic acid) and its oxidised state (dehydroascorbic acid) across the menstrual cycle demonstrated that ascorbic acid concentration and total antioxidant plasma status were greatest during ovulation when oestrogen peaks and in the midluteal phase, with dehydroascorbic acid greatest at menstruation and the midfollicular phases (Michos et al. 2006).

From this study it is concluded that in eumenorrhoeic women antioxidant responses are modulated in concert with oestrogen and may offer protection in times of particular need.

Whether vitamin C and/or vitamin E supplementation could offer protection from damaging levels of oxidative stress and inflammatory responses, particularly after increased or unaccustomed exercise or other situations of ischaemia/reperfusion, in postmenopausal women is open to conjecture. However, in a study of more than 34,000 postmenopausal women only dietary vitamin E was associated with reduced coronary disease (proposed to be related to LDL oxidation) but isolated vitamin supplementation was not (Kushi et al. 1996).

Furthermore, antioxidant vitamin supplementation can reduce adaptations to endurance training as well as hinder the cellular adaptation to become more oxidant resistant, including upregulation of endogenous antioxidant systems (For review see Petrnelij and Coombes (2011)). There are, however, conflicting results, probably due to varying levels of supplementation, training status, exercise type, load and measure of oxidation status. It can be tentatively concluded that high doses of individual antioxidant vitamins, in most well-nourished (non-deficient) individuals, will not enhance physical performance, and although they may reduce exercise related oxidation there is no clear evidence that this confers any recovery or health advantage (Peternelj and Coombes 2011).

An interesting finding was made in a study comparing antioxidant capacity and muscle enzyme leakage after exhausting exercise on low and high CHO diets across the menstrual cycle (Klapcinska et al. 2002). A number of antioxidant enzyme systems were improved on the low CHO diet supported by reduced membrane leakage of creatine kinase into plasma, with no significant menstrual cycle phase effects. The authors attributed the improvement in antioxidant function to the greater vitamin E, selenium and haem iron consumed on the low CHO diet (Klapcinska et al. 2002), although changes in the fatty acid composition of the diet or other nutrients cannot be discounted.

The limited available data suggest that further research is warranted to assess positive or negative effects of antioxidant vitamin supplementation in a systematic manner, particularly in women during specific phases of the menstrual cycle while heavily training, and in those with low circulating sex hormones.

Soy and Isoflavones

Soy is the predominant dietary source of isoflavones, one of several classes of phytoestrogens (oestrogen mimickers derived from plants which can bind to oestrogen receptors) (Cederroth and Nef 2009). Although some have found beneficial metabolic effects (including lower body mass index (BMI), higher high density lipoproteins (HDL), lower low density lipoproteins (LDL), lower blood glucose and insulin) in postmenopausal women who consume soy or soy-based purified phytoestrogens, this is not universally observed (Cederroth and Nef 2009). Furthermore there has been

some concern that due to its oestrogen-like functionality, it may be promote breast cancer, thus those at risk or diagnosed have been advised to avoid phytoestrogens. In premenopausal women soy phytoestrogens (45 mg isoflavones) have been observed to decrease FSH and LH and a greater concentration of oestrogen has been observed in the follicular phase with 1 month of daily supplementation (Cassidy et al. 1994). However, the follicular phase and menstrual cycle was lengthened and the progestin peak delayed. This is somewhat at odds with earlier concerns regarding phytoestrogens and cancer propagation, and may infer a reduced risk of cancer due to less total time over a woman's life in the luteal phase. Additionally, cholesterol was observed to be lowered in these premenopausal women consuming phytoestrogens (Cassidy et al. 1994). There may be different longer term effects than those observed over the short term, as some adaptation may occur. In support of this is a study in which 100 mg of soy isoflavones were given for 1 year and no alteration in menstrual cycle length or hormone levels was observed (Maskarinec et al. 2002).

In a crossover study with young, eumenorrhoeic women receiving soy (52 mg isoflavones) or placebo "cookies" daily for one menstrual cycle, in addition to greater progesterone concentration 3 days before ovulation, the ratio of a marker of bone resorption/bone formation was higher at the midluteal phase (Zittermann et al. 2004). Whether this response would be observed with longer-term dietary intakes in young women and if this would have long-term negative consequences in terms of bone health is unknown. In contrast, in postmenopausal women a positive correlation has been observed between mineral bone density and phytoestrogen intake; however, this correlation was not observed in premenopausal women (Mei et al. 2001).

In a study with teenage swimmers, all with normal menstrual cycles, supplementation (26 days) with *Lippia citriodora* (lemon verbena) extract, in a beverage which also contained vitamins C and E, was observed to increase glutathione peroxidase and reductase activities in red blood cells, and superoxide dismutase activity in lymphocytes, to a greater extent after exercise than with just a beverage with vitamins C and E. This extract contains two phytoestrogens which have the potential to bind with oestrogen receptors. 17-β-oestradiol and testosterone were observed to be lower and sex hormone-binding globulin to be greater with the extract, in the basal condition as well as after exercise (Mestre-Alfaro et al. 2011). Although this phytoestrogen containing extract enhances antioxidant systems, it is questionable whether this group of young, regularly training and competing women would benefit from or be negatively impacted by the reduction in circulating, free, sex-hormones.

In support of phytoestrogens having antioxidant functionality, similar to oestrogen, a study in which daily consumption of soy milk (113–207 mg/day isoflavones for one menstrual cycle reduced lipid peroxidation in premenopausal women, with a greater effect in older women with lower doses (Nhan et al. 2005).

Another source of isoflavones is red clover. Results with supplementation with this source of isoflavone extract have been inconsistent. In one study 86 mg isoflavones were consumed per day, for three menstrual cycles, by premenopausal women and no alterations in cholesterol or cholesterol subtractions or other blood parameters were observed (Blakesmith et al. 2003). In another study, a similar amount of red clover

isoflavones was consumed by premenopausal as well as postmenopausal women for 1 month (Campbell et al. 2004). They did, however, observe an increase in HDL cholesterol with supplementation, but this was only significant in postmenopausal women.

Although there have been some positive effects observed, particularly in postmenopausal women who use phytoestrogens as an alternative to hormone replacement therapy, long term risk and health benefits are unclear (Moreira et al. 2014; Patisaul and Jefferson 2010). Even less is known as to whether phytoestrogen supplementation enhances or reduces exercise training adaptations, including ROS signalling and endogenous antioxidant systems in this growing segment of the population.

Fish Oil

It has been proposed that enhancement of endothelial nitric oxide (NO) production and down-regulation of acute phase cytokines by oestrogen and fish oil may play a role in deterring the development or progression of Alzheimer's disease (McCarty 1999). The omega 3 fatty acids in fish have been proposed to reduce inflammation via inhibitory effects on Interleukin-1 (IL-1) and Interleukin-6 (IL-6) and may have a positive effect on endothelial NO production. Oestrogen can also increase endothelial NO formation and has an inhibitory effect on IL-6, both reducing inflammation. It has been suggested that some of the other negative effects of menopause may also be attributed to this increased inflammation (McCarty 1999). This being the case fish oil supplementation may be particularly beneficial in postmenopausal women.

A case has also been made for fish oil supplementation in premenopausal women who have premenstrual symptoms (PMS). It has been suggested that more rigid red blood cells result from linoleic acid insufficiency, or altered metabolism, thereby reducing prostaglandin E1 (PGE1) synthesis, which could make red blood cells less deformable. This could result in greater intracapillary pressures needed for blood flow, resulting in fluid movement into the extravascular compartment (Simpson 1988). If this could account for some of the PMS symptoms, then it is reasoned that by enhancing PGE1 synthesis through precursor fatty acids (e.g., found in fish oil or evening primrose oil) then the red blood cells would be more able to move through the capillaries at lower pressures and reduce fluid filtration and retention.

In a recent double blind, crossover study daily fish oil tablet (80 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) consumption for 3 months reduced premenstrual pain and ibuprofen use (Rahbar et al. 2012). Others have found similar results in combination with B-12 supplementation (Deutch et al. 2000). In a review of efficacy of treatment for dysmenorrhoea the use of fish oil was concluded to be "possibly effective", strength of recommendation "B" (Morrow and Naumburg 2009).

Although the strength of evidence is moderate, enhancing dietary intakes of fish or other sources of omega 3-rich foods or supplements have little to no known negative effects and may prove efficacious, for those with PMS and in postmenopausal or amenorrhoeic women. One cautionary note regarding fish or fish oil supplements, where the source of the fish and purity is unclear, is the possibility that mercury

levels could pose health risks if consumed on a regular basis. However, it appears that supplements may not pose more of a risk of mercury toxicity than regular fish consumption (Foran et al. 2003; Hightower and Moore 2003).

Vitamin D/Calcium

Vitamin D and calcium are important for fertility (Stumpf and Denny 1989) and vitamin D is positively correlated with FSH concentration (Jukic et al. 2015). Decreasing calcium concentration and increases in parathyroid hormone have been theorised to play a role in premenstrual syndrome and supplementation may decrease symptoms (Thys-Jacobs 2000) and low vitamin D in the luteal phase may be involved (Thys-Jacobs et al. 2007). However, oestrogen plays a role in calcium regulation (Pitkin et al. 1978) and simply supplementing with calcium and or vitamin D will unlikely compensate for the lack of oestrogen in amenorrhoeic athletes (Baer et al. 1992), or postmenopausal women. The decreasing bone mineral density in athletes without menstrual cycles and the increase in bone density after resumption of menstruation (Drinkwater et al. 1986) are evidence hereof.

Branched Chain Amino Acids (BCAA)

There appears to be an effect of oestrogen on BCAA metabolism, such that the breakdown of these to keto-acids (leading to further catabolism for energy or gluconeogenesis) is inhibited and, thus, these amino acids are preserved for protein synthesis (Obayashi et al. 2004; Shimomura et al. 2001; Kobayashi et al. 1997). As the majority of this work has been conducted in animals it is unclear to what extent this applies to women, and if so, is there a menstrual cycle effect such that when oestrogen is low should protein intakes be increased, particularly when total energy and protein intakes are low and energy expenditure is high, such as often the case in endurance female athletes. In males, supplementing with oestrogen improved nitrogen balance during endurance exercise training (Hamadeh et al. 2005a). Implications for postmenopausal and amenorrhoeic athletes are as yet unclear. Further research is warranted to determine the applicability of these findings to women, with and without menses or on varying forms of hormonal contraception, and the extent to which possible alterations in BCAA metabolism influence muscle growth and repair.

Table 6.2 Summary of practical applications of nutrients with respect to female sex hormone alteration

Practical applications
Lower resting muscle glycogen in the follicular phase can be overcome by CHO loading but an increase in total energy intake may be required.
Pre-exercise feeding and/or CHO ingestion negate the oestrogen-induced reduction in gluconeogenesis during endurance exercise (>50 % VO_2max).
Female athletes need to pay extra attention to recovery nutrition in the luteal phase to offset the increase in protein catabolism.
Oestrogen and progesterone affect the hormonal and neural control of thirst, sodium regulation, and fluid retention, increasing the risk of hyponatraemia during the luteal phase of the menstrual cycle.
Hormone therapy in menopausal women lowers the threshold for osmotic AVP release, increased basal plasma volume expansion and decreased urine output, resulting in greater fluid retention.
Oestrogen enhances antioxidant capacity in females.
Supplementing with dietary sources of antioxidants may be prudent in those with amenorrhoea or in menopause, but may still not compensate for lack of oestrogen.
Fish oil (omega-3 fatty acid source) may aid in inflammatory disorders such as dysmenorrhoea and those associated with menopause.
Vitamin D and calcium play a role in fertility, possibly in dysmenorrhoea as well as bone health; however, they cannot fully compensate for lack of oestrogen.
Branched chain amino acid oxidation may be greater when oestrogen is low; this may have dietary implications for in those with amenorrhoea or in menopause, particularly when training regularly and/ or on low energy diets.

Conclusions

There may well be menstrual cycle and/or female sex hormone effects on the metabolism of other nutrients or supplements of particular importance to women engaged in regular physical training, but research is limited. We focus on those with the most significant effects and summarise these in Table 6.2. We encourage future researchers to explore the specific effects and nutrient interactions modified by normal fluctuations and alterations in female sex hormones. As the majority of acute response and training studies delineating the impact of nutrients on exercise tolerance and impact have been conducted in males, recommendations for females are often based on male responses. We, as researchers that have undertaken intervention studies with females in varying phases of the menstrual cycle, realise the difficulties and time commitment necessary for this type of work and implore granting bodies to commit dedicated funds for more systematic study such that the knowledge base concerning women eventually equals that of men.

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