Sex Hormones, Exercise and Women

Scientific and Clinical Aspects

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This work is dedicated to my good friend and mentor, the late Dr. Atko Viru, of Tartu University, Estonia.

Preface

In the late 1970s, medical science was beginning to understand that exercise training, while normally an extremely positive physiological stimulus, could also have some drawbacks. Landmark research studies by scientists such as Dr. Barbara Drinkwater, Dr. Anne Loucks, and Dr. Michelle Warren, as well as others, demonstrated that exercise training could be a causative factor in disrupting the endocrine control of a woman's reproductive system leading to the development of "athletic amenorrhea" (secondary amenorrhea). This medical condition is now recognized as part of the conditions associated with the Female Athlete Triad.

The basic premise of the research work on the development of athletic amenorrhea in women can be conceptualized as follows:

Exercise → Female Reproductive Hormones → Physiologic Consequences (negative)

That is, aspects of exercise and exercise training modulate the functioning of the female reproductive hormones. This modulating influence can be highly negative, leading to low estrogen and progesterone states and disruption of normal ovary function and menstruation. Contemporary research has demonstrated that the critical aspects initiating the sequence of such events are energy availability (i.e., development of a low energy availability state; recently designated as part of the Relative Energy Deficiency in Sports condition [RED-S] by an International Olympic Committee Medical Commission).

As a young professional, I found the research on athletic amenorrhea an exciting and fascinating aspect of exercise endocrinology. But my curiosity also caused me to think about the relationship in a different fashion and ask the question—if exercise affects reproductive hormones, could the reproductive hormones have physiological effects unrelated to reproduction that influences the capacity of women to exercise? This seemed a logical question to me as many hormones have more than one physiological effect/impact, and structurally many reproductive hormones have

chemical structures similar to many metabolic and water balance hormones. In other words, I wondered:

Female Reproductive Hormones → Exercise → Physiologic Consequences (negative/positive?)

After studying the research literature, it was apparent that animal researchers had been asking this question and seeing that the female reproductive hormones did affect physiological systems and processes that affected exercise capacity. At that time, nearly 40 years ago, the human-based literature was extremely sparse. With that, I and a number of other researchers began to pursue the question of whether the female reproductive hormones have physiological impacts on the bodily systems that are essential to the exercise capacity of women exercisers.

In asking this question, to myself, the underlying premise was not to examine women in order to see why in some activities men are better. But, more to understanding the unique physiology of women and whether female sex hormones might account for some of the variance in physiological performance between amenorrheic and eumenorrheic women, and within women across the life span as they experience menarche to menopause. That has been my interest in pursuing this absorbing topic and why I wanted to develop this book.

This book was developed with the hope that the select group of professionals writing the various chapters could address this last question. Like nearly all written works, this one could be improved and be made better, but I am extremely proud and thankful to the international collection of authors who contributed and put forth so much hard work. Each discussed topic provides current insight into the state-of-the-art research in the respective topic area. It is hoped the reader will be as excited and fascinated after reading the individual topics as the authors were in writing them. I also hope the insights provided herein will inspire new researchers to ask questions about the roles of female sex hormones in exercise and pursue investigations to seek answers to those questions.

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Acknowledgments I wish to acknowledge the support of my graduate students who certainly helped me bring this to completion. You are a great group of young professionals. My sincere thanks to all the authors involved with this project. They were wonderful to work with and I appreciate their professionalism. I also wish to sincerely thank my family for their support while I worked on this project.

Prologue

The unique beauty of sports lies in the exceptional performances which result from physical, psychological, and technical excellence. We cheer on our favorites, tagging along with the huge excitement leading up to the big events. What limits and records will be broken? What will we see that has never been done before? For so many, it is hard to picture what it is like being a top athlete, but it is almost like an obsession aiming for the margins that can take you further, higher, or be smarter. Often this leads to a game in which one pushes themselves closer and closer to the limit. The golden limit where you must get comfortable as an athlete in order to be competitive, but where it is also so very close to the small steps that can set you back. Bigtime!

As a female elite athlete for one and a half decades, I worshiped this state of mind. This life surrounded by my fellow athletes, teammates, and competitors pursuing the same dream. This might seem like the perfect setup, living the dream with people fully motivated for exceeding their former limits. So, is there a problem?

We know that intense training at this level, leading to high performances at elite competitions, leads to unique strength, stamina, and technical execution. Yet it is a paradox that the same training in some cases leads to negative hormonal changes, energy deficiency, injuries, or physiological drawbacks. The debate on how to encourage and facilitate development toward this excellency while balancing it in such a way that is not unhealthy both in a short- and longtime perspective is still not resolved and as a topic is hotter than ever before in the research community.

While training as a top athlete, I was lucky to be able to pursue a dream of becoming a scientist/medical doctor. This gave me the unique chance to experience and reflect on the load me and my fellow athletes put on ourselves while reaching for the goal of performing at our best. Surprisingly, the knowledge of female physiology, excessive training, and both short- and long-term effects is extremely limited, which unfortunately has led to the loss of talent, health, and unredeemed potential. Looking ahead, we need more knowledge, understanding, awareness, and increased research about female athletes and their physiology to both increase their performance and support them in a long-term perspective. This way we might facilitate both winners in sports and winners in life.

With this book, world leading scientists provide their insights into the unique physiology of women and the effect of their reproductive hormones, leading to a better understanding of the conditions related to the responses and adaptations of women to exercise. For everyone working with and around female athletes and women who exercise, in my opinion, this should be mandatory reading. Congratulations to the authors and the editor for their excellent efforts.

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Chapter 1
The Hypothalamic–Pituitary–Ovarian Axis, Menstrual and Oral Contraceptive Cycles: Regulation and Function in the Context of Exercise and Sport

Ritva S. Mikkonen, Johanna K. Ihalainen, Hope C. Davis-Wilson, and Anthony C. Hackney

Introduction

Over the past few generations, female* participation in sports and exercise has continued to increase resulting in a greater need for research in female physiology. More specifically, work is still needed regarding the benefits and consequences of exercise on reproductive endocrinology as well as the effects of reproductive hormones on exercise and performance. The female reproductive system is a complex physiological system consisting of several hormonal and regulatory components. Thus, it is imperative for exercise scientists who wish to study females to have a strong knowledge base of the controlling regulatory system, referred to as the hypothalamic–pituitary–ovarian (HPO) axis. The intent of this chapter is to provide background information about female sex steroids as well as the endocrine basics of the female reproductive system. This chapter focuses on providing a brief review

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of the essential endocrinology of the menstrual cycle, menstrual dysfunction, and hormonal contraceptive (HC) use as well as brief information regarding the effects of the menstrual cycle and HC use on exercise. In addition, a summary of "best practice" methodology for taking into consideration the menstrual cycle and HC in sport and exercise, both research and practice, is included. **Nota Bene:* In this chapter, we use the terms "women" or "female" as they are used in the studies presented. However, we encourage the reader to consider that transgender and gender-diverse individuals may also menstruate and/or have unique hormonal profiles.

Female Sex Steroids

The female life cycle is associated with several hormonal milestones in which estrogen and progesterone play significant roles including menarche, pregnancy, perimenopause, and the transition into menopause, as well as the use of exogenous sex hormones including hormonal contraceptives and hormonal replacement therapy. All these events and interventions alter the levels and fluctuations of sex hormones and are discussed in this book. Female sex steroids (hormones), including estrogen and progesterone, have typically been defined by their role in reproductive function. Previously, it was assumed that the targets for these hormones were limited to the reproductive system including the breast, uterus, and ovary in women (Turgeon et al. 2006). Relatively recently, however, the functions of sex steroid hormones have been recognized to target tissues in the vascular system, central nervous system, gastrointestinal tract, immune system, skin, kidney, and lung (Wierman 2007). This information has changed our understanding of normal physiology and has influenced research regarding the potential sex-based differences in responses to exercise.

Estrogens

Estrogens are a group of similarly structured steroid hormones that are produced primarily in the ovaries of females. Three estrogens are present in significant quantities in the plasma of the human female: estradiol-β-17, estrone, and estriol. Estradiol-β-17 is the principal estrogen produced and released due to HPO-axis activity at the ovaries and has a higher relative estrogenic potency than other estrogens. Estradiol-β-17 is the estrogen responsible for primary and secondary female sex characteristics and contributes reproductive function (Wierman 2007). As such, estradiol-β-17 is the main estrogen discussed in this chapter. Briefly, estrone is the primary estrogen in a woman's body after menopause, while estriol is the primary estrogen during pregnancy. Estrone and estriol are produced locally in target tissue (peripheral conversion) such as adipose cells.

Estrogens have physiological roles in both males and females, including soft tissue, skeletal muscle, and the epidermis (Wierman 2007). In general, estrogens

promote proliferation and growth of specific cells. During childhood, only minimal quantities of estrogens are secreted. At puberty, a significant increase in pituitary gonadotropic hormones is observed (Apter 1980). During this time, the size of the ovaries, fallopian tubes, uterus, and vagina increases remarkably. Estrogens inhibit osteoclast activity in the bones and stimulate bone growth, thus estradiol-β-17 also plays an essential role in maximizing and maintaining bone density, which is why estradiol-β-17 deficiency can have detrimental consequences for a woman's bone health (Väänänen and Härkönen 1996). Estrogens cause the deposition of increased quantities of fat in the subcutaneous tissue, and as a result, the fat percentage of females is considerably higher than in males. Estrogens increase whole-body metabolic rate slightly but only about one-third as much as testosterone. Research indicates that resting and exercise metabolism (lipolysis, glycogen sparing) are affected by estradiol-β-17. For example, physiological estradiol-β-17 can increase lipolysis and inhibit glycogen utilization during rest and acute exercise (Hackney 1999, 2021; Hackney et al. 2022). It is thought that estradiol-β-17 may also directly alter enzymatic activity or indirectly affect insulin sensitivity thereby affecting glycogen usage (Bunt 1990).

With aging, estrogen levels begin to decline. During the first year of menopause, an average decrease in estrogens of 80% occurs (Viña et al. 2006), which is accompanied by a loss of strength and muscle mass (Phillips et al. 1993). Declines in estrogen are also associated with decreased cardiovascular health, and estrogen has been studied extensively for its potential cardioprotective activity (Iorga et al. 2017). Importantly, estrogens regulate several other functions throughout female and male target tissues through direct and indirect impacts on other neuroendocrine agents (Bunt 1990). Importantly, decreases in basal estradiol-β-17 are associated with several negative physiological outcomes in athletes (Pirke et al. 1985), non-athletic women of reproductive age (Golden and Carlson 2008; Klein et al. 2019), and menopausal/postmenopausal women (Phillips et al. 1993; Sirola and Rikkonen 2005). These observations emphasize the importance of estrogens for health, performance, and functional capacity.

Progestogen

Progesterone is the major progestogen (steroid hormone classification) and is produced predominantly by the ovaries, but it is also produced locally in some tissues. The term "progestin" is often used to denote a synthetic progesterone (Sitruk-Ware and El-Etr 2013). As such, to differentiate the synthetic hormones from natural progesterone, we will use progestin in the present chapter for all synthetic molecules as opposed to the natural hormone progesterone. The name progestin can be used interchangeably with progestogen, progestagen, gestogen, and gestagen.

Progesterone acts through binding to intracellular progesterone receptors (PRs) that have been identified in several tissues both in and outside of the female reproductive tract (Conneely and Lydon 2000). The function of progesterone is primarily to

prepare the uterus for pregnancy by stabilizing the endometrial lining and preparing the breast for lactation (Filicori 1999). In addition, progesterone has important effects on the central nervous system, vascular, and other target tissues (Mani et al. 1997) (please see other chapters in this book for details). Moreover, progesterone has the potential to effect energy metabolism by increasing fat oxidation (Redman et al. 2005). When progesterone concentrations are high, progesterone can inhibit the binding of estrogen to an estrogen receptor (ER) by blocking the binding site. This causes the conversion of estradiol-β-17 to estrone, a less active form of estrogen (Erickson et al. 1985).

Hypothalamic–Pituitary–Ovarian Axis

The hypothalamus is a small region of the brain located near the pituitary gland at the base of the brain, while the ovaries are located on either side of the uterus against the pelvic wall. Together, the hypothalamus, pituitary, and ovaries make up the hypothalamic–pituitary–ovarian (HPO) axis (see Fig. 1.1). Regulation of the female reproductive system consists of complex and dynamic interactions between neuroendocrine feedback loops of the hypothalamus, pituitary, and ovary. Although there is debate about whether the hypothalamus or pituitary is the most important regulator of the female reproductive system, there is no denying that all three neuroendocrine glands must work together to ensure proper functioning (Sam and Frohman 2008).

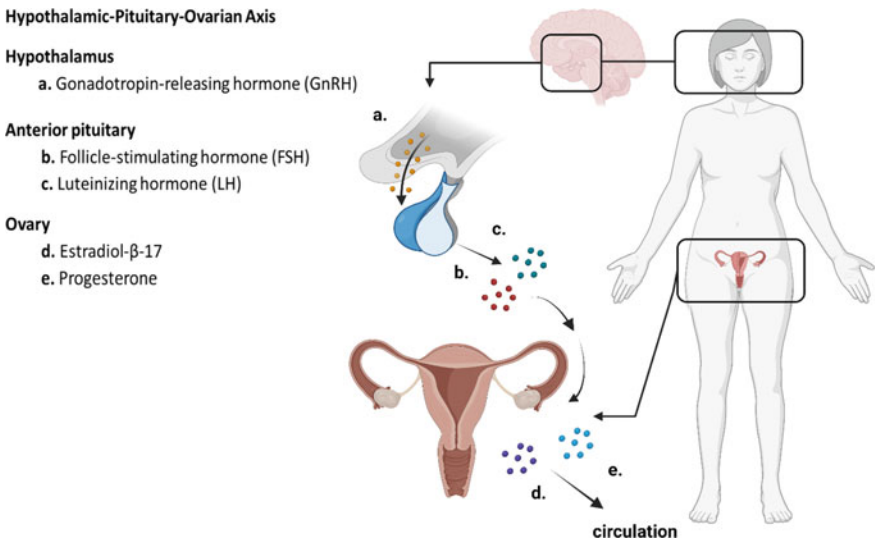

Fig. 1.1 Female hormonal system known as the hypothalamic–pituitary–ovarian axis

The HPO-axis feedback loops are dependent on sufficient energy and nutrients and are regulated by stress (Veldhuis et al. 1985) (emotional and/or physical) and/or the conditions such as low energy availability (an imbalance in energy consumed vs. energy expended) (Elliott-Sale et al. 2018; Hakimi and Cameron 2017). Disruptions to normal hormone concentrations may be observed even after only a few days of decreased energy intake (Loucks and Thuma 2003), acute stress (Chrousos and Gold 1992), or a combination (Strock et al. 2020). Prolonged exposure to stress and low energy intake may ultimately be manifested as menstrual dysfunction (discussed later). Briefly, proper functioning of the reproductive system is critical not only to reproductive health, but overall health in women as evidenced by the myriad of health-related issues that often accompany decreased levels of estrogens that occur with amenorrhea and menopause (female reproductive senescence).

Hypothalamic Hormones

Current research suggests that a set of brain peptides (i.e., neuropeptides) encoded by the Kiss1 gene, known more commonly as kisspeptin, may be an important upstream regulator of where gonadotropin-releasing hormone (GnRH) release (Skorupskaite et al. 2014). Indeed, the kisspeptin system is reported to serve as a "gatekeeper" for the secretion of gonadotropins, ovulation, and the metabolic regulation of fertility as well as the onset of puberty (Pinilla et al. 2012; Roa et al. 2008). Kisspeptin neurons in the hypothalamus modulate the prepubescent LH surge that occurs in females as well as the actions of sex steroids on GnRH neurons (Skorupskaite et al. 2014). Metabolic disruptions (e.g., inadequate nutrition) can decrease kisspeptin expression, which in turn can suppress reproductive functioning (Castellano et al. 2005; Fernandez-Fernandez et al. 2006).

The signaling process for the menstrual cycle begins in the hypothalamus, where gonadotropin-releasing hormone (GnRH) is released into the bloodstream and travels to the pituitary gland. The pituitary responds by releasing gonadotropin hormones, specifically luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In healthy women, GnRH is released in a pulsatile manner, and consequently, FSH and LH are released in a similar pulsatile pattern from the anterior pituitary (Herbison 2018).

Pituitary Hormones

The pituitary release of FSH and LH results in binding to the ovarian receptors for these hormones, which stimulates the production and secretion of both estrogen and progesterone (Ferin 1996). Specifically, within the ovary, LH binds to LH receptor sites on the thecal cells. When stimulated, thecal cells convert available cholesterol into androgens (McNatty et al. 1979). These androgens are then transported to the

granulosa cells where FSH binds to FSH receptors, thus stimulating the conversion of androgens into estrogen (specifically estradiol-β-17) via aromatase enzymes (Hillier 1987).

Ovarian Hormones

As noted, the processes described above result in the release of sex steroid hormones progesterone and estradiol-β-17 at the ovary as well as the designation of which follicle will complete ovulation. Follicular maturation and development occur via complex processes involving interconnected intra- and extra-ovarian events. These events initiate ovulation of a mature oocyte and transformation of the ruptured follicle into a corpus luteum. The changes in progesterone and estradiol-β-17 that are typically observed during the menstrual cycle are described later in this chapter.

Other Key Regulators of the HPO Axis

The HPO axis is also influenced by the hypothalamic–pituitary–adrenal (HPA) axis, which plays a critical role in regulating stress via glucocorticoids, and energy balance (Elliott-Sale et al. 2018). Similarly, the activin–follistatin–inhibin axis (AFI) influences HPO-axis function. Granulosa cells produce inhibin and activin. Inhibin inhibits FSH secretion in remaining non-dominant follicles, while activin stimulates FSH and increases the sensitivity of FSH at the ovary (Kitaoka et al. 1988). Follistatin inhibits activin and is released by the anterior pituitary (Muttukrishna et al. 2004). In addition to pituitary and ovarian regulation, follistatin and inhibin also have roles in physiological processes including bone metabolism and hematopoiesis (Makanji et al. 2014).

The Menstrual Cycle

Cyclic ovarian function spans the time between puberty (and the onset of menarche) and menopause. Both puberty and the time spanning perimenopause through menopause are transitional periods of increasing or decreasing ovarian activity, respectively, that occur over several years. The age of menarche is genetically determined, controlled by the central nervous system, and may be correlated with attaining a critical body weight (Karapanou and Papadimitriou 2010). The fluctuating production and release of reproductive hormones over approximately 28 days and ranging from 21 to 35 days is known as the menstrual cycle. The menstrual cycle can be divided into two basic phases: the low-estrogen (follicular) and high-estrogen (luteal)

phases, which are divided by ovulation (~mid-cycle). The menstrual cycle can also be divided into four more distinct phases, as shown in Fig. 1.2 and defined below:

Phase 1: The cycle begins with menses (menstrual bleeding or bloody discharge), and this phase lasts an average of 5 days (Elliott-Sale et al. 2021). During this phase, estrogen and progesterone levels are low, but FSH and LH levels begin to rise slowly, causing new follicle growth and estrogen release from the ovaries (Hall and Guyton 2006). Menses mark the first day of the menstrual cycle and are the start of the follicular phase. As the follicular phase progresses, the dominant follicle is selected. FSH increases and estrogen remains low due to regression of the corpus luteum from the previous cycle. With the increased sensitivity of FSH due to FSH receptors on the granulosa cells, a dominant follicle is selected and begins to secrete estrogen.

Phase 2: Just before ovulation, the highest estrogen levels of the menstrual cycle are observed, while a significant increase in LH levels occurs (Elliott-Sale et al. 2021). This surge in LH levels is essential for ovulation (Hall and Guyton 2006).

Phase 3: Ovulation occurs and a mature egg is released from the ovary and travels down the fallopian tube, while the formation of the corpus luteum occurs (Hall and Guyton 2006). Next, a positive feedback loop emerges as increasing estrogen levels from the follicle stimulate the LH surge characteristic of the luteal phase. Following ovulation, progesterone is released in a pulsatile manner from the follicle in response to LH. The follicle then becomes the corpus luteum within the uterus (Vande Wiele et al. 1970). If fertilization occurs, the embryo remains in the endometrium and develops into a fetus.

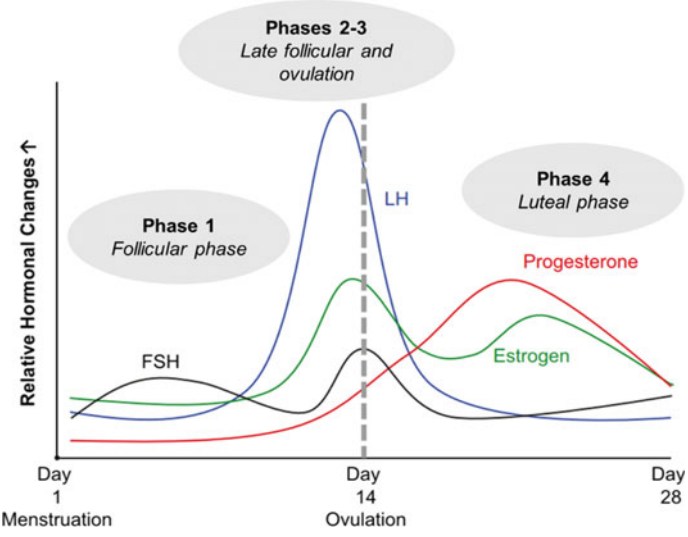

Fig. 1.2 Key regulatory hormone changes associated with the menstrual cycle in a healthy eumenorrheic woman, including the identified phases of the menstrual cycle

Phase 4: The corpus luteum begins to secrete estrogen and progesterone. Estrogen levels are relatively high and accompanied by the highest levels of progesterone observed during the cycle (Elliott-Sale et al. 2021). High concentrations of estrogen and progesterone inhibit and reduce the secretion of FSH and LH from the pituitary gland (Hall and Guyton 2006). Toward the end of the cycle, if fertilization does not occur, the corpus luteum begins to atrophy and its hormone secretion decreases. This is accompanied by a fall in estrogen and progesterone and the onset of menstruation (bleeding/bloody discharge). Simultaneously, this triggers the secretion of hormones by the hypothalamus and pituitary gland a few days before the start of a new cycle (Hall and Guyton 2006). Figure 1.2 gives an illustrative display of the major circulating hormonal changes over the menstrual cycle and highlights these specific and hormonally unique phases. It should be noted that this "textbook" hormonal profile can be affected by several factors and that measuring hormonal profiles in a cohort of "naturally menstruating women" is likely to reveal individual hormonal profiles that may not be identical from cycle to cycle (MacNutt et al. 2012).

Menstrual cycle, sport and exercise

Exercise performance (both strength and endurance) may be slightly reduced during the early -follicular phase of the menstrual cycle in comparison with the other phases (McNulty et al. 2020). This might be explained by premenstrual and menstrual symptoms that are linked to the late luteal phase (phase 4) and early-follicular phase (phase 1). Unfortunately, the existing literature on this topic is relatively limited and lacking in quality (McNulty et al. 2020), particularly in elite athletes (Meignié et al. 2021). Solli et al. (2020) used questionnaires to investigate how elite Norwegian endurance athletes experience their menstrual cycle with regard to athletic performance. Of 140 athletes, 50–71% reported changes in performance over the menstrual cycle. Most of these athletes reported performance decrements 1–4 days prior to menstruation or during menstruation. This was accompanied by several symptoms including stomach pain, bloating, and mood changes. Although 80% of athletes reported menstrual pain, only 20% of athletes indicated that they changed their planned training due to this pain, while roughly half of the athletes used pain medications (Solli et al. 2020).

In addition to the bleeding phase, another "critical" phase associated with negative experiences on exercise performance is the second half of the menstrual cycle also known as the luteal phase. Premenstrual syndrome (PMS), which may begin 7–10 days before menstrual bleeding, is characterized by several possible symptoms including mood disturbances, difficulty sleeping, muscle, and joint pain, bloating, constipation, diarrhea, headache, etc. Some 85–90% of women are affected by at least one symptom (Halbreich et al. 2003), while the daily activities of some 15–20% of women are affected by PMS symptoms (Yonkers et al. 2008). For some women, PMS symptoms are more severe and/or debilitating in nature. Premenstrual dysphoric disorder (PMDD) affects between 2 and 8% of the population (Matsumoto et al. 2013). Symptoms associated with PMS may be present during menstrual bleeding

including stomach pain, cramps, headache, and back pain that can negatively influence or impede training (Martin et al. 2018), whereas subjective experiences of these symptoms are variable. Menstrual cramps/pain and heavy menstrual bleeding may be present during a "regular" or "normal" cycle; however, if these symptoms affect daily life, they should be discussed with a healthcare professional. It is important to note that not all women experience negative symptoms related to their menstrual cycle.

Menstrual Dysfunction

The menstrual cycle is a sign of health and homeostasis in women of reproductive age that are not using hormonal contraceptives and are not pregnant or nursing. As discussed in more detail in later chapters, physical and psychological stress as well as other conditions including poor nutritional status can affect the menstrual cycle. Maintenance of a regular menstrual cycle requires a healthy and normally functioning hypothalamic–pituitary–ovarian axis and uterus. A healthcare professional can/should be consulted with questions about the menstrual cycle, irregularities, and related symptoms. Table 1.1 summarizes the most common menstrual cycle-related terminology.

The lack of a menstrual cycle, a long cycle, or an irregular cycle may indicate energy imbalance (low energy availability or obesity), lack of recovery, or other gynecological illness. Low energy availability and lack of recovery in sports are often associated with impaired HPO-axis function and low estrogen (Allaway et al. 2016). Over time low-estrogen (and other hormonal changes associated with menstrual dysfunction) affects bone and muscle health as well as endothelial function ultimately affecting performance and functional capacity. It is important that coaches and practitioners working with female athletes recognize that the negative symptoms of low energy availability may not be present immediately. As such, it is important to discuss the characteristics of a normal menstrual cycle as well as signs of menstrual dysfunction and to encourage athletes to seek help if signs of menstrual dysfunction arise. Ultimately, the underlying cause or causes of menstrual dysfunction should always be investigated by a healthcare professional.

Elite athletes as well as recreational athletes who are training with high training volume quantities are at risk for menstrual disturbance due to their high training volume and associated high level of energy expenditure, which may be accompanied by low energy intake (Mountjoy et al. 2014). Although the absence of menstruation (amenorrhea) is usually correctable by factors such as increasing energy availability, amenorrhea can have long-term health effects on, for example, bone health (Mountjoy et al. 2014). Because amenorrhea is one of the most easily identifiable signs of relative energy deficiency in sport (RED-S) in women (Mountjoy et al. 2014), it is important that the atmosphere in each coaching relationship and team allows for discussion on the topic. A Swedish study found that coaches still communicate to young endurance athletes that missing a period is a sign of a lean elite athlete or a sufficiently strenuous

Table 1.1 Menstrual cycle-related terms and their recommended definitions in research (modified from (Elliott-Sale et al. 2021))

Term	Definition
Eumenorrhea	Menstrual cycle length is 21–35 days resulting in ≥ 9 consecutive periods per year. There is evidence of LH surge and correct hormonal profile and no HC use 3 months prior
Primary amenorrhea	Failure to reach menarche by age 15 years when the development of secondary sexual characteristics is evident or failure to reach menarche by age 14 years when no secondary sexual characteristics are present
Secondary amenorrhea	Absence of more than three consecutive periods in non-pregnant women with past menses that may be caused by gynecological illness or low energy availability
Oligomenorrhea	Menstrual cycle length is > 35 days
Polymenorrhea	Menstrual cycle length is < 21 days
Anovulation	Menstrual bleeding without ovulation
Luteal phase deficiency	Menstrual cycles with < 16 nmol·L^{-1} of progesterone based on a single luteal phase progesterone measurement
Primary dysmenorrhea	Menstrual bleeding is accompanied by significant pain from the first menstrual period (concomitantly other symptoms may be present such as nausea, vomiting, diarrhea, fatigue, fever, irritability, muscle pain, dizziness, and/or headache)
Secondary dysmenorrhea	Previously unpainful menstrual bleeding that typically is secondary to gynecological illness (concomitantly other symptoms may be present such as nausea, vomiting, diarrhea, fatigue, fever, irritability, muscle pain, dizziness, and/or headache)
Menorrhagia	Menstrual bleeding that is abnormally heavy (>80 ml) or prolonged (> 7 days) and negatively affects daily function

workout(s) (Höök et al. 2021). On the contrary, a regular menstrual cycle is a sign of a woman's homeostasis (if the woman is not pregnant/breastfeeding or using hormonal contraception) and amenorrhea should always be taken seriously.

Hormonal Contraceptives

Two kinds of hormonal contraception exist: One prevents fertilization and the other prevents implantation and pregnancy. Importantly, several other reasons exist for hormonal contraceptive use, both gynecological and otherwise. From a pharmacological point of view, hormonal contraceptive methods utilize either a combination of estrogen (typically ethinyl estradiol, natural estradiol, or one of its derivatives) and progestin or progestin only. The route of administration for hormonal contraceptives can be oral, intramuscular, subcutaneous, transdermal, intravaginal, and

intrauterine. The most commonly used reversible methods of HC are oral contraceptives (OCs, pills); however, the most effective reversible methods of contraceptives are intrauterine devices (IUDs) and capsules, as they do not involve user errors, i.e., forgetting a pill or insertion/removal of a hormonal ring. In addition to the effectiveness of hormonal contraception methods (Lopez et al. 2013), contraceptive users are generally interested in information regarding safety, side effects, and cost. Importantly, users are often interested in ease of use and effectiveness for the treatment of menstrual disorders rather than preventing pregnancy alone (Westhoff et al. 2007).

The choice of contraceptive method (hormonal or otherwise) should be based on a realistic evaluation of an individual's health, needs, and wishes. This decision should be made in consultation with a healthcare professional with whom the individual feels safe sharing personal information. Understanding the reasons why women use contraceptives is important to accurately inform an individual's decision to start, stop, or switch between different contraceptive options. The suitability of a contraceptive method, including subjective experience of possible side effects, improves the continuity of use and effectiveness.

It is important to note that the bleeding that occurs during inactive, pill, or ring-free days in individuals using HCs is not actually considered "menstrual bleeding" or a "period". This bleeding is referred to as withdrawal bleeding and is caused by a drop in exogenous hormone levels that causes the endometrium to shed. As such, the bleeding that occurs in individuals using hormonal contraceptives is not an indicator of health and homeostasis in the same way as menstrual bleeding (Menses Requires Energy: A Review of How Disordered Eating, Excessive Exercise, and High Stress Lead to Menstrual Irregularities 2020). Notably, HCs may be used to help "recover" a cycle in cases of menstrual dysfunction, but HC use does nothing to treat or address low energy availability or associated comorbidities such as decreased bone health (Cobb et al. 2007). When addressing menstrual dysfunction, low energy availability and management of both physical and psychological stress are essential; however, it is also important to exclude other gynecological or endocrinological illnesses (Southmayd et al. 2017).

Oral Contraceptives

Most oral contraceptives (OCs) are composed of at least one estrogen and one progestin (synthetic progestogens), although the types and concentrations vary from pill to pill. These combined OCs can be monophasic or multiphasic. In combined OCs, progestin causes a decrease in pituitary gonadotropin secretion, which is enhanced by estrogen. Progestins prevent pregnancy by preventing ovulation, while estrogens control menstrual bleeding (Baird and Glasier 2010; Cooper et al. 2022).

Monophasic OCs deliver a constant amount of estrogen and progestin each day for 21–24 days. This is followed by 4–7 days with no pill or a placebo, to promote compliance. Alternatively, monophasic OCs can be used without breaks for a prolonged duration, if so indicated or desired. There are no known disadvantages to prolonged

use of monophasic OCs in terms of effectiveness in preventing pregnancy or side effects (Kroll et al. 2010; Machado et al. 2010). In fact, the US Food and Drug Administration (FDA) approved the 24/4, 84/7, and 365-day regimens in 2003 (Sitruk-Ware and El-Etr 2013). In addition to monophasic OCs, intramuscular, subcutaneous, transdermal, intravaginal, and intrauterine HCs are classified as monophasic.

Multiphasic oral contraceptives alter the ratio of progestin to estrogen in pills during the 21-day cycle, which reduces the total monthly dose of progestin in each cycle, but may require a higher dose of estrogen (Baird and Glasier 2010). Multiphasic pills are either biphasic or triphasic. Biphasic OCs deliver a different amount of estrogen and progestin over two phases; e.g., for days 7–10 and days 11–14. The final seven days of the cycle included no pill or a placebo to improve efficacy. Triphasic OCs deliver a different amount of estrogen and progestin for each week of your cycle thus "mimicking" a natural cycle. Different formulations dictate the length of each phase. Like monophasic and biphasic OCs, the final week (seven days) includes no pill or a placebo to improve efficacy.

Depending on the specific HC and individual situation, there may be slight variations in instructions for use. As such, it is best to consult your healthcare professional for instructions and advice regarding specific HC formulations.

Estrogens

Most combined HCs contain ethinyl estradiol (EE), which has a stronger effect than natural estrogen (estradiol). Compounds such as estradiol valerate and estradiol hemihydrate are metabolized into natural estrogen. The estrogens in HCs inhibit follicular development through negative feedback on the anterior pituitary, which results in blunted FSH secretion although the effects of progesterone on this negative feedback are stronger (Cooper et al. 2022). Thus far, no differences have been observed between the efficacy or contraindications of different estrogens used in HCs.

Progestins

There are four generations of progestins that are classified based on when they first became available and as well as their different estrogenic, pregestational, and androgenic characteristics, i.e., their affinity for estrogen, androgen, and progesterone receptors. For example, hormonal contraceptives containing anti-androgenic properties reduce the effect of the endogenous androgen that are effective in treating polycystic ovary syndrome, hirsutism, and acne (Powell 2017). Progestin from HCs induces a negative feedback loop at the hypothalamus by decreasing the pulse frequency of gonadotropin-releasing hormone, which decreases the secretion of FSH

and LH. A lack of developing follicles results in no increase in estradiol levels (typically produced by the follicle). This negative feedback is accompanied by a lack of positive feedback by estrogen to stimulate LH secretion and effectively prevents ovulation (release of the follicle) (Cooper et al. 2022). The types of progestin used in HCs are more variable than that of estrogens, and the side effects associated with HCs are often attributed to the progestin they contain. As such, switching to a different progestin may be indicated in the case of undesired HC-induced side effects. It is important to note that newer progestins are not necessarily better than older progestins (Cooper et al. 2022) although third- and fourth-generation progestins are associated with fewer side effects than earlier generation progestins.

Progestogen-Only Hormonal Contraceptives

As the name would suggest, progestogen only hormonal contraceptives, colloquially known as "mini pills", contain only progestin (e.g., norethindrone or levonorgestrel) and do not contain estrogen (Baird and Glasier 2010). The primary mechanism for progestin only HC in preventing pregnancy is its ability to change cervical mucus and make it hostile to the transport of sperm (Baird and Glasier 2010; Grimes et al. 2013). It is important that progestogen only hormonal contraceptives are taken at the same time of day and without any breaks (or forgotten pills) to maintain efficacy (Grimes et al. 2013). Progestin only pills may be less effective than combination OCs as ovulation is not consistently inhibited (Grimes et al. 2013; Spencer et al. 2009). Nevertheless, when used according to instructions, progestogen only OCs are equally as effective as combined OCs (Trussell 2011).

Intrauterine Devices (IUDs)

Intrauterine devices (IUDs) are effective in preventing pregnancy, and their use does not require remembering to take a daily pill. The hormonal IUD contains progestin only. An IUD can be inserted at any time during the menstrual cycle, although checking for pregnancy prior to insertion may be indicated (Bergin et al. 2012). The hormonal IUD contains progestin only and it makes the cervical mucus thicker rendering it difficult for sperm to pass through the uterine organs. Changes in the lining of the uterus prevent implantation, while ovulation itself may be inhibited to varying degrees (Apter et al. 2014; Lewis et al. 2010; Overview | Long-Acting Reversible Contraception | Guidance | NICE 2019). A non-hormonal copper IUD is also available and discussed briefly later in this chapter.

Possible Side Effects and Adverse Effects of Hormonal Contraceptives

As with all medications, HC use may be accompanied by adverse side effects. These adverse side effects typically diminish with continued use of the same method within three to five months (Barr 2010). Most women (76%) report side effects including breast tenderness, decreased sexual desire, depressive symptoms, and mood swings while using hormonal contraceptives (Tiihonen 2012). The most common side effects include irregular bleeding or spotting, especially during the first months of HC use (Gallo et al. 2013).

Combined HC use may affect mood. For example, sexual desire may be impacted, although research indicates that changes in sexual desire due to combined HC use are individual and may be related to desire before the commencement of combined HC use (Burrows et al. 2012). A causal link between combined HCs and depression has not been established, although patients should be evaluated individually for risk. Migraine with aura is an absolute contraindication for combined HC use. If the incidence of migraine without aura increases or becomes worse with combined HC use, discontinuation is recommended (Champaloux et al. 2017).

There are some potentially more severe adverse side effects associated with HC use. An increased risk for venous thrombosis, for example, is associated with the use of combined OCs; however, this risk is lower than the risk of pregnancy-related venous thrombosis. For women using combined HCs containing levonorgestrel, norethisterone acetate, or norgestimate, venous thromboembolism (deep vein thrombosis) risk is relatively small, although previous deep vein thrombosis or a first-degree relative who has had deep vein thrombosis is considered an absolute contraindication to combined HC use. Likewise, previous myocardial or cerebral infarction is an absolute contraindication for combined HC use. Combined HCs do not increase the risk of ischemic stroke and myocardial infarction in non-smokers under 35 years of age although combined HC use may increase the metabolic risk factors for these diseases (Piltonen et al. 2012; Sitruk-Ware and Nath 2011). Indeed, being overweight, obesity, and smoking increase the risk for deep vein thrombosis and stroke as well as metabolic risk. As such, IUDs or condoms may be recommended for these populations.

Combined HCs are associated with a slight increase in risk for breast cancer. This risk decreases to baseline within 5 years of combined HC cessation (Gierisch et al. 2013). A meta-analysis revealed that cervical cancer risk is increased after 5 years of combined HC use (Moreno et al. 2002); however, these results did not take into account other contributing factors such as smoking and should be interpreted with caution.

Progestin-only oral HCs are associated with slightly different adverse side effects in comparison with combined HCs. For example, breakthrough bleeding and prolonged withdrawal bleeding is more common with progestin-only oral HCs compared to combined HCs (Grimes et al. 2013; Spencer et al. 2009). Changes in mood may be associated with progestin-only oral HCs. Like combined HCs, sexual

desire may be affected by progestin-only HCs, whereas the effect appears to be individual and research on this topic is limited (Burrows et al. 2012; Ford et al. 2012). A causal link between progestin-only oral HCs and depression has not been established, although it is recommended that patients be evaluated individually for risk. Additional side effects reported with progestin-only HCs include skin oiliness and acne (Spencer et al. 2009), breast tenderness, and headache (Chi 1993). Research regarding progestin-only HCs and cancer risk does not, to our knowledge, exist.

In terms of hormonal IUDs, the first 6 months of hormonal IUD use may be accompanied by breakthrough bleeding, bloating, breast tenderness, mild acne, and oily hair (Overview | Long-Acting Reversible Contraception | Guidance | NICE 2019). In addition, functional (spontaneous) ovarian cysts may occur although these typically resolve on their own (Inki et al. 2002; Nahum et al. 2015). Copper IUDs may increase bleeding volume and duration in addition to pain associated with menstrual bleeding (Overview | Long-Acting Reversible Contraception | Guidance | NICE 2019).

Most of the adverse side effects associated with HC use are minor, and HCs remain an easy, noninvasive, reversible, and relatively low-risk way to prevent unwanted pregnancy and treat several gynecological issues. Some medications may interfere with or interact with HCs, and several contraindications to HC use exist that should be taken into consideration in cooperation with a qualified healthcare professional. Indeed, a thorough evaluation of each individual situation is necessary when selecting and prescribing hormonal contraceptive doses and delivery methods.

Non-contraceptive Benefits of HCs

Most women use HCs to prevent pregnancy, but approximately 14% use HCs for non-contraceptive reasons only (Jones 2011). Indeed, HCs have considerable non-contraceptive benefits including reduction in heavy menstrual bleeding and fibroids; reduced dysmenorrhea and pelvic pain from endometriosis; decreased risk of endometrial, ovarian, and colorectal cancer; reduced risk of pelvic inflammatory disease and ectopic pregnancy; and reduced physical and emotional symptoms associated with premenstrual dysphoric disorder (PMDD). Additional benefits include improvement in suffering from menstrual migraines; treatment of hyperandrogenism that may be related to polycystic ovarian syndrome (PCOS); treatment of endometrial hyperplasia and carcinoma; endometrial protection during estrogen replacement; and promotion of healthy vaginal flora (Bahamondes et al. 2015; Brant et al. 2017; Cooper et al. 2022; Maguire and Westhoff 2011; Schindler 2013). Furthermore, iron deficiency anemia is less common since HC users tend to bleed less (Milman et al. 1992). The non-contraceptive benefits associated with HCs can improve the health and well-being of users. Furthermore, after cessation of combined HC use, a natural cycle of normal duration typically returns (Duijkers et al. 2005).

Non-hormonal Contraceptive Methods

Hormonal contraceptives may not be indicated or desired by all women. Fortunately, non-hormonal options for contraception are available including male and female condoms, the diaphragm, spermicides, and vaginal gels. These methods do not influence HPO-axis function. A long-term hormone-free option for contraception is the copper IUD. A copper IUD is a small piece of flexible plastic in the shape of the letter "T" that has copper wrapped around it. Copper IUDs locally release copper ions, which change the lining of the uterus and cervical mucus to prevent sperm from reaching the egg, prevent sperm from fertilizing the egg, or alternatively may prevent implantation (Overview | Long-Acting Reversible Contraception | Guidance | NICE 2019). Copper IUDs do not, however, affect ovulation. Typically, copper IUDs (with varying amounts of copper) work effectively for 5 years after insertion; however, the FDA (U.S. Food and Drug Administration has approved a copper IUD with 380 mm2 copper that can be used for 10 years and up to 12 years in women of all ages (Espey and Ogburn 2011; Practice Bulletin No. 121: Long-Acting Reversible Contraception: Implants and Intrauterine Devices 2011). Copper IUDs do not influence HPO-axis function.

Hormonal Contraceptives and Exercise—Sport

The prevalence of HC use is 35–45% in the general population (Lindh et al. 2017) and 40–70% in elite athletes (Brynhildsen et al. 1997; Martin et al. 2018; Torstveit and Sundgot-Borgen 2005; Lindh et al. 2017). As implied earlier, the reasons for HC use extend beyond preventing pregnancy and may include a desire to decrease symptoms related to the menstrual cycle, decrease menstrual bleeding, or a need to modify the timing of withdrawal bleeding. Regardless of the reason for using or not using HCs, the choice to use should be up to the individual and should be made with a healthcare professional providing information regarding the risks and benefits of different doses and delivery methods. The family planning benefits of all forms of contraception are important.

The influence of HC use on exercise performance and training adaptations requires additional research. Several studies report that HCs may have a small effect on training responses and adaptations, but individual differences are apparent (Elliott-Sale et al. 2020; Knowles et al. 2019; Martin et al. 2018). Likewise, it is difficult to determine whether or not the reasons for HC use (e.g., cramping. bleeding, mood swings) might have been more detrimental to exercise participation or training than the possible side effects of HC use. Solli et al. (2020) reported that approximately 25% of HC users had at some point stopped using and/or changed their HC because they had experienced negative side effects or effects on their performance (Solli et al. 2020). Martin et al. (2018) reported that the most common reasons to change the type of HC or to stop using HC were weight gain, changes in mood, changed the need for

contraception, headache, forgetting to take pills, and increased or increased bleeding (Martin et al. 2018)

There are no fit-for-purpose recommendations regarding what kind of HC should be used for athletes, while the effects of HC on performance and body composition are variable and quite possibly individual. Different formulations, reasons for use, and sports requirements make it difficult to weigh the potential harms and benefits regarding possible side effects and performance on a group level. A meta-analysis by Elliott-Sale et al. reports that HC may have a small negative effect on performance at the group level. This finding is echoed by Knowles et al. who found that HC users tended to have smaller gains in strength and muscle mass (Knowles et al. 2019). Even so, the performance of women taking OC does not appear to vary significantly during different phases of the cycle (Elliott-Sale et al. 2020). Ultimately, the quality and quantity of current research do not support the avoidance of HC in athletic populations.

Information regarding the effects of both hormonal and copper IUDs on athletic performance is non-existent (Henderson and Scribbans 2020). It can be hypothesized that the non-contraceptive benefits of hormonal IUDs may support exercise and sports participation in populations where negative symptoms associated with the menstrual cycle would otherwise be a barrier to exercise or sports participation.

Female Hormones in the Laboratory and on the Field

Female sex steroids are important for health and performance, while stimuli such as exercise, nutrition, and stress influence the endogenous hormonal milieu of females. While a significant amount of work has already been done to investigate the effects of the menstrual cycle and hormonal contraceptive use on exercise and performance, additional high-quality and well-controlled research is required in order to more clearly elucidate the effects of endogenous hormonal milieu and exogenous hormone use (i.e., hormonal contraceptives), particularly on training responses and adaptations.

Recording and monitoring the menstrual cycle in research and the field (see Fig. 1.3) will improve our understanding of the influence of endogenous hormonal profiles on exercise and performance. Inclusion of hormonal analyses, particularly in research settings, is imperative. Open communication about menstrual cycle characteristics and symptoms needs to be normalized in sports, whereas educating coaches and athletes about menstrual cycles and HC use is essential. Furthermore, facilitating discussions between sports and health professionals may help in the selection of the best possible HC for each individual athlete. In addition, communicating about the potential individual risks and benefits of HC use as well as alternative methods for contraception should be openly discussed as family planning is also an important part of physically active and athletic female lives.

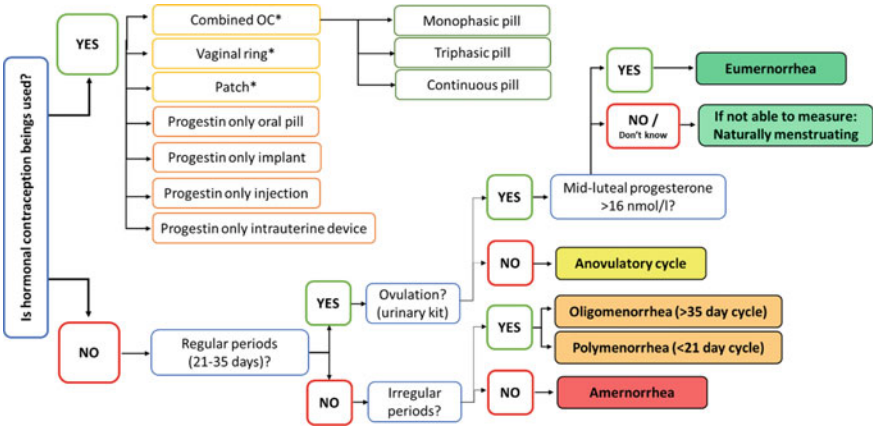

Fig. 1.3 How to assess the menstrual status of a female. When hormonal contraception is not used, the possible use of a copper IUD should be checked. * = contains both estrogen and progestin. Modified from (Elliott-Sale et al. 2021)

Summary and Conclusions

The HPO axis is the major regulator of the female reproductive system and health that also has a significant influence on the performance and overall well-being of active women. This regulation begins when GnRH is released from the hypothalamus at the onset of puberty, which stimulates LH and FSH production at the anterior pituitary. These hormones then bind to ovarian receptors, stimulating the release of the female reproductive hormones including estrogen and progesterone. This regulation process is quite precise and complicated, and several upstream regulators (e.g., brain peptide) such as kisspeptin control it.

Regulation of the reproductive axis can also be influenced by HCs, which are used by females worldwide to prevent unwanted pregnancy or treat various gynecological illnesses. HCs work by increasing estrogen concentrations during the follicular phase of a female's cycle. High-estrogen levels then prevent the mid-cycle gonadotropin surge necessary for ovulation. HCs are still considered somewhat controversial due to potentially adverse side effects (as well as due to some societal and cultural issues), and more research should be conducted on HC use in the future to learn more about these side effects. Lastly, endogenous hormone profile and use of exogenous hormones should always be considered in exercise and performance-related research, while discussions about menstrual cycles and HC use should be normalized in sports settings.

References

Allaway HCM, Southmayd EA, De Souza MJ. The physiology of functional hypothalamic amenorrhea associated with energy deficiency in exercising women and in women with anorexia nervosa. Horm Mol Biol Clin Invest. 2016;25(2):91–119. https://doi.org/10.1515/HMBCI-2015-0053.

Apter D. Serum steroids and pituitary hormones in female puberty: a partly longitudinal study. Clin Endocrinol. 1980;12(2):107–20. https://doi.org/10.1111/J.1365-2265.1980.TB02125.X.

Apter D, Gemzell-Danielsson K, Hauck B, Rosen K, Zurth C. Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies. Fertil Steril 2014;101(6). https://doi.org/10.1016/J.FERTNSTERT.2014.03.004

Bahamondes L, Bahamondes MV, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update. 2015;21(5):640–51. https://doi.org/10.1093/HUMUPD/DMV023.

Baird DT, Glasier AF. Hormonal Contraception 2010;328(21):1543–49. https://doi.org/10.1056/NEJM199305273282108.

Barr NG. Managing adverse effects of hormonal contraceptives. Am Fam Phys 2010;82(12):1499–1506. https://www.aafp.org/afp/2010/1215/p1499.html

Bergin A, Tristan S, Terplan M, Gilliam ML, Whitaker AK. A missed opportunity for care: two-visit IUD insertion protocols inhibit placement. Contraception. 2012;86(6):694–7. https://doi.org/10.1016/J.CONTRACEPTION.2012.05.011.

Brant AR, Ye PP, Teng SJ, Lotke PS. Non-contraceptive benefits of hormonal contraception: Established benefits and new findings. Curr Obstet Gynecol Rep 2017;6(2):109–117. https://doi.org/10.1007/S13669-017-0205-3

Brynhildsen JO, Hammar J, Hammar ML. Does the menstrual cycle and use of oral contraceptives influence the risk of low back pain? A prospective study among female soccer players. Scand J Med Sci Sports. 1997;7(6):348–53. https://doi.org/10.1111/J.1600-0838.1997.TB00165.X.

Bunt JC. Metabolic actions of estradiol: significance for acute and chronic exercise responses. Med Sci Sports Exerc 1990;22(3):286–290. http://www.ncbi.nlm.nih.gov/pubmed/2199750.

Burrows LJ, Basha M, Goldstein AT. The effects of hormonal contraceptives on female sexuality: a review. J Sex Med. 2012;9(9):2213–23. https://doi.org/10.1111/J.1743-6109.2012.02848.X.

Castellano JM, Navarro VM, Fernández-Fernández R, Nogueiras R, Tovar S, Roa J, Vazquez MJ, Vigo E, Casanueva FF, Aguilar E, Pinilla L, Dieguez C, Tena-Sempere M. Changes in hypothalamic KiSS-1 system and restoration of pubertal activation of the reproductive axis by Kisspeptin in Undernutrition. Endocrinology. 2005;146(9):3917–25. https://doi.org/10.1210/en.2005-0337.

Champaloux SW, Tepper NK, Monsour M, Curtis KM, Whiteman MK, Marchbanks PA, Jamieson DJ. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. Am J Obstet Gynecol. 2017;216(5):489.e1-489.e7. https://doi.org/10.1016/J.AJOG.2016.12.019.

Chi, IC. The safety and efficacy issues of progestin-only oral contraceptives—An epidemiologic perspective. Contraception 1993;47(1):1–21. https://doi.org/10.1016/0010-7824(93)90105-G.

Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992;267(9):1244–1252. https://doi.org/10.1001/jama.1992.03480090092034.

Cobb KL, Bachrach LK, Sowers M, Nieves J, Greendale GA, Kent KK, Brown BW, Pettit K, Harper DM, Kelsey JL. The effect of oral contraceptives on bone mass and stress fractures in female runners. Med Sci Sports Exerc. 2007;39(9):1464–73. https://doi.org/10.1249/mss.0b013e318074e532.

Conneely OM, Lydon JP. Progesterone receptors in reproduction: Functional impact of the A and B isoforms. Steroids. 2000;65(10–11):571–7. https://doi.org/10.1016/S0039-128X(00)00115-X.

Cooper DB, Patel P, Mahdy H. Oral contraceptive pills. Hist Intellect Property 50 Objects 2022;224–231. https://doi.org/10.5005/jp/books/12894_19.

Duijkers IJM, Engels L, Klipping C. Length of the menstrual cycle after discontinuation of oral contraceptives. Gynecol Endocrinol Official J Int Soc Gynecol Endocrinol. 2005;20(2):74–9. https://doi.org/10.1080/09513590400021011.

Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, Ackerman KE. Endocrine effects of relative energy deficiency in sport. Int J Sport Nutr Exerc Metab. 2018;28(4):335–49. https://doi.org/10.1123/ijsnem.2018-0127[doi].

Elliott-Sale KJ, McNulty KL, Ansdell P, Goodall S, Hicks KM, Thomas K. Swinton PA, Dolan E. The effects of oral contraceptives on exercise performance in women: A systematic review and meta-analysis. In: Sports medicine. Berlin: Springer; 2020. p. 1–28 https://doi.org/10.1007/s40279-020-01317-5.

Elliott-Sale KJ, Minahan CL, de Jonge XAKJKJ, Ackerman KE, Sipilä S, Constantini NW, Lebrun CM, Hackney AC Methodological considerations for studies in sport and exercise science with women as participants: A working guide for standards of practice for research on women 2021;51(5). https://pubmed.ncbi.nlm.nih.gov/33725341/.

Erickson GF, Magoffin DA, Dyer CA, Hofeditz C. The ovarian androgen producing cells: a review of structure/function relationships. Endocr Rev. 1985;6(3):371–99. https://doi.org/10.1210/EDRV-6-3-371.

Espey E, Ogburn T. Long-acting reversible contraceptives: intrauterine devices and the contraceptive implant. Obstet Gynecol. 2011;117(3):705–19. https://doi.org/10.1097/AOG.0B013E31820CE2F0.

Ferin M. The menstrual cycle: An integrative view. Reproductive endocrinology, surgery and technology. In: Adashi EYRZ, Rock JA (Eds) 1996.

Fernandez-Fernandez R, Martini AC, Navarro VM, Castellano JM, Dieguez C, Aguilar E, Pinilla L, Tena-Sempere M. Novel signals for the integration of energy balance and reproduction. Mol Cell Endocrinol. 2006;254–255:127–32. https://doi.org/10.1016/j.mce.2006.04.026.

Filicori M. The role of luteinizing hormone in folliculogenesis and ovulation induction. Fertil Steril. 1999;71(3):405–14. https://doi.org/10.1016/S0015-0282(98)00482-8.

Ford O, Lethaby A, Roberts H, Mol BWJ. Progesterone for premenstrual syndrome. Cochrane Database Syst Rev 2012(3). https://doi.org/10.1002/14651858.CD003415.PUB4

Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 μg versus >20 μg estrogen combined oral contraceptives for contraception. In: Cochrane database of systematic reviews, vol. 2013, Issue 8. Cochrane Database systematic review; 2013. https://doi.org/10.1002/14651858.CD003989.pub5.

Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev Publ Am Assoc Can Res Cosponsored Am Soc Prev Oncol. 2013;22(11):1931–43. https://doi.org/10.1158/1055-9965.EPI-13-0298.

Golden NH, Carlson JL. The pathophysiology of amenorrhea in the adolescent. Ann N Y Acad Sci. 2008;1135:163–78. https://doi.org/10.1196/ANNALS.1429.014.

Grimes DA, Lopez LM, O'Brien PA. Raymond EG. Progestin-only pills for contraception. Cochrane Database Syst Rev 2013;(11). https://doi.org/10.1002/14651858.CD007541.PUB3.

Hackney AC. Influence of oestrogen on muscle glycogen utilization during exercise. Acta Physiol Scand. 1999;167(3):273–4. https://doi.org/10.1046/j.1365-201X.1999.00605.x.

Hackney AC. Menstrual cycle hormonal changes and energy substrate metabolism in exercising women: A perspective. Int J Environ Res Publ Health 2021;18(19). https://doi.org/10.3390/ijerph181910024.

Hackney AC, Koltun KJ, Williett HN. Menstrual cycle hormonal changes: Estradiol-β-17 and progesterone interactions on exercise fat oxidation. Endocrine. 2022. https://doi.org/10.1007/S12020-022-02998-W.

Hakimi O, Cameron L-C. Effect of exercise on ovulation: A systematic review. Sports Med. 2017;47:1555–67. https://doi.org/10.1007/s40279-016-0669-8.

Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). Psychoneuroendocrinology. 2003;28(SUPPL. 3):1–23. https://doi.org/10.1016/S0306-4530(03)00098-2.

Hall JE, Guyton AC. Guyton and hall: Textbook of medical physiology (11th ed). Elsevier-Health Sciences Division;2006.

Henderson, ZJ, Scribbans TD. Intrauterine contraception and athletic performance. Health Fitness J Can, 2020;13(2):37–45. https://doi.org/10.14288/HFJC.V13I2.308

Herbison AE. The gonadotropin-releasing hormone pulse generator. In: Endocrinology, vol. 159, Issue 11. Oxford University Press;2018, p. 3723–36. https://doi.org/10.1210/en.2018-00653

Hillier SG. Intrafollicular paracrine function of ovarian androgen. J Steroid Biochem. 1987;27(1–3):351–7. https://doi.org/10.1016/0022-4731(87)90327-X.

Höök M, Bergström M, Sæther SA, McGawley K. Do elite sport first, get your period back later. Are barriers to communication hindering female athletes? Int J Environ Res Publ Health 2021;18(22). https://doi.org/10.3390/IJERPH182212075.

Inki P, Hurskainen R, Palo P, Ekholm E, Grenman S, Kivelä A, Kujansuu E, Teperi J, Yliskoski M, Paavonen J. Comparison of ovarian cyst formation in women using the levonorgestrel-releasing intrauterine system versus hysterectomy. Ultrasound Obstet Gynecol Official J Int Soc Ultrasound Obstet Gynecol 2002;20(4):381–385. https://doi.org/10.1046/J.1469-0705.2002.00805.X.

Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ. 2017;8(1):33. https://doi.org/10.1186/s13293-017-0152-8.

Jones RK. Beyond birth control: the overlooked benefits of oral contraceptive pills 2011. https://sci-hub.do/https://www.guttmacher.org/sites/default/files/report_pdf/beyond-birth-control.pdf?utm_source=baytoday.ca&utm_campaign=baytoday.ca%3Aoutbound&utm_medium=referral

Karapanou O, Papadimitriou A. Determinants of menarche. Reprod Biol Endocrinol. 2010;8(1):1–8. https://doi.org/10.1186/1477-7827-8-115.

Kitaoka M, Kojima I, Ogata E. Activin-A: a modulator of multiple types of anterior pituitary cells. Biochem Biophys Res Commun. 1988;157(1):48–54. https://doi.org/10.1016/S0006-291X(88)80009-3.

Klein DA, Paradise SL, Reeder RM. Amenorrhea: A systematic approach to diagnosis and management. Am Fam Physician. 2019;100(1):39–48. https://doi.org/10.2310/obg.19117.

Knowles OE, Aisbett B, Main LC, Drinkwater EJ, Orellana L, Lamon S. Resistance training and skeletal muscle protein metabolism in eumenorrheic females: Implications for researchers and practitioners. Sports Med. 2019;49(11):1637–50. https://doi.org/10.1007/s40279-019-01132-7.

Kroll R, Reape KZ, Margolis M. The efficacy and safety of a low-dose, 91-day, extended-regimen oral contraceptive with continuous ethinyl estradiol. Contraception. 2010;81(1):41–8. https://doi.org/10.1016/J.CONTRACEPTION.2009.07.003.

Lewis RA, Taylor D, Natavio MF, Melamed A, Felix J, Mishell D. Effects of the levonorgestrel-releasing intrauterine system on cervical mucus quality and sperm penetrability. Contraception. 2010;82(6):491–6. https://doi.org/10.1016/J.CONTRACEPTION.2010.06.006.

Lindh I, Skjeldestad FE, Gemzell-Danielsson K, Heikinheimo O, Hognert H, Milsom I, Lidegaard Ø. Contraceptive use in the Nordic countries. Acta Obstet Gynecol Scand. 2017;96(1):19–28. https://doi.org/10.1111/AOGS.13055.

Lopez LM, Steiner M, Grimes DA, Hilgenberg D, Schulz KF. Strategies for communicating contraceptive effectiveness. Cochrane Database Syst Rev 2013;(4). https://doi.org/10.1002/14651858.CD006964.PUB3.

Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab. 2003;88(1):297–311. https://doi.org/10.1210/jc.2002-020369.

Machado RB, de Melo NR, Maia H. Bleeding patterns and menstrual-related symptoms with the continuous use of a contraceptive combination of ethinylestradiol and drospirenone: a randomized study. Contraception. 2010;81(3):215–22. https://doi.org/10.1016/J.CONTRACEPTION.2009.10.010.

MacNutt MJ, De Souza MJ, Tomczak SE, Homer JL, Sheel AW. Resting and exercise ventilatory chemosensitivity across the menstrual cycle. J Appl Physiol. 2012;112(5):737–47. https://doi.org/10.1152/japplphysiol.00727.2011.

Maguire K, Westhoff C. The state of hormonal contraception today: Established and emerging noncontraceptive health benefits. Am J Obstet Gynecol. 2011;205(4):S4. https://doi.org/10.1016/J.AJOG.2011.06.056.

Makanji Y, Zhu J, Mishra R, Holmquist C, Wong WPS, Schwartz NB, Mayo KE, Woodruff TK. Inhibin at 90: From discovery to clinical application, a historical review. Endocr Rev. 2014;35(5):747–94. https://doi.org/10.1210/er.2014-1003.

Mani SK, Blaustein JD, O'Malley BW. Progesterone receptor function from a behavioral perspective. Horm Behav. 1997;31(3):244–55. https://doi.org/10.1006/HBEH.1997.1393.

Martin D, Sale C, Cooper SB, Elliott-Sale KJ. Period prevalence and perceived side effects of hormonal contraceptive use and the menstrual cycle in elite athletes. Int J Sports Physiol Perform. 2018;13(7):926–32. https://doi.org/10.1123/ijspp.2017-0330[doi].

Matsumoto T, Asakura H, Hayashi T. Biopsychosocial aspects of premenstrual syndrome and premenstrual dysphoric disorder. Gynecol Endocrinol Official J Int Soc Gynecol Endocrinol. 2013;29(1):67–73. https://doi.org/10.3109/09513590.2012.705383.

McNatty KP, Makris A, De Grazia C, Osathanondh R, Ryan KJ. The production of progesterone, androgens and oestrogens by human granulosa cells in vitro and in vivo. J Steroid Biochem. 1979;11(1C):775–9. https://doi.org/10.1016/0022-4731(79)90011-6.

McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S., Thomas K, Hicks KM. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: A systematic review and meta-analysis. In: Sports medicine. Berlin: Springer;2020. p. 1–15. https://doi.org/10.1007/s40279-020-01319-3.

Meignié A, Duclos M, Carling C, Orhant E, Provost P, Toussaint JF, Antero J. The effects of menstrual cycle phase on elite athlete performance: A critical and systematic review. Frontiers Physiol 2021;12. https://doi.org/10.3389/FPHYS.2021.654585/PDF.

Menses Requires Energy: A Review of How Disordered Eating, Excessive Exercise, and High Stress Lead to Menstrual Irregularities, 42 Clinical Therapeutics 401 (2020). https://doi.org/10.1016/j.clinthera.2020.01.016.

Milman N, Kirchhoff M, JØrgensen T. Iron status markers, serum ferritin and hemoglobin in 1359 Danish women in relation to menstruation, hormonal contraception, parity, and postmenopausal hormone treatment. Ann Hematol 1992;65(2), 96–102. https://doi.org/10.1007/BF01698138.

Moreno V, Bosch FX, Muñoz N, Meijer CJLM, Shah KV, Walboomers JMM, Herrero R, Franceschi S. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet (london, England). 2002;359(9312):1085–92. https://doi.org/10.1016/S0140-6736(02)08150-3.

Mountjoy M, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, Meyer N, Sherman R, Steffen K, Budgett R, Ljungqvist A. The IOC consensus statement: Beyond the Female athlete triad-relative energy deficiency in sport (RED-S). Br J Sports Med. 2014;48(7):491–7. https://doi.org/10.1136/bjsports-2014-093502.

Muttukrishna S, Tannetta D, Groome N, Sargent I. Activin and follistatin in female reproduction. Mol Cell Endocrinol. 2004;225(1–2):45–56. https://doi.org/10.1016/J.MCE.2004.02.012.

Nahum GG, Kaunitz AM, Rosen K, Schmelter T, Lynen R. Ovarian cysts: presence and persistence with use of a 13.5mg levonorgestrel-releasing intrauterine system. Contraception, 2015;91(5):412–417. https://doi.org/10.1016/J.CONTRACEPTION.2015.01.021.

Overview | Long-acting reversible contraception | Guidance | NICE, (2019) (Testimony of National institute for health and care excellence). https://www.nice.org.uk/guidance/CG30.

Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci. 1993;84(1):95–8. https://doi.org/10.1042/cs0840095.

Piltonen T, Puurunen J, Hedberg P, Ruokonen A, Mutt SJ, Herzig KH, Nissinen A, Morin-Papunen L, Tapanainen JS. Oral, transdermal and vaginal combined contraceptives induce an increase in

markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weight women: a randomized study. Hum Reprod (oxford, England). 2012;27(10):3046–56. https://doi.org/10.1093/HUMREP/DES225.

Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M (2012). Kisspeptins and reproduction: Physiological roles and regulatory mechanisms. In: *Physiological Reviews* (Vol. 92, Issue 3, pp. 1235–1316). American Physiological Society Bethesda, MD. https://doi.org/10.1152/physrev.00037.2010

Pirke KM, Schweiger U, Lemmel W, Krieg JC, Berger M. The influence of dieting on the menstrual cycle of healthy young women. J Clin Endocrinol Metab. 1985;60(6):1174–9. https://doi.org/10.1210/jcem-60-6-1174.

Powell A. Choosing the right oral contraceptive pill for teens. Pediatr Clin North Am. 2017;64(2):343–58. https://doi.org/10.1016/J.PCL.2016.11.005.

Practice bulletin no. 121: Long-acting reversible contraception: Implants and intrauterine devices. Obstet Gynecol. 2011;118(1):184–96. https://doi.org/10.1097/AOG.0B013E318227F05E.

Redman LM, Scroop GC, Westlander G, Norman RJ. Effect of a synthetic progestin on the exercise status of sedentary young women. J Clin Endocrinol Metab. 2005;90(7):3830–7. https://doi.org/10.1210/JC.2004-2401.

Roa, J., Aguilar, E., Dieguez, C., Pinilla, L., & Tena-Sempere, M. (2008). New frontiers in kisspeptin/GPR54 physiology as fundamental gatekeepers of reproductive function. In *Frontiers in Neuroendocrinology* (Vol. 29, Issue 1, pp. 48–69). Academic Press. https://doi.org/10.1016/j.yfrne.2007.07.002

Sam S, Frohman LA. Normal physiology of hypothalamic pituitary regulation. Endocrinol Metab Clin North Am. 2008;37(1):1–22. https://doi.org/10.1016/J.ECL.2007.10.007.

Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab. 2013;11(1):41–7. https://doi.org/10.5812/ijem.4158.

Sirola J, Rikkonen T. Muscle performance after the menopause. J Br Menopause Soc. 2005;11(2):45–50. https://doi.org/10.1258/136218005775544561.

Sitruk-Ware, R., & El-Etr, M. (2013). Progesterone and related progestins: potential new health benefits. *Climacteric : The Journal of the International Menopause Society*, *16 Suppl 1*(S1), 69–78. https://doi.org/10.3109/13697137.2013.802556

Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. Rev Endocr Metab Disord. 2011;12(2):63–75. https://doi.org/10.1007/S11154-011-9182-4.

Skorupskaite K, George JT, Anderson RA. The kisspeptin-GnRH pathway in human reproductive health and disease. Hum Reprod Update. 2014;20(4):485–500. https://doi.org/10.1093/HUMUPD/DMU009.

Solli GS, Sandbakk SB, Noordhof DA, Ihalainen JK, Sandbakk Ø. Changes in self-reported physical fitness, performance, and side effects across the phases of the menstrual cycle among competitive endurance athletes. Int J Sports Physiol Perform. 2020;15(9):1324–33. https://doi.org/10.1123/ijspp.2019-0616.

Southmayd EA, Hellmers AC, De Souza MJ. Food versus pharmacy: assessment of nutritional and pharmacological strategies to improve bone health in energy-deficient exercising women. Curr Osteoporos Rep. 2017;15(5):459–72. https://doi.org/10.1007/S11914-017-0393-9.

Spencer AL, Bonnema R, McNamara MC. Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications. Am J Med. 2009;122(6):497–506. https://doi.org/10.1016/J.AMJMED.2009.01.016.

Strock NCA, De Souza MJ, Williams NI. Eating behaviours related to psychological stress are associated with functional hypothalamic amenorrhoea in exercising women. J Sports Sci. 2020;38(21):2396–406. https://doi.org/10.1080/02640414.2020.1786297.

Tiihonen, M. (2012). *Naisten kokemuksia hormonivalmisteista: tutkimus hormonaalisesta ehkäisystä ja vaihdevuosien hormonihoidosta.* https://sci-hub.do/https://erepo.uef.fi/bitstream/handle/123456789/10626/urn_isbn_978-952-61-0683-0.pdf?sequence=1

Torstveit MK, Sundgot-Borgen J. Participation in leanness sports but not training volume is associated with menstrual dysfunction: a national survey of 1276 elite athletes and controls. Br J Sports Med. 2005;39(3):141–7. https://doi.org/10.1136/BJSM.2003.011338.

Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(5):397–404. https://doi.org/10.1016/J.CONTRACEPTION.2011.01.021.

Turgeon JL, Carr MC, Maki PM, Mendelsohn ME, Wise PM. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: Insights from basic science and clinical studies. Endocr Rev. 2006;27(6):575–605. https://doi.org/10.1210/ER.2005-0020.

Väänänen, H. K., & Härkönen, P. L. (1996). Estrogen and bone metabolism. *Maturitas*, *23*(SUPPL.), S65–S69. https://doi.org/10.1016/0378-5122(96)01015-8

Vande Wiele RL, Bogumil J, Dyrenfurth I, Ferin M, Jewelewicz R, Warren M, Rizkallah T, Mikhail G. Mechanisms regulating the menstrual cycle in women. Recent Prog Horm Res. 1970;26:63–103. https://doi.org/10.1016/B978-0-12-571126-5.50006-6.

Veldhuis JD, Evans WS, Demers LM, Thorner MO, Wakat D, Rogol AD. Altered neuroendocrine regulation of gonadotropin secretion in women distance runners. J Clin Endocrinol Metab. 1985;61(3):557–63. https://doi.org/10.1210/jcem-61-3-557.

Viña J, Sastre J, Pallardó FV, Gambini J, Borrás C. Role of mitochondrial oxidative stress to explain the different longevity between genders: protective effect of estrogens. Free Radical Res. 2006;40(12):1359–65. https://doi.org/10.1080/10715760600952851.

Westhoff CL, Heartwell S, Edwards S, Zieman M, Stuart G, Cwiak C, Davis A, Robilotto T, Cushman L, Kalmuss D. Oral contraceptive discontinuation: Do side effects matter? Am J Obstet Gynecol. 2007;196(4):412.e1-412.e7. https://doi.org/10.1016/J.AJOG.2006.12.015.

Wierman ME. Sex steroid effects at target tissues: Mechanisms of action. Am J Physiol Adv Physiol Educ. 2007;31(1):26–33. https://doi.org/10.1152/ADVAN.00086.2006/ASSET/IMAGES/LARGE/ZU10010723690012.JPEG.

Yonkers KA, O'Brien PS, Eriksson E. Premenstrual syndrome. The Lancet. 2008;371(9619):1200–10. https://doi.org/10.1016/S0140-6736(08)60527-9.

Chapter 2
Sex Hormones and Substrate Metabolism During Endurance Exercise

Laurie Isacco and Nathalie Boisseau

Abbreviations

AMPC	Cyclic adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
ANP	Atrial natriuretic peptide
β-HAD	β-Hydroxy acyl-CoA dehydrogenase
CPT-I	Carnitine palmitoyletransferase I
CS	Citrate synthase
CHO	Carbohydrates
E2	17β-Estradiol
EE	Ethinyl estradiol
ER	Estrogen receptors
FFA	Free fatty acids
FFM	Fat-free mass
FP	Follicular phase
GH	Growth hormone
GLUT4	Glucose transporter type 4
GMPC	Cyclic guanosine monophosphate
HRT	Hormone replacement therapy
IGF-1	Insulin-like growth factor 1
IMCL	Intramyocellular lipid
LP	Luteal phase
LPL	Lipoprotein lipase
MCAD	Medium-chain acyl-CoA dehydrogenase

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MLOR	Maximal lipid oxidation rates
mRNA	Messenger ribonucleic acid
OC	Oral contraceptives
OC+	Oral contraceptive users
OC-	Oral contraceptive non-users
PDK4	Pyruvate dehydrogenase kinase isozyme 4
PGC-1α	Peroxisome proliferator-activated receptor- γ coactivator 1α
PPAR	Peroxisome proliferator-activated receptor
Ra	Rate of appearance
Rd	Rate of disappearance
RER	Respiratory exchange ratio
SREBP-1c	Sterol regulatory element-binding protein-1c
VO_{2max}	Maximal oxygen consumption

Introduction

Carbohydrates (CHO) and fat are the main energy sources mobilized to meet the energy demands during muscle contraction, whereas protein contribution is lower. Their relative implication is modulated by different parameters. Although exercise intensity and duration are the main determinants of fuel selection, age, diet, physical activity level, weight status, and sex also can influence their use (Brooks and Mercier 1994; Jeukendrup and Wallis 2005). All these variables have been extensively studied in athletes for performance enhancement and also in people with chronic diseases with the aim of improving health and quality of life (Lambert et al. 1997; Bordenave et al. 2008).

Today, sex-related differences, due to the presence of sex-specific steroids, in substrate utilization during exercise are widely acknowledged. Indeed, estrogen and progesterone interact directly and/or indirectly with the tissues and organs involved in energy metabolism, such as muscle, liver, and adipose tissue. In women, the natural ovarian hormone fluctuations during the menstrual cycle and pregnancy, the drastic decrease in steroid concentrations at menopause, and the use of oral contraceptives (OC) or hormone replacement therapy (HRT) can all influence substrate metabolism during endurance exercise (Isacco et al. 2012a, b; Boisseau and Isacco 2021).

This chapter aims to present an overview of the sex differences in substrate metabolism during endurance exercise and to specifically discuss the effects of the menstrual cycle, OC, pregnancy, menopause, and HRT on these adaptations.

Sex Differences in Substrate Metabolism During Endurance Exercise

To avoid any bias, before any comparison of exercise-induced metabolic responses between men and women, the populations' age and training status should be matched and the diet and time since the last training bout must be controlled. The maximal oxygen consumption (VO_{2max}) can be used to match the groups' cardiorespiratory fitness level; however, VO_{2max} should be expressed relative to fat-free mass (FFM) and not per kilogram of body mass because women have approximately 5 to 8% more body fat than men (Carter et al. 2001a, b; Tarnopolsky 2008). If all these variables are not taken into account, conflicting results may be obtained, as already reported (Costill et al. 1976; Froberg and Pedersen 1984; Blatchford et al. 1985). Another inherent issue is the potential heterogeneity of the hormonal status in the women's group. Different variables, such as the menstrual cycle phase, oligo-amenorrhea, amenorrhea, OC use and type, menopause, and HRT type (to mention just a few), have to be finely controlled to avoid intra-group discrepancies. Therefore, it is easy to understand why research on exercise-induced health improvement or performance enhancement is predominantly performed in men and why results obtained in men are frequently applied also to women.

Carbohydrate Metabolism

Many studies investigated sex differences in substrate oxidation rates during moderate-intensity endurance exercise, most of the time in young subjects (~18–30 year old). Overall, through respiratory exchange ratio (RER) measurement, they revealed that, at a given relative work intensity, reliance on whole-body CHO oxidation to support energy demands is lower in women than men (Tarnopolsky et al. 1990a, b; Tarnopolsky et al. 1995; Romijn et al. 2000; Carter et al. 2001a, b; Devries et al. 2006; Tremblay et al. 2010). Similarly, stable isotope-based measurement of hepatic glucose turnover showed that women rely less on CHO stores than men, as indicated by the lower glucose rate of appearance (Ra), disappearance (Rd), and metabolic clearance (Carter et al. 2001a, b; Devries et al. 2006). The origin of this adaptation is still unknown and could be explained by the lower liver glycogenolysis and/or gluconeogenesis in women than in men. Conversely, it is not clear whether skeletal muscle glycogen stores are spared in women during moderate-intensity endurance exercise. Some studies did not find any sex difference in muscle CHO utilization after a single bout of cycling exercise (Tarnopolsky et al. 1995; Roepstorff et al. 2002; Zehnder et al. 2005), whereas others observed higher net (from muscle biopsies) or estimated glycogen use in men during a running exercise (Tarnopolsky et al. 1990a, b; Carter et al. 2001a, b). Studies on glycogen repletion following exercise showed that post-exercise CHO supplementation leads to a similar increase in muscle glycogen in both sexes (Kuipers et al. 1989; Tarnopolsky, Bosman et al.

1997). However, from a practical point of view, the amount of CHO needed to similarly optimize the muscle glycogen stores in men and women (12 g kg^{-1} d^{-1}) would induce a weight gain in women and would be antinomic with performance (James et al. 2001).

Fat Metabolism

For the same relative exercise intensity, women show greater reliance on fat than men, as indicated by their lower RER (Tarnopolsky 2008). In their recent meta-analysis, Cano et al. (2022) highlighted some controversial findings concerning sex-related differences in fuel oxidation during moderate aerobic exercise. This may be explained by poor control of the basal fat mass percentage, training, and nutritional status among studies, but also by differences in the used methods and population characteristics. Cano et al. confirmed the sexual dimorphism in substrate utilization when considering sedentary/recreationally active individuals, but highlighted controversial findings in athletes. The lack of difference sometimes observed between men and women athletes in fat oxidation during prolonged exercise could be explained by the increased ability of men athletes to oxidize lipid sources per minute (Cano et al. 2022). Overall, as the body fat is generally higher in women, it could theoretically lead to greater free fatty acid (FFA) availability and fat oxidation than in men. However, a decrease in body fat mass favors lipolytic sensitivity. Therefore, lipolytic responsiveness is enhanced in subjects with low body fat mass (Klein et al. 1994) and decreased in people with obesity (Wolfe et al. 1987).

While stable isotope-based methods show higher lipolysis (*i.e.,* higher glycerol Ra) in women than in men during moderate-intensity prolonged exercise (Carter et al. 2001a, b), it is not possible to accurately estimate the specific role of FFA or intramyocellular lipids (IMCL) in the total fat oxidation rates. IMCL concentrations at rest are higher in women than in men (Roepstorff et al. 2002, 2006; Devries et al. 2007; Tarnopolsky et al. 2007) due to the higher lipid droplet content and not due to their larger size (Tarnopolsky et al. 2007). However, it is still unclear whether IMCL utilization is higher (Roepstorff et al. 2002, 2006; Steffensen et al. 2002), lower (Zehnder et al. 2005) or similar (White et al. 2003; Devries et al. 2007) in women and men during moderate-intensity prolonged exercise. FFA utilization is not different in endurance-trained women and men at 25%, 65%, and 85% of VO_{2max} (Romijn et al. 2000) and also in untrained subjects during a single bout of exercise (90 min) performed at 45% VO_{2max} (Burguera et al. 2000). Only Roepstorff et al. (2002) found a greater amount of oxidized FFA in women than in men after 1 h of a 90-min cycling exercise performed at 60% VO_{2max}.

In a population of sedentary individuals with overweight or obesity, the absolute peak fat oxidation rate was higher in men than women; however, the difference between sexes disappeared when values were compared relative to FFM. In addition, the peak fat oxidation and the corresponding relative exercise intensity were lower

in sedentary individuals with overweight than in leaner and/or physically active individuals (Bogdanis et al. 2008).

Estrogen-Induced Sex Differences in Substrate Metabolism

Studies in rodents and humans suggest that estrogens have a significant role in regulating substrate metabolism at rest and during endurance exercise (Sladek 1974; Kendrick et al. 1987; Tarnopolsky 2008; Maher et al. 2010; Vieira-Potter et al. 2015).

Animals supplemented with 17β-estradiol (E2) showed a higher activity of lipoprotein lipase (LPL) (Ellis et al. 1994), carnitine palmitoyl transferase I (CPT-I), and short-chain β-hydroxy acyl-CoA dehydrogenase (β-HAD) (Campbell and Febbraio 2001) in skeletal muscle and reduced hepatic glycogen utilization compared with untreated controls (Kendrick et al. 1987; Hatta et al. 1988; Campbell and Febbraio 2001). However, no difference is observed in β-HAD (McKenzie et al. 2000), CPT-I (Berthon et al. 1998) or LPL (Kiens et al. 2004) activities between men supplemented with E2 and women.

E2 administration to men (Carter et al. 2001a, b; Devries et al. 2005; Hamadeh et al. 2005) or to women with amenorrhea (Ruby et al. 1997) decreases RER, CHO kinetics, and oxidation rates and increases plasma FFA concentrations and fat oxidation rates during moderate-intensity prolonged exercise (Ruby et al. 1997; Carter et al. 2001a, b; Devries et al. 2005; Hamadeh et al. 2005). No effect is observed on whole-body lipolysis (Ruby et al. 1997; Carter et al. 2001a, b) or on muscle glycogen utilization (Tarnopolsky et al. 2001; Devries et al. 2005). Pharmacological suppression and replacement of ovarian hormones in women showed that E2 decreases CHO oxidation rates by reducing muscle glycogen utilization and Rd (muscle uptake) (D'Eon et al. 2002).

E2 increases the messenger ribonucleic acid (mRNA) expression of peroxisome proliferator-activated receptor < and β (PPAR-<, PPAR-β), sterol regulatory element-binding protein-1c (SREBP-1c), CPT-I, glucose transporter type 4 (GLUT4), and glycogen synthase (Tarnopolsky 2008). E2 supplementation in men upregulates peroxisome proliferator-activated receptor-γ coactivator 1 α (PGC-1α) and the microRNA miR-29b (predicted to regulate PGC-1α), leading to increased mitochondrial gene expression of medium-chain acyl-CoA dehydrogenase (MCAD) that is involved in lipid utilization (Maher et al. 2010) (see Table 2.1).

Protein Metabolism

It has been demonstrated that urea nitrogen excretion in urine (a marker of protein catabolism) increases only in men after exercise (treadmill running for 15.5 km) (Tarnopolsky et al. 1990a, b). Similarly, the results of studies using isotopic markers (L-[1-13C]-leucine) indicate that in protracted exercise, amino acid (at least leucine)

Table 2.1 Effects of 17β-estradiol (E2) on substrate metabolism in human and rodent models

E2 supplementation and substrate metabolism		
Population/model	Effects	References
Amenorrheic women	↓ RER during exercise	Ruby et al. (1997)
Men	↓ RER during exercise	Carter et al. (2001a, b), Devries et al. (2005), Hamadeh et al. (2005)
Men	↓ CHO oxidation during exercise	Hamadeh et al. (2005)
	↑ Fat oxidation during exercise	Hamadeh et al. (2005)
	↑ FFA during exercise	Ruby et al. (1997)
	↓ Ra of glucose during exercise (also in women)	Carter et al. (2001a, b), Devries et al. (2005), Ruby et al. (1997)
	↓ Rd of glucose during exercise	Carter et al. (2001a, b), Devries et al. (2005)
	↓ Resting adipose tissue activity	Ellis et al. (1994)
Rats	↑ LPL activity in muscle during exercise	Ellis et al. (1994)
	↑ CPT-I, β-HAD	Campbell and Febbraio (2001)
Female rats	↑ Glycogen synthase, citrate synthase	Beckett et al. (2002)
Sex differences		
Tissue	*Effects*	*References*
Muscle	CPT-I ♂ = ♀	Berthon et al. (1998)
	β-HAD ♂ = ♀	Carter et al. (2001a, b)
	Muscle LPL activity ♂ = ♀	Kiens et al. (2004)
E2 supplementation in men		
Tissue	*Effects*	*References*
Muscle RNA levels	↑ PPAR-α, PPAR-β	Tarnopolsky et al. (2008)
	↑ CPT-I, SREBP-1c	Tarnopolsky et al. (2008)
	↑ GLUT4	Tarnopolsky et al. (2008)
Muscle protein and RNA levels	↑ MCAD (↑ PGC-1α mRNA, ↓ microRNA miR-29b)	Maher et al. (2010)

utilization is higher in men than women (Lamont et al. 2001), even after 38 days of endurance training (McKenzie et al. 2000). Glycogen sparing in the liver might explain the difference in amino acid utilization between sexes because no sex-specific difference in the activity of branched-chain 2-oxoacid dehydrogenase, the enzyme that limits the oxidation of branched amino acids, has been reported (McKenzie et al. 2000). Specifically, in women, glycogen sparing might reduce tricarboxylic acid

cycle activity and consequently decrease amino acid oxidation via an anaplerotic effect.

Menstrual Cycle and Substrate Metabolism During Endurance Exercise

Fluctuations of Ovarian Hormones During the Menstrual Cycle

Female sexual maturity is characterized by an increase in ovarian hormone concentrations leading to the appearance of the menstrual cycle and secondary sexual characteristics. The menstrual cycle is one of the most important biological rhythms in women. Estrogen (17β-estradiol, estrone, and estriol) and progesterone are the two main ovarian hormones of the menstrual cycle, and they fluctuate predictably during 23–35 days (Reilly 2000). They are mainly secreted by the ovaries and to a lesser extent by the adrenal glands (Lebrun 1994).

The menstrual cycle is divided into two distinct phases: follicular phase (FP) (early, mid, and late) and luteal phase (LP) (early, mid, and late) separated by ovulation. The FP begins on the first day of the menses and continues until ovulation. The LP begins after ovulation and lasts, on average, fourteen days until the next menses (Constantini et al. 2005). The estrogen/progesterone ratio is different across the menstrual cycle: (i) low-estrogen and progesterone concentrations in the early FP, (ii) high-estrogen and low progesterone concentrations during ovulation, and (iii) high-estrogen and progesterone concentrations in the mid LP (Constantini et al. 2005).

Natural Ovarian Hormones and Substrate Metabolism During Endurance Exercise

Although the main function of ovarian hormones is to support reproduction, they also influence directly or indirectly other physiological systems, particularly energy metabolism at rest and during exercise where estrogen and progesterone may have antagonistic functions (Constantini et al. 2005; Oosthuyse and Bosch 2010).

As previously discussed (see "Estrogen-induced sex differences in substrate metabolism" section), studies in animals and humans on estrogen effect on substrate metabolism suggest that the hormonal fluctuations during the menstrual cycle could influence substrate metabolism in women.

In humans, most studies did not find any difference in substrate metabolism at rest between FP and LP (Heiling and Jensen 1992; Jensen et al. 1994; Piers et al. 1995; Horton et al. 2002; Uranga et al. 2005; Magkos et al. 2006). However, Hackney (1990) reported that the resting muscle glycogen content in the *vastus lateralis* is

higher in mid-LP than in mid-FP, suggesting a glycogen sparing effect during LP (Hackney 1990). Conflicting results have been obtained when studying the menstrual cycle effect on CHO and fat metabolism during exercise in humans (Hackney 2021). In the late 1980s, Nicklas et al. reported higher muscle glycogen content in LP than FP after depletion exercise (Nicklas et al. 1989). Similarly, muscle glycogen sparing effect during cycling at approximately 70% VO_{2max} for 60 min was observed during the LP compared with the FP (Hackney 1999).

In regularly menstruating women, glucose Ra and Rd and CHO oxidation rates were lower and fat oxidation rates higher in LP than FP during a 25-min cycling exercise performed at 90% of the lactate threshold (Zderic et al. 2001). Similarly, women displayed lower glucose Ra and Rd and lower total glycogen utilization in LP than FP during endurance exercise (90-min cycling at 65% VO_{2max}) (Devries et al. 2006). Thus, according to these studies, the higher E2 plasma levels in LP promote muscle glycogen storage and sparing during exercise (Devries et al. 2006; Oosthuyse and Bosch 2010). This is strengthened by the finding that E2 increases muscle glycogen synthase activity (Beckett et al. 2002). Glycogen sparing during the LP could be associated with and explained by enhanced reliance on lipid metabolism (Dombovy et al. 1987; Hackney 1999; Oosthuyse and Bosch 2010). Recently, Willett et al. showed that young eumenorrheic physically active women use more fat and less CHO in the LP than the FP during running sessions at 65% of VO_{2max}. They directly associated these results with changes in resting E2 concentrations (Willett et al. 2021).

However, other studies did not find any difference in substrate metabolism between FP and LP during endurance exercise (De Souza et al. 1990; Kanaley et al. 1992; Horton et al. 2002, 2006; Suh et al. 2002, 2003; Hulton et al. 2021). Similar RER values were obtained in FP and LP during maximal and submaximal exercises (De Souza et al. 1990), and the different menstrual cycle phases did not have any effect on substrate metabolism during a treadmill run performed at 70% VO_{2max} until exhaustion (Bailey et al. 2000). Similarly, neither menstrual cycle phase nor menstrual status (amenorrheic vs eumenorrheic women) influenced CHO and fat oxidation rates during a 90-min run performed at 60% VO_{2max} (Kanaley et al. 1992). However, pharmaceutically manipulated sex hormone concentrations may influence fuel utilization during exercise in eumenorrheic and oligomenorrheic women. In this population, high circulating sex steroid concentrations resulted in enhanced fat oxidation and reduced CHO oxidation during endurance running (60 min at 65% VO_{2max}) compared with low hormonal concentrations (Hackney et al. 2000). However, the naturally occurring fluctuations in estrogen and progesterone during the menstrual cycle did not affect peak fat oxidation rate and maximal fat oxidation intensity (measured during a graded exercise test) in fasting young eumenorrheic women (Frandsen et al. 2020).

Using stable isotopic tracers, no difference was found in whole-body substrate oxidation rates between FP and LP (Horton et al. 2002, 2006; Suh et al. 2002, 2003; Jacobs et al. 2005). Likewise, RER and glucose kinetics (Horton et al. 2002), as well as glycerol and FFA rates (Horton et al. 2006), were comparable between menstrual cycle phases during a 90-min cycling exercise at 50% VO_{2max}. Finally,

similar substrate oxidation rates, glucose, and lipid kinetics were observed in LP and FP during cycling at 45% and 65% VO_{2max} for 60 min (Suh et al. 2002, 2003; Jacobs et al. 2005).

The Estrogen/Progesterone Ratio

As noted earlier, the results of studies on the effect of the menstrual cycle on fuel metabolism during endurance exercise are often contradictory (Hackney 2021). This could be partially explained by the complex balance between estrogen and progesterone concentrations, their direct and indirect activities, and their fluctuations during the menstrual cycle. Some authors emphasized that estrogen inhibits gluconeogenesis (Matute and Kalkhoff 1973), favors glycogen storage, increases lipolysis, and promotes fat oxidation (Constantini et al. 2005). Progesterone antagonizes estrogen pro-lipolytic effects but also shifts substrate metabolism toward fat utilization via its CHO-sparing effects (Constantini et al. 2005). Accordingly, D'Eon et al. (2002) hypothesized that the decreased glucose kinetics in women is most likely an estrogen-associated effect and progesterone seems to potentiate it. However, more than the individual and isolated effects of estrogen and progesterone on substrate metabolism, their interaction seems to be critical. Indeed, in 2002, D'Eon et al. proposed that the estrogen/progesterone ratio and the magnitude of the increase in estrogen from FP to LP need to be sufficiently elevated (i.e., twofold or more) to lead to metabolic changes. Jacobs et al. (2005) and Horton et al. (2006) emphasized that the magnitude of estrogen upregulation and particularly the increase in the estrogen/progesterone ratio are important factors in determining the final effect of these ovarian hormones on fat metabolism. This was later confirmed by Oosthuyse and Bosch (2010) who also suggested that intra- and interindividual variations in ovarian hormones could partially explain the discrepancies among studies (Oosthuyse and Bosch 2010). Recently, Hackney et al. reported that in eumenorrheic women, the changes in estrogen/progesterone ratio along the menstrual cycle (from early FP to LP) influence fat oxidation during endurance exercise. Specifically, the estrogen/progesterone ratio variation was positively correlated with the fat oxidation variation during 1-h running at 65% VO_{2max}. This means that in eumenorrheic women, a higher increase in sex steroid hormone concentrations from early FP to LP is associated with a greater reliance on fat during endurance exercise (Hackney et al. 2022). The hormonal fluctuations may differ in the same woman from one cycle to the other and also among women. Some women have important hormonal changes during the menstrual cycle, whereas others have small fluctuations (i.e., responders vs. non-responders) (Hackney 2021). In addition, as highlighted by Elliott-Sale et al., it is crucial to propose a clear and definitive terminology on the menstrual status and to standardize the methods to accurately define and identify the different menstrual cycle phases (i.e., early FP, late FP, etc.) (Elliott-Sale et al. 2021). Overall, the hormonal change magnitude should be considered when studying the menstrual cycle effects on substrate metabolism (Boisseau and Isacco 2021). Nevertheless,

more work is needed to better understand the complex interactions between ovarian hormones and their effect on energy metabolism during prolonged exercise.

Non-Ovarian Hormones

Natural ovarian hormones not only directly influence substrate metabolism during endurance exercise, but also have some indirect effects through complex interactions with non-steroid hormones, such as insulin, catecholamine, growth hormone (GH), and cortisol (McKerns et al. 1958; Reinke et al. 1972; Matute and Kalkhoff 1973; Sladek 1974; Bunt 1990; Bonen et al. 1991; Bemben et al. 1992). For instance, estrogen supplementation in rats increases sensitivity to catecholamine and hormone-sensitive lipase activity (Benoit et al. 1982). Moreover, according to Bonen et al. (1991), the most significant effect of estrogen on substrate metabolism is through an estrogen-mediated decrease in insulin sensitivity. Therefore, the effects of ovarian hormones on non-steroid hormones during the menstrual cycle may partially explain the substrate oxidation differences observed between FP and LP in some studies. Indeed, the increase in cortisol (Genazzani et al. 1975) and GH concentrations (Horton et al. 2002) as well as in sympathetic activity (Minson et al. 2000) associated with the reduction in insulin action (Escalante Pulido and Alpizar Salazar 1999) observed in LP could favor higher fat oxidation and lower CHO oxidation during endurance exercise.

Exercise Intensity

Exercise intensity is the main factor affecting substrate oxidation during exercise (Brooks and Mercier 1994). The menstrual cycle-dependent effects of female steroid hormones on fuel metabolism are also influenced by exercise intensity. For instance, the lower CHO and higher fat oxidation rates observed in mid-LP (compared with mid-FP) at low and moderate exercise intensities (10-min treadmill run at 35% and 60% VO_{2max}) disappear at higher exercise intensity (75% VO_{2max}) (Hackney et al. 1994). On the other hand, the effect of estrogen on hepatic glucose output was detected only when the exercise intensity was sufficiently elevated to increase the demand of glucose utilization above a certain level (Horton et al. 2002). Thus, at approximately 50% VO_{2max} (25.1 ml min^{-1} kg^{-1}), plasma glucose kinetics and CHO oxidation rates are lower in LP than in FP. Conversely, no difference is observed when individuals cycle at 42% VO_{2max} (20.2 ml min^{-1} kg^{-1}) (Zderic et al. 2001). Likewise, glucose Ra is not different between menstrual cycle phases at 20.2 ml min^{-1} kg^{-1} (Horton et al. 2002). Conversely, it is significantly higher in early FP than in mid-LP at 70% VO_{2max} (36.8 ml min^{-1} kg^{-1}) (Campbell et al. 2001) and at 65% VO_{2max} (25.4 ml min^{-1} kg^{-1}) (Devries et al. 2006). As highlighted by Oosthuyse and Bosch (2010), substrate metabolism differences during the menstrual cycle partially depend on the energy demand, and higher intensity exercise leads to increased endogenous glucose production.

As blood lactate levels are a frequently used marker of exercise intensity and/or performance, a major question was whether its blood concentration in response to exercise varies between menstrual cycle phases. In 1981, Jurkowski et al. found higher blood lactate concentrations in the FP than LP after heavy (66% of maximal power output) and exhaustive (90% of maximal power output) exercise (Jurkowski et al. 1981). However, in their review, Smekal et al. (2007) highlighted the inconsistency concerning the menstrual cycle effects on blood lactate among studies. This could be mainly due to study design differences, such as exercise intensity, nutritional status, and sample characteristics (Berend et al. 1994).

The nutritional status also affects substrate oxidation rates and may contribute to regulating the cross talk between ovarian hormones and exercise intensity/energy demands; see next section (Oosthuyse and Bosch 2010).

Nutritional Status

When investigating substrate metabolism during exercise, nutritional status is an important variable because fed conditions could blunt differences in substrate utilization between menstrual cycle phases; however, most studies are performed after an overnight fast, possibly due to protocol standardization (Campbell et al. 2001; Zderic et al. 2001; Devries et al. 2006).

In women depleted in CHO, plasma glucose concentrations are maintained during submaximal bicycle exercise (90 min at 63% VO_{2max}) in FP, while they progressively decrease (70 and 90 min of exercise) in LP (Lavoie et al. 1987). Conversely, CHO loading can overcome glucose kinetic and muscle glycogen sparing differences in LP and FP (McLay et al. 2007). Similarly, lower CHO and higher fat oxidation rates in LP than in FP at rest and during exercise (cycle ergometer at 30, 50, and 70% VO_{2max}) are observed after a low CHO diet in comparison with a high CHO diet for three days (Wenz et al. 1997). According to Oosthuyse and Bosch (2010), glucose kinetics varies during the menstrual cycle when exercise is high enough to influence endogenous glucose production. Energy intake may modify this relationship. For instance, Campbell et al. (2001) showed that consumption of energy drinks during exercise masks differences in glucose Ra between FP and LP. The authors suggested that upon energy drink ingestion, glucose Ra is mostly determined by exogenous glucose absorption and this could blunt menstrual cycle-related differences (Campbell et al. 2001). Accordingly, no difference in substrate metabolism between menstrual cycle phases is observed when exercise is performed in postprandial conditions (Suh et al. 2002). Similarly, a study on the effects of menstrual cycle phases and diet (CHO loading compared with isoenergetic normal diet: 8.4 g kg^{-1} d^{-1} CHO versus 5.2 g kg^{-1} d^{-1} CHO for three days) on muscle glycogen content and substrate oxidation rates during exercise (75-min cycling at 45% to 75% VO_{2max} followed by a 16 km time trial) showed lower resting glycogen concentrations in mid-FP than mid-LP. Conversely, substrate utilization during exercise was not affected by the menstrual cycle phases (McLay et al. 2007). Thus, CHO loading leads to similar substrate utilization during exercise, despite lower glycogen storage

in mid-FP. Interestingly, in a recent study, Hulton et al. (2021) did not observe any difference in hormonal, metabolite, or substrate utilization patterns between menstrual cycle phases in eumenorrheic women during moderate prolonged exercise in hyperglycemic conditions (i.e., supraphysiologic glucose dose) (Hulton et al. 2021). Overall, Moore and colleagues suggested that it is too early to recommend sex-specific guidelines concerning CHO and protein requirements, but emphasized the need for additional research in which energy intake and hormonal status in women are rigorously controlled (Moore et al. 2021).

Discrepancies remain concerning the effect of menstrual cycle-related hormone fluctuations on substrate oxidation rates during endurance exercise. They could be explained by differences in the experimental protocols (mainly, exercise duration and intensity), but also by the many variables that can influence substrate metabolism during exercise (Jeukendrup 2003; Jeukendrup and Wallis 2005). Although some of them have been discussed here (exercise intensity, diet), studies on the effect of the prior physical activity level or weight status are still scarce.

Oral Contraceptive Effects on Substrate Metabolism During Endurance Exercise

Oral Contraceptive Formulations

Many adult women of childbearing age use hormonal agents to regulate menstrual cycles and for birth control. Different contraceptive options are available to women, and OC remains one of the most popular forms of birth control (de Melo et al. 2004). OC's primary aim is to avoid pregnancy, but they can also be used to control the menstrual cycle and premenstrual symptoms and to improve bone health (Snow-Harter 1994; Bennell et al. 1999; Burrows and Peters 2007). Three different OC types (monophasic, biphasic, and triphasic) that usually combine ethinyl estradiol (EE) and progestin are currently available. Monophasic OCs provide constant synthetic steroid hormone concentrations and are easy to use. In triphasic OC, synthetic steroid hormone concentrations change three times to mimic the natural menstrual cycle. Biphasic OCs (two different hormone concentrations) are less frequently prescribed and do not present any real advantage compared with monophasic and triphasic OCs (Bennell et al. 1999; Burrows and Peters 2007). For women sensitive to estrogen, progestin-only OC is an option.

EE concentrations have drastically changed since OC's introduction in the early 1960s. In the beginning, they were close to 150 μg and progestin components could reach 250 μg. Rapidly, EE concentrations decreased to 50 μg to offset the negative effects (insulin resistance and dyslipidemia). Today, low-dose (EE: 20–30 μg) OCs are mostly prescribed (Benagiano et al. 2008). Recently, more natural compounds, such as estradiol and estradiol valerate, have been introduced (Sitruk-Ware and Nath 2011), but studies on their effect on substrate metabolism during exercise are

not available yet. Progestin concentrations are more variable, and the compounds currently used in OC have different estrogenic, progestogenic, and androgenic effects (Constantini et al. 2005). New-generation progestin compounds have been developed in the last few years to minimize their side effects on insulin resistance, glucose intolerance, plasma cholesterol, and triglycerides. The effects of synthetic progestin compounds currently vary depending on their androgenicity. Norgestrel and levonorgestrel show the highest androgenic activities, while norethindrone is weaker (Constantini et al. 2005). Newer OC formulations with reduced EE and progestin doses and novel molecules with safer profiles are now available on the market (Shufelt and Bairey Merz 2009).

Synthetic Ovarian Hormone Affects on Substrate Metabolism During Endurance Exercise

Due to the specific hormone nature and concentrations, OC may affect energy metabolism (Fig. 2.1). Surprisingly, although weight gain is one of the most common side effects reported by women using OC, data on OC influence relative to energy balance, and specifically on substrate metabolism at rest and/or during exercise, are scarce (Metz et al. 2022). Jensen and Levine (1998) did not find any difference in lipolysis and substrate oxidation rates at rest and during epinephrine infusion between eumenorrheic women (OC−) and women taking OC (OC+) (Jensen and Levine 1998). However, other authors observed substrate metabolism alterations in OC+. For instance, during 30 min of treadmill exercise at 40% VO_{2max}, OC+ women showed higher FFA and lower glucose plasma concentrations without any difference in RER compared with OC- women (Bonen et al. 1991). Likewise, OC+ women exhibited lower glucose levels and CHO oxidation rates during a 90-min treadmill run at 50% VO_{2max}, suggesting increased CHO sparing in OC + women (Bemben et al. 1992).

A comparison of two OC with 35 μg EE and different progestin concentrations (low-progestin concentrations: 500 μg; and high-progestin concentrations: 1000 μg of norethisterone) showed no difference in metabolic parameters at rest. Conversely, RER was significantly lower in women using the high-progestin OC than in women using the low-progestin OC throughout the steady-state exercise test (20 min at 75% VO_{2max}) (Redman et al. 2005). The authors proposed that high-progestin level is associated with insulin resistance, glucose intolerance, and reduced muscle glycogen utilization (Sutter-Dub and Vergnaud 1982; Campbell and Febbraio 2002; Picard et al. 2002). Moreover, progestin could increase fat oxidation rates by reducing the availability of glucose-6-phosphate for glycolysis (Redman et al. 2005). It should be noted that norethisterone binds to progesterone receptors but also androgen receptors (with low affinity) and therefore exerts both progestogenic and androgenic effects (Redman et al. 2005).

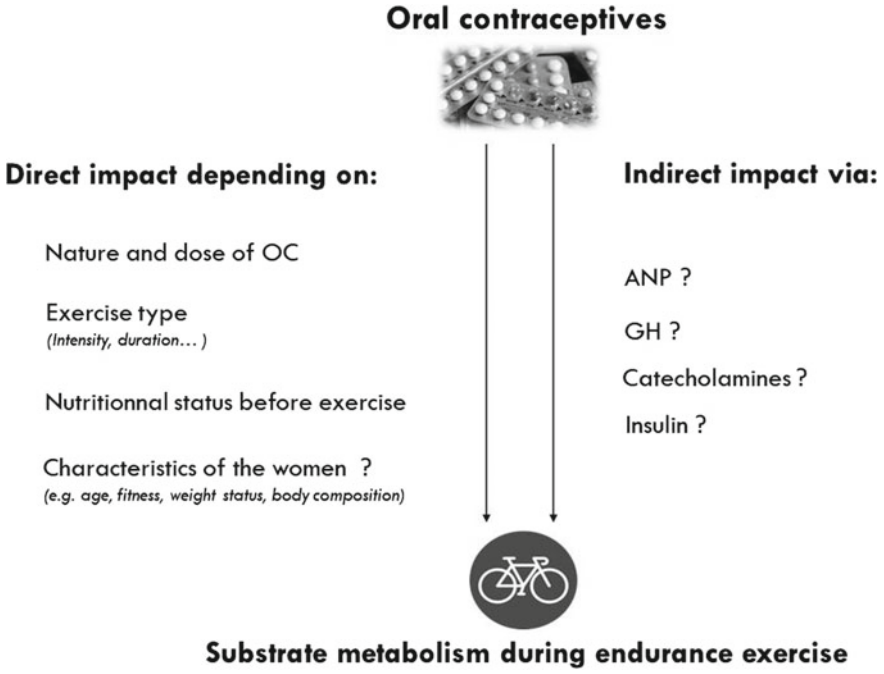

Fig. 2.1 Direct and indirect effects of oral contraceptives on substrate metabolism during endurance exercise. ANP = atrial natriuretic peptide; GH = growth hormone; OC = oral contraceptives; ? denotes additional studies are needed

Analysis of the effect of triphasic OC (4-month treatment) on lipid mobilization and utilization during endurance exercise (60-min cycling at 45% VO_{2max} and 65% VO_{2max}) showed that in OC+ women, lipid mobilization increases during exercise without any change in fat oxidation rates (Casazza et al. 2004). The authors suggested that FFA re-esterification could explain these results (Jacobs et al. 2005). They also demonstrated that OC use decreases glucose flux without any change in CHO and fat oxidation rates during prolonged cycling (Suh et al. 2003). Similarly, Isacco and collaborators did not find any difference in RER, CHO, and fat oxidation rates between OC users and non-users during endurance exercise (45-min cycling at 65% VO_{2max}) (Isacco et al. 2012a, b). They also reported that OC use increases fat mobilization; however, this effect is blunted when lipolytic activity is stimulated by exercise (Isacco et al. 2014).

Due to their specific nature and concentrations, the synthetic ovarian hormones contained in OC may influence substrate metabolism during exercise. More studies are necessary, but it seems that OC use may increase lipolytic activity during endurance exercise without any effect on substrate utilization (Bonen et al. 1991; Suh et al. 2003; Casazza et al. 2004; Isacco et al. 2012a, b; Isacco et al. 2014).

Oral Contraceptive Effects on Non-ovarian Hormone Responses

Some specific non-ovarian hormone changes may be involved in the substrate metabolism differences observed in OC users and non-users (Fig. 2.1).

Growth hormone (GH)

Like natural ovarian hormones, synthetic steroids can exert their effects directly or indirectly through non-steroid hormone actions. In the early 1990s, it was suggested that hormones contained in OC may affect plasma GH concentrations and thus substrate metabolism. Indeed, higher plasma GH concentrations were observed in OC+ than in OC- women during exercise (Bonen et al. 1991). Similarly, GH concentrations increase at 10 and 20 min of exercise in OC + women (Bemben et al. 1992). GH concentrations are also higher during continuous (20 min at 60% VO_{2max}) and intermittent cycling (higher than 80% VO_{2max} for the same duration) in OC + women (Bernardes and Radomski 1998). Finally, GH concentrations are higher from the 15th minute of exercise (30-min cycling at 60% VO_{2max}) in OC + than in OC- women without any difference in glucose tolerance (Boisseau et al. 2001).

As GH reduces glucose uptake and favors lipolysis (Norrelund 2005), it was proposed that such differences in plasma GH concentrations in OC + and OC- women may lead to opposite substrate metabolism activity (Bonen et al. 1991; Bemben et al. 1992; Boisseau et al. 2001). However, no or little effect of OC use was observed in substrate utilization, although higher GH concentrations have been associated with increased plasma FFA levels (Bonen et al. 1991) and reduced plasma glucose concentrations (Bonen et al. 1991; Bemben et al. 1992). Bonen and coworkers (1991) suggested that reduced GH efficiency, lower receptor sensitivity, and/or transport bias in OC+ women could explain these results. Thus, the increase in plasma GH concentrations observed in OC users seems not to be associated with changes in GH activity.

On the other hand, like Casazza et al. (2004), Isacco et al. (2014) did not find any difference in plasma GH concentrations between OC + and OC- women, despite higher plasma glycerol and FFA concentrations in OC + women, suggesting greater lipid mobilization during prolonged cycling (Isacco et al. 2014). The authors hypothesized that as GH requires 2 to 3 h to promote lipolysis, its effect is most likely negligible during the exercise trial (45 min) and the recovery period (2 h), and the difference in lipolytic activity between groups cannot be explained only by OC effect on GH.

Atrial natriuretic peptide (ANP)

ANP has an important lipolytic action through a specific pathway (cyclic guanosine monophosphate—GMPc—and protein kinase G) that is independent of the signaling cascade regulated by catecholamines and insulin (cyclic adenosine monophosphate—AMPc—and protein kinase A) (Sengenes et al. 2003; Moro et al. 2004; Lafontan et al. 2005; Sengenes et al. 2005; Koppo et al. 2010). Studies in animals reported that E2 can affect plasma ANP concentrations. Specifically, the combined administration of estradiol and progesterone enhances ANP gene expression in a

dose-dependent manner in ovariectomized female rats (Hong et al. 1992). Moreover, estradiol administration in follitropin-receptor knockout mice, in which the ANP system is impaired, increases ANP synthesis (Belo et al. 2008). In humans, ANP concentrations are higher in women than in men, mainly due to ovarian hormones (Clark et al. 1990). Similarly, three months of HRT increases plasma ANP concentrations in postmenopausal women, thus emphasizing the role of female steroids in plasma ANP level regulation (Maffei et al. 2001). As the biological activities of synthetic ovarian hormones in OC are more potent than those of natural hormones, OC could increase plasma ANP concentrations. Indeed, Davidson et al. reported greater ANP concentrations in OC + than in OC- women (Davidson et al. 1988). Noradrenaline and ANP concentrations are higher also in women taking new-generation OC compared with non-users, whereas plasma insulin, GH, and adrenaline levels are comparable between groups (Isacco et al. 2014). These hormonal responses, and particularly the higher ANP concentrations at baseline and throughout exercise, may partly explain the difference in lipid mobilization between groups (Isacco et al. 2014).

Nutritional Status

As already mentioned, nutrition is an important factor for fuel selection during endurance exercise. Most studies have investigated the effects of OCs in fed or fast conditions (Bonen et al. 1991; Bemben et al. 1992; Suh et al. 2003; Casazza, et al. 2004; Jacobs et al. 2005; Redman et al. 2005) and only one in both conditions (Isacco et al. 2012a, b).

Analysis of the effect of a high CHO diet (80% of CHO) and glucose ingestion (2 g kg^{-1}) on substrate oxidation rates during cycling (120 min at 57% VO_{2max}) showed that the high CHO diet and glucose ingestion favor CHO utilization. However, no difference was observed in fuel selection between OC + and OC- women (Tremblay et al. 2010). Some studies reported higher lipid mobilization in OC+ than in OC- women during exercise performed in postprandial conditions (Bonen et al. 1991; Casazza et al. 2004). However, these studies did not take into account the potential effects of food intake and daytime variations that may influence hormonal responses and energy metabolism. Consequently, Isacco et al. investigated the interaction of OC use and nutritional status on substrate metabolism in women during prolonged cycling exercise (45 min at 65% VO_{2max}). Lipid mobilization and utilization were increased in the fasting condition compared with the fed state, without any effect on the hormonal status (Isacco et al. 2012a, b). OC use favors lipolysis in the postprandial state, but this effect is blunted when lipolytic activity is stimulated by exercise. Thus, it seems that exercise per se masks the OC-induced greater postprandial lipid mobilization (Isacco et al. 2014). In conclusion, the nutritional status must be specified when interpreting OC effects on substrate metabolism, and more studies are needed to clarify this interaction.

Maximal Lipid Oxidation Rate

Increased lipid oxidation favors body weight management and glycogen sparing, thus delaying fatigue during endurance exercise (Romijn et al. 1993; Kelley 2005). This is particularly important both for performance and health strategies. Higher lipid mobilization (Bonen et al. 1991; Casazza et al. 2004; Jacobs et al. 2005; Isacco et al. 2014) without any difference in fat oxidation rates during endurance exercise (Bemben et al. 1992; Isacco et al. 2012a, b) has been reported in OC+ compared with OC- women. Moreover, in each individual, the maximal lipid oxidation rate is elicited by a specific exercise intensity. This could be used to individualize training programs for people wishing to maximize their lipid utilization and/or to identify subjects with metabolic impairments (Perez-Martin et al. 2001; Achten et al. 2002). OC + women display higher maximal lipid oxidation rates at higher intensity of exercise than OC- women (Isacco et al. 2015). Therefore, as the synthetic steroids currently used in OC formulations could affect the maximal lipid oxidation rate and the intensity at which it occurs, the exercise intensity that elicits the maximal lipid oxidation rate has to be targeted to highlight potential metabolic differences in OC + and OC- women (Isacco et al. 2015). It is worth noting that anthropometric measures and body composition (total fat mass, fat mass localization, FFM) could not explain the difference between groups that were matched for these characteristics, age, and physical activity level. To explain the differences in maximal lipid oxidation rates and the corresponding intensity between OC+ and OC- women, it has been hypothesized that EE has a more potent effect than E2. Moreover, the activities of natural and synthetic estrogens are mediated by the two major isoforms of estrogen receptors (ERα and ERβ) that elicit antagonist effects on metabolism. Increased glucose tolerance, as well as lipid mobilization and utilization, is associated with ERα activity, while ERβ stimulation leads to lipogenesis and insulin resistance (Oosthuyse and Bosch 2012). EE binds with a high affinity to ERα and with a twofold lower affinity to ERβ. Conversely, natural estrogen displays comparable binding affinities for both ERs (Tremollieres 2012).

Pregnancy

In the first weeks/months of pregnancy, many women (athletes and also active women) often perform physical activity. However, few data have been published on energy metabolism and substrate utilization during exercise in pregnancy, due to the many variables that must be taken into account (*e.g.,* type of exercise, training level, diet, gestation duration) (Bessinger and McMurray 2003).

In pregnant women, the resting metabolic rate increases progressively due to pregnancy-related changes (higher ventilation, cardiovascular activity, uterine/placental modifications, and fetal growth) (McMurray et al. 1993). Literature data suggest that substrate (CHO/fat) utilization and RER during exercise are comparable in pregnant and non-pregnant women (Bessinger et al. 2002). In addition,

no difference in RER values (treadmill walk at 65% of the predicted maximal heart rate for 30 min at the same time of the day) was observed in women at different gestation times (22 and 33 weeks) and after delivery (14 weeks postpartum) (Bessinger et al. 2002). Other studies suggested that RER is higher in pregnant women (versus non-pregnant controls), possibly due to higher CHO utilization in pregnancy (Artal et al. 1986). These differences could be linked to the fact that metabolic acidosis is more frequent in pregnant women who perform exercise at levels above the onset of blood lactate accumulation (Wolfe et al. 1998). In this condition, RER might not be a good marker of muscle metabolism due to the higher CO_2 output and the consequent "artificial" increase of the VCO_2/VO_2 ratio, particularly at high exercise intensity. Therefore, without data obtained using methods not based on RER quantification, it is not possible to draw firm conclusions about the effect pregnancy has on substrate utilization during exercise.

During pregnancy, blood glucose concentration, liver glucose release, and insulin levels are increased, whereas liver glycogen storage is decreased (Bo et al. 2016). However, very little information is available on glucose homeostasis during prolonged exercise in pregnancy. Several groups found that blood glucose concentration decrease is faster and more important in pregnant than in non-pregnant women (Soultanakis et al. 1996). This decrease in blood glucose (in the absence of RER changes) may be explained by a disparity between glucose production and uptake, possibly because skeletal muscle glucose uptake is too high relative to glucose production in the liver or because glucose production in the liver is reduced during pregnancy (Bessinger and McMurray 2003). In agreement, Bessinger et al. (2002) suggested that glycogenolysis and gluconeogenesis in the liver cannot meet the exercise-induced energy demand during pregnancy.

Menopause Affects on Substrate Metabolism During Endurance Exercise

Menopause

Menopause signals the end of the fertile phase in women and is defined retrospectively after 12 months of amenorrhea. The transition to menopause corresponds to a decrease in sex steroid hormones, and plasma estrogen reaches similar levels as in men (i.e., 6–24 ng l^{-1}) (Simpson et al. 2002). Menopause changes also favor adiposity gain. The Study of Women's Health Across the Nation (SWAN), in which 800 women were followed for six years through the menopausal period, reported an average increase of 3.4 kg in fat mass and 5.7 cm in waist circumference (Sowers et al. 2007). Estrogen and body fat mass changes in postmenopausal women might also alter substrate metabolism during endurance exercise.

Sex Differences in Substrate Metabolism During Endurance Exercise in Older Individuals

The RER and fat oxidation rates adjusted for VO_2 are not different in 70-year-old men and 66-year-old (menopausal) women during a 30-min cycling bout at 45% VO_{2max} (Toth et al. 1998). This indicates that the higher reliance on fat as substrate in premenopausal women than in men decreases after menopause, mainly due to the reduction in plasma E2 and, to a lesser extent, progesterone levels. However, during a 40-min cycling exercise at 50% VO_{2max}, RER is lower and fat oxidation rates (adjusted for FFM) are higher in postmenopausal women with obesity than in men with obesity (aged 57 ± 1 years) (Numao et al. 2009), despite similar E2 resting serum concentrations in both groups and higher plasma FFA levels in men. The exercise-induced higher increase in E2 plasma concentrations observed in premenopausal women compared with men (Horton et al. 1998) might still occur in postmenopausal women with obesity, and this could explain the higher fat oxidation rates (Numao et al. 2009).

Menopause and Substrate Metabolism During Endurance Exercise: Comparison Between Pre- and Postmenopausal Women

As menopause leads to a significant decrease in estrogen circulating levels, it is not surprising that menopause is associated with lower whole-body fat oxidation rates at rest (Lovejoy et al. 2008). Moreover, postmenopausal women show lower fat oxidation rates ($g.min^{-1}$ kg FFM^{-1}) and energy expenditure (kcal min^{-1}) during a cycling exercise (45 min at 50% VO_{2max}) than premenopausal women. This could further contribute to reducing the capacity of substrate utilization by skeletal muscle after menopause (Abildgaard et al. 2013). The reduction in lean body mass seems to be a critical factor to explain the lower fat oxidation rates and energy expenditure in postmenopausal women because they are closely correlated. Interestingly, differences in whole-body fat oxidation rates are not reflected in the mRNA expression levels at rest, or factors involved in fat oxidation rates and energy expenditure regulation, such as CPT-I, citrate synthase (CS), PPARα, β-HAD, PGC-1, and pyruvate dehydrogenase kinase isozyme 4 (PDK4) (Abildgaard, Pedersen et al. 2013). Also, the activity of important oxidative enzymes (β-HAD and CS) is unchanged by the menopausal status. However, the same authors found that exercise-induced adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in skeletal muscle is lower in postmenopausal women than in premenopausal women. Although it was only a trend, this finding is compatible with earlier results showing that AMPK is activated by estrogen (D'Eon et al. 2005, 2008).

Exercise training is one of the most effective approaches to counteract the adverse effects of menopause. Dupuit et al. noted that in postmenopausal women, moderate-intensity continuous training and high-intensity interval training (combined or not with resistance training) significantly increase fat oxidation rates during an acute moderate-intensity prolonged exercise and also during recovery (Dupuit et al. 2020).

Menopause, Hormone Replacement Therapy, and Substrate Metabolism During Endurance Exercise

HRT, also commonly known as hormone replacement therapy (i.e., 0.625–1.250 mg.day^{-1} of estrogen), is widely used for controlling menopausal symptoms and for preventing bone loss (Yasui et al. 2003).

Different studies showed that HRT increases exercise-induced fat oxidation rates in postmenopausal women due to its action on the concentration and activity of lipolytic hormones (Bjorntorp 1996; Kohrt et al. 1998; O'Sullivan et al. 1998). During endurance exercise, plasma levels of lipolytic hormones, such as cortisol or GH, are higher in postmenopausal HRT users than in non-users (Johnson, et al. 1997; Kraemer et al. 1998). However, in response to an acute running exercise (30 min on a treadmill) performed at 80% VO_{2max}, no difference in fat oxidation rates was observed between women taking (aged 53 ± 3 years) or not (aged 49 ± 3 years) HRT (Johnson et al. 2002). The higher exercise intensity of this protocol may probably explain the difference from the other studies because lipid metabolism decreases with exercise intensity (Brooks and Mercier 1994). Thus, an exercise session performed at 80% of VO_{2max} (or greater) may blunt the difference in exercise-induced fat oxidation rates in women either taking or not HRT.

The estrogen administration route (oral or transdermal) also could affect energy metabolism and fuel selection (O'Sullivan et al. 1998; dos Reis et al. 2003; Lwin et al. 2008). In a crossover design study involving postmenopausal women (aged 57 ± 1 years), oral HRT was associated with decreased fat oxidation rates, increased body fat mass, and decreased lean body mass at rest compared with transdermal HRT (both for 24 weeks) (O'Sullivan et al. 1998). In addition, 24-h indirect calorimetry measurements clearly showed a decrease in fat oxidation rates at rest in postmenopausal (aged 51 ± 4 years) women who received oral estrogen treatment (0.625 mg.day^{-1} conjugated equine estrogen) for two months (Lwin et al. 2008). Oral estrogens could thus increase fat deposition by reducing fat oxidation, explaining why HRT generally causes weight/fat gain. Upon exposure to high-estrogen concentrations, the production of enzymes involved in fat oxidation is decreased (Weinstein et al. 1986; Gower et al. 2002) and that of enzymes involved in lipogenesis is increased in the liver (Mandour et al. 1977). Data from studies in rodents also show that pharmacological doses of estrogen inhibit both mRNA and protein expression of CPT-I (Lwin et al. 2008) and may limit hormone-sensitive lipase activity (Gower et al. 2002). In contrast, transdermal estrogen administration does not affect fat oxidation rates

(O'Sullivan and Ho 1995; O'Sullivan et al. 1998; dos Reis et al. 2003). The liver accounts for approximately 25% of whole-body resting metabolism (Konarzewski and Diamond 1995) and oxidizes more fat than skeletal muscle. Estrogens pass through the liver upon oral, but not transdermal administration, thus increasing GH and GH-binding protein levels and decreasing insulin-like growth factor 1 (IGF-1). This alters substrate metabolism and, indirectly, body composition (Hoffman et al. 1995; O'Sullivan et al. 1998). It could also explain why fat oxidation rates increase in postmenopausal women who take transdermal estrogen and decrease in women taking oral estrogen (dos Reis et al. 2003). Unfortunately, to date all studies investigating the influence of the administration route have been performed at rest and never during endurance exercise.

Recent data indicate that HRT does not really protect postmenopausal women against cardiovascular diseases and may even increase the risk of stroke (Boardman et al. 2015). Furthermore, HRT favors breast cancer development (Lupo et al. 2015), which led to a reduction in its use (Kocjan and Prelevic 2003). However, these results should be interpreted with caution, because in most of these studies women took conjugated estrogen rather than low E2 concentrations by transdermal administration. Thus, the estrogen type also could explain the different HRT effects on substrate metabolism.

In conclusion, more studies are required on HRT administration route and formulation (estrogen type and content) to precisely determine the risk/benefice ratio in postmenopausal women.

Conclusion

Sexual dimorphism in fuel metabolism during endurance exercise has been extensively studied in view of improving performance or health; however, data only on women are scarce. This is mainly due to the hormonal fluctuations throughout the women's life span and thus to the difficulties in standardizing research protocols.

The current literature findings indicate that sex and menopause affect substrate metabolism during endurance exercise. Results on the effects of the menstrual cycle, OC, and pregnancy are less consistent. Methodological differences in exercise modalities (intensity, duration), ovarian hormone concentrations, OC type, diet, physical activity level, and weight status may partially explain these discrepancies. Moreover, the activities of natural and synthetic ovarian hormones are complex and tissue specific and may have direct and indirect effects on substrate metabolism. For instance, we recently reported that the hormonal status may influence fat mass localization in women and that depending on the women's characteristics (e.g., weight status), fat mass localization may in turn modulate fat oxidation during endurance exercise (Isacco et al. 2020, 2021).

In a society where physical activity promotion is becoming a health challenge, it is relevant to pursue research focused on women. Investigating the impact of sex, menstrual cycle, OC, pregnancy, and menopause (including HRT) on metabolic

parameters during endurance exercise will lead to better performance management and health benefits for this population.

References

Abildgaard J, Pedersen AT, Green CJ, Harder-Lauridsen NM, Solomon TP, Thomsen C, Juul A, Pedersen M, Pedersen JT, Mortensen OH, Pilegaard H, Pedersen BK, Lindegaard B. Menopause is associated with decreased whole body fat oxidation during exercise. Am J Physiol Endocrinol Metab. 2013;304(11):E1227-1236.

Achten J, Gleeson M, Jeukendrup AE. Determination of the exercise intensity that elicits maximal fat oxidation. Med Sci Sports Exerc. 2002;34(1):92–7.

Artal R, Wiswell R, Romem Y, Dorey F. Pulmonary responses to exercise in pregnancy. Am J Obstet Gynecol. 1986;154(2):378–83.

Bailey SP, Zacher CM, Mittleman KD. Effect of menstrual cycle phase on carbohydrate supplementation during prolonged exercise to fatigue. J Appl Physiol. 2000;88(2):690–7.

Beckett T, Tchernof A, Toth MJ. Effect of ovariectomy and estradiol replacement on skeletal muscle enzyme activity in female rats. Metabolism. 2002;51(11):1397–401.

Belo NO, Sairam MR, Dos Reis AM. Impairment of the natriuretic peptide system in follitropin receptor knockout mice and reversal by estradiol: implications for obesity-associated hypertension in menopause. Endocrinology. 2008;149(3):1399–406.

Bemben DA, Boileau RA, Bahr JM, Nelson RA, Misner JE. Effects of oral contraceptives on hormonal and metabolic responses during exercise. Med Sci Sports Exerc. 1992;24(4):434–41.

Benagiano G, Bastianelli C, Farris M. Hormonal contraception: present and future. Drugs Today (barc). 2008;44(12):905–23.

Bennell K, White S, Crossley K. The oral contraceptive pill: a revolution for sportswomen? Br J Sports Med. 1999;33(4):231–8.

Benoit V, Valette A, Mercier L, Meignen JM, Boyer J. Potentiation of epinephrine-induced lipolysis in fat cells from estrogen-treated rats. Biochem Biophys Res Commun. 1982;109(4):1186–91.

Berend JZ, Brammeier MR, Jones NA, Holliman SC, Hackney AC. Effect of the menstrual cycle phase and diet on blood lactate responses to exercise. Biol Sport. 1994;11(4):241–8.

Bernardes RP, Radomski MW. Growth hormone responses to continuous and intermittent exercise in females under oral contraceptive therapy. Eur J Appl Physiol Occup Physiol. 1998;79(1):24–9.

Berthon PM, Howlett RA, Heigenhauser GJ, Spriet LL. Human skeletal muscle carnitine palmitoyltransferase I activity determined in isolated intact mitochondria. J Appl Physiol (1985) 1998;85(1):148–153.

Bessinger RC, McMurray RG. Substrate utilization and hormonal responses to exercise in pregnancy. Clin Obstet Gynecol. 2003;46(2):467–78.

Bessinger RC, McMurray RG, Hackney AC. Substrate utilization and hormonal responses to moderate intensity exercise during pregnancy and after delivery. Am J Obstet Gynecol. 2002;186(4):757–64.

Bjorntorp P. The regulation of adipose tissue distribution in humans. Int J Obes Relat Metab Disord. 1996;20(4):291–302.

Blatchford FK, Knowlton RG, Schneider DA. Plasma FFA responses to prolonged walking in untrained men and women. Eur J Appl Physiol Occup Physiol. 1985;53(4):343–7.

Bo K, Artal R, Barakat R, Brown W, Dooley M, Evenson KR, Haakstad LAH, Larsen K, Kayser B, Kinnunen TI, Mottola MF, Nygaard I, van Poppel M, Stuge B, Davies GAL, Commission IOCM. Exercise and pregnancy in recreational and elite athletes: 2016 evidence summary from the IOC expert group meeting, Lausanne. Part 2-the effect of exercise on the fetus, labour and birth. Br J Sports Med. 2016;50(21):1297–305.

Boardman HM, Hartley L, Eisinga A, Main C, Roque i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015;3:CD002229.

Bogdanis GC, Vangelakoudi A, Maridaki M. Peak fat oxidation rate during walking in sedentary overweight men and women. J Sports Sci Med. 2008;7(4):525–31.

Boisseau N, Rannou F, Delamarche P, Bentue-Ferrer D, Gratas-Delamarche A. Glucose tolerance during moderate prolonged exercise in women with oral contraceptives as compared to non-users. J Sports Med Phys Fitness. 2001;41(2):203–9.

Boisseau N, Isacco L. Substrate metabolism during exercise: sexual dimorphism and women's specificities. Eur J Sport Sci 2021:1–21.

Bonen A, Haynes FW, Graham TE. Substrate and hormonal responses to exercise in women using oral contraceptives. J Appl Physiol. 1991;70(5):1917–27.

Bordenave S, Metz L, Flavier S, Lambert K, Ghanassia E, Dupuy AM, Michel F, Puech-Cathala AM, Raynaud E, Brun JF, Mercier J. Training-induced improvement in lipid oxidation in type 2 diabetes mellitus is related to alterations in muscle mitochondrial activity. Effect of endurance training in type 2 diabetes. Diabetes Metab. 2008;34(2):162–8.

Brooks GA, Mercier J. Balance of carbohydrate and lipid utilization during exercise: the "crossover" concept. J Appl Physiol. 1994;76(6):2253–61.

Bunt JC. Metabolic actions of estradiol: significance for acute and chronic exercise responses. Med Sci Sports Exerc. 1990;22(3):286–90.

Burguera B, Proctor D, Dietz N, Guo Z, Joyner M, Jensen MD. Leg free fatty acid kinetics during exercise in men and women. Am J Physiol Endocrinol Metab. 2000;278(1):E113-117.

Burrows M, Peters CE. The influence of oral contraceptives on athletic performance in female athletes. Sports Med. 2007;37(7):557–74.

Campbell SE, Febbraio MA. Effect of ovarian hormones on mitochondrial enzyme activity in the fat oxidation pathway of skeletal muscle. Am J Physiol Endocrinol Metab. 2001;281(4):E803-808.

Campbell SE, Febbraio MA. Effect of the ovarian hormones on GLUT4 expression and contraction-stimulated glucose uptake. Am J Physiol Endocrinol Metab. 2002;282(5):E1139-1146.

Campbell SE, Angus DJ, Febbraio MA. Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. Am J Physiol Endocrinol Metab. 2001;281(4):E817-825.

Cano A, Ventura L, Martinez G, Cugusi L, Caria M, Deriu F, Manca A. Analysis of sex-based differences in energy substrate utilization during moderate-intensity aerobic exercise. Eur J Appl Physiol. 2022;122(1):29–70.

Carter SL, Rennie C, Tarnopolsky MA. Substrate utilization during endurance exercise in men and women after endurance training. Am J Physiol Endocrinol Metab. 2001b;280(6):E898-907.

Carter S, McKenzie S, Mourtzakis M, Mahoney DJ, Tarnopolsky MA. Short-term 17beta-estradiol decreases glucose R(a) but not whole body metabolism during endurance exercise. J Appl Physiol 2001a;(1985) 90(1):139–146.

Casazza GA, Jacobs KA, Suh SH, Miller BF, Horning MA, Brooks GA. Menstrual cycle phase and oral contraceptive effects on triglyceride mobilization during exercise. J Appl Physiol. 2004;97(1):302–9.

Clark BA, Elahi D, Epstein FH. The influence of gender, age, and the menstrual cycle on plasma atrial natriuretic peptide. J Clin Endocrinol Metab. 1990;70(2):349–52.

Constantini NW, Dubnov G, Lebrun CM. The menstrual cycle and sport performance. Clin Sports Med 2005;24(2):e51–82, xiii-xiv.

Costill DL, Daniels J, Evans W, Fink W, Krahenbuhl G, Saltin B. Skeletal muscle enzymes and fiber composition in male and female track athletes. J Appl Physiol. 1976;40(2):149–54.

Davidson BJ, Rea CD, Valenzuela GJ. Atrial natriuretic peptide, plasma renin activity, and aldosterone in women on estrogen therapy and with premenstrual syndrome. Fertil Steril. 1988;50(5):743–6.

de Melo NR, Aldrighi JM, Faggion D Jr, Reyes VR, Souza JB, Fernandes CE, Larson E. A prospective open-label study to evaluate the effects of the oral contraceptive Harmonet (gestodene75/EE20) on body fat. Contraception. 2004;70(1):65–71.

De Souza MJ, Maguire MS, Rubin KR, Maresh CM. Effects of menstrual phase and amenorrhea on exercise performance in runners. Med Sci Sports Exerc. 1990;22(5):575–80.

D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise carbohydrate metabolism by estrogen and progesterone in women. Am J Physiol Endocrinol Metab. 2002;283(5):E1046-1055.

D'Eon TM, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. J Biol Chem. 2005;280(43):35983–91.

D'Eon TM, Rogers NH, Stancheva ZS, Greenberg AS. Estradiol and the estradiol metabolite, 2-hydroxyestradiol, activate AMP-activated protein kinase in C2C12 myotubes. Obesity (silver Spring). 2008;16(6):1284–8.

Devries MC, Hamadeh MJ, Graham TE, Tarnopolsky MA. 17beta-estradiol supplementation decreases glucose rate of appearance and disappearance with no effect on glycogen utilization during moderate intensity exercise in men. J Clin Endocrinol Metab. 2005;90(11):6218–25.

Devries MC, Hamadeh MJ, Phillips SM, Tarnopolsky MA. Menstrual cycle phase and sex influence muscle glycogen utilization and glucose turnover during moderate-intensity endurance exercise. Am J Physiol Regul Integr Comp Physiol. 2006;291(4):R1120-1128.

Devries MC, Lowther SA, Glover AW, Hamadeh MJ, Tarnopolsky MA. IMCL area density, but not IMCL utilization, is higher in women during moderate-intensity endurance exercise, compared with men. Am J Physiol Regul Integr Comp Physiol. 2007;293(6):R2336-2342.

Dombovy ML, Bonekat HW, Williams TJ, Staats BA. Exercise performance and ventilatory response in the menstrual cycle. Med Sci Sports Exerc. 1987;19(2):111–7.

dos Reis CM, de Melo NR, Meirelles ES, Vezozzo DP, Halpern A. Body composition, visceral fat distribution and fat oxidation in postmenopausal women using oral or transdermal oestrogen. Maturitas. 2003;46(1):59–68.

Dupuit M, Rance M, Morel C, Bouillon P, Pereira B, Bonnet A, Maillard F, Duclos M, Boisseau N. Moderate-intensity continuous training or high-intensity interval training with or without resistance training for altering body composition in postmenopausal women. Med Sci Sports Exerc. 2020;52(3):736–45.

Elliott-Sale KJ, Minahan CL, de Jonge X, Ackerman KE, Sipila S, Constantini NW, Lebrun CM, Hackney AC. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51(5):843–61.

Ellis GS, Lanza-Jacoby S, Gow A, Kendrick ZV. Effects of estradiol on lipoprotein lipase activity and lipid availability in exercised male rats. J Appl Physiol. 1994;77(1):209–15.

Escalante Pulido JM, Alpizar Salazar M. Changes in insulin sensitivity, secretion and glucose effectiveness during menstrual cycle. Arch Med Res. 1999;30(1):19–22.

Frandsen J, Pistoljevic N, Quesada JP, Amaro-Gahete FJ, Ritz C, Larsen S, Dela F, Helge JW. Menstrual cycle phase does not affect whole body peak fat oxidation rate during a graded exercise test. J Appl Physiol (1985) 2020;128(3):681–687.

Froberg K, Pedersen PK. Sex differences in endurance capacity and metabolic response to prolonged, heavy exercise. Eur J Appl Physiol Occup Physiol. 1984;52(4):446–50.

Genazzani AR, Lemarchand-Beraud T, Aubert ML, Felber JP. Pattern of plasma ACTH, hGH, and cortisol during menstrual cycle. J Clin Endocrinol Metab. 1975;41(3):431–7.

Gower BA, Nagy TR, Blaylock ML, Wang C, Nyman L. Estradiol may limit lipid oxidation via Cpt 1 expression and hormonal mechanisms. Obes Res. 2002;10(3):167–72.

Hackney AC. Effects of the menstrual cycle on resting muscle glycogen content. Horm Metab Res. 1990;22(12):647.

Hackney AC. Influence of oestrogen on muscle glycogen utilization during exercise. Acta Physiol Scand. 1999;167(3):273–4.

Hackney AC, McCracken-Compton MA, Ainsworth B. Substrate responses to submaximal exercise in the midfollicular and midluteal phases of the menstrual cycle. Int J Sport Nutr. 1994;4(3):299–308.

Hackney AC, Muoio D, Meyer WR. The effect of sex steroid hormones on substrate oxidation during prolonged submaximal exercise in women. Jpn J Physiol. 2000;50(5):489–94.

Hackney AC, Koltun KJ, Williett HN. Menstrual cycle hormonal changes: estradiol-beta-17 and progesterone interactions on exercise fat oxidation. Endocrine 2022.

Hackney AC. Menstrual cycle hormonal changes and energy substrate metabolism in exercising women: a perspective. Int J Environ Res Public Health 2021;18(19)

Hamadeh MJ, Devries MC, Tarnopolsky MA. Estrogen supplementation reduces whole body leucine and carbohydrate oxidation and increases lipid oxidation in men during endurance exercise. J Clin Endocrinol Metab. 2005;90(6):3592–9.

Hatta H, Atomi Y, Shinohara S, Yamamoto Y, Yamada S. The effects of ovarian hormones on glucose and fatty acid oxidation during exercise in female ovariectomized rats. Horm Metab Res. 1988;20(10):609–11.

Heiling VJ, Jensen MD. Free fatty acid metabolism in the follicular and luteal phases of the menstrual cycle. J Clin Endocrinol Metab. 1992;74(4):806–10.

Hoffman DM, O'Sullivan AJ, Freund J, Ho KK. Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism. J Clin Endocrinol Metab. 1995;80(1):72–7.

Hong M, Yan Q, Tao B, Boersma A, Han KK, Vantyghem MC, Racadot A, Lefebvre J. Estradiol, progesterone and testosterone exposures affect the atrial natriuretic peptide gene expression in vivo in rats. Biol Chem Hoppe Seyler. 1992;373(4):213–8.

Horton TJ, Pagliassotti MJ, Hobbs K, Hill JO. Fuel metabolism in men and women during and after long-duration exercise. J Appl Physiol. 1998;85(5):1823–32.

Horton TJ, Miller EK, Glueck D, Tench K. No effect of menstrual cycle phase on glucose kinetics and fuel oxidation during moderate-intensity exercise. Am J Physiol Endocrinol Metab. 2002;282(4):E752-762.

Horton TJ, Miller EK, Bourret K. No effect of menstrual cycle phase on glycerol or palmitate kinetics during 90 min of moderate exercise. J Appl Physiol (1985) 2006;100(3):917–925.

Hulton AT, Malone JJ, Campbell IT, MacLaren DPM. The effect of the menstrual cycle and hyperglycaemia on hormonal and metabolic responses during exercise. Eur J Appl Physiol 2021.

Isacco L, Duche P, Boisseau N. Influence of hormonal status on substrate utilization at rest and during exercise in the female population. Sports Med. 2012a;42(4):327–42.

Isacco L, Thivel D, Pelle AM, Zouhal H, Duclos M, Duche P, Boisseau N. Oral contraception and energy intake in women: impact on substrate oxidation during exercise. Appl Physiol Nutr Metab. 2012b;37(4):646–56.

Isacco L, Thivel D, Pereira B, Duclos M, Boisseau N. Maximal fat oxidation, but not aerobic capacity, is affected by oral contraceptive use in young healthy women. Eur J Appl Physiol. 2015;115(5):937–45.

Isacco L, Ennequin G, Boisseau N. Effect of fat mass localization on fat oxidation during endurance exercise in women. Front Physiol. 2020;11: 585137.

Isacco L, Thivel D, Meddahi-Pelle A, Lemoine-Morel S, Duclos M, Boisseau N. Exercise per se masks oral contraceptive-induced postprandial lipid mobilization. Appl Physiol Nutr Metab 2014:1–8.

Isacco L, Ennequin G, Boisseau N. Influence of the different hormonal status changes during their life on fat mass localisation in women: a narrative review. Arch Physiol Biochem 2021:1–6.

Jacobs KA, Casazza GA, Suh SH, Horning MA, Brooks GA. Fatty acid reesterification but not oxidation is increased by oral contraceptive use in women. J Appl Physiol. 2005;98(5):1720–31.

James AP, Lorraine M, Cullen D, Goodman C, Dawson B, Palmer TN, Fournier PA. Muscle glycogen supercompensation: absence of a gender-related difference. Eur J Appl Physiol. 2001;85(6):533–8.

Jensen MD, Levine J. Effects of oral contraceptives on free fatty acid metabolism in women. Metabolism. 1998;47(3):280–4.
Jensen MD, Martin ML, Cryer PE, Roust LR. Effects of estrogen on free fatty acid metabolism in humans. Am J Physiol. 1994;266(6 Pt 1):E914-920.
Jeukendrup AE. Modulation of carbohydrate and fat utilization by diet, exercise and environment. Biochem Soc Trans. 2003;31(Pt 6):1270–3.
Jeukendrup AE, Wallis GA. Measurement of substrate oxidation during exercise by means of gas exchange measurements. Int J Sports Med. 2005;26(Suppl 1):S28-37.
Johnson LG, Kraemer RR, Haltom R, Kraemer GR, Gaines HE, Castracane VD. Effects of estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol responses to exercise in postmenopausal women. Fertil Steril. 1997;68(5):836–43.
Johnson LG, Kraemer RR, Kraemer GR, Haltom RW, Cordill AE, Welsch MA, Durand RJ, Castracane VD. Substrate utilization during exercise in postmenopausal women on hormone replacement therapy. Eur J Appl Physiol. 2002;88(3):282–7.
Jurkowski JE, Jones NL, Toews CJ, Sutton JR. Effects of menstrual cycle on blood lactate, O2 delivery, and performance during exercise. J Appl Physiol Respir Environ Exerc Physiol. 1981;51(6):1493–9.
Kanaley JA, Boileau RA, Bahr JA, Misner JE, Nelson RA. Substrate oxidation and GH responses to exercise are independent of menstrual phase and status. Med Sci Sports Exerc. 1992;24(8):873–80.
Kelley DE. Skeletal muscle fat oxidation: timing and flexibility are everything. J Clin Invest. 2005;115(7):1699–702.
Kendrick ZV, Steffen CA, Rumsey WL, Goldberg DI. Effect of estradiol on tissue glycogen metabolism in exercised oophorectomized rats. J Appl Physiol. 1987;63(2):492–6.
Kiens B, Roepstorff C, Glatz JF, Bonen A, Schjerling P, Knudsen J, Nielsen JN. Lipid-binding proteins and lipoprotein lipase activity in human skeletal muscle: influence of physical activity and gender. J Appl Physiol (1985) 2004;97(4):1209–1218.
Klein S, Coyle EF, Wolfe RR. Fat metabolism during low-intensity exercise in endurance-trained and untrained men. Am J Physiol. 1994;267(6 Pt 1):E934-940.
Kocjan T, Prelevic GM. Hormone replacement therapy update: who should we be prescribing this to now? Curr Opin Obstet Gynecol. 2003;15(6):459–64.
Kohrt WM, Ehsani AA, Birge SJ Jr. HRT preserves increases in bone mineral density and reductions in body fat after a supervised exercise program. J Appl Physiol. 1998;84(5):1506–12.
Konarzewski M, Diamond JM. Evolution of basal metabolic rate and organ masses in laboratory mice. Evolution. 1995;49:1239–48.
Koppo K, Larrouy D, Marques MA, Berlan M, Bajzova M, Polak J, Van de Voorde J, Bulow J, Lafontan M, Crampes F, Langin D, Stich V, de Glisezinski I. Lipid mobilization in subcutaneous adipose tissue during exercise in lean and obese humans. Roles of insulin and natriuretic peptides. Am J Physiol Endocrinol Metab. 2010;299(2):E258-265.
Kraemer RR, Johnson LG, Haltom R, Kraemer GR, Gaines H, Drapcho M, Gimple T, Castracane VD. Effects of hormone replacement on growth hormone and prolactin exercise responses in postmenopausal women. J Appl Physiol. 1998;84(2):703–8.
Kuipers H, Saris WH, Brouns F, Keizer HA, ten Bosch C. Glycogen synthesis during exercise and rest with carbohydrate feeding in males and females. Int J Sports Med. 1989;10(Suppl 1):S63-67.
Lafontan M, Moro C, Sengenes C, Galitzky J, Crampes F, Berlan M. An unsuspected metabolic role for atrial natriuretic peptides: the control of lipolysis, lipid mobilization, and systemic nonesterified fatty acids levels in humans. Arterioscler Thromb Vasc Biol. 2005;25(10):2032–42.
Lambert EV, Hawley JA, Goedecke J, Noakes TD, Dennis SC. Nutritional strategies for promoting fat utilization and delaying the onset of fatigue during prolonged exercise. J Sports Sci. 1997;15(3):315–24.
Lamont LS, McCullough AJ, Kalhan SC. Gender differences in leucine, but not lysine, kinetics. J Appl Physiol (1985) 2001;91(1):357–362.

Lavoie JM, Dionne N, Helie R, Brisson GR. Menstrual cycle phase dissociation of blood glucose homeostasis during exercise. J Appl Physiol (1985) 1987;62(3):1084–1089.
Lebrun CM. The effect of the phase of the menstrual cycle and the birth control pill on athletic performance. Clin Sports Med. 1994;13(2):419–41.
Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (lond). 2008;32(6):949–58.
Lupo M, Dains JE, Madsen LT. Hormone replacement therapy: an increased risk of recurrence and mortality for breast cancer patients? J Adv Pract Oncol. 2015;6(4):322–30.
Lwin R, Darnell B, Oster R, Lawrence J, Foster J, Azziz R, Gower BA. Effect of oral estrogen on substrate utilization in postmenopausal women. Fertil Steril. 2008;90(4):1275–8.
Maffei S, Del Ry S, Prontera C, Clerico A. Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. Clin Sci (lond). 2001;101(5):447–53.
Magkos F, Patterson BW, Mittendorfer B. No effect of menstrual cycle phase on basal very-low-density lipoprotein triglyceride and apolipoprotein B-100 kinetics. Am J Physiol Endocrinol Metab. 2006;291(6):E1243-1249.
Maher AC, Akhtar M, Vockley J, Tarnopolsky MA. Women have higher protein content of beta-oxidation enzymes in skeletal muscle than men. PLoS ONE. 2010;5(8): e12025.
Mandour T, Kissebah AH, Wynn V. Mechanism of oestrogen and progesterone effects on lipid and carbohydrate metabolism: alteration in the insulin: glucagon molar ratio and hepatic enzyme activity. Eur J Clin Invest. 1977;7(3):181–7.
Matute ML, Kalkhoff RK. Sex steroid influence on hepatic gluconeogenesis and glucogen formation. Endocrinology. 1973;92(3):762–8.
McKerns KW, Coulomb B, Kaleita E, De Renzo EC. Some effects of in vivo administered estrogens on glucose metabolism and adrenal cortical secretion in vitro. Endocrinology. 1958;63(6):709–22.
McKenzie S, Phillips SM, Carter SL, Lowther S, Gibala MJ, Tarnopolsky MA. Endurance exercise training attenuates leucine oxidation and BCOAD activation during exercise in humans. Am J Physiol Endocrinol Metab. 2000;278(4):E580-587.
McLay RT, Thomson CD, Williams SM, Rehrer NJ. Carbohydrate loading and female endurance athletes: effect of menstrual-cycle phase. Int J Sport Nutr Exerc Metab. 2007;17(2):189–205.
McMurray RG, Mottola MF, Wolfe LA, Artal R, Millar L, Pivarnik JM. Recent advances in understanding maternal and fetal responses to exercise. Med Sci Sports Exerc. 1993;25(12):1305–21.
Metz L, Isacco L, Redman LM. Effect of oral contraceptives on energy balance in women: a review of current knowledge and potential cellular mechanisms. Metabolism. 2022;126: 154919.
Minson CT, Halliwill JR, Young TM, Joyner MJ. Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. Circulation. 2000;102(13):1473–6.
Moore DR, Sygo J, Morton JP. Fuelling the female athlete: carbohydrate and protein recommendations. Eur J Sport Sci 2021:1–13.
Moro C, Crampes F, Sengenes C. Atrial natriuretic peptide contributes to the physiological control of lipid mobilization in humans. FASEB J. 2004;18:908–10.
Nicklas BJ, Hackney AC, Sharp RL. The menstrual cycle and exercise: performance, muscle glycogen, and substrate responses. Int J Sports Med. 1989;10(4):264–9.
Norrelund H. Consequences of growth hormone deficiency for intermediary metabolism and effects of replacement. Front Horm Res. 2005;33:103–20.
Numao S, Hayashi Y, Katayama Y, Matsuo T, Tanaka K. Sex differences in substrate oxidation during aerobic exercise in obese men and postmenopausal obese women. Metabolism. 2009;58(9):1312–9.
Oosthuyse T, Bosch AN. The effect of the menstrual cycle on exercise metabolism: implications for exercise performance in eumenorrhoeic women. Sports Med. 2010;40(3):207–27.
Oosthuyse T, Bosch AN. Oestrogen's regulation of fat metabolism during exercise and gender specific effects. Curr Opin Pharmacol. 2012;12(3):363–71.
O'Sullivan AJ, Ho KK. A comparison of the effects of oral and transdermal estrogen replacement on insulin sensitivity in postmenopausal women. J Clin Endocrinol Metab. 1995;80(6):1783–8.

O'Sullivan AJ, Crampton LJ, Freund J, Ho KK. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. J Clin Invest. 1998;102(5):1035–40.

Perez-Martin A, Dumortier M, Raynaud E, Brun JF, Fedou C, Bringer J, Mercier J. Balance of substrate oxidation during submaximal exercise in lean and obese people. Diabetes Metab. 2001;27(4 Pt 1):466–74.

Picard F, Wanatabe M, Schoonjans K, Lydon J, O'Malley BW, Auwerx J. Progesterone receptor knockout mice have an improved glucose homeostasis secondary to beta -cell proliferation. Proc Natl Acad Sci U S A. 2002;99(24):15644–8.

Piers LS, Diggavi SN, Rijskamp J, van Raaij JM, Shetty PS, Hautvast JG. Resting metabolic rate and thermic effect of a meal in the follicular and luteal phases of the menstrual cycle in well-nourished Indian women. Am J Clin Nutr. 1995;61(2):296–302.

Redman LM, Scroop GC, Westlander G, Norman RJ. Effect of a synthetic progestin on the exercise status of sedentary young women. J Clin Endocrinol Metab. 2005;90(7):3830–7.

Reilly T. The menstrual cycle and human performance: an overview. Biol Rhythm Res. 2000;31(1):29–40.

Reinke U, Ansah B, Voigt KD. Effect of the menstrual cycle on carbohydrate and lipid metabolism in normal females. Acta Endocrinol (copenh). 1972;69(4):762–8.

Roepstorff C, Steffensen CH, Madsen M, Stallknecht B, Kanstrup IL, Richter EA, Kiens B. Gender differences in substrate utilization during submaximal exercise in endurance-trained subjects. Am J Physiol Endocrinol Metab. 2002;282(2):E435-447.

Roepstorff C, Donsmark M, Thiele M, Vistisen B, Stewart G, Vissing K, Schjerling P, Hardie DG, Galbo H, Kiens B. Sex differences in hormone-sensitive lipase expression, activity, and phosphorylation in skeletal muscle at rest and during exercise. Am J Physiol Endocrinol Metab. 2006;291(5):E1106-1114.

Romijn JA, Coyle EF, Sidossis LS, Gastaldelli A, Horowitz JF, Endert E, Wolfe RR. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am J Physiol. 1993;265(3 Pt 1):E380-391.

Romijn JA, Coyle EF, Sidossis LS, Rosenblatt J, Wolfe RR. Substrate metabolism during different exercise intensities in endurance-trained women. J Appl Physiol. 2000;88(5):1707–14.

Ruby BC, Robergs RA, Waters DL, Burge M, Mermier C, Stolarczyk L. Effects of estradiol on substrate turnover during exercise in amenorrheic females. Med Sci Sports Exerc. 1997;29(9):1160–9.

Sengenes C, Bouloumie A, Hauner H, Berlan M, Busse R, Lafontan M, Galitzky J. Involvement of a cGMP-dependent pathway in the natriuretic peptide-mediated hormone-sensitive lipase phosphorylation in human adipocytes. J Biol Chem. 2003;278(49):48617–26.

Sengenes C, Moro C, Galitzky J, Berlan M, Lafontan M. Natriuretic peptides: a new lipolytic pathway in human fat cells. Med Sci (Paris) 2005;21 Spec No:29–33.

Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. J Am Coll Cardiol. 2009;53(3):221–31.

Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, Speed C, Jones M. Aromatase–a brief overview. Annu Rev Physiol. 2002;64:93–127.

Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. Rev Endocr Metab Disord. 2011;12(2):63–75.

Sladek CD. Gluconeogenesis and hepatic glycogen formation in relation to the rat estrous cycle. Horm Metab Res. 1974;6(3):217–21.

Smekal G, von Duvillard SP, Frigo P, Tegelhofer T, Pokan R, Hofmann P, Tschan H, Baron R, Wonisch M, Renezeder K, Bachl N. Menstrual cycle: no effect on exercise cardiorespiratory variables or blood lactate concentration. Med Sci Sports Exerc. 2007;39(7):1098–106.

Snow-Harter. Bone health and prevention of osteoporosis in active and athletic women. Clin Sports Med 1994;13(2):389–404.

Soultanakis HN, Artal R, Wiswell RA. Prolonged exercise in pregnancy: glucose homeostasis, ventilatory and cardiovascular responses. Semin Perinatol. 1996;20(4):315–27.

Sowers M, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, Yosef M, Symons J. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab. 2007;92(3):895–901.

Steffensen CH, Roepstorff C, Madsen M, Kiens B. Myocellular triacylglycerol breakdown in females but not in males during exercise. Am J Physiol Endocrinol Metab. 2002;282(3):E634-642.

Suh SH, Casazza GA, Horning MA, Miller BF, Brooks GA. Luteal and follicular glucose fluxes during rest and exercise in 3-h postabsorptive women. J Appl Physiol. 2002;93(1):42–50.

Suh SH, Casazza GA, Horning MA, Miller BF, Brooks GA. Effects of oral contraceptives on glucose flux and substrate oxidation rates during rest and exercise. J Appl Physiol. 2003;94(1):285–94.

Sutter-Dub MT, Vergnaud MT. Progesterone and glucose metabolism in the female rat adipocyte: effect on hexokinase activity. J Endocrinol. 1982;95(3):369–75.

Tarnopolsky MA. Sex differences in exercise metabolism and the role of 17-beta estradiol. Med Sci Sports Exerc. 2008;40(4):648–54.

Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR. Gender differences in substrate for endurance exercise. J Appl Physiol. 1990a;68(1):302–8.

Tarnopolsky MA, Rennie CD, Robertshaw HA, Fedak-Tarnopolsky SN, Devries MC, Hamadeh MJ. Influence of endurance exercise training and sex on intramyocellular lipid and mitochondrial ultrastructure, substrate use, and mitochondrial enzyme activity. Am J Physiol Regul Integr Comp Physiol. 2007;292(3):R1271-1278.

Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR. Gender differences in substrate for endurance exercise. J Appl Physiol (1985) 1990b;68(1):302–308.

Tarnopolsky MA, Atkinson SA, Phillips SM, MacDougall JD. Carbohydrate loading and metabolism during exercise in men and women. J Appl Physiol (1985) 1995;78(4):1360–1368.

Tarnopolsky MA, Bosman M, Macdonald JR, Vandeputte D, Martin J, Roy BD. Postexercise protein-carbohydrate and carbohydrate supplements increase muscle glycogen in men and women. J Appl Physiol (1985) 1997;83(6):1877–1883.

Tarnopolsky MA, Zawada C, Richmond LB, Carter S, Shearer J, Graham T, Phillips SM. Gender differences in carbohydrate loading are related to energy intake. J Appl Physiol (1985) 2001;91(1):225–230.

Toth MJ, Gardner AW, Arciero PJ, Calles-Escandon J, Poehlman ET. Gender differences in fat oxidation and sympathetic nervous system activity at rest and during submaximal exercise in older individuals. Clin Sci (lond). 1998;95(1):59–66.

Tremblay J, Peronnet F, Massicotte D, Lavoie C. Carbohydrate supplementation and sex differences in fuel selection during exercise. Med Sci Sports Exerc. 2010;42(7):1314–23.

Tremollieres F. Oral combined contraception: is there any difference between ethinyl-estradiol and estradiol? Gynecol Obstet Fertil. 2012;40(2):109–15.

Uranga AP, Levine J, Jensen M. Isotope tracer measures of meal fatty acid metabolism: reproducibility and effects of the menstrual cycle. Am J Physiol Endocrinol Metab. 2005;288(3):E547-555.

Vieira-Potter VJ, Zidon TM, Padilla J. Exercise and estrogen make fat cells "Fit." Exerc Sport Sci Rev. 2015;43(3):172–8.

Weinstein I, Cook GA, Heimberg M. Regulation by oestrogen of carnitine palmitoyltransferase in hepatic mitochondria. Biochem J. 1986;237(2):593–6.

Wenz M, Berend JZ, Lynch NA, Chappell S, Hackney AC. Substrate oxidation at rest and during exercise: effects of menstrual cycle phase and diet composition. J Physiol Pharmacol. 1997;48(4):851–60.

White LJ, Ferguson MA, McCoy SC, Kim H. Intramyocellular lipid changes in men and women during aerobic exercise: a (1)H-magnetic resonance spectroscopy study. J Clin Endocrinol Metab. 2003;88(12):5638–43.

Willett HN, Koltun KJ, Hackney AC. Influence of menstrual cycle estradiol-beta-17 fluctuations on energy substrate utilization-oxidation during aerobic, endurance exercise. Int J Environ Res Publ Health 2021;18(13).

Wolfe RR, Peters EJ, Klein S, Holland OB, Rosenblatt J, Gary H Jr. Effect of short-term fasting on lipolytic responsiveness in normal and obese human subjects. Am J Physiol. 1987;252(2 Pt 1):E189-196.

Wolfe LA, Kemp JG, Heenan AP, Preston RJ, Ohtake PJ. Acid-base regulation and control of ventilation in human pregnancy. Can J Physiol Pharmacol. 1998;76(9):815–27.

Yasui T, Uemura H, Takikawa M, Irahara M. Hormone replacement therapy in postmenopausal women. J Med Invest. 2003;50(3–4):136–45.

Zderic TW, Coggan AR, Ruby BC. Glucose kinetics and substrate oxidation during exercise in the follicular and luteal phases. J Appl Physiol. 2001;90(2):447–53.

Zehnder M, Ith M, Kreis R, Saris W, Boutellier U, Boesch C. Gender-specific usage of intramyocellular lipids and glycogen during exercise. Med Sci Sports Exerc. 2005;37(9):1517–24.

Chapter 3
Effects of Sex Hormones and Exercise on Adipose Tissue

Victoria J. Vieira-Potter

Overview of Functions of Adipose Tissue

In the human body, adipose (i.e., fat) tissue makes up between five and upward of 50 % of total body mass. In severe cases of obesity, adipose tissue can make up over 80 % of body mass. However ~20 % of the mass of an average adult male constitutes adipose tissue, this percentage is much greater among age-matched females, who have an average body fat mass of ~28 % (Thompson et al. 2012). The major function of adipose tissue is energy storage in the form of lipid as triacylglycerol (TAG), which is the most efficiently stored source of energy. Indeed, total body adipose tissue supplies up to ~800,000 kcal of energy, whereas energy stored as glycogen in skeletal muscle and liver combined supplies only a fraction of that amount of energy. If the amount of energy stored in adipose tissue was to be stored as glycogen, it would take up ~500 % more volume (Frayn et al. 2003). Thus, energy storage in adipose tissue allows for survival over relatively long periods of inadequate energy intake and is therefore a key evolutionarily advantageous feature.

While it has long been thought that the total number of adipocytes over the course of a lifetime is constant, newer evidence suggests that cell turnover does occur, albeit not at the rate of some other human cell types. Estimates are that the half-life of an adipocyte is ~300–400 days (Strawford et al. 2004) but more studies are necessary to validate that estimate. What is evident is that turnover does occur, counter to previous belief. Because of the body's almost constant reliance on a shift between adipocyte storage and lipolysis, the adipocyte cell is one that is plastic (adaptability) throughout its life and has tremendous capacity to expand and shrink depending on the circumstance. This plasticity requires considerable remodeling to accommodate these cycles of expansion and shrinking. This remodeling is achieved with the help

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of resident and acquired immune cells, such as macrophages. This may help explain, teleologically, why adipose tissue is a major site of immune cell localization, a topic to be discussed in more detail later.

Aside from its important energy storage role, adipose tissue serves many other essential functions such as organ structural support and temperature regulation/insulation. Moreover, it is now appreciated that the adipose tissue plays important roles in immune and endocrine function and serves as an important mediator of immunity and energy balance. These more recently discovered functions of adipose tissue have led to its classification as an endocrine organ and the emergence of a new field of study called "immunometabolism", which investigates these interactions between the immune and endocrine systems (Ferrante 2013). Exercise and female sex hormones, as well as a variety of other biological and behavioral factors, profoundly affect the endocrine functions of adipose tissue. While the implications of this are only beginning to be investigated, it is quite possible that the influence of various factors (e.g., exercise, aging, sex hormones) on systemic metabolic health may be driven by changes that occur in the adipose tissue. Moreover, the sex differences that exist in age-related metabolism and metabolic responses to exercise training may be at least partially explained by sex hormone-mediated differences in adipose tissue metabolism.

The adipose tissue is a heterogeneous organ that is broadly classified as either "white" (i.e., WAT), accounting for ~95–99 % of total body fat mass and serving the main functions of energy storage and lipid mobilization, or "brown" (i.e., BAT), accounting for only a fraction of total body fat mass and functioning mainly to regulate body temperature via adaptive thermogenesis (Peirce et al. 2014). Unlike WAT, the major role of BAT is not in energy storage, but rather, energy dissipation as heat. The distinguishing characteristic of BAT is that it is mitochondria-dense and contains a multi-locular phenotype such that lipid is stored as tiny droplets throughout the cell rather than as the one large droplet which is characteristic of adipocytes from WAT. The mitochondria found in brown adipocytes are unique in that they contain a high concentration of uncoupling protein-1 (UCP-1), a protein that uncouples oxidative phosphorylation from energy (i.e., ATP) production. This allows the brown adipocyte to produce heat rather than trapping substrate energy in a utilizable form. However, intriguing new research suggests that there is a great deal of plasticity in the major adipose tissue depots, such that some resident cells in WAT have the ability to take on a phenotype reminiscent of adipocytes from BAT; these cells have been classified as "brite" or "beige" adipocytes. This phenotype change, characterized in part by increased UCP-1 expression, may enhance fat metabolism, facilitate weight loss, and improve insulin sensitivity. On the other hand, it is likely that cells with similar plasticity are present in BAT such that they may, under certain environmental conditions (e.g., chronic energy overload as in obesity), take on a phenotype more similar to adipoctyes from WAT. This process in BAT, whereby adipocytes store more lipid and take on characteristics more similar to white adipocytes, has been described as "whitening" (Shimizu et al. 2014). Notably, both exercise and female sex hormones are among the growing list of factors that may influence "beigeing" of

WAT. On the other hand, physical inactivity, obesity, and estrogen loss may trigger "whitening" of BAT, which may have negative effects on overall metabolic health.

Effects of Exercise and Estrogen on Adipocyte Lipolysis

Given its primary role in lipid energy storage, WAT is particularly important during fasting and exercise, especially when glycogen becomes limited. It is during fasting and endurance exercise that the process of adipocyte lipolysis becomes highly activated. Lipolysis is the major process that occurs uniquely in adipose tissue whereby the energy stored as lipid can be mobilized for use by other tissues. It is largely hormone driven and is dependent upon the specific physiological condition (Fig. 3.1). During the fed state, the hormone insulin potently suppresses adipose tissue lipolysis, whereas during the fasted state, when insulin levels are low and glucagon levels are high, lipolysis occurs unabated, resulting in an increase in circulating non-esterified free fatty acids (NEFAs) which serve as an important fuel for the energy-requiring skeletal and cardiac muscle cells. The mechanism of lipolysis involves increased activity of hormone sensitive lipase (HSL), an enzyme potently inhibited by insulin and activated by glucagon. On the other hand, during the fed state, insulin promotes fat storage in adipocytes by activating the enzyme lipoprotein lipase (LPL) (Wang and Eckel 2009) and inhibiting HSL. Not only does insulin increase TAG storage via LPL, but it also potentiates an increase in re-esterification of fatty acids in adipocytes for reasons that are not entirely clear (Frayn et al. 1994). In addition to being inhibited by insulin, adipocyte lipolysis is stimulated strongly by catecholamines (e.g., epinephrine and norepinephrine) which are released during exercise and which result in beta-adrenergic receptor (AR)-mediated mobilization of lipid (Hjemdahl and Linde 1983). Briefly, catecholamines bind to adipocyte cell surface adrenergic receptors, triggering intracellular signaling events culminating in the phosphorylation of HSL by protein kinase A (PKA); phosphorylated HSL mediates the hydrolysis of TAG molecules, resulting in the release of NEFAs and free glycerol from the adipocyte. Lipid droplet proteins such as perilipin are also important regulators of lipolysis and, when active, allow for the hydrolysis of lipid droplets within adipocytes. Other important players in the stimulation of lipolysis are adipose triglyceride lipase (ATGL) and comparative gene identification-58 (CG158). ATGL is a TAG hydrolase and the rate-limiting enzyme that promotes the catabolism of fat in both adipose and non-adipose tissues. Efficient ATGL activity requires activation by CG158, and upon stimulation of ATGL, release of fatty acids is increased. Alternatively, insulin, which decreases during exercise, deactivates both HSL and lipid droplet proteins, thereby inhibiting lipolysis.

In addition to stimulating lipolysis, beta$_3$ AR stimulation in particular is a potent stimulus for browning of WAT (i.e., increased UCP-1 and mitochondrial biogenesis). During exercise, there is a strong positive relationship between adipocyte lipolysis and systemic fatty acid oxidation. In fact, net whole-body fat oxidation is determined by many factors that regulate both WAT lipolysis and skeletal muscle oxidative

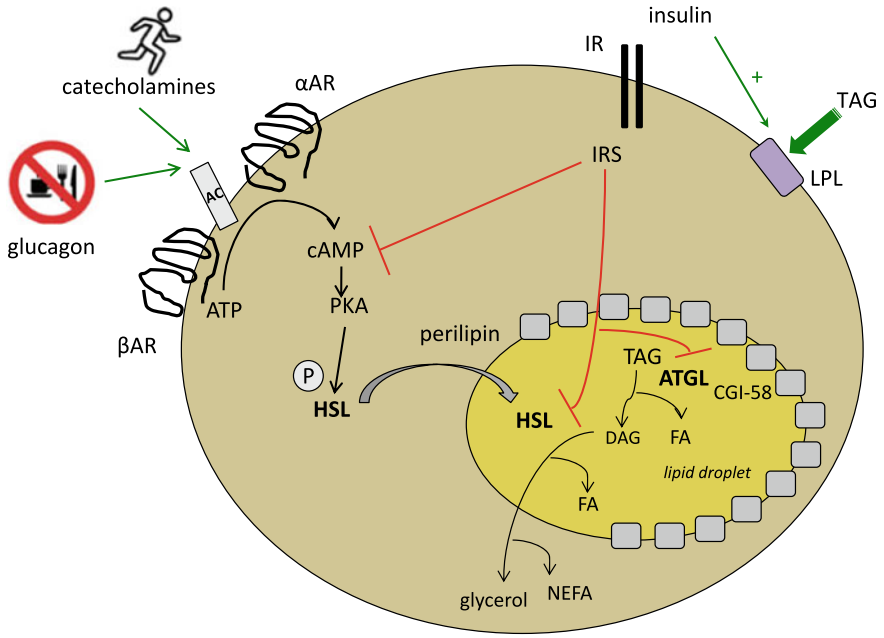

Fig. 3.1 Hormonal regulation of adipocyte lipolysis. Hormones released during exercise (i.e., catecholamines) and fasting (i.e., glucagon) bind to and activate membrane-bound ARs which trigger an AC-mediated increase in cAMP. cAMP activates PKA which phosphorylates and activates HSL to catalyze the hydrolysis of TAG stored in the lipid droplet; cAMP also activates perilipin allowing it to dissociate from the lipid droplet and thus facilitate lipolysis. During the fed state, insulin allows the adipocyte to take up fatty acids for storage via the activation of LPL and suppresses adipocyte lipolysis via activation of IRS, which leads to reduced cAMP/HSL activation. Insulin also inhibits ATGL which is another important lipase located in the lipid droplet which works closely with CGI-58. *AR* adrenergic receptor, *AC* adenylate cyclase, *cAMP* cyclic AMP, *PKA* protein kinase A, *HSL* hormone sensitive lipase, *IR* insulin receptor, *IRS* insulin receptor substrate, *TAG* triacylglycerol, *DAG* diacylglycerol, *FA* fatty acid, *NEFA* non-esterified fatty acid, and *LPL* lipoprotein lipase.

capacity. With a net negative energy balance, fatty acid utilization increases to meet energy demands, and adipocytes shrink. As blood glucose levels become limited (e.g., during endurance exercise), WAT lipolysis increases as the body relies more heavily on fatty acid oxidation (Thompson et al. 2012). Thus, WAT lipolysis and skeletal muscle fatty acid oxidation are tightly linked such that WAT lipolysis increases the plasma NEFA concentration, and NEFAs are taken up by exercising muscles in a concentration-dependent manner. NEFA oxidation is dependent on both the intensity and the duration of the exercise. Given its near constant reliance on endocrine factors which regulate the flux between storage and lipolysis, and its primary role in secreting NEFAs into the circulation for transport throughout the body, it is not surprising that adipose tissue is among the most highly vascularized tissues in the human body. In fact, during resting conditions, blood perfusion is even greater in adipose tissue than in skeletal muscle (Thompson et al. 2012). During exercise, blood flow to both adipose

tissue as well as skeletal muscle increases significantly. Undeniably, increased blood flow to adipose tissue during exercise is critical for neuroendocrine control of lipid kinetics and NEFA mobilization to exercising skeletal muscle (Lambadiari et al. 2015).

Exercise training may facilitate adaptations in adipose tissue lipolysis (Ogasawara et al. 2015) and fat oxidation to maximize fat utilization and preserve glycogen stores (Vicente-Salar et al. 2015). The importance of exercise-mediated regulation of adipocyte lipolysis is illustrated by evidence in rodents, which suggests that exercise training-induced cardiac tissue adaptations do not occur when adipose tissue lipolysis is prevented via genetic knockdown of ATGL (Foryst-Ludwig et al. 2015). And, acute and chronic exercise may differentially affect lipolysis. For example, the cellular machinery associated with adipose tissue lipolysis undergoes significant and unique molecular changes with both acute and chronic exercise training (Ogasawara et al. 2015). There have been limited studies on how different types and intensities of exercise affect these changes. However, in one study of eumenorrheic women who were examined for substrate metabolism during a submaximal exercise bout at two different menstrual cycle phases (i.e., mid-folicular characterized by higher estrogen levels and mid-luteal characterized by lower estrogen levels), significant differences in substrate utilization were noted. Specifically, carbohydrate oxidation was higher during the follicular (i.e., high estrogen) phase compared to luteal (i.e., lower estrogen) phase. Correspondingly, lipid oxidation was higher during the luteal phase. Interestingly, at a greater exercise intensity, there were no longer significant differences in fuel utilization during menstrual phases suggesting that female sex hormones may affect fuel utilization during moderate but not intense exercise (Hackney et al. 1994).

Although sex differences have been appreciated, how estrogen affects adipose tissue-specific exercise training adaptations is completely unknown. While one study in humans failed to demonstrate significant sex differences between fatty acid and glycerol mobilization during rest or moderate-intensity exercise (Bulow et al. 2006), another study investigating the effects of short-term submaximal exercise on lipid mobilization showed that women have a more pronounced exercise-driven lipid mobilization response (Hellstrom et al. 1996). Although estrogen has been shown to enhance adipocyte lipolysis and fatty acid oxidation, postmenopausal women develop dyslipidemia, which may be related to an increase in basal lipolysis. Wohlers and Spangenburg, in mice, showed that loss of ovarian function results in increased ATGL protein content and decreased perilipin content, these differences compared to control, sham-operated animals associated with increased NEFA and glycerol levels, suggestive of increased basal lipolysis. Those differences were partially normalized with estrogen treatment, but not by exercise (Wohlers and Spangenburg 2010). In addition, premenopausal females have greater sensitivity to insulin's antilipolytic effect in adipose tissue causing them to be more resistant to adipose tissue loss (Luglio 2014). Interestingly, during endurance exercise, females may actually have a greater preference toward fat oxidation than males, which associates with greater glycogen preservation. That is, females may be more metabolically flexible than males. Along those same lines, there is also some evidence that females have greater

skeletal muscle intramyocellular lipid (IMCL) content and that a greater percentage of their IMCL stores associate directly with mitochondria following exercise, suggestive of a greater capacity to utilize those lipid stores (Devries 2016). Mechanistically, some data suggest that women are more sensitive to the lipolytic action of epinephrine compared to men (Katzer et al. 2021), which may be due to ARs being affected by sex and/or estrogen. Some studies show that estrogen affects AR density on adipocytes. Catecholamine-stimulated lipolysis occurs through activation of beta ARs, whereas alpha AR activity inhibits lipolysis (Fig. 3.1). In fact, at least one human study showed that the greater rate of lipolysis in women upon epinephrine stimulation was due to lower alpha AR-mediated inhibition of lipolysis. Other studies have shown that estrogen, via estrogen receptor alpha (ERα) signaling, upregulates the expression of alpha AR, thus attenuating lipolysis and potentiating fat storage in the absence of beta AR stimulation. More detail on how ERs may affect AR signaling will be described later on. In sum, definitive data on whether sex differences exist in exercise-mediated adipose tissue lipolysis are inconclusive and require further study.

Factors Affecting Adipose Tissue Distribution

WAT is classified broadly as subcutaneous and visceral depots. Visceral WAT describes that surrounding the internal organs, whereas subcutaneous lies just beneath the skin throughout the body. Subcutaneous WAT is stored primarily around the hips and buttocks. The visceral intra-abdominal depot is most metabolically detrimental in that it associates strongly with insulin resistance and dyslipidemia. Estrogen appears to drive subcutaneous adipose tissue storage and estrogen-mediated adipose tissue distribution is thought to explain why females characteristically store fat in subcutaneous (e.g., hip, gluteal regions), whereas males tend to store fat viscerally. Other evidence that estrogen increases subcutaneous fat storage is that male-to-female transsexual individuals receiving estrogen therapy increase subcutaneous but not visceral fat deposition (Luglio 2014). This estrogen-dependent fat distribution pattern is considered metabolically protective and likely explains why premenopausal women are less likely to experience adverse obesity-associated metabolic outcomes compared to age-matched men (Lapid et al. 2014). Mechanistically, this might be due to the fact that subcutaneous fat is more insulin sensitive and thus serves an important blood glucose regulatory role. Equally important, this sex difference dissipates with age, when postmenopausal females begin to accumulate more visceral fat in the abdominal region concomitant with the natural cessation of ovarian hormones, including 17-β-estradiol (to be referred to simply as “estrogen” throughout this chapter). Also, in postmenopausal women who experience gains in adiposity with cessation of ovarian hormone production, estrogen replacement reduces visceral, but not subcutaneous fat storage (Mattiasson et al. 2002). Interestingly, despite increasing adipose tissue blood flow similarly in visceral and subcutaneous depots, catecholamine-driven lipolytic activation is greater in intra-abdominal compared to subcutaneous WAT (Enevoldsen et al. 2000). For this reason, exercise is particularly

beneficial in reducing visceral fat and thus improving metabolic syndrome symptoms, such as dyslipidemia. The sex difference in adipose tissue distribution may also help explain why women compared to men are less responsive to exercise training in terms of body fat reduction.

As indicated above, the major sex difference in lipid metabolism and adipose tissue distribution is that lipid metabolism in females drives fat storage in subcutaneous WAT depots with the majority being deposited in lower body regions, whereas males tend to favor central storage of lipid where it can be oxidized more readily (Varlamov et al. 2014). The earliest reports that ovarian hormones, particularly estrogen, can directly affect body fat levels via signaling specifically in adipocytes were from 1978 by Wade and Gray, who found that estrogen binds to a protein receptor in the cytosolic fraction of both white and brown adipose tissue depots (Wade and Gray 1978). It has also been appreciated since the 1980s that estrogen acts directly in the brain to augment food intake and stimulate voluntary exercise and acts directly in adipocytes to decrease LPL activity and therefore limit excess lipid storage in adipose tissue (Wade et al. 1985). The aromatase knockout mouse supports the notion that estrogen loss causes visceral WAT accumulation. In that rodent model in which endogenous estrogens cannot be synthesized, obesity is characterized by significant adipose accumulation in central (i.e., gonadal and intrarenal) depots (Endlich et al. 2013).

The sex difference in body fat content and distribution really begins to manifest during puberty, when increasing estrogen drives accretion of adipose tissue mass in females. Mechanistically, this may be due to an estrogen-mediated stimulation of pre-adipocyte differentiation in adipose tissue (Lapid et al. 2014). This effect of estrogen on adipose tissue development is not surprising since adipose tissue is essential for female reproductive capabilities. The increase in adipose tissue during pubertal development in females is a key factor which determines when reproductive maturity is reached. Notably, whereas a critical adiposity threshold needs to be reached in order for females to reach sexual maturity, this is not true for males. Leptin, a hormone produced and secreted by adipose tissue to be discussed in greater detail later, appears to be critical in this regard and is a powerful example of the importance of adipose tissue as an endocrine organ (Chehab et al. 1997). There is also sexual dimorphism in the effects of excess adipose tissue during development such that it potentiates early pubertal development in young females, whereas the opposite is true in young males where excess adiposity delays puberty (Crocker et al. 2014).

The important role of adipose tissue on female reproductive capabilities is also demonstrated by the fact that even moderate weight loss of 10–15 % of ideal body weight induces amenorrhea. Higher body fat percentage (26–28 %) in mature women has been thought to be necessary for regular ovulatory cycles and may influence reproductive ability in three major ways: (1) directly as adipose tissue is a source of estrogen via aromatization of androgen to estrogen by the aromatase enzyme present in adipose tissue; (2) shifting estrogen metabolism in such a way that influences its potency; (3) indirectly by changing the binding affinity of sex hormone binding globulin which binds estrogen, thus limiting its biological activity (Frisch 1991). It appears that ~22 % body fat is necessary to maintain a regular menstrual cycle

although some have reported regular cycles in athletes with <17 % body fat (Ramos and Warren 1995).

These sex differences in the relationship between adiposity and reproductive development are clearly related to differences in several endocrine factors, arguably the most important of which being estrogen. This is illustrated by the enhancement of body fat gain in the subcutaneous region in early pregnancy (even in the absence of caloric increase), a period characterized by high levels of estrogen (O'Sullivan 2009). Estrogen's ability to enhance efficient fat storage in women is metabolically beneficial in preparation for fertility, fetal development, and lactation. Estrogen's ability to drive efficient fat storage may be in part due to its effect to suppress postprandial lipid oxidation (O'Sullivan et al. 2001). Taken together, estrogen promotes efficient fat storage, especially in subcutaneous depots, and potentiates lower rates of lipid oxidation, thus favoring energy retention in adipose tissue. Estrogen also appears to suppress visceral adipose tissue accumulation by suppressing de novo lipogenesis in this depot. The alpha form of the ER directs the feminizing effects of estrogen, and likely, the propensity toward subcutaneous over visceral fat accumulation. Because this is the potent reproductive form of the ER, it is more highly expressed in female adipose tissue compared to male adipose tissue, whereas ERβ is equally expressed in adipose tissue between sexes. Unfortunately, ERα also mediates the cancer-promoting effects of estrogen (e.g., breast, uterine, and ovarian cancers may be triggered by chronically elevated ER alpha activation). We will now discuss the important and divergent roles played by these specific ER forms.

Role of Estrogen Receptors in Adipose Tissue Metabolism

The multitude of estrogen's effects on physiological and endocrine processes is virtually all mediated via its specific receptors. The best characterized receptors are the alpha and beta forms which are both classical nuclear receptors; it is estrogen receptor alpha (ERα) that is most heavily expressed in adipose tissue and likely modulates some of estrogen's metabolic effects on this tissue. But ERs α and β are expressed throughout the body and brain and ERα is thought to drive many global effects of estrogen, including adipose tissue deposition and fuel partitioning (Rettberg et al. 2014). Although the classical (i.e., genomic) pathway is thought to mediate most of estrogen's actions in the body, it is now known that non-genomic signaling also occurs. Via activation of membrane-bound ERs, estrogen (and possibly other ER ligands) can trigger a signaling cascade including PKA and mitogen-activated protein kinase (MAPK) cascades, which may facilitate cellular nitric oxide production and/or increase glucose transporter (i.e., GLUT4) translocation, thus improving insulin signaling (Wehling et al. 2006). The important role of adipose tissue ERα in mediating effects of estrogen is illustrated by rodent studies involving mice null for this receptor, which experience significant adiposity gains and disturbances in metabolic health. Studies of mutant mice with ERα selectively knocked out of adipose tissue recapitulates the adverse metabolic phenotype induced by removing ovarian

estrogen production, suggesting that many of the adipose tissue-specific adverse effects of estrogen loss are mediated through loss of signaling through this receptor. Indeed, rodent models lacking ERα are more susceptible to obesity, inflammation, and insulin resistance. Moreover, one study showed in aged female mice, that whole-body ERα knockout mice, although fatter than age-matched wild-type and ER beta knockout mice before surgery, did not gain weight following ovariectomy, much unlike the wild-type and ER beta knockout counterparts (Zidon et al. 2020). In terms of mechanism, it was recently shown that ERα is protective on adipocyte mitochondrial function (Zhou et al. 2020), an important component of adipocyte health that protects against adipose tissue inflammation and insulin resistance. Unfortunately, though, as noted above, this form of the ER also mediates estrogen's cancer-promoting actions. Together, these studies demonstrate the metabolically protective role of estrogen, signaling through ERα, in adipose tissue. The well-known sex difference in systemic insulin sensitivity, where premenopausal women have significantly greater sensitivity than age-matched men, is likely driven by enhanced insulin sensitivity of adipose tissue in females; and this is likely mediated, at least in part, by ERα (Davis et al. 2013). Indeed, isolated adipocytes from the intra-abdominal region of females have been shown to have greater sensitivity to insulin compared to those from the same region in males (Kim et al. 2014).

While the vast majority of research attention over the past few decades has been focused on ERα, ERβ is also expressed in adipose tissue. However, unlike ERα, ERβ appears to be expressed at equal abundance in both male and female adipose tissue. Only recently has it been studied for its actions in adipose tissue. This is likely due to early studies showing no robust phenotype secondary to genetic ablation of ERβ. However genetic deletion of ERα, or even fat pad-specific down-regulation, causes obesity and adipocyte hypertrophy (Davis et al. 2013), genetic ablation of ERβ did not seem to robustly affect susceptibility to obesity or cause insulin resistance. However, there may have been technical problems with early ERβ knockout mouse models, which may have prevented conclusive determinations about its physiological role from being made. Since 2010, several animal studies have shown that selective ERβ ligands have obesity-reducing effects (Yepuru et al. 2010; Ponnusamy et al. 2017; Miao et al. 2016; Sasayama et al. 2017; González-Granillo et al. 2020). Together, these preclinical studies indicate that antiobesity effects of selective ERβ ligands may be mediated by enhanced mitochondrial activity in adipocytes. It is possible that, among females, ERβ becomes even more important metabolically following menopause, when estrogen levels are low. That hypothesis is supported by recent rodent work, which demonstrates that lack of ER beta exacerbates the metabolic effects of estrogen depletion (i.e., rodent ovariectomy). It is probable that more emphasis will be placed on targeting ERβ to safely and effectively improve adipocyte health, but the research on this is still in its infancy.

It is well established that exercise training is among the most effective strategies to improve systemic insulin sensitivity. Given the role of ERα in enhancing insulin sensitivity, one study investigated the effect of exercise training on ERα expression in skeletal muscle. Interestingly, that study showed that exercise increased muscle ERα expression, but only in female rats; later work showed this effect to be muscle cell

type specific with increases being most evident in gastrocnemius muscle (Lemoine et al. 2002). Interestingly, even in adult men, exercise has been shown to increase skeletal muscle ERα (Wiik et al. 2005). Whether exercise-mediated changes in ERs are related to its insulin-sensitizing effects has not been addressed but is an intriguing idea. While exercise is thought to mostly improve skeletal muscle insulin sensitivity, data also suggest that exercise enhances adipocyte insulin sensitivity. More studies are necessary to determine if the effects of exercise on adipocyte ERα and ERβ expression are mechanistically linked to its beneficial effects on adipocyte insulin sensitivity and metabolism. One published study performed on male rodents only did not show an increase in adipose tissue ERα (Metz et al. 2016), but a more recent study in male mice showed that, while exercise did not affect adipose tissue ERα, it did significantly increase adipose tissue ERβ beta expression, yet had no effect on ERβ in skeletal muscle or liver (Winn et al. 2019). This may be due to exercise-mediated lipolysis, since other studies have since shown that the lipolytic stimulator and $beta_3$ AR ligand, CL316, 243 also increase ERβ protein expression in adipose tissue (Queathem et al. 2021). While skeletal muscle-specific insulin-sensitizing effects of exercise are well known, the effects of exercise on adipose tissue insulin sensitivity have received less attention. However, there is evidence in female rodents that aerobic fitness improves adipose tissue sensitivity across WAT and BAT depots. Remarkably, the adipose tissue insulin sensitivity difference between high and low-aerobically fit rats in that study was even more robust than that observed in skeletal muscle (Park et al. 2016). The extent to which adipose tissue estrogen signaling affects the insulin-sensitizing role of exercise training on adipose tissue remains largely unknown. But, given the evidence that exercise increases ER expression on adipocytes, and the evidence of the critical role ERs play in adipocyte mitochondrial activity, lend support for an important role of estrogen signaling in exercise-mediated adaptations.

Effects of Exercise and Estrogen on Brown Adipose Tissue (BAT)

While the vast majority of adipose tissue in the human body is WAT, as mentioned earlier, BAT also exists and has received significant attention recently. Until around 2007, it was thought that adult humans did not have physiologically relevant amounts of BAT. However, with new technologies allowing for BAT metabolic detection, now it is known that we do harbor some BAT. Further, although making up only a fraction of total adipose tissue mass, it appears to be very relevant from a metabolic standpoint. Due to its reliance on mitochondrial fatty acid oxidation that occurs in its specialized adipocytes to produce heat, BAT contributes to energy expenditure. In addition, studies have demonstrated that BAT activity also improves glucose homeostasis. While the major stimulus for BAT activity is cold, since the realization that functional BAT exists in adult humans, a growing body of research has investigated alternative mechanisms to activate BAT. This new research emphasis has been

partially driven by the possibility of targeting BAT as an obesity-mitigating therapeutic. The mechanism behind the classic BAT stimulus, cold exposure, involves activation of the sympathetic nervous system (SNS). Upon SNS activation, norepinephrine (NE) is released into the circulation and binds to β-adrenergic receptors on the surface of brown adipocytes. This binding triggers an activation cascade involving G-proteins and adenylate cyclase activation, which ultimately results in lipolysis; the fatty acids released activate UCP-1, which then uncouples oxidative phosphorylation, and produces heat. Simultaneously, NE stimulates BAT glucose uptake—it is the stimulation of glucose uptake that allows positron emission tomography/computed tomography (PET/CT) scan technology to detect BAT activity and it is this technology that allowed for the discovery that human adults have functional BAT.

Falling under the physiological adaptationprinciple of hormesis, low levels of reactive oxygen species (ROS) have been shown to be, not only not detrimental, but *necessary* for the proper thermogenic functioning of BAT (Ro et al. 2015). When chemical antioxidants are over-expressed in BAT adipocytes, UCP-1 expression, and the associated thermogenesis, is suppressed. On the other hand, excessive ROS caused by dysfunctional mitochondria lead to oxidative damage, which impairs proper BAT function. Exercise may act to enhance "mitohormesis." Mitohormesis applies the definition of hormesis (i.e., *the process by which exposure to a low dose of a mild stressor promotes adaptive changes which enhance the capacity to tolerate subsequent stressors*) specifically to the mitochondria, suggesting that mitochondrial stress leads to healthy adaptations allowing the mitochondria to maintain cellular homeostasis upon subsequent stress (Merry and Ristow 2015). Exercise may promote this process by inducing low levels of ROS that then enhance oxidative metabolism. Since exercise stimulates the SNS and catecholamine release (i.e., NE and epinephrine), it has been hypothesized that exercise may activate BAT. That hypothesis was tested in rodent studies. In one such study, mitochondria were harvested from BAT of trained and untrained rats both before and after an exhaustive exercise bout (Gohil et al. 1984). What was found was that exercise actually reduced the oxidative capacity of BAT. However, early animal studies revealed that exercise-trained rats have greater capacity for NE-stimulated BAT thermogenesis (Hirata 1982a, b); that is, those findings suggested that exercise may not activate BAT per se, but may increase its sensitivity to stimulated activity. However, this line of research has produced conflicting results. In fact, several studies using a variety of exercise modalities have reported that exercise training reduces the SNS response in BAT (Richard et al. 1992; Nozu et al. 1992; Yamashita et al. 1993; Larue-Achagiotis et al. 1995). This is quite the opposite of what happens with exercise training in skeletal muscle (Joseph et al. 2006). While some investigators who have reported that BAT thermogenic activity increases following exercise training in mice (Oh-ishi et al. 1996), others have reported an exercise-mediated reduction in BAT thermogenesis (Leblanc et al. 1982). This latter finding perhaps makes more physiological sense, as the authors speculate that an exercise-mediated reduction in thermogenesis would prevent energy wasting. Recent studies have confirmed that latter theory that exercise is more likely to reduce than activate BAT activity. While there is a noticeable gap

in the animal literature on the metabolic effects of BAT between ~1990 and 2007, there has been a resurgence of basic animal studies on BAT activity following the discoveries between the years 2007 and 2009 that human adults indeed harbor thermogenically active BAT (Sanchez-Delgado et al. 2015). It has since been discovered that BAT activity decreases with age, correlates inversely with BMI and obesity, and is greater among premenopausal women compared to age-matched men (Sanchez-Delgado et al. 2015). In a cross-sectional study of adult males, cold-induced BAT activation was significantly lower among exercise-trained compared to weight and sex-matched sedentary controls (Vosselman et al. 2015). A renewed interest in the potential effect of exercise to increase non-exercise thermogenesis came about after a comprehensive study led by Speigelman and colleagues in 2012, in which it was found that exercise induced skeletal muscle secretion of a hormone (irisin) that was shown to increase UCP-1 expression in WAT in humans and animals (Bostrom et al. 2012).

A very interesting observation was made that adipocytes from BAT express ERα and that this receptor is essential for brown adipogenesis. A study of human fetal BAT demonstrated that it expresses both ERα and β, with ERα being the predominant form. This not only suggests that, like WAT, BAT is regulated by estrogens but also implicates estrogen as playing a role in BAT development (Velickovic et al. 2014). Thus, it is perhaps not surprising that females have more BAT than males and that estrogen regulates BAT thermogenesis (Martinez de Morentin et al. 2014). It also appears that there is sexual dimorphism in mitochondrial function of BAT such that female BAT has greater mitochondrial content and is less susceptible to oxidative stress (Nadal-Casellas et al. 2012); these protective characteristics are lost with ovariectomy in rodents and only partially restored with estrogen replacement, suggesting estrogen as well as other ovarian hormones may protect BAT mitochondrial function (Nadal-Casellas et al. 2011). It has been hypothesized that post-ovariectomy weight gain in rodents, and possibly, weight gain postmenopause in humans, is due in part to reduced BAT activity. Interestingly, early evidence cited that estrogen may increase energy expenditure independent of increased physical activity by increasing adaptive thermogenesis in BAT. While not all preclinical studies have supported this hypothesis (Nigro et al. 2014), it is possible that estrogens regulate BAT thermogenesis and that loss of estrogen signaling affects energy homeostasis in part by reducing non-activity energy expenditure via BAT activity (Martinez de Morentin et al. 2014). It is also important to note that estrogen is an antioxidant and increases gene expression of natural antioxidant molecules which may protect adipocytes from mitochondrial oxidative stress. This point will be discussed further in the section to follow.

Mitochondrial Function and Browning of WAT (*Can Exercise and Estrogen Make Fat Cells Fit?*)

While BAT is characteristically the mitochondria-dense depot, all adipocytes contain mitochondria. In fact, mitochondria are essential for many adipocyte functions including lipolysis, triglyceride re-esterification and storage, and adipokine production. And, it has been appreciated since the early 1990s that exercise training induces mitochondrial adaptations in WAT that are similar to those that occur in skeletal muscle (Stallknecht et al. 1991). It appears that the exercise-mediated increase in mitochondrial biogenesis in adipose is driven by catecholaminergic mechanisms. Moreover, "healthy" adipoctyes are known to have highly functional mitochondria, whereas "unhealthy" adipocytes are characterized by a profile of high inflammatory/oxidative stress associated with dysfunctional mitochondria (Vieira-Potter et al. 2015). Thus, it is possible that exercise training enhances adipocyte function in part via its positive effects on adipocyte mitochondria. This may help explain the evidence that exercise training mitigates metabolic dysfunction by enhancing adipocyte differentiation in BAT and/or increasing WAT browning (Xu et al. 2011). A recent elegant study showed that the transplantation of subcutaneous WAT from exercise-trained rodents into sedentary, insulin-resistant rodents led to remarkable improvements in insulin sensitivity in the recipient rodents (Stanford et al. 2013). Moreover, that study showed the increased insulin-stimulated glucose disposal in the recipient mice was not due to increased glucose uptake into the transplanted fat; rather, those mice experienced increased glucose uptake into skeletal muscle and BAT, strongly suggesting an exercise-induced endocrine effect of the WAT. This suggests that exercise may affect the endocrine function of brown and WAT to facilitate systemic metabolic enhancements.

It is well established that exercise upregulates skeletal muscle peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1-α), which is linked to mitochondrial biogenesis, angiogenesis, and fiber-type switching. Moreover, in individuals with type 2 diabetes, skeletal muscle PGC-1α mRNA levels are reduced (Patti et al. 2003), whereas the attenuated levels are restored by various types of exercise ranging from acute to chronic endurance (Summermatter and Handschin 2012). In one study, mice with upregulated PGC-1α were not only resistant to obesity and diabetes but also had a prolonged lifespan (Bostrom et al. 2012). Human white adipocytes transfected with PGC-1α present increased levels of UCP-1, suggesting PGC-1α can remodel WAT into BAT (i.e., browning of WAT) (Tiraby et al. 2003). Importantly, exercise may also increase adipose tissue PGC-1α. One study (Sutherland et al. 2009) demonstrated that 2 h of daily swimming exercise training for a month led to increases in markers of WAT mitochondrial biogenesis such as cytochrome-C oxidase (COXIV) and Core1 expressions and citrate synthase activity, which are all driven by increased PGC-1α and mitochondrial transcription factor A (Tfam). Recently, the newly identified "exercise hormone", irisin (as described above) has received much attention due to its potential browning effect on WAT. The Fndc5 gene stimulated by PGC1-α in exercising muscle forms irisin,

which is secreted into circulation, and stimulates a biological program making WAT more like BAT via upregulated PGC-1α and UCP-1 expression. Spiegelman and Bostrom (Bostrom et al. 2012) demonstrated that exercise (i.e., voluntary wheel running and swimming) in mice drives the subcutaneous and visceral fat pads into a thermogenic gene program (e.g., enhanced mitochondrial content and increased levels of UCP-1 gene expression) via triggering an increase in circulating irisin. Exercise-mediated adaptations in adipose tissue mitochondria appear to require nitric oxide (NO) signaling via an endothelial NO synthase (eNOS)-dependent mechanism. Moreover, it has been suggested that an exercise-mediated increase in eNOS activity may explain its protective effects on adipose tissue immunometabolism (i.e., reduced inflammation, enhanced mitochondrial function, increased sensitivity to antilipolytic effect of insulin), although eliminating eNOS per se does not increase adipose tissue inflammation under sedentary conditions (Jurrissen et al. 2016).

Estrogen may have similar effects on adipocyte mitochondria as those induced by exercise. ERα plays an important role in eNOS regulation (Sun et al. 2016) and may explain estrogen's role in increasing mitochondrial biogenesis (Zhou et al. 2020) and protecting against mitochondrial stress (Duckles and Krause 2011). The newly appreciated effect of exercise to increase adipose tissue ER beta expression, combined with studies showing that activation of ER beta induces adipocyte browning and mitochondrial activity, suggests that both ERs may play important roles, and that estrogen and exercise may work synergistically to improve adipocyte health. In fact, early evidence that genetic manipulation of the ERs using mouse models affects the responsiveness to $beta_3$ AR ligand-induced browning supports this idea. Further, the fact that there are newly appreciated sex differences in the sensitivity to adipose tissue browning, and that these sex differences are dependent on adipose tissue depot (where there are also differences in ER expression levels), further supports a critical role of ER expression in responsiveness to lipolytic stimulation, whether it be through catecholamine or $beta_3$ AR agonist-induction. The relationships between estrogen availability and adaptations to exercise in adipose tissue, and how such relationships may affect sex-specific effects of exercise on adipose tissue health, is an area of investigation that certainly required further exploration.

Roles Played by Exercise and Estrogen in Adiposity Reduction

The importance of exercise and total physical activity on adiposity reduction in states of energy surplus (e.g., obesity) is controversial. Although epidemiological data from the National Weight Control Registry demonstrate that exercise at the quantity of at least 1 h per day is a strong predictor of successful long-term weight loss, some researchers argue that calorie reduction is more effective in inducing an energy deficit resulting in weight loss. Some researchers suggest that exercise in the absence of dietary restriction results in compensatory dietary intake, thereby

mitigating exercise-mediated weight loss (Thomas et al. 2012). From an energy balance standpoint, any net energy deficit (i.e., due to dietary or exercise-mediated deficit) will result in a reduction in adipose (and lean) mass. Accordingly, in order for exercise to reduce total adiposity, it must induce an energy deficit that is not replaced by dietary energy. The direct versus indirect effects of exercise on adiposity are difficult to separate. That is, it is possible that exercise affects adipose tissue both by inducing an energy deficit that triggers mobilization to satisfy that need and by more directly affecting adipocyte metabolism. It does appear that adipocyte lipolysis and skeletal muscle fat oxidation are higher, even during the resting state, following endurance exercise and that protein degradation is downregulated (Vicente-Salar et al. 2015). This suggests that training adaptations may occur in adipose tissue that are unique from the energy deficit effects of exercise. The mitochondrial adaptations in adipose tissue, and enhanced sensitivity to hormone-regulated lipolysis, described in the above sections, would certainly serve as examples of these exercise-specific effects.

In general, exercise training significantly reduces mean adipocyte size and adipocyte lipid content, as well as increases WAT gene expression of important metabolically protective proteins such as GLUT4 and PGC1-α, suggesting that exercise may facilitate exercise-mediated fat mobilization which is necessary for fat loss. On the other hand, in many cases, adipocyte molecular changes that occur with exercise training are independent of any exercise-mediated weight loss (Stanford et al. 2015). One study even showed that exercise training led to significantly greater gene expression changes in subcutaneous WAT compared to exercise-induced changes in skeletal muscle (Stanford et al. 2013). Thus, an important consideration in evaluating the literature on the role of exercise in weight loss is that exercise affects the "quality" of adipose tissue even in instances when exercise training does not lead to total adipose tissue reduction. In this next section, the idea that adipose tissue is an endocrine organ will be discussed in greater detail to allow for a more in-depth investigation of how exercise might affect the "quality" (e.g., regulatory function, insulin sensitivity, inflammation, endocrine role, etc.) of adipose tissue. Further, the idea that sex differences may exist in these attributes of adipose tissue will be discussed, along with a discussion of how the effects of exercise may differ depending on sex and other factors.

Adipose Tissue as an Endocrine Organ Susceptible to Inflammation

Research over the past two decades has revealed the adipose tissue as an immune site harboring a unique collection of cells (Giordano et al. 2014). In fact, mature adipocytes make up only ~50 % of WAT and that the remaining ~50 % comprises the stromal vascular cell (SVC) fraction which includes pre-adipocytes, fibroblasts, immune cells, endothelial cells, and smooth muscle cells (van Harmelen et al. 2005;

Gesta et al. 2007) allowing WAT to serve functions to maintain vascular, metabolic, endocrine, and immunological homeostasis, in addition to energy storage and mobilization. The idea that WAT is little more than a storage depot was challenged in 1994 with the groundbreaking discovery of the hormone leptin (Halaas et al. 1995). Leptin is produced and secreted by adipocytes, and its major role is in regulating whole-body energy balance through its interaction with receptors in the ventral medial region of the hypothalamus (Campfield et al. 1996). While the major role of leptin is to act as a lipostat both suppressing appetite and increasing thermogenesis, it also has a multitude of other effects that span many physiological processes. Importantly, leptin is also at the interface between the body's energy reserves and reproduction, highlighting the vital role that adipose tissue plays in female reproduction (Thong et al. 2000). The first indication of the importance of adipose-derived leptin in reproduction came with the discovery that the few humans born with a genetic defect preventing them from producing leptin are not only obese due to disturbed energy balance regulation, but do not reach sexual maturity. It is now known that leptin receptors are expressed not only in brain but also in human ovaries (Thong et al. 2000) and other tissues. There is also a sexual dimorphism in circulating leptin such that women have greater levels than men, even when the greater total adiposity in women is accounted for. In healthy women, leptin increases during the luteal phase of the menstrual cycle (Thong et al. 2000). Moreover, this rise in leptin parallels ovarian hormones, suggesting a relationship between sex hormones and leptin production, although mechanisms remain unknown. Interestingly, exercise-induced amenorrhea, which is very common among reproductive-aged females undergoing intense training, associates with an absence of diurnal leptin rhythm (Thong et al. 2000) which is accompanied by reduced basal metabolic rate. In amenorrheic athletes, it has been hypothesized that their significantly lower circulating leptin levels are attributed to their low body fat content; however, studies have demonstrated that the lower leptin levels during amenorrhea are not fully accounted for by lower percent body fat, suggesting that another factor is responsible for leptin suppression in these individuals. Other factors that may play a role are low total energy intake and low circulating insulin (which has been shown to increase adipose tissue leptin gene expression). Importantly, exogenous leptin administration alone is not effective in restoring reproductive function in amenorrheic women unless sufficient glucose is available. Clearly, the relationships between reproductive capabilities, metabolism, and leptin are complex and not fully understood.

While low leptin levels associate with amenorrhea, obesity results in high leptin levels which has been shown to be a causative feature of obesity-related breast cancer (Schmidt et al. 2015). Since aromatase enzyme is present in adipose tissue, adipose tissue produces estrogen, which is produced from an androgen precursor. For this reason, adipose tissue is the major tissue responsible for estrogen production postmenopause. Moreover, excess local estrogen production in mammary tissue of obese women is thought to contribute to the increased risk of breast cancer among obese women (Howe et al. 2013).

In addition to leptin, many adipose tissue-derived hormones, cytokines, and chemokines have been discovered and are collectively called "adipokines". The

immunometabolic processes which occur in adipose tissue directly affect somatic metabolic function (Ferrante 2013). Because of this rich immune cell composition which includes adaptive (e.g., B and T lymphocytes) as well as innate immune cells (e.g., macrophages, dendritic cells, mast cells, eosinophils), adipose tissue is now classified as an immune organ, the latest organ to be classified as such (Bloor and Symonds 2014). Modulating adipose tissue inflammation can independently affect whole-body metabolic function (Xu et al. 2013; Ko et al. 2014; Miao et al. 2014).

Chronic inflammation in WAT links obesity with insulin resistance and obesity-related metabolic disease (Osborn and Olefsky 2012). This relationship was first recognized with the discovery that WAT produces and secretes the pro-inflammatory cytokine, tumor necrosis factor (TNF)-α in rodent models of obesity (Hotamisligil et al. 1993). Although, there is evidence of immune cells in WAT as far back as the 1950s (Laqueur and Harrison 1951), with the adipose-derived TNF-α discovery, it was learned that inflammation actually causes insulin resistance in adipose tissue through a mechanism involving inhibition of serine/threonine phosphorylation of the docking protein, insulin receptor substrate (IRS)-1 (Hotamisligil et al. 1993). Other immune cells arising from the WAT including interleukin (IL)-6 (Kern et al. 2001), resistin (Cherneva et al. 2013), IL-1β (Gao et al. 2014), and interferon (IFN)-γ (O'Rourke et al. 2012) also directly modulate insulin sensitivity locally and systemically. Also noteworthy is that adipose tissue secretes not only inflammatory cytokines but also anti-inflammatory and insulin-sensitizing proteins such as adiponectin (Yamauchi et al. 2001) and IL-10 (Speaker et al. 2014). These secretions arise from the adipocytes themselves (e.g., adiponectin, leptin, resistin, visfatin), as well as from other infiltrating and resident immune cells including adipose tissue macrophages (e.g., IL-10, TNF-α) and T lymphocytes (e.g., IFN-γ). It is thought that macrophages , mostly recruited from blood monocytes, are mostly responsible for the inflammatory cytokines present in obese WAT (Weisberg et al. 2003). Research in this area of adipose tissue immune cell production and release has been reviewed extensively (Fain 2006), and it can be concluded that a diverse array of immune cell interactions occurs in WAT that are orchestrated by a growing list of adipose mediated secretions. One of the major conclusions from that body of work is that adipose tissue macrophage phenotype is a key determinant of the inflammatory status of the tissue. Thus, it is important to briefly summarize the concept of macrophage phenotype.

Macrophages have been classically classified into two broad classes based on their secretion profile and surface markers: M1 or "classical" and M2 or "alternative". Newer findings suggest that there are actually many more subgroups (Natoli and Monticelli 2014). It is recognized that macrophages can readily change state based on the local tissue environment (Sorisky et al. 2013). Especially under nutrient dense conditions, inflammatory (i.e., M1) macrophages infiltrate WAT and, like the inflammatory cytokines they secrete, negatively affect insulin resistance. Macrophages and monocytes are present in obese as well as lean WAT (Feuerer et al. 2009), although the prevalence increases with WAT expansion (Weisberg et al. 2003). In fact, it is estimated that ~10 % of the SVC fraction from lean WAT may be made up of macrophages, whereas this number increases to ~40–50 % in obese WAT

(McNelis and Olefsky 2014). The M1 macrophage plays a central role in host defense against bacterial and viral infections (i.e., innate immunity), while the M2 macrophage is associated with anti-inflammatory reactions and plays roles in tissue remodeling, fibrosis, and tumor progression (Natoli and Monticelli 2014); these classical macrophage roles also dictate their function in WAT. While the majority of macrophages present in obese WAT are of the classical M1 phenotype, those present in lean WAT tend to M2 (Feuerer et al. 2009).

Effects of Exercise and Estrogen on Adipose Tissue Inflammation

Certainly, by way of reducing total WAT, exercise can serve to counter obesity-associated WAT inflammation (Tchernof and Despres 2013). However, the anti-inflammatory effects of exercise go beyond simply reducing total adiposity since weight loss-independent, exercise-mediated reductions in WAT inflammation have been documented in humans (Bruun et al. 2006) and rodents (Bradley et al. 2008; Vieira et al. 2009). One study investigated the effects of a 15-week exercise intervention (i.e., 2–3 h of moderate-intensity walking, swimming, or aerobics, 5 days per week) on weight loss, insulin sensitivity, and inflammation (systemic, as well as gene expression in WAT and skeletal muscle biopsy samples) in severely obese subjects (Bruun et al. 2006). Those subjects experienced improvements in insulin sensitivity and reduced systemic inflammation (Bruun et al. 2006). Importantly, that study also found that WAT inflammation decreased with exercise, an effect that was not found in the skeletal muscle. In a similar study with animals, a reduction in WAT gene expression of CD68 and CD14 (macrophage markers) and TNF-α were observed in morbidly obese rats exposed to acute swimming exercise for 12 weeks (Oliveira et al. 2013). Similarly, in obese mice, moderate exercise training (6 or 12 weeks of treadmill running) lowered systemic and as well as WAT inflammation, anti-inflammatory effects that predicted improvements in insulin resistance and hepatic steatosis (Vieira et al. 2009). Another group showed that 6 weeks of voluntary wheel running exercise decreased WAT inflammation in obese mice, even in the presence of high fat diet (Bradley et al. 2008). Likewise, in genetically obese rats, endurance exercise training in combination with the drug, metformin positively altered WAT secretion and plasma concentrations of leptin and IL-10, shifting the WAT toward an anti-inflammatory phenotype (Jenkins et al. 2012). In another study using high fat diet-fed mice by Kawanishi et al., exercise training resulted in a marked reduction in WAT inflammation despite not weight-reducing effect of exercise (Kawanishi et al. 2010). Those authors went on to show that exercise was associated, not only with a reduction in total WAT macrophage content but with an M1 → M2 macrophage phenotype switch, which may help explain its anti-inflammatory effect (Kawanishi et al. 2010). Acute exercise has also been reported to have anti-inflammatory effects in WAT: a mild–moderate

3-h exercise bout reduced inflammation in the epididymal WAT (a major visceral fat depot) of rats as indicated by decreased mRNA levels of inflammatory cytokines including TNF-α and IL-1β. Similar to the study by Kawanishi et al., there was also a switch in macrophage phenotype from pro-inflammatory anti-inflammatory phenotype in that study, suggesting that the mechanism may involve the acute hormonal/physiological/immunological changes associated with exercise (Oliveira et al. 2013).

Exercise may also facilitate interactions between adipocytes and immune cells in adipose tissue, although more studies are necessary in this area. Adipocyte lipolysis was discussed in detail above and it well appreciated that exercise profoundly affects lipolysis, both acutely and perhaps induces chronic adaptations in this regard. Interestingly, macrophages also are capable of undergoing lipolysis, although they exhibit intracellular lipolysis mediated through lipophagy (Singh et al. 2009) unlike adipocytes, which exhibit extracellular lipolysis. These processes may work in concert to regulate lipid trafficking and metabolism (Xu et al. 2013). Mice lacking CGI-58, the lipid droplet-associated protein described above, have dysfunctional lipophagy in macrophages. And downregulation of this protein increased inflammation via inflammasome activation via a mechanism involving macrophage-produced ROS (Miao et al. 2014). Animals lacking CGI-58 also experience a suppression of PPARγ-dependent mitochondrial function, which leads to increased ROS release from mitochondria. That study by Miao et al. demonstrated a PPARγ-mitochondria-ROS-inflammation pathway in macrophages (Miao et al. 2014) and offers a good example of how adipocyte and macrophage function may be united via lipid metabolism pathways. Given the evidence cited above that exercise may improve mitochondrial function in adipose tissue, it is possible that exercise may improve adipose tissue function by limiting inflammation by improving the phenotype of both mitochondria and adipose resident immune cells.

In one study, Rahman and colleagues reported that suppression of the inflammasome NLRP3 was associated with an improved metabolic phenotype in addition to suppression of inflammation. An interesting and unexpected finding from that study was that lower inflammatory activation was also associated with improved adipocyte mitochondrial function. Indeed, mitochondrial dysfunction is emerging as an important trigger of inflammation and oxidative stress in many tissues including WAT. Hahn and coworkers used an adipocyte cell line, 3T3-L1, to elucidate mechanisms by which inflammatory cytokines may affect mitochondrial metabolism. Every pro-inflammatory cytokine investigated in that study, TNF-α, IL-6, and IL-1β, impaired adipocyte mitochondrial function as indicated by reduced gene expression of mitochondrial biogenesis indicators, PGC1α and eNOS. Inflammation also induced mitochondrial fragmentation and dysregulated mitochondrial fusion (Hahn et al. 2014). Since free fatty acids were shown to directly decrease CGI-58 expression in macrophages, via way of enhancing lipolytic regulation, exercise may also reduce the availability of potentially lipotoxic fatty acids which can cause inflammatory macrophage activation and insulin resistance.

Another research study has demonstrated that the transcriptional regulator of fasting lipolysis, IRF4, enhances adipocyte lipolysis and suppresses macrophage

inflammation (Fabrizi et al. 2014); and mice with a myeloid-specific deletion of IRF4 are insulin resistant. Thus, IRF4 may serve as a communication link between adipocytes and macrophages that regulates lipid handling in adipocytes by promoting adipocyte lipolysis while also decreasing classical M1 macrophage activation (Fabrizi et al. 2014). The effects of exercise training on IRF4 remain unknown, but this may serve as another potential mechanism by which exercise enhances lipolytic regulation and reduces inflammation. Saturated free fatty acids have been reported to activate DNA methyltransferase (DNAMT) enzymes (Yang et al. 2014) which may mechanistically link fatty acid exposure to inflammation. DNAMT3b was shown by those researchers to directly methylate PPARλ at its promoter region, thereby leading to M1 macrophage polarization. The trigger may be macrophage ROS production, as ROS led to oxidative damage of phospholipids, protein, and DNA. Thus, cross talk exists between macrophage-derived cytokines and adipocytes, as well as between adipocyte mitochondria and macrophages themselves. This cycle of ROS production and inflammatory activation clearly potentiates inflammatory cascades. On the other hand, enhancing mitochondrial fatty acid oxidation may decrease inflammation. Activation of macrophage AMP-activated protein kinase (AMPK), an important cellular fuel gauge and regulator of lipid metabolism, can significantly abrogate inflammatory signaling events (Filippov et al. 2013). Interestingly, estrogen is also known to activate AMPK (D'Eon et al. 2005) as well as reduce adipose tissue inflammation where exercise has strikingly similar effects (Higa et al. 2014).

Another possible mechanism by which exercise reduces WAT inflammation involves paracrine effects due to proteins secreted into the circulation by skeletal muscle cells (i.e., myokines) upon an exercise stimulus. Similar to adipokines, myokines have been shown to exhibit their effects both locally and peripherally. IL-6 (interleukin-6) is one such recently identified myokine that has shown potential in possessing a protective metabolic role. IL-6 may exert beneficial metabolic effects via enhancement of lipolysis and mitigation of the inflammatory response in WAT (Pedersen and Hojman 2012). Interestingly, IL-6 is commonly secreted by enlarged adipocytes and has been associated with reduced insulin action in WAT and systemically (Fried et al. 1998). However, Pedersen et al. (Petersen and Pedersen 2005) demonstrated that IL-6 may be a protective factor produced by exercising muscle cells and released into the circulation during and after exercise. Indeed, plasma IL-6 level increases exponentially with exercise and is related to exercise intensity, duration, mass muscle recruited, and endurance capacity of an individual. Produced by both type I and II muscle fibers, IL-6 acts to regulate glucose and lipid metabolism. In skeletal muscle, IL-6 activates AMPK and PI3 kinase to enhance glucose uptake and fat oxidation and also exerts effects in a hormone-like fashion affecting other tissues such as liver (e.g., hepatic glucose production) and WAT (e.g., enhanced lipolysis). Notably, IL-6 lessens circulating TNF-α levels, implying an anti-inflammatory role. Starkie et al. (Starkie et al. 2003) used a model of low-grade inflammation established with a low dose of *E. coli* endotoxin administered to healthy individuals. The TNF-α response induced by endotoxin was totally blunted by a 3-h bout of cycling exercise

or an infusion with recombinant human IL-6. Consistent with those multiple beneficial effects, mice with IL-6 deficiency develop obesity and insulin resistance, effects that are reversed with IL-6 administration (Wallenius et al. 2002). Thus, provocation of an increase in muscle IL-6 secretion may help explain some of the metabolic and anti-inflammatory effects of exercise.

Similar to anti-inflammatory effects of myokines during exercise, adipocyte-released adiponectin levels, which are inversely proportional to abdominal fat mass and insulin resistance, significantly increase with both acute and short-term aerobic exercise training (Saunders et al. 2012). Adiponectin inhibits nuclear factor kB (NFkB), an essential transcription factor for the expression of inflammatory and stress-related proteins (Villarreal-Molina and Antuna-Puente 2012). What is counterintuitive is that adiponectin has been shown to stimulate rapid TNF-α secretion in human and mouse macrophages. This, in turn, stimulates IL-10, an anti-inflammatory cytokine, thus creating tolerance to further LPS (lipopolysaccharides) stimulation (Tsatsanis et al. 2005). Thus, regular exercise training may protect against chronic low-grade systemic inflammation as well as adipocyte inflammation via the increased secretion of immunomodulatory factors such as adiponectin from adipocytes, and IL-6 produced by skeletal muscle cells.

WAT browning, which was described above as being associated with improved insulin sensitivity, is also associated with reduced inflammation, offering yet another hypothetical mechanism by which exercise is anti-inflammatory. A possible mechanism between browning and suppressed inflammation may be that PGC-1α directly suppresses ROS in WAT (St-Pierre et al. 2006). ROS are often associated with obesity-associated diseases; they increase oxidative stress and trigger inflammatory cytokine production (St-Pierre et al. 2006). Anti-inflammatory effects of PGC-1α have been demonstrated in vitro using skeletal muscle cell lines. That is, enhanced expression of PGC-1α in C2C12 myotubes suppressed inflammatory cytokine production (Handschin et al. 2007). It is possible that, via upregulation of PGC-1 in WAT, exercise may reduce WAT inflammation, thus constituting another possible anti-inflammatory mechanism.

Quite similar to what happens to adipose tissue with obesity, ovarian estrogen deprivation via ovariectomy induces inflammation in adipose tissue (Vieira-Potter et al. 2012), and this can be effectively mitigated with estrogen replacement (Bluher 2013). Exercise training is equally effective as estrogen replacement in preventing fat gain post-ovariectomy (Endlich et al. 2013) but whether exercise mitigates ovariectomy-induced adipose tissue inflammation does not appear to have been investigated.

Role of Sex in Exercise-Mediated Adipose Tissue Responses

It is well appreciated that there are sex differences in metabolic responses to exercise. During exercise, women utilize proportionally more lipid and less carbohydrate than men, are better preservers of hepatic glycogen, and exhibit lower hepatic

glucose production (Varlamov et al. 2014). Moreover, premenopausal women, when compared to age-matched men, have greater substrate flexibility exemplified by their ability to attenuate use of carbohydrate at high altitude (Braun et al. 2000). The mechanism is thought to involve estrogen-mediated enhancements of adipocyte lipolysis (Braun and Horton 2001). Not surprisingly, WAT from estrogen-sufficient female rodents has greater mitochondrial content, and visceral WAT is more sensitive to lipolytic stimulation and induction of browning (Queathem et al. 2021). Estrogens have been shown to directly suppress triglyceride synthesis by both reducing lipogenesis in liver and increasing WAT lipolysis (Varlamov et al. 2014; Gao et al. 2006). Indeed, lipolysis rates are unequivocally greater in young women compared to age-matched men, with rates of FFA release being ~40 % greater in women than men relative to energy needs and independent of differences in relative rats of fat oxidation (Santosa and Jensen 2015). The sex differential metabolic responses during exercise may be due to differences in sympathetic nerve activity or muscle fiber-type distribution (Varlamov et al. 2014). For example, over 3000 genes are differentially expressed in male and female skeletal muscle. One skeletal muscle sex difference is that females tend to have more slower-twitch fibers; this is thought to be responsible for their increased endurance and greater oxidative capacity (Haizlip et al. 2015). Interestingly, estrogen loss impairs glucose uptake during exercise (Bostrom et al. 2012). In rodents, ovariectomy reduces key oxidative enzymes in skeletal muscle, whereas estrogen replacement prevents this (Campbell and Febbraio 2001).

Aging in both sexes induces a change in body composition characterized by greater adiposity and less lean mass (Calles-Escandon and Poehlman 1997), and age-related physical activity reduction is at least partially responsible for these changes. Alterations in fat oxidation are also a contributing factor; clearly, it is difficult to differentiate cause and effect among the compilation of factors that occur with aging including less relative lean mass, physical inactivity, and hormone changes. Skeletal muscle-specific effects (i.e., age-related sarcopenia) also likely play an important role. Research suggests that female reproductive hormones are permissive to fatty acid oxidation, and their decline during menopause contributes to the reduction in fatty acid metabolism seen in this population. This may help explain the shift in body fat distribution toward an increase in visceral adiposity (Tchernof et al. 1998). In addition, hormone replacement therapy has been shown to reduce visceral adipose tissue postmenopause (Sites et al. 2001). Not surprisingly, exercise training has been shown to be particularly therapeutic and preventative regarding this constellation of risk factors associated with aging in women. In rodents, ovariectomy increases adiposity across depots, whereas both estrogen replacement and exercise prevent these effects (Shinoda et al. 2002).

Summary

The adipose tissue is an essential organ that not only serves as the body's main energy storage reservoir but also fulfills many other essential physiological roles

including but not limited to organ protection, energy balance regulation, neuroendocrine control, immune homeostasis, and thermoregulation. Although the vast majority of adipose tissue in the human body is considered white (i.e., WAT), with its primary function being energy storage in a unified lipid droplet that makes up most of the cell, brown (i.e., BAT) is now known to exist in the adult human, albeit only representing a fraction of total body fat. BAT is different from WAT in that its main function is thermoregulation, which it carries out by producing heat via uncoupling of mitochondrial oxidative phosphorylation. To do this, adipocytes from BAT have a multi-locular phenotype and contain many mitochondria which contain UCP-1; these specialized mitochondria oxidize fatty acids, which are stored in close proximity in the numerous small lipid droplets which surround them. Important sex differences exist in BAT in that females tend to have more of it, and BAT from females tends to be more active than that from males. Interestingly, estrogen receptors are expressed on adipocytes from both WAT and BAT and estrogen is thought to be an important signal required for pre-adipocyte differentiation in both types of fat. WAT is subclassified into visceral and subcutaneous depots, with excess visceral being most metabolically detrimental. Subcutaneous, on the other hand, associates with a healthier overall metabolic phenotype, and estrogen is the major driver of subcutaneous WAT deposition. This may help explain the significantly greater insulin sensitivity among females compared to males. Indeed, despite having greater body fat percentage compared to males, females are more insulin sensitive and this appears consistent across species. Females also tend to be protected against the increase in insulin resistance associated with high fat diet, which appears to be due to estrogen. Postmenopausal women as well as ovariectomized experimental animals develop increased visceral adiposity and severe metabolic dysfunction, whereas premenopausal women characteristically exemplify a gynoid versus android body fat distribution profile.

Adipocyte lipolysis is the major physiological process that occurs in adipose tissue which allows its stored energy to be released for use by other tissues. It is largely driven by the hormonal milieu induced by either fasting or exercise, but estrogen is known to also be a powerful modulator of adipoctye lipolysis. Estrogen's ability to suppress adipocyte lipolysis may explain why it is more difficult for females to reduce total body adiposity with diet and exercise and also why postmenopausal women experience dysregulated lipolysis which associates with the development of insulin resistance. Indeed, women are more sensitive in terms of insulin-mediated suppression of lipolysis (Varlamov et al. 2014).

Most of the established metabolic effects of estrogen on adipose tissue are mediated through its major receptors, ERα and ERβ. Via these receptors, estrogen improves adipose tissue health by reducing inflammation, de novo lipogenesis, and insulin resistance and improving mitochondrial function. Intriguingly, there is much overlap between the beneficial effects of estrogen and exercise on adipose tissue metabolic health and function. But, it is not beneficial among postmenopausal women who experience the negative effects of loss of adipocyte estrogen signaling.

In conclusion, estrogen profoundly affects adipose tissue throughout the lifespan, from its very development in utero, to its function throughout adolescence, the reproductive stage, and aging. While estrogen replacement therapy remains controversial,

most of the negative effects of menopause and/or estrogen loss via ovariectomy in rodents can be minimized or completely rescued with estrogen therapy. While the mechanisms by which exercise and/or estrogen reduce adipose tissue inflammation are not fully understood, one hypothesis is that both may directly affect macrophage phenotype by causing a shift from inflammatory to anti-inflammatory activation (Kawanishi et al. 2010; Toniolo et al. 2015). It is also possible that estrogen signaling enhances mitochondrial activity and function, and improves metabolic flexibility, contributing to more insulin sensitive and less inflamed adipose tissue.

References

Bloor ID, Symonds ME. Sexual dimorphism in white and brown adipose tissue with obesity and inflammation. Horm Behav. 2014;66(1):95–103.

Bluher M. Importance of estrogen receptors in adipose tissue function. Mol Metabol. 2013;2(3):130–2.

Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481(7382):463–8.

Bradley RL, Jeon JY, Liu FF, Maratos-Flier E. Voluntary exercise improves insulin sensitivity and adipose tissue inflammation in diet-induced obese mice. Am J Physiol Endocrinol Metab. 2008;295(3):E586–94.

Braun B, Horton T. Endocrine regulation of exercise substrate utilization in women compared to men. Exerc Sport Sci Rev. 2001;29(4):149–54.

Braun B, Mawson JT, Muza SR, Dominick SB, Brooks GA, Horning MA, et al. Women at altitude: carbohydrate utilization during exercise at 4,300 m. J Appl Physiol (1985). 2000;88(1):246–56.

Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. Am J Physiol Endocrinol Metab. 2006;290(5):E961–7.

Bulow J, Gjeraa K, Enevoldsen LH, Simonsen L. Lipid mobilization from human abdominal, subcutaneous adipose tissue is independent of sex during steady-state exercise. Clin Physiol Funct Imaging. 2006;26(4):205–11.

Calles-Escandon J, Poehlman ET. Aging, fat oxidation and exercise. Aging. 1997;9(1-2):57–63.

Campbell SE, Febbraio MA. Effects of ovarian hormones on exercise metabolism. Curr Opin Clin Nutr Metab Care. 2001;4(6):515–20.

Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. OB protein: a peripheral signal linking adiposity and central neural networks. Appetite. 1996;26(3):302.

Chehab FF, Mounzih K, Lu R, Lim ME. Early onset of reproductive function in normal female mice treated with leptin. Science. 1997;275(5296):88–90.

Cherneva RV, Georgiev OB, Petrova DS, Mondeshki TL, Ruseva SR, Cakova AD, et al. Resistin—the link between adipose tissue dysfunction and insulin resistance in patients with obstructive sleep apnea. J Diab Metab Disord. 2013;12(1):5.

Crocker MK, Stern EA, Sedaka NM, Shomaker LB, Brady SM, Ali AH, et al. Sexual dimorphisms in the associations of BMI and body fat with indices of pubertal development in girls and boys. J Clin Endocrinol Metab. 2014;99(8):E1519–29.

Davis KE, Neinast MD, Sun K, Bills JD, Zehr JA, Zeve D, Hahne LD, et al. The sexually dimorphic role of adipose and adipocyte estrogen receptors in modulating adipose tissue expansion, inflammation, and fibrosis. Mol Metab. 2013;2(3):227–42.

D'Eon TM, Souza SC, Aronovitz M, Obin MS, Fried SK, Greenberg AS. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. J Biol Chem. 2005;280(43):35983–91.

Devries MC. Sex-based differences in endurance exercise muscle metabolism: impact on exercise and nutritional strategies to optimize health and performance in women. Exp Physiol. 2016;101(2):243–9.

Duckles SP, Krause DN. Mechanisms of cerebrovascular protection: oestrogen, inflammation and mitochondria. Acta Physiol (Oxf). 2011;203(1):149–54.

Endlich PW, Claudio ER, da Silva Goncalves WL, Gouvea SA, Moyses MR, de Abreu GR. Swimming training prevents fat deposition and decreases angiotensin II-induced coronary vasoconstriction in ovariectomized rats. Peptides. 2013;47:29–35.

Enevoldsen LH, Stallknecht B, Fluckey JD, Galbo H. Effect of exercise training on in vivo lipolysis in intra-abdominal adipose tissue in rats. Am J Physiol Endocrinol Metab. 2000;279(3):E585–92.

Fabrizi M, Marchetti V, Mavilio M, Marino A, Casagrande V, Cavalera M, et al. IL-21 is a major negative regulator of IRF4-dependent lipolysis affecting Tregs in adipose tissue and systemic insulin sensitivity. Diabetes. 2014.

Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm. 2006;74:443–77.

Ferrante Jr AW. Macrophages, fat, and the emergence of immunometabolism. J Clin Invest. 2013;123(12):4992–3.

Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med. 2009;15(8):930–9.

Filippov S, Pinkosky SL, Lister RJ, Pawloski C, Hanselman JC, Cramer CT, et al. ETC-1002 regulates immune response, leukocyte homing, and adipose tissue inflammation via LKB1-dependent activation of macrophage AMPK. J Lipid Res. 2013;54(8):2095–108.

Foryst-Ludwig A, Kreissl MC, Benz V, Brix S, Smeir E, Ban Z, et al. Adipose tissue lipolysis promotes exercise-induced cardiac hypertrophy involving the lipokine C16:1n7-palmitoleate. J Biol Chem. 2015;290(39):23603–15.

Frayn KN, Shadid S, Hamlani R, Humphreys SM, Clark ML, Fielding BA, et al. Regulation of fatty acid movement in human adipose tissue in the postabsorptive-to-postprandial transition. Am J Physiol. 1994;266(3 Pt 1):E308–17.

Frayn KN, Karpe F, Fielding BA, Macdonald IA, Coppack SW. Integrative physiology of human adipose tissue. Int J Obes Relat Metab Disord. 2003;27(8):875–88.

Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab. 1998;83(3):847–50.

Frisch RE. Body weight, body fat, and ovulation. Trends Endocrinol Metab. 1991;2(5):191–7.

Gao H, Bryzgalova G, Hedman E, Khan A, Efendic S, Gustafsson JA, et al. Long-term administration of estradiol decreases expression of hepatic lipogenic genes and improves insulin sensitivity in ob/ob mice: a possible mechanism is through direct regulation of signal transducer and activator of transcription 3. Mol Endocrinol. 2006;20(6):1287–99.

Gao D, Madi M, Ding C, Fok M, Steele T, Ford C, et al. Interleukin-1beta mediates macrophage-induced impairment of insulin signaling in human primary adipocytes. Am J Physiol Endocrinol Metab. 2014.

Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. Cell. 2007;131(2):242–56.

Giordano A, Smorlesi A, Frontini A, Barbatelli G, Cinti S. White, brown and pink adipocytes: the extraordinary plasticity of the adipose organ. Eur J Endocrinol. 2014;170(5):R159–71.

Gohil K, Henderson S, Terblanche SE, Brooks GA, Packer L. Effects of training and exhaustive exercise on the mitochondrial oxidative capacity of brown adipose tissue. Biosci Rep. 1984;4(11):987–93.

González-Granillo M, Savva C, Li X, et al. Selective estrogen receptor (ER) beta activation provokes a redistribution of fat mass and modifies hepatic triglyceride composition in obese male mice. Mol Cell Endocrinol. 2020;502:110672. https://doi.org/10.1016/j.mce.2019.110672.

Hackney AC, McCracken-Compton MA, Ainsworth B. Substrate responses to submaximal exercise in the midfollicular and midluteal phases of the menstrual cycle. Int J Sport Nutr. 1994;4(3):299–308.

Hahn WS, Kuzmicic J, Burrill JS, Donoghue MA, Foncea R, Jensen MD, et al. Proinflammatory cytokines differentially regulate adipocyte mitochondrial metabolism, oxidative stress, and dynamics. Am J Physiol Endocrinol Metab. 2014;306(9):E1033–45.

Haizlip KM, Harrison BC, Leinwand LA. Sex-based differences in skeletal muscle kinetics and fiber-type composition. Physiology. 2015;30(1):30–9.

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science. 1995;269(5223):543–6.

Handschin C, Choi CS, Chin S, Kim S, Kawamori D, Kurpad AJ, et al. Abnormal glucose homeostasis in skeletal muscle-specific PGC-1alpha knockout mice reveals skeletal muscle-pancreatic beta cell crosstalk. J Clin Invest. 2007;117(11):3463–74.

Hellstrom L, Blaak E, Hagstrom-Toft E. Gender differences in adrenergic regulation of lipid mobilization during exercise. Int J Sports Med. 1996;17(6):439–47.

Higa TS, Spinola AV, Fonseca-Alaniz MH, Evangelista FS. Remodeling of white adipose tissue metabolism by physical training prevents insulin resistance. Life Sci. 2014;103(1):41–8.

Hirata K. Blood flow to brown adipose tissue and norepinephrine- induced calorigenesis in physically trained rats. Jpn J Physiol. 1982a;32(2):279–91.

Hirata K. Enhanced calorigenesis in brown adipose tissue in physically trained rats. Jpn J Physiol. 1982b;32(4):647–53.

Hjemdahl P, Linde B. Influence of circulating NE and Epi on adipose tissue vascular resistance and lipolysis in humans. Am J Physiol. 1983;245(3):H447–52.

Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87–91.

Howe LR, Subbaramaiah K, Hudis CA, Dannenberg AJ. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. Clin Cancer Res. 2013;19(22):6074–83.

Jenkins NT, Padilla J, Arce-Esquivel AA, Bayless DS, Martin JS, Leidy HJ, et al. Effects of endurance exercise training, metformin, and their combination on adipose tissue leptin and IL-10 secretion in OLETF rats. J Appl Physiol. 2012;113(12):1873–83.

Joseph AM, Pilegaard H, Litvintsev A, Leick L, Hood DA. Control of gene expression and mitochondrial biogenesis in the muscular adaptation to endurance exercise. Essays Biochem. 2006;42:13–29.

Jurrissen TJ, Sheldon RD, Gastecki ML, Woodford ML, Zidon TM, Rector RS, et al. Ablation of eNOS does not promote adipose tissue inflammation. Am J Physiol Regul Integr Comp Physiol. 2016;310(8):744–51.

Kawanishi N, Yano H, Yokogawa Y, Suzuki K. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. Exerc Immunol Rev. 2010;16:105–18.

Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280(5):E745–51.

Kim JH, Cho HT, Kim YJ. The role of estrogen in adipose tissue metabolism: insights into glucose homeostasis regulation. Endocr J. 2014;61(11):1055–67.

Ko SH, Lee JK, Lee HJ, Ye SK, Kim HS, Chung MH. 8-Oxo-2'-deoxyguanosine ameliorates features of metabolic syndrome in obese mice. Biochem Biophys Res Commun. 2014;443(2):610–6.

Lambadiari V, Triantafyllou K, Dimitriadis GD. Insulin action in muscle and adipose tissue in type 2 diabetes: the significance of blood flow. World J Diabetes. 2015;6(4):626–33.

Lapid K, Lim A, Clegg DJ, Zeve D, Graff JM. Oestrogen signalling in white adipose progenitor cells inhibits differentiation into brown adipose and smooth muscle cells. Nat Commun. 2014;5:5196.
Laqueur GL, Harrison MB. Glandular adipose tissue associated with cytotoxic suprarenal contraction and diabetes mellitus. Am J Pathol. 1951;27(2):231–45.
Larue-Achagiotis C, Rieth N, Goubern M, Laury MC, Louis-Sylvestre J. Exercise-training reduces BAT thermogenesis in rats. Physiol Behav. 1995;57(5):1013–7.
Leblanc J, Dussault J, Lupien D, Richard D. Effect of diet and exercise on norepinephrine-induced thermogenesis in male and female rats. J Appl Physiol. 1982;52(3):556–61.
Lemoine S, Granier P, Tiffoche C, Berthon PM, Rannou-Bekono F, Thieulant ML, et al. Effect of endurance training on oestrogen receptor alpha transcripts in rat skeletal muscle. Acta Physiol Scand. 2002;174(3):283–9.
Luglio HF. Estrogen and body weight regulation in women: the role of estrogen receptor alpha (ER-alpha) on adipocyte lipolysis. Acta Med Indones. 2014;46(4):333–8.
Martinez de Morentin PB, Gonzalez-Garcia I, Martins L, Lage R, Fernandez-Mallo D, Martinez-Sanchez N, et al. Estradiol regulates brown adipose tissue thermogenesis via hypothalamic AMPK. Cell Metab. 2014;20(1):41–53.
Mattiasson I, Rendell M, Tornquist C, Jeppsson S, Hulthen UL. Effects of estrogen replacement therapy on abdominal fat compartments as related to glucose and lipid metabolism in early postmenopausal women. Horm Metab Res. 2002;34(10):583–8.
McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. Immunity. 2014;41(1):36–48.
Merry TL, Ristow M. Mitohormesis in exercise training. Free Radic Biol Med. 2015;pii:S0891-5849(15)01141-7.
Metz L, Gerbaix M, Masgrau A, Guillet C, Walrand S, Boisseau N, et al. Nutritional and exercise interventions variably affect estrogen receptor expression in the adipose tissue of male rats. Nutr Res. 2016;36(3):280–9.
Miao H, Ou J, Ma Y, Guo F, Yang Z, Wiggins M, et al. Macrophage CGI-58 deficiency activates ROS-inflammasome pathway to promote insulin resistance in mice. Cell Rep. 2014;7(1):223–35.
Miao YF, Su W, Dai YB, et al. An ERbeta agonist induces browning of subcutaneous abdominal fat pad in obese female mice. Sci Rep. 2016;6:38579. https://doi.org/10.1038/srep38579.
Nadal-Casellas A, Proenza AM, Llado I, Gianotti M. Effects of ovariectomy and 17-beta estradiol replacement on rat brown adipose tissue mitochondrial function. Steroids. 2011;76(10-11):1051–6.
Nadal-Casellas A, Bauza-Thorbrugge M, Proenza AM, Gianotti M, Llado I. Sex-dependent differences in rat brown adipose tissue mitochondrial biogenesis and insulin signaling parameters in response to an obesogenic diet. Mol Cell Biochem. 2012;373(1-2):125–35.
Natoli G, Monticelli S. Macrophage activation: glancing into diversity. Immunity. 2014;40(2):175–7.
Nigro M, Santos AT, Barthem CS, Louzada RA, Fortunato RS, Ketzer LA, et al. A change in liver metabolism but not in brown adipose tissue thermogenesis is an early event in ovariectomy-induced obesity in rats. Endocrinology. 2014;155(8):2881–91.
Nozu T, Kikuchi K, Ogawa K, Kuroshima A. Effects of running training on in vitro brown adipose tissue thermogenesis in rats. Int J Biometeorol. 1992;36(2):88–92.
Ogasawara J, Izawa T, Sakurai T, Sakurai T, Shirato K, Ishibashi Y, et al. The molecular mechanism underlying continuous exercise training-induced adaptive changes of lipolysis in white adipose cells. J Obes. 2015;2015:473430.
Oh-ishi S, Kizaki T, Toshinai K, Haga S, Fukuda K, Nagata N, et al. Swimming training improves brown-adipose-tissue activity in young and old mice. Mech Ageing Dev. 1996;89(2):67–78.
Oliveira AG, Araujo TG, Carvalho BM, Guadagnini D, Rocha GZ, Bagarolli RA, et al. Acute exercise induces a phenotypic switch in adipose tissue macrophage polarization in diet-induced obese rats. Obesity. 2013.
O'Rourke RW, White AE, Metcalf MD, Winters BR, Diggs BS, Zhu X, et al. Systemic inflammation and insulin sensitivity in obese IFN-gamma knockout mice. Metabolism. 2012;61(8):1152–61.

Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012;18(3):363–74.
O'Sullivan AJ. Does oestrogen allow women to store fat more efficiently? A biological advantage for fertility and gestation. Obes Rev. 2009;10(2):168–77.
O'Sullivan AJ, Martin A, Brown MA. Efficient fat storage in premenopausal women and in early pregnancy: a role for estrogen. J Clin Endocrinol Metab. 2001;86(10):4951–6.
Park YM, Rector RS, Thyfault JP, Zidon TM, Padilla J, Welly RJ, et al. Effects of ovariectomy and intrinsic aerobic capacity on tissue-specific insulin sensitivity. Am J Physiol Endocrinol Metab. 2016;310(3):190–9.
Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. Proc Natl Acad Sci U S A. 2003;100(14):8466–71.
Pedersen L, Hojman P. Muscle-to-organ cross talk mediated by myokines. Adipocyte. 2012;1(3):164–7.
Peirce V, Carobbio S, Vidal-Puig A. The different shades of fat. Nature. 2014;510(7503):76–83.
Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005;98(4):1154–62.
Ponnusamy S, Tran QT, Harvey I, et al. Pharmacologic activation of estrogen receptor beta increases mitochondrial function, energy expenditure, and brown adipose tissue. FASEB J. 2017;31(1):266–81. https://doi.org/10.1096/fj.201600787RR.
Queathem ED, Welly RJ, Clart LM, et al. White adipose tissue depots respond to chronic beta-3 adrenergic receptor activation in a sexually dimorphic and depot divergent manner. Cells. 2021;10(12). https://doi.org/10.3390/cells10123453.
Ramos RH, Warren MP. The interrelationships of body fat, exercise, and hormonal status and their impact on reproduction and bone health. Semin Perinatol. 1995;19(3):163–70.
Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol. 2014;35(1):8–30.
Richard D, Labrie A, Rivest S. Tissue specificity of SNS response to exercise in mice exposed to low temperatures. Am J Physiol. 1992;262(5 Pt 2):R921–5.
Ro SH, Semple I, Ho A, Park HW, Lee JH. Sestrin2, a regulator of thermogenesis and mitohormesis in brown adipose tissue. Front Endocrinol (Lausanne). 2015;6:114.
Sanchez-Delgado G, Martinez-Tellez B, Olza J, Aguilera CM, Gil A, Ruiz JR. Role of exercise in the activation of brown adipose tissue. Ann Nutr Metab. 2015;67(1):21–32.
Santosa S, Jensen MD. The sexual dimorphism of lipid kinetics in humans. Front Endocrinol (Lausanne). 2015;6:103.
Sasayama D, Sugiyama N, Yonekubo S, et al. Novel oestrogen receptor beta-selective ligand reduces obesity and depressive-like behaviour in ovariectomized mice. Sci Rep. 2017;7(1):4663. https://doi.org/10.1038/s41598-017-04946-5.
Saunders TJ, Palombella A, McGuire KA, Janiszewski PM, Despres JP, Ross R. Acute exercise increases adiponectin levels in abdominally obese men. J Nutr Metabol. 2012;2012:148729.
Schmidt S, Monk JM, Robinson LE, Mourtzakis M. The integrative role of leptin, oestrogen and the insulin family in obesity-associated breast cancer: potential effects of exercise. Obes Rev. 2015;16(6):473–87.
Shimizu I, Aprahamian T, Kikuchi R, Shimizu A, Papanicolaou KN, MacLauchlan S, et al. Vascular rarefaction mediates whitening of brown fat in obesity. J Clin Invest. 2014;124(5):2099–112.
Shinoda M, Latour MG, Lavoie JM. Effects of physical training on body composition and organ weights in ovariectomized and hyperestrogenic rats. Int J Obes Relat Metab Disord. 2002;26(3):335–43.
Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, et al. Autophagy regulates lipid metabolism. Nature. 2009;458(7242):1131–5.
Sites CK, Brochu M, Tchernof A, Poehlman ET. Relationship between hormone replacement therapy use with body fat distribution and insulin sensitivity in obese postmenopausal women. Metabolism. 2001;50(7):835–40.

Sorisky A, Molgat AS, Gagnon A. Macrophage-induced adipose tissue dysfunction and the preadipocyte: should I stay (and differentiate) or should I go? Adv Nutr. 2013;4(1):67–75.
Speaker KJ, Cox SS, Paton MM, Serebrakian A, Maslanik T, Greenwood BN, et al. Six weeks of voluntary wheel running modulates inflammatory protein (MCP-1, IL-6, and IL-10) and DAMP (Hsp72) responses to acute stress in white adipose tissue of lean rats. Brain Behav Immun. 2014;39:87–98.
Stallknecht B, Vinten J, Ploug T, Galbo H. Increased activities of mitochondrial enzymes in white adipose tissue in trained rats. Am J Physiol. 1991;261(3 Pt 1):E410–4.
Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest. 2013;123(1):215–23.
Stanford KI, Middelbeek RJ, Goodyear LJ. Exercise effects on white adipose tissue: beiging and metabolic adaptations. Diabetes. 2015;64(7):2361–8.
Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. FASEB J. 2003;17(8):884–6.
St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jager S, et al. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell. 2006;127(2):397–408.
Strawford A, Antelo F, Christiansen M, Hellerstein MK. Adipose tissue triglyceride turnover, de novo lipogenesis, and cell proliferation in humans measured with ^2H_2O. Am J Physiol Endocrinol Metab. 2004;286(4):E577–88.
Summermatter S, Handschin C. PGC-1alpha and exercise in the control of body weight. Int J Obes (Lond). 2012;36(11):1428–35.
Sun T, Cao L, Ping NN, Wu Y, Liu DZ, Cao YX. Formononetin upregulates nitric oxide synthase in arterial endothelium through estrogen receptors and MAPK pathways. J Pharm Pharmacol. 2016;68(3):342–51.
Sutherland LN, Bomhof MR, Capozzi LC, Basaraba SA, Wright DC. Exercise and adrenaline increase PGC-1{alpha} mRNA expression in rat adipose tissue. J Physiol. 2009;587(Pt 7):1607–17.
Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359–404.
Tchernof A, Calles-Escandon J, Sites CK, Poehlman ET. Menopause, central body fatness, and insulin resistance: effects of hormone-replacement therapy. Coron Artery Dis. 1998;9(8):503–11.
Thomas DM, Bouchard C, Church T, Slentz C, Kraus WE, Redman LM, et al. Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. Obes Rev. 2012;13(10):835–47.
Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. Physiol Rev. 2012;92(1):157–91.
Thong FS, McLean C, Graham TE. Plasma leptin in female athletes: relationship with body fat, reproductive, nutritional, and endocrine factors. J Appl Physiol. 2000;88(6):2037–44.
Tiraby C, Tavernier G, Lefort C, Larrouy D, Bouillaud F, Ricquier D, et al. Acquirement of brown fat cell features by human white adipocytes. J Biol Chem. 2003;278(35):33370–6.
Toniolo A, Fadini GP, Tedesco S, Cappellari R, Vegeto E, Maggi A, et al. Alternative activation of human macrophages is rescued by estrogen treatment in vitro and impaired by menopausal status. J Clin Endocrinol Metab. 2015;100(1):E50–8.
Tsatsanis C, Zacharioudaki V, Androulidaki A, Dermitzaki E, Charalampopoulos I, Minas V, et al. Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. Biochem Biophys Res Commun. 2005;335(4):1254–63.
van Harmelen V, Skurk T, Hauner H. Primary culture and differentiation of human adipocyte precursor cells. Methods Mol Med. 2005;107:125–35.
Varlamov O, Bethea CL, Roberts Jr CT. Sex-specific differences in lipid and glucose metabolism. Front Endocrinol (Lausanne). 2014;5:241.

Velickovic K, Cvoro A, Srdic B, Stokic E, Markelic M, Golic I, et al. Expression and subcellular localization of estrogen receptors alpha and beta in human fetal brown adipose tissue. J Clin Endocrinol Metab. 2014.

Vicente-Salar N, Urdampilleta Otegui A, Roche CE. Endurance training in fasting conditions: biological adaptations and body weight management. Nutr Hosp. 2015;32(n06):2409–20.

Vieira Potter VJ, Strissel KJ, Xie C, Chang E, Bennett G, Defuria J, et al. Adipose tissue inflammation and reduced insulin sensitivity in ovariectomized mice occurs in the absence of increased adiposity. Endocrinology. 2012;153(9):4266–77.

Vieira VJ, Valentine RJ, Wilund KR, Antao N, Baynard T, Woods JA. Effects of exercise and low-fat diet on adipose tissue inflammation and metabolic complications in obese mice. Am J Physiol Endocrinol Metab. 2009;296(5):E1164–71.

Vieira-Potter VJ, Zidon TM, Padilla J. Exercise and estrogen make fat cells "Fit". Exerc Sport Sci Rev. 2015;43(3):172–8.

Villarreal-Molina MT, Antuna-Puente B. Adiponectin: anti-inflammatory and cardioprotective effects. Biochimie. 2012;94(10):2143–9.

Vosselman MJ, Hoeks J, Brans B, Pallubinsky H, Nascimento EB, van der Lans AA, et al. Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. Int J Obes (Lond). 2015;39(12):1696–702.

Wade GN, Gray JM. Cytoplasmic 17 beta-[3H]estradiol binding in rat adipose tissues. Endocrinology. 1978;103(5):1695–701.

Wade GN, Gray JM, Bartness TJ. Gonadal influences on adiposity. Int J Obes. 1985;9 Suppl 1:83–92.

Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL, et al. Interleukin-6-deficient mice develop mature-onset obesity. Nat Med. 2002;8(1):75–9.

Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab. 2009;297(2):E271–88.

Wehling M, Schultz A, Losel R. Nongenomic actions of estrogens: exciting opportunities for pharmacology. Maturitas. 2006;54(4):321–6.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796–808.

Wiik A, Gustafsson T, Esbjornsson M, Johansson O, Ekman M, Sundberg CJ, et al. Expression of oestrogen receptor alpha and beta is higher in skeletal muscle of highly endurance-trained than of moderately active men. Acta Physiol Scand. 2005;184(2):105–12.

Winn NC, Jurrissen TJ, Grunewald ZI, et al. Estrogen receptor-alpha signaling maintains immunometabolic function in males and is obligatory for exercise-induced amelioration of nonalcoholic fatty liver. Am J Physiol Endocrinol Metab. 2019;316(2):E156–67. https://doi.org/10.1152/ajpendo.00259.2018.

Wohlers LM, Spangenburg EE. 17beta-estradiol supplementation attenuates ovariectomy-induced increases in ATGL signaling and reduced perilipin expression in visceral adipose tissue. J Cell Biochem. 2010;110(2):420–7.

Xu X, Ying Z, Cai M, Xu Z, Li Y, Jiang SY, et al. Exercise ameliorates high-fat diet-induced metabolic and vascular dysfunction, and increases adipocyte progenitor cell population in brown adipose tissue. Am J Physiol Regul Integr Comp Physiol. 2011;300(5):R1115–25.

Xu X, Grijalva A, Skowronski A, van Eijk M, Serlie MJ, Ferrante Jr AW. Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. Cell Metab. 2013;18(6):816–30.

Yamashita H, Yamamoto M, Sato Y, Izawa T, Komabayashi T, Saito D, et al. Effect of running training on uncoupling protein mRNA expression in rat brown adipose tissue. Int J Biometeorol. 1993;37(1):61–4.

Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7(8):941–6.

Yang X, Wang X, Liu D, Yu L, Xue B, Shi H. Epigenetic regulation of macrophage polarization by DNA methyltransferase 3b. Mol Endocrinol. 2014;28(4):565–74.

Yepuru M, Eswaraka J, Kearbey JD, et al. Estrogen receptor-{beta}-selective ligands alleviate high-fat diet- and ovariectomy-induced obesity in mice. J Biol Chem. 2010;285(41):31292–303. https://doi.org/10.1074/jbc.M110.147850.

Zhou Z, Moore TM, Drew BG, Ribas V, Wanagat J, Civelek M, et al. Estrogen receptor α controls metabolism in white and brown adipocytes by regulating Polg1 and mitochondrial remodeling. Sci Transl Med. 2020;12(555):eaax8096.

Chapter 4
Sex Hormones and Their Impact on the Respiratory Responses to Exercise and the Environment

Maren K. Porter and Joseph W. Duke

Abbreviations

$A\text{-}aDO_2$	Alveolar-to-arterial difference in PO_2
SaO_2	Arterial O_2 saturation
pH	Blood acidity
BSA	Body surface area
fb	Breathing frequency
CO_2	Carbon dioxide
EELV	End-expiratory lung volume
EILV	End-inspiratory lung volume
$P_{ET}CO_2$	End-tidal partial pressure of CO_2
FP	Follicular phase
HCVR	Hypercapnic ventilatory response
HVR	Hypoxic ventilatory response
LP	Luteal phase
MPA	Medroxyprogesterone
OC	Oral contraceptives
O_2	Oxygen
$PaCO_2$	Partial pressure of CO_2 in arterial blood
PaO_2	Partial pressure of O_2 in arterial blood
PAO_2	Partial pressure of O_2 in the alveolus
VO_2	Peak, peak aerobic capacity
Pb	Power of breathing
V_T	Tidal volume
Wb	Work of breathing

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Introduction

The respiratory system plays an integral role in the first two steps of the oxygen (O_2) transport system. Specifically, it is responsible for the bulk flow of atmospheric air into the lungs and then diffusion of O_2 from alveoli into the pulmonary capillary blood, thereby maintaining a sufficiently high arterial partial pressure of O_2 (PaO_2). Additionally, the respiratory system plays a prominent role in regulating the partial pressure of carbon dioxide ($PaCO_2$) in the arterial blood, as well as maintaining blood acidity, i.e., pH. These objectives are accomplished by choosing an ideal breathing pattern, i.e., tidal volume and breathing frequency, and operating lung volumes, i.e., end-expiratory, and end-inspiratory lung volumes, such that the processes are as energetically efficient as possible. The respiratory system is also intimately linked with the cardiovascular system and pulmonary vascular pressure, and resistance must remain low to keep right heart work low and prevent damage to the alveolar-capillary blood gas interface. Damage to this interface would inevitably have a negative impact on the respiratory system's diffusive ability.

This system is highly integrated and tightly regulated within a narrow range under a variety of physiologic conditions. Aerobic exercise using a significant proportion of total body mass (e.g., running or cycling) significantly increases O_2 demand, which results in compensatory changes to increase O_2 transport. Simulated or natural terrestrial environments like high altitude or hypo- or hyperthermia also place challenges on O_2 transport and delivery which are met by altering respiratory system activity. There are an infinite number of physiologic and pathophysiologic factors that alter, transiently or permanently, the responses of the respiratory system. These factors may also positively or negatively impact the system's ability to function in its primary roles described above. To this end, there are also a number of neurochemical factors—hormones and neurotransmitters—altered naturally or pharmacologically, which are known to interact with and affect the respiratory system. Specific to this chapter is the role of sex hormones, i.e., progesterone and estrogen, which vary throughout the menstrual cycle with and without oral contraceptive (OC) use in women that may affect respiratory function. It is possible (and likely) that the normal variations in progesterone and estrogen, via a naturally occurring menstrual cycle or from OC use, in women alters ventilatory responses to exercise and/or in response to changes in PaO_2 and $PaCO_2$ and/or airway function. Understanding these influences would be of great interest to scientists and clinicians working in the respiratory physiology area. Table 4.1 provides an overview of the hypothesized or confirmed effects of altered sex hormones; i.e., progesterone and estrogen, on aspects of respiratory function.

Accordingly, this chapter reviews the pertinent scientific and clinical literature investigating the effects of sex hormones in women, specifically estrogens and progestogens, on various parameters of the respiratory system. Unfortunately, much of this work is yet to be done; therefore, differences between men and women will also be briefly discussed herein. Table 4.2 outlines some important sex-based differences in respiratory structure and function that largely drive the differing physiology. Because it is the sex hormone progesterone that likely mediates critical changes in

Table 4.1 Overview of the impact of sex hormones on respiratory function at rest and during exercise

	Luteal phase	Follicular phase	Supporting references	Dissenting references
Physiology	Progesterone at highest concentration	Progesterone at lowest concentration	–	–
	Estrogen at lower concentration than at late-follicular phase/ovulation	Estrogen at higher concentration than at late-follicular phase/ovulation	–	–
Impact on respiration	Greater ventilation at rest	Lower ventilation at rest	(Das 1998; MacNutt et al. 2012; Schoene et al. 1981; Takano 1984; Takano et al. 1981; Williams and Krahenbuhl 1997)	(Beidleman et al. 1999; da Silva et al. 2006; Freemas et al. 2020; Hackney et al. 1991; Lebrun 1993; Matsuo et al. 2003; Regensteiner et al. 1990; Smekal et al. 2007; White et al. 1983)
	Greater ventilation at exercise	Lower ventilation at exercise	(Schoene et al. 1981; Williams and Krahenbuhl 1997)	(Beidleman et al. 1999; Bryner et al. 1996; Casazza et al. 2002; De Souza et al. 1990; Dombovy et al. 1987; Freemas et al. 2020; Hackney et al. 1991; Lebrun 1993; Lebrun et al. 2003; Matsuo et al. 2003; Regensteiner et al. 1990; Smekal et al. 2007)

(continued)

Table 4.1 (continued)

	Luteal phase	Follicular phase	Supporting references	Dissenting references
	Greater hypoxic ventilatory response[a]	Lesser hypoxic ventilatory response	(Schoene et al. 1981; Takano 1984; White et al. 1983)	(Beidleman et al. 1999; Dombovy et al. 1987; MacNutt et al. 2012; Regensteiner et al. 1990)
	Greater hypercapnic ventilatory response[a]	Lower hypercapnic ventilatory response	(Byrne-Quinn et al. 1971; Dombovy et al. 1987; Dutton et al. 1989; Harms and Stager 1995; Martin et al. 1978; Schoene et al. 1981; Williams and Krahenbuhl 1997)	(Beidleman et al. 1999; MacNutt et al. 2012; Regensteiner et al. 1990; Slatkovska et al. 2006; Takano et al. 1981; White et al. 1983)
	Lower CO_2 threshold	Higher CO_2 threshold	(Beidleman et al. 1999; MacNutt et al. 2012)	(Dombovy et al. 1987; Dutton et al. 1989; Regensteiner et al. 1990; Slatkovska et al. 2006; Takano et al. 1981)
Overall implications	Greater Wb and Pb at rest and exercise	Lesser Wb and Pb at rest and exercise	–	

Review of the hypothesized and confirmed changes in respiratory responses as a result of changing sex hormone concentrations
[a]Exaggerated changes in athletes
See list of abbreviations at beginning of chapter for definitions

ventilatory drive, nearly all studies described here compare ventilatory parameters only between the luteal and follicular phases because this is when progesterone is at its highest and lowest, respectively, i.e., when the effect would be its greatest. In this chapter, we will discuss the following major areas: ventilation at rest and in response to exercise, breathing patterns and respiratory mechanics at rest and during exercise, pulmonary gas exchange efficiency, and ventilatory chemoresponsiveness. Within each section, we will discuss sex differences, the impact of changes in sex hormones, i.e., across the menstrual cycle, and the effect of OC use if data are available.

Other chapters in this book outline, in detail, the changes in sex hormones during a normal menstrual cycle as well as with OC use. Therefore, the reader is referred to that chapter for specific information on those topics.

Table 4.2 Overview of respiratory structural and functional differences between men and women

	Female	Male	Supporting references	Dissenting references
Anatomical difference	Smaller lungs	Larger lungs	(Miller et al. 2005; Quanjer et al. 2012)	–
	Smaller central airways	Larger central airways	(Dominelli et al. 2018; Peters et al. 2020, 2021; Sheel et al. 2009)	–
	Prismatic rib cage/lung shape	Pyramidal rib cage/lung shape	(Bellemare and Jeanneret 2006; García-Martínez et al. 2016, 2019; Torres-Tamayo et al. 2018)	–
	Less alveoli	More alveoli	–	–
Physiologic differences	Lesser ventilation during exercise	Greater ventilation during exercise	(Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2004, 2009; MacNutt et al. 2012; Matsuo et al. 2003; Molgat-Seon et al. 2018a, 2018b, 2019; Olfert et al. 2004; Peters et al. 2021; Wilkie et al. 2015); Fig. 4.1	–
	Greater intrathoracic pressure generation during exercise	Lesser intrathoracic pressure generation during exercise	(Dominelli et al. 2015b)	–
	Increased fb for matched ventilation at rest	Decreased fb for matched ventilation at rest	(Guenette et al. 2009; Molgat-Seon et al. 2018b)	(Bryner et al. 1996; Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Mitchell et al. 2018; Peters et al. 2021; Wilkie et al. 2015)

(continued)

Table 4.2 (continued)

	Female	Male	Supporting references	Dissenting references
	Decreased V_T for matched ventilation	Increased V_T for matched ventilation	(Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2009; Mitchell et al. 2018; Molgat-Seon et al. 2018b; Peters et al. 2021; Wilkie et al. 2015), Fig. 4.1	–
	Greater EELV and EILV during exercise	Lesser EELV and EILV during exercise	(Dominelli et al. 2015a; Guenette et al. 2007); Fig. 4.2a, b	(Cory et al. 2015; Dominelli et al. 2015b, 2017; Mitchell et al. 2018; Molgat-Seon et al. 2018b; Peters et al. 2021)
	Greater Pb during exercise at or above 50 L/min	Lesser Pb during exercise at or above 50L/min	(Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2007, 2009; Mann et al. 2020; Molgat-Seon et al. 2018b; Peters et al. 2021); Fig. 4.3	–
	Greater A-aDO_2 during near-maximal exercise	Lesser A-aDO_2 during near-maximal exercise	(Dominelli et al. 2013; Harms et al. 1998); Fig. 4.4a, b	(Duke et al. 2014, 2020; Hopkins et al. 2000; Olfert et al. 2004)
	EIAH induction at lower exercise intensities	EIAH induction at higher exercise intensities	(Dominelli et al. 2013; Harms et al. 1998)	–
	Lower CO_2 threshold	Greater CO_2 threshold	(Beidleman et al. 1999; MacNutt et al. 2012)	–
	Lower hypercapnic ventilatory response	Greater hypercapnic ventilatory response	(MacNutt et al. 2012; White et al. 1983)	(Aitken et al. 1986; Rebuck et al. 1973)

Review of the hypothesized and confirmed impacts of biological sex on respiratory structure and function in adult humans
See list of abbreviations at beginning of chapter for definitions

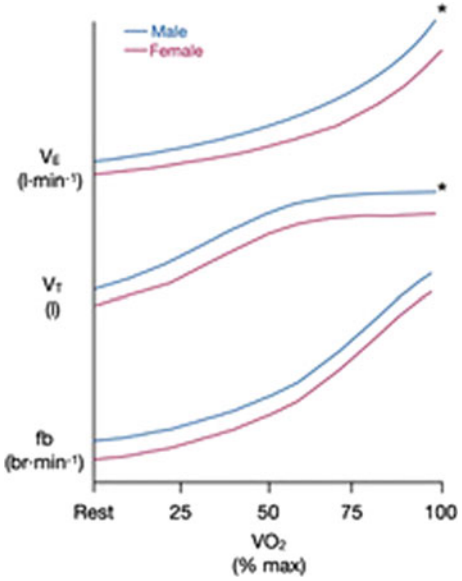

Fig. 4.1 Ventilation and ventilatory patterns at rest and during exercise. Ventilation (V_E) increases linearly during exercise in both men (blue) and women (purple) until the ventilatory threshold is reached. Thereafter, V_E increases curvilinearly with increasing exercise intensity. There is no difference in V_E between men and women at rest and during mild- and moderate-intensity exercise. However, men have a greater V_E during high-intensity and maximal exercise (*). Tidal volume (V_T) increases linearly during exercise until the volume reaches approximately 60% of one's vital capacity and plateaus thereafter. There is no effect of sex on V_T at rest, but men have a greater V_T during exercise for a given level of V_E. Breathing frequency (fb) increases linearly with exercise until the ventilatory threshold is reached. Thereafter, there is an approximately curvilinear increase. There is no difference between men and women on fb at rest or during exercise. This figure was adapted from previous work (Dominelli and Molgat-Seon 2022)

Effect of Sex and Sex Hormones on Resting and Exercise Ventilatory Parameters

Rest and Exercise Ventilation

Effect of Sex

The impact of sex on respiratory structure and function is well known with there being a variety of differences in respiratory system morphology (Dominelli and Molgat-Seon 2022; LoMauro and Aliverti 2018). The important differences include women having smaller lungs than men, even when corrected for height (Miller et al. 2005; Quanjer et al. 2012) and having smaller central airways, i.e., trachea to ~ fifth generation bronchi, (Dominelli et al. 2018; Peters et al. 2020, 2021; Sheel et al. 2009).

Additionally, thoracic geometry appears to differ between men and women. Women appear to have a more "prismatic" rib cage and lung shape with men having a more "pyramidal" rib cage and lung shape (Bellemare and Jeanneret 2006; García-Martínez et al. 2016, 2019; Torres-Tamayo et al. 2018). Further discussion of these differences is beyond the scope of the current chapter, but the interested reader is referred to our colleagues' excellent reviews on the topic (Dominelli and Molgat-Seon 2022; Dominelli et al. 2019). The relevance of these sex-based morphometric differences in the respiratory system is that they are, largely, the basis for all sex-based differences in ventilation at rest and the ventilatory responses to exercise. Additionally, they serve as the foundation for altered responses and functionality resulting from variations in sex hormones across the menstrual cycle and/or OC use.

Previous work comparing resting ventilation between men and women has been equivocal with some reporting no difference (Duke et al. 2014, 2020; Guenette et al. 2004; Matsuo et al. 2003; Olfert et al. 2004; Sébert 1983; White et al. 1983) and others reporting that women have lower resting ventilation (MacNutt et al. 2012). Figure 4.1 provides an overview of ventilation at rest and during exercise between men and women. Regardless of whether resting ventilation was statistically different between men and women, most studies have reported a difference of only 1–4 L/min (Duke et al. 2014, 2020; Guenette et al. 2004; MacNutt et al. 2012; Matsuo et al. 2003; Olfert et al. 2004; Sébert 1983; White et al. 1983), which would have a physiologically meaningless impact on respiratory muscle energetics. Body surface area (BSA) affects the metabolic rate, i.e., oxygen consumption (VO_2) and carbon dioxide (CO_2) production, which in turn would have an effect on ventilation at rest, so it may be more appropriate to express ventilation, at rest or during exercise, corrected for BSA. When done, the differences in resting ventilation between men and women are either reduced (Sébert 1983; White et al. 1983) or completely abolished (Guenette et al. 2004; MacNutt et al. 2012).

On the contrary, there is a clear consensus on the difference in ventilation during severe and/or maximal exercise between men and women with men having greater ventilation than women (Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2004, 2009; MacNutt et al. 2012; Matsuo et al. 2003; Molgat-Seon et al. 2018a, 2018b, 2019; Olfert et al. 2004; Peters et al. 2021; Wilkie et al. 2015) (Fig. 4.1). Again, correcting ventilation during exercise for BSA narrows the difference between men and women, but to a much lesser extent than during rest (Cory et al. 2015; Dominelli et al. 2015a, 2015b; Guenette et al. 2004, 2009; MacNutt et al. 2012; Olfert et al. 2004; Wilkie et al. 2015). The underlying cause for the lower ventilation during maximum exercise in women is due to several contributing factors. The primary cause for this difference is lung size, with men having larger lungs than women. However, there is a clear effect of sex on airway diameter such that the smaller airways lead to a greater airflow resistance and, thus, lesser airflow. This makes it difficult for most women to match the ventilation of their male counterparts without generating extraordinarily high intrathoracic pressures, which would be energetically costly (see below). As it is, women do generate greater intrathoracic pressures than men during exercise and still have significantly lower ventilation (Dominelli et al. 2015b).

Effect of Sex Hormones

As described above, experimentally, progesterone is a ventilatory stimulant, so it stands to reason that the normal fluctuations in progesterone that occur throughout the normal menstrual cycle would affect resting and exercise ventilation such that ventilation under any condition would be highest during the luteal phase (LP) and lowest in the follicular phase (FP). The effect of the menstrual cycle phase, i.e., sex hormones, on resting ventilation has been extensively studied, but there is a lack of agreement in the current literature. Several studies have demonstrated greater ventilation at rest during the LP compared to the FP (Das 1998; MacNutt et al. 2012; Schoene et al. 1981; Takano 1984; Takano et al. 1981; Williams and Krahenbuhl 1997), while others observed no difference between these phases (Beidleman et al. 1999; da Silva et al. 2006; Freemas et al. 2020; Hackney et al. 1991; Lebrun 1993; Matsuo et al. 2003; Regensteiner et al. 1990; Smekal et al. 2007; White et al. 1983). Precisely why these findings conflict could be due to a multitude of factors including, but not limited to, training status, research/exercise protocol used, and how the menstrual cycle was monitored, which would impact the researchers' ability to accurately determine what menstrual cycle phase a woman was in such that some could have failed to study individuals when progesterone was at its absolute highest or lowest.

The consensus on the effect of the menstrual cycle phase on ventilation during near-maximal or maximal exercise is that there is no effect (Beidleman et al. 1999; Bryner et al. 1996; Casazza et al. 2002; De Souza et al. 1990; Dombovy et al. 1987; Freemas et al. 2020; Hackney et al. 1991; Lebrun 1993; Lebrun et al. 2003; Matsuo et al. 2003; Regensteiner et al. 1990; Smekal et al. 2007). However, a recent study demonstrated that ventilation was greater during exercise at 10% below the gas exchange threshold during the LP compared to the FP (Freemas et al. 2020), but this difference was ~ 3 L/min. The lack of an effect persisted while subjects exercised while breathing hypoxic gas (15% O_2) at sea level (MacNutt et al. 2012) or while in a simulated hypobaric environment [4,300 m; (Beidleman et al. 2017)]. However, others (Schoene et al. 1981; Williams and Krahenbuhl 1997) have reported ventilation during exercise was greater during the LP compared to the FP. Why these findings conflict with the majority of the current literature is most likely due to one or more of the factors noted above. It is peculiar, though, that progesterone provided to men elicited an increased ventilatory response to exercise and sleep (Skatrud et al. 1978). Likewise, progesterone has been used, successfully, as a therapeutic for obstructive sleep apnea and Chronic Obstructive Pulmonary Disease (Dempsey et al. 1986; Kimura et al. 1988; Skatrud et al. 1980; Tatsumi et al. 1986). Nonetheless, the lack of an effect in normally menstruating women ultimately demonstrates the complexity of ventilatory regulation. In general, humans will maintain blood gas (PaO_2, $PaCO_2$, pH) homeostasis with the most economical ventilatory pattern possible, i.e., will not breathe more than is needed. Thus, it would appear that changes in sex hormones in normally menstruating women are insufficient to disrupt this balance. It is also likely that the feedforward and feedback mechanisms regulating exercise-induced

ventilatory drive are too dominant and robust to be altered by sex hormones in normal physiologic concentrations.

Effects of OC Use

The impact of OC use on athletic performance, the metabolic rate at rest and during exercise, and the ventilatory responses to exercise and the environment are only recently being studied extensively. Currently, only a few published studies have examined these parameters. Much more work is still needed in this area particularly because of the various types of OC currently used by women. OCs are either synthetic progesterone only or a combination of synthetic estrogen–progesterone and are either monophasic with the same level(s) of synthetic hormone in each pill or are multiphasic with varying level(s) of synthetic hormones in each pill (see other chapters' discussion). Nettlefold et al. (2007) studied women who were regularly taking monophasic OC and found no difference in resting ventilation between the active and inactive pill phases, which represent the LP and FP, respectively. Casazza et al. (2002) studied eumenorrheic women before and after 4 months of triphasic OC use and found no difference in ventilation during peak exercise between the active and inactive pill phases. Similarly, Lebrun et al. (2003) studied highly active women (peak aerobic capacity (VO_2 peak) > 50 mL/kg/min), while they were on a triphasic OC and found no difference in ventilation during peak (i.e., near maximal) exercise.

Ventilatory Pattern and Respiratory Mechanics

Effect of Sex

Ventilatory patterns are an important consideration when attempting to gain a thorough understanding of the respiratory responses to exercise. The general term "ventilatory pattern" refers to the breathing frequency (fb) and tidal volume (V_T) used to attain a given ventilation, as well as the operating lung volumes at which an individual breathes. In general, ventilatory patterns are variable between individuals, regardless of sex, as patterns are typically individually "selected" to be the most economical for that individual. However, due to structural differences in the respiratory system between sexes, it is considered that women take smaller, more frequent breaths (i.e., smaller V_T and greater fb) than their male counterparts. Nonetheless, previous work has demonstrated that fb during exercise is not different between men and women (Bryner et al. 1996; Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Mitchell et al. 2018; Peters et al. 2021; Wilkie et al. 2015), but a few showing fb to be greater in women compared to men (Guenette et al. 2009; Molgat-Seon et al. 2018b). Parallel to this, women typically have a smaller V_T than men during exercise (Cory et al. 2015; Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2009; Mitchell et al. 2018;

Molgat-Seon et al. 2018b; Peters et al. 2021; Wilkie et al. 2015). Figure 4.1 illustrates differences in breathing patterns (i.e., V_T and fb) between men and women.

Operating lung volumes refers to where on the continuum of lung volumes between total lung capacity (i.e., lungs completely full) and residual volume (i.e., lungs "empty") an individual is breathing. This is a complex and complicated area of respiratory physiology, but only a brief introduction is provided, and the reader is directed to several in-depth reviews on the topic (Johnson et al. 1999; Sheel and Romer 2012). Operating lung volumes are quantified by obtaining the volume of air in the lungs at end-inspiration (end-inspiratory lung volume; EILV) and the volume of air left in the lungs at end-expiration (end-expiratory lung volume; EELV) at rest or during exercise and are expressed as an absolute volume and/or as a proportion of total lung capacity or vital capacity. Because of the characteristics of the lung tissue and chest wall, at rest individuals breathe at approximately halfway between total lung capacity and residual volume and energetic cost of ventilation is minimal. When one begins to exercise, ventilation increases by increasing fb and expanding V_T. The latter is achieved by decreasing EELV, i.e., exhaling more completely, to optimize the length-tension relationship of the respiratory muscles and increasing EILV, i.e., inhaling more completely. Operating lung volumes are a proxy of respiratory mechanics and have implications for the energetic cost and mechanical work (or power) of breathing, i.e., the work of breathing (Wb) because breathing closer to total lung capacity and/or residual volume alters the pressure required to expand/contract the respiratory tissues (Agostoni and Hyatt 1986; Cross et al. 2021; Otis 1964). Accordingly, previous work has compared EELV and EILV at rest and during exercise between men and women.

Several prior studies have compared operating lung volumes during exercise between men and women. Specifically, Guenette et al. (2007) observed women to have a greater EELV (42 ± 8 versus 35 ± 5% of vital capacity) and EILV ($88 \pm$ versus 82 ± 7% of vital capacity) compared to men. Likewise, Dominelli et al. (2015a) also found EELV to be significantly greater in women compared to men during maximum exercise but found no difference in EILV. The majority of previous work, however, found no sex-based differences on EELV or EILV during exercise (Cory et al. 2015; Dominelli et al. 2015b, 2017; Mitchell et al. 2018; Molgat-Seon et al. 2018b; Peters et al. 2021). Figure 4.2a displays how operating lung volumes change during progressive exercise in men and women. Figure 4.2b displays the representative maximum and tidal flow-volume loops at rest and during maximal exercise in men and women. Note that women have a lesser "area" in the4.ir maximum flow-volume curve (thick, black line), which makes them more susceptible to developing mechanical ventilatory constraints. The reason for the lack of an effect of sex is likely due to variability between individuals, regardless of sex, as operating lung volumes are selected to optimize ventilation while being energetically efficient. However, when generalizing differences in breathing patterns between sexes, one should consider the exercise stimulus, i.e., constant load exercise, graded exercise test to volitional fatigue, etc., as these may influence the ability (or not) to observe a difference between men and women.

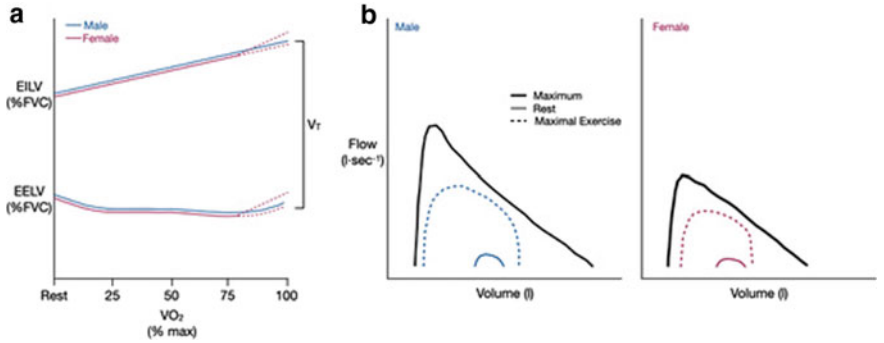

Fig. 4.2 Operating lung volumes at rest and during exercise. Operating lung volumes **a**, i.e., end-inspiratory lung volume (EILV) and end-expiratory lung volumes (EELV), change with increasing exercise intensity. In both men (blue) and women (purple), EILV increases linearly toward total lung capacity with increasing exercise intensity. The shaded region on the line representing the women illustrates that one study has reported a significantly greater EILV in athletic women compared to athletic men (Guenette et al. 2007). EELV decreases toward residual volume at the onset of exercise and then levels off during moderate-intensity exercise before finally increasing back toward functional residual capacity. The shaded region on the line representing women illustrates that two studies (Dominelli et al. 2015a; Guenette et al. 2007) report a significantly greater EELV in women compared to men during high-intensity exercise. Flow-volume loops (**b**) for representative men (left; blue) and women (right; purple) are also displayed. This figure was adapted from previous work (Dominelli and Molgat-Seon 2022; Molgat-Seon et al. 2018c). The solid, thick black line represents the maximum flow-volume loop, the solid, thin, colored (blue or purple) line represents a tidal flow-volume loop at rest, and the dashed, thin, colored (blue or purple) line represents a tidal flow-volume loop at maximum exercise

A popular area of research in respiratory physiology is quantifying the Wb (mechanical cost per breath) and the power of breathing (mechanical cost over a minute; Pb). Several methods can be used to quantify the Wb and Pb, with each having important advantages and disadvantages (Cross et al. 2021). These details are beyond the scope of the current chapter, but work comparing men and women on the Wb and Pb during exercise has greatly furthered our understanding of sex-based differences in the respiratory responses to exercise. No prior work has examined the effect of sex on the Wb, but has, instead, focused on the Pb. That work has unanimously demonstrated that women have a greater Pb than men during exercise when ventilation is greater than or equal to 50 L/min (Dominelli et al. 2015a, 2015b, 2017; Guenette et al. 2007, 2009; Mann et al. 2020; Molgat-Seon et al. 2018b; Peters et al. 2021). Figure 4.3 displays changes in Pb during exercise in men and women. It is generally accepted that the greater Pb in women is due to a greater resistive Pb, i.e., an increased mechanical cost to move air, as a result of women having smaller central airways than men (Dominelli et al. 2018; Peters et al. 2020, 2021; Sheel et al. 2009).

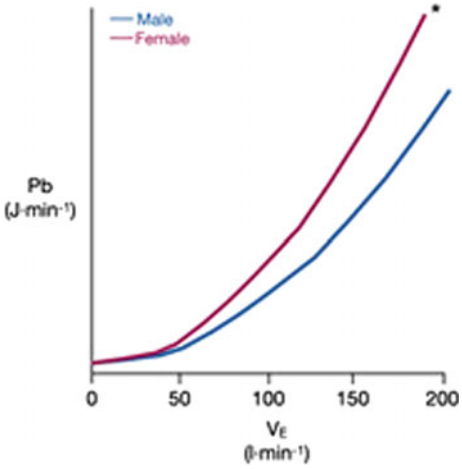

Fig. 4.3 Power of breathing at rest and during exercise**.** The power of breathing (Pb) increases with ventilation (V_E) in a curvilinear manner in both men (blue) and women (purple). Above a V_E ~ 50 l/min, women have a significantly greater Pb compared to men (*). This figure was adapted from previous work (Peters et al. 2021)

Effect of Sex Hormones

The effect of the menstrual cycle phase on the ventilatory patterns during exercise has not been a focus of prior research. The possible reason is that exercise elicits an extremely large drive to breathe, which can only be overridden voluntarily, i.e., the individual choosing to adjust their breathing patterns. However, the few studies that have reported fb and V_T at rest or during exercise have reported no difference between these parameters during the LP and FP (Bryner et al. 1996; Das 1998; MacNutt et al. 2012). Thus, not only does the total ventilation not change across the menstrual cycle, but neither does the strategy utilized to attain that ventilation. Only Nettlefold et al. (2007) have reported fb and V_T at rest in women using OC and reported no effect of pill phase (active versus inactive) on these parameters.

Similarly, Bryner et al. (1996) found no difference in fb during maximal exercise between pill phases. At present, no studies have examined the effect of OC use on EILV, EELV, or the Wb/Pb. More work is needed in this area, but the likely outcome is that there will be no effect of sex hormones (endogenous or exogenous) on these parameters due to the inherent variability in fb, V_T, EILV, and EELV combined with the minimal effect on ventilation during exercise. However, one area of future work that may demonstrate an effect of sex hormones is that of respiratory muscle contractility. Please see other chapters in this book for details concerning how sex hormones impact tension development of the skeletal (locomotor) muscles, regrettably, similar work has not been carried out in the respiratory muscles.

Pulmonary Gas Exchange

Effect of Sex

The primary role of the respiratory system is to serve as the gas exchanger between the pulmonary capillary blood and the environment. Pulmonary gas exchange is imperfect in all humans; the degree of imperfection, i.e., the inefficiency, of the system is quantified as the difference in the partial pressure of O_2 in the alveolar air (PAO_2) and that in the arterial blood (PaO_2) and referred to as the A-aDO_2. "Perfect" pulmonary gas exchange would be defined as complete equilibration of O_2 between the alveolar air and the pulmonary capillary blood—quantified as an A-aDO_2 of 0 mmHg. In general, the A-aDO_2 is 0−10 mmHg at rest, with the presence of a patent foramen ovale largely assumed to explain the variation in resting A-aDO_2 (Duke et al. 2020; Elliott et al. 2015; Lovering et al. 2011), which is a remnant of the fetal circulation. For a thorough review of the topic, the interested reader is directed to a recent review (Lovering et al. 2016). Regardless of the magnitude at rest, it is well known that the A-aDO_2 increases three–fivefold, i.e., to 20–25 mmHg, during maximal exercise. The cause(s) of the increased A-aDO_2 during exercise is beyond the scope of this review, but the interested reader is referred to the seminal review on this topic (Dempsey and Wagner 1999).

The vast majority of the studies examining pulmonary gas exchange efficiency at rest and during exercise have been conducted primarily in men. Recently, though, there has been a concerted effort to better understand the impact that biological sex has on various aspects of physiology, including pulmonary gas exchange. The seminal work comparing pulmonary gas exchange between sexes has suggested that women have a greater A-aDO_2 during near-maximal exercise compared to men and develop exercise-induced arterial hypoxemia at lower relative exercise intensities than men (Dominelli et al. 2013; Harms et al. 1998). However, this work did not study men and, rather, referred to historical data on men. Hopkins et al. (2000) found women to have a similar PaO_2 and A-aDO_2 during maximal exercise compared to historical male data. Figure 4.4a illustrates A-aDO_2 in men and women at rest and during graded exercise. Olfert et al. (2004) and Duke et al. (2014) did study both men and women and found no difference in the A-aDO_2 between sexes during near-maximal exercise breathing air and hypoxic gas (12.5% and 12% O_2, respectively). More recently, Duke et al. (2020) demonstrated no effect of sex on the A-aDO_2, while individuals breathed air and varying levels of hypoxic gas (16%, 14%, 12%, and 10% O_2) at rest. Figure 4.4b illustrates the A-aDO_2 in men and women at rest breathing varying levels of hypoxic gas.

The available literature suggests some disagreement on whether or not women have worse pulmonary gas exchange than men. However, in those studies that have directly compared men and women, there was no impact of sex (Duke et al. 2014, 2020; Olfert et al. 2004), but more work in larger cohorts with a wide range of fitness levels is needed. One important aspect of pulmonary gas exchange that does

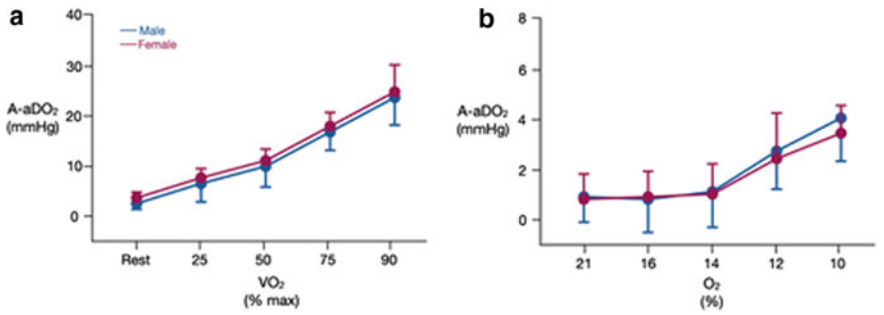

Fig. 4.4 Impact of sex on pulmonary gas exchange efficiency. The alveolar-to-arterial difference in the partial pressure of O2 (A-aDO2) does not differ between men (blue) and women (purple) at rest and during exercise (**a**). Likewise, the A-aDO2 does not differ between men (blue) and women (purple) at rest while breathing room air (21% O2) or at varying levels of hypoxic gas (**b**). These figures were adapted from previous work (Duke et al. 2014, 2020; Lovering et al. 2013)

appear different between sexes is the incidence of exercise-induced arterial hypoxemia [i.e., decreased PaO_2 and/or arterial O_2 saturation (SaO_2) during exercise]. Women, particularly those that are aerobically trained, appear to develop exercise-induced arterial hypoxemia at lower exercise intensities than their male counterparts (Dominelli et al. 2013; Harms et al. 1998). The accepted reason is that women have a greater mechanical ventilatory constraint than men; e.g., expiratory flow limitation. In essence, mechanical constraints to ventilation would result in an inadequate hyperventilatory response to exercise, which would likely contribute to the fall in PaO_2 and SaO_2. To test this hypothesis, some have used low-density gas (i.e., 80% helium and 20% O_2) during exercise to alleviate or abolish the mechanical ventilatory constraints that are present. When done, exercise-induced arterial hypoxemia, if present, goes away or is significantly reduced (Dominelli et al. 2013).

At present, no studies have examined the effect of sex hormones either via changes during the menstrual cycle or from OC use. However, it has been suggested that variations in sex hormones via the menstrual cycle or from OC use alter ventilatory chemoresponsiveness (see below), which could then impact pulmonary gas exchange, but this work has yet to be complete. At present, there is no evidence to suggest that the menstrual cycle phase has an effect on exercise performance, respiratory exchange ratio, and/or blood lactate accumulation during exercise (Smekal et al. 2007). Therefore, any potential effect of sex hormones on pulmonary gas exchange efficiency would either be minimal or of no functional consequence. Nevertheless, many studies still need to be conducted to better understand the basic sex differences, as well as the effect of the menstrual cycle phase, in the area of pulmonary gas exchange. Fortunately, there has been a significant push in the scientific community to either include women in studies and/or study women specifically so hopefully, the data addressing this important area of respiratory physiology are forthcoming.

Effect of Sex and Sex Hormones on Ventilatory Chemoresponsiveness

Ventilatory output in response to changes in PaO_2 and $PaCO_2$ is coordinated in the respiratory control center in the brain stem and is done with input from central and various peripheral chemoreceptors. Sex hormones exert their effect on ventilation at the level of the central nervous system by specifically altering the set point (the point at which ventilation begins to increase) or ventilatory gain (the output from a given change) (Behan et al. 2003; Behan and Wenninger 2008; Dempsey et al. 1986). Accordingly, it is generally accepted that alterations in ventilatory chemoresponsiveness, as a result of varying levels of progesterone and estrogen through the menstrual cycle or as a consequence of OC use, represent the most robust sex hormone-induced respiratory system changes. Exogenous progesterone in healthy men is a ventilatory stimulant (Skatrud et al. 1980) and an effective treatment for patients with breathing disorders like Chronic Obstructive Pulmonary Disease and/or obstructive sleep apnea (Dempsey et al. 1986; Kimura et al. 1988; Skatrud et al. 1980; Tatsumi et al. 1986). In contrast, estrogen alone does not appear to alter the hypoxic ventilatory response (HVR) or hypercapnic ventilatory response (HCVR), but when combined with progesterone appears to potentiate the progesterone-induced changes in ventilation (Brodeur et al. 1986; Regensteiner et al. 1990; Tatsumi et al. 1997) likely by inducing progesterone receptor expression (Brodeur et al. 1986). The studies referenced above are important contributions to this area of study as they have described how ventilation is affected by sex hormones. However, these studies have largely used pharmacological doses of sex hormones to evoke and quantify a compensatory effect on ventilation and/or ventilatory responsiveness.

Effect of Sex

Differences in the ventilatory responses between men and women to hypoxia and/or hypercapnia have been largely equivocal. Specifically, the HVR is either lesser (Aitken et al. 1986; Mortola and Saiki 1996; Tatsumi et al. 1991) or greater (Hirshman et al. 1975; White et al. 1983) in men compared to women or not different (Dahan et al. 1998; Guenette et al. 2004; Jensen et al. 2004; Jordan et al. 2000; Loeppky et al. 2001; Sajkov et al. 1997; Sarton et al. 1999). Similarly, the HCVR has been shown to be either greater (MacNutt et al. 2012; White et al. 1983) or not different (Aitken et al. 1986; Rebuck et al. 1973) in men compared to women. There are several potential explanations for variable results between men and women on HVR, including differences in the methodology used to quantify chemoresponsiveness, but the most prominent and relevant to the current text is that not all have characterized the menstrual cycle phase in which the women were studied.

Hypoxic Ventilatory Response

Effect of Sex Hormones

The data on how and if HVR varies across the menstrual cycle are, at present, not clear. Recently, MacNutt et al. (2012) conducted a thorough study on the impact of the menstrual cycle phase and ventilatory responses to exercise and alveolar hypoxia/hypercapnia. They reported no alteration in the isocapnic HVR between the LP and FP in moderate to well-trained women (VO_2 peak = 43.4 ± 9.5 mL/kg/min) across the menstrual cycle. Similarly, others (Beidleman et al. 1999; Dombovy et al. 1987; Regensteiner et al. 1990) have observed no difference in HVR in women between the LP and FP. Regensteiner et al. (1990) also examined the effect of medroxyprogesterone (MPA) supplementation on HVR and still did not observe a significant difference between the LP and FP. However, some have reported a significantly greater HVR in the LP compared to FP. Specifically, Schoene et al. (1981) studied the HVR in athletic (VO_2 peak = 49.6 ± 5.2 mL/kg/min) and non-athletic (35.2 ± 4.2 mL/kg/min) eumenorrheic women between the LP and FP. The researchers found the HVR to be greater in the LP compared to the FP in all women. Figure 4.5a illustrates how HVR varies between the LP and LP in women and men. Interestingly, Schoene et al. (1981) also found the HVR to be lower in the LP in athletes compared to non-athletes, demonstrating a clear effect of training status on ventilatory chemoresponsiveness that has also been observed in men (Harms and Stager 1995). White et al. (1983) studied the HVR in women during the LP and FP, as well as in men. They reported a significantly greater HVR in the LP compared to the FP in women and a significantly greater HVR in men compared to women in the FP only, i.e., FP was the lowest, LP was in the middle, and men were the highest. Similarly, Takano (Takano 1984) observed a significantly greater HVR in the LP compared to the FP.

There are a few potential reasons as to why there is a lack of agreement on the effect of the menstrual cycle phase, i.e., high, or low levels of progesterone, on the HVR. First, there is significant heterogeneity in the fitness levels of women being studied. Because endurance training attenuates the HVR (Harms and Stager 1995), comparing fit women with unfit men may bias the results in favor of a difference in HVR. Second, the method by which HVR is determined varies between studies. Nearly, all studies utilize an isocapnic test that requires a substantial resting period (up to 30 min) to establish a true resting ventilation before decreasing the proportion of O_2 in the inspirate; i.e., flowing 100% nitrogen into a gas reservoir, lowering the percent O_2 from 21 to 5% over 5-10 min. Additionally, the means by which a numerical value is obtained and stated as the HVR is assessed differently between studies. One method (i.e., "A" method) quantifies HVR based on the shape of the hyperbolic relationship between ventilation and PAO_2 (Weil et al. 1970). The greater the "A" value, the greater the ventilatory response to decreased O_2 level (i.e., PAO_2). The second method (i.e., "slope" method) quantifies HVR as the slope of the least squares regression line between SaO_2 and ventilation such that the HVR units are

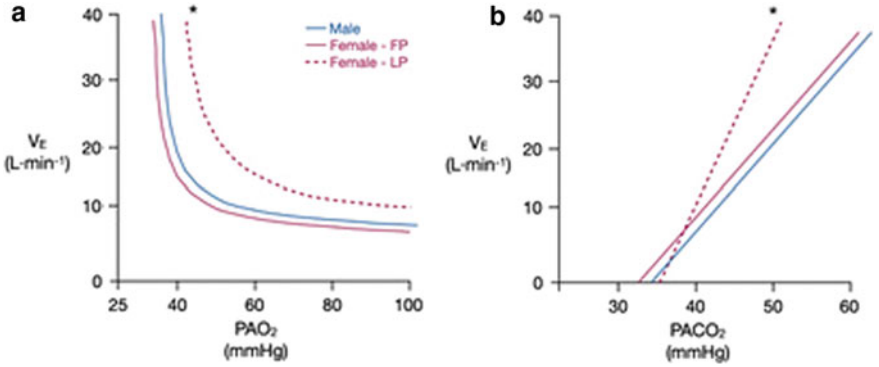

Fig. 4.5 Hypoxic and hypercapnic ventilatory responses between men and women and across the menstrual cycle. The hypoxic ventilation response (**a**) is greater in women during the luteal phase (LP; dashed, purple line) compared to the follicular phase (FP; solid, purple line) (*). Men (solid, blue line) have a similar hypoxic ventilatory response to women in the FP. The hypercapnic ventilatory response (**b**) is greater in women during the LP (dashed, purple line) compared to the FP (solid, purple line) (*). Men (solid, blue line) have a similar hypercapnic ventilatory response to women in their FP. This figure was adapted from previous work (Schoene et al. 1981)

liters per minute per % fall in SaO_2 and reported as positive numbers by convention. Generally, researchers tend to rely on the slope method more frequently than the "A" method because of ease of computation, but a strong agreement has been reported between methods [$r = 0.70-0.97$; (Moore et al. 1984; Townsend et al. 2002)]. Nevertheless, it is conceivable that an individual may have a high "A" parameter, but a low slope value (Townsend et al. 2002).

Effect of OC Use

The impact of various OCs on the HVR has not been rigorously studied. Regensteiner et al. (1989) have the only study to date to investigate the effect of OC use, per se, on the HVR. They studied postmenopausal women while they took estrogen, progesterone, or both (i.e., in actuality a hormone replacement therapy intervention) and found only the combination of hormones to have a significant effect on HVR. Clearly, more work needs to be done in this area to better elucidate the effect, if any, OC use has on the HVR.

Hypercapnic Ventilatory Response

Effect of Sex Hormones

Similar to HVR, findings on changes in HCVR across the menstrual cycle remain inconclusive. MacNutt et al. (2012) used a standard rebreathing method without prior hyperventilation to assess CO_2 sensitivity, i.e., HCVR quantified as the slope of the least squares regression line between ventilation and the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$). Using this method, they found no difference in HCVR across menstrual cycle phases. Similarly, no difference in HCVR between the LP and FP has been reported by others (Beidleman et al. 1999; White et al. 1983), as well as Regensteiner et al. (1990) even during MPA supplementation. Slatkovska et al. (2006) and Takano et al. (1981) also found no difference in HCVR between the LP and FP when done using both hypoxic and hyperoxic HCVR protocols. However, several other studies have reported HCVR to be greater in the LP compared to the FP (Dombovy et al. 1987; Dutton et al. 1989; Schoene et al. 1981; Williams and Krahenbuhl 1997). Figure 4.5b illustrates how HCVR varies between the LP and LP in women and men. Similar to HVR, there appears to be a fitness effect on HCVR because only the non-athletic women demonstrated a menstrual cycle phase effect (Byrne-Quinn et al. 1971; Harms and Stager 1995; Martin et al. 1978; Schoene et al. 1981).

There are multiple methodological ways to assess the HCVR and a main point of difference is whether or not the subjects perform a prior hyperventilation before the rebreathing aspect of the procedure. This is done to lower $P_{ET}CO_2$ from ~ 40 to 20–25 Torr and would allow one to observe and measure basal ventilation, as well as observe and quantify the CO_2 threshold, that is the $P_{ET}CO_2$ at which ventilation increases linearly (Duffin 2011; Mateika et al. 2003). Why a researcher would or would not choose to use a select HCVR protocol with a prior hyperventilation in their research design is beyond the scope of this chapter, but the interested reader is directed to reviews on the topic (Duffin 2011; Duffin et al. 2000). Nevertheless, the appropriate interpretation of alterations in the CO_2 threshold is that a lower threshold implies an enhanced chemoresponsiveness to hypercapnia, while a higher threshold implies a delayed or depressed chemoresponsiveness to hypercapnia. Similar to HCVR and HVR, findings on the CO_2 threshold have been equivocal. The CO_2 threshold is lower in women compared to men (Beidleman et al. 1999; MacNutt et al. 2012). Additionally, MacNutt et al. (2012) and Beidleman et al. (1999) found the CO_2 threshold to be significantly lower in the LP compared to the FP, while others have observed there to be no difference in CO_2 threshold between the LP and FP (Dombovy et al. 1987; Dutton et al. 1989; Regensteiner et al. 1990; Slatkovska et al. 2006; Takano et al. 1981) even with MPA supplementation (Regensteiner et al. 1990).

Effect of OC Use

The impact of various OCs on the HCVR has not been rigorously studied. Nettlefold et al. (2007) studied the hyperoxic and hypoxic HCVR in 12 women who were taking various monophasic OCs during the active and inactive pill phase, i.e., the LP and FP, respectively. They found no difference between pill phases in CO_2 threshold or slope for either HCVR test. The only other study that investigated the effect of OC, per se, did so in postmenopausal women taking estrogen, progesterone, or both (Regensteiner et al. 1989). They found no effect on CO_2 threshold or HCVR slope for estrogen or progesterone alone. However, when taking both estrogen and progesterone they observed a decreased CO_2 threshold and a significantly steeper HCVR slope. Clearly, more work needs to be done in this area with a particular focus on the different types of OCs.

Summary

In summary, the data discussed above outline the current knowledge and understanding of some of the sex differences in the responses of the respiratory system to exercise and the environment, as well as describe the available (but limited) literature examining the effects of changes in sex hormones on these respiratory system responses. At present, the existing data are largely inconclusive in several important areas such as ventilation at rest and the ventilatory response to hypoxia and hypercapnia. This is probably due to the variability of hormonal levels in subjects within and between studies, fitness level of subjects, and differences in testing procedure and protocols being used. Additionally, the variability, i.e., individuality, of responses to hormones also provides another degree of complexity. Despite this, the data agree that there is an effect of sex on the ventilatory response to exercise. As described at length above, this is due to women having smaller lungs and airways compared to men. Similarly, changes in sex hormones via the menstrual cycle or with OC use do not appear to affect the ventilatory responses to exercise. Nevertheless, the understanding of basic sex differences and the effect of variations in sex hormones on these ventilatory parameters is incomplete, but these data may be forthcoming with the increased focus on including women as participants in research studies. Future work should focus on developing consistency in research protocols and rigorously monitoring the menstrual cycle to ensure that measurements are taken during the time of the greatest and lowest concentration of progesterone. Additionally, it would be helpful to gain an understanding of how the responses described above do or do not vary during the ovulatory phase of the menstrual cycle, which has not been examined in exercise studies.

References

Agostoni E, Hyatt RE. Static behavior of the respiratory system. In: Macklem PT, Mead J, editors. Handbook of physiology. Bethesda; American Physiological Society: 1986.

Aitken ML, Franklin JL, Pierson DJ, Schoene RB. Influence of body size and gender on control of ventilation. J Appl Physiol. 1986;60(6):1894–9.

Behan M, Zabka AG, Thomas CF, Mitchell GS. Sex steroid hormones and the neural control of breathing. Respir Physiol Neurobiol. 2003;136:249–63.

Behan M, Wenninger JM. Sex steroidal hormones and respiratory control. Respir Physiol Neurobiol. 2008;164:213–21.

Beidleman BA, Rock PB, Muza SR, Fulco CS, Forte VA, Cymerman A. Exercise VE and physical performance at altitude are not affected by the menstrual cycle phase. J Appl Physiol. 1999;86(5):1519–26.

Beidleman BA, Fulco CS, Cadarette BS, Cymerman A, Buller MJ, Salgado RM, Posch AM, Staab JE, Sils IV, Yurkevicius BR, Luippold AJ, Welles AP, Muza SR. Is normobaric hypoxia an effective treatment for sustaining previously acquired altitude acclimatization? J Appl Physiol. 2017;123(5):1214–27.

Bellemare F, Jeanneret A. Sex differences in thoracic adaptation to pulmonary hyperinflation in cystic fibrosis. Eur Respir J. 2006;29(1):98–107.

Brodeur P, Mockus M, McCullough R, Moore LG. Progesterone receptors and ventilatory stimulation by progestin. J Appl Physiol. 1986;60(2):590–5.

Bryner RW, Toffle RC, Ullrich IH, Yeater RA. Effect of low dose oral contraceptives on exercise performance. Br J Sports Med. 1996;30(1):36–40.

Byrne-Quinn E, Weil JV, Sodal IE, Filley GF, Grover RF. Ventilatory control in the athlete. J Appl Physiol. 1971;30(1):91–8.

Casazza GA, Suh SH, Miller BF, Navazio FM, Brooks GA. Effects of oral contraceptives on peak exercise capacity. J Appl Physiol. 2002;93(5):1698–702.

Cory JM, Schaeffer MR, Wilkie SS, Ramsook AH, Puyat JH, Arbour B, Basran R, Lam M, Les C, MacDonald B, Jensen D, Guenette JA. Sex differences in the intensity and qualitative dimensions of exertional dyspnea in physically active young adults. J Appl Physiol. 2015;119(9):998–1006.

Cross TJ, Gideon EA, Morris SJ, Coriell CL, Hubbard CD, Duke JW. A comparison of methods used to quantify the work of breathing during exercise. J Appl Physiol. 2021;131(3):1123–33.

Da Silva SB, de Viana ESR, de Sousa MBC. Changes in peak expiratory flow and respiratory strength during the menstrual cycle. Respir Physiol Neurobiol. 2006; 150(2–3): 211–219.

Dahan AM, Sarton E, Teppema L, Olievier C. Sex-related differences in the influence of morphine on ventilatory control in humans. Anesthesiology. 1998;88(4):903–13.

Das TK. Effects of the menstrual cycle on timing and depth of breathing at rest. Indian J Physiol Pharmacol. 1998;42(4):498–502.

De Souza MJ, Maguire MS, Rubin KR, Maresh CM. Effects of menstrual phase and amenorrhea on exercise performance in runners. Med Sci Sports Exerc. 1990;22(5):575–80.

Dempsey JA, Olson EB, Skatrud JB. Hormones and neurochemicals in the regulation of breathing. In: Cherniak NS, Widdicombe JG, (editors). Handbook of physiology: the respiratory system: control of breathing. Washington, DC; American Physiological Society: 1986.

Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. J Appl Physiol. 1999;87(6):1997–2006.

Dominelli PB, Foster GE, Dominelli GS, Henderson WR, Koehle MS, McKenzie DC, Sheel AW. Exercise-induced arterial hypoxaemia and the mechanics of breathing in healthy young women. J Physiol. 2013;591(12):3017–34.

Dominelli PB, Molgat-Seon Y, Bingham D, Swartz PM, Road JD, Foster GE, Sheel AW. Dysanapsis and the resistive work of breathing during exercise in healthy men and women. J Appl Physiol. 2015a;119(10):1105–13.

Dominelli PB, Render JN, Molgat-Seon Y, Foster GE, Romer LM, Sheel AW. Oxygen cost of exercise hyperpnoea is greater in women compared with men. J Physiol. 2015b;593(8):1965–79.

Dominelli PB, Molgat-Seon Y, Griesdale DEG, Peters CM, Blouin J-S, Sekhon M, Dominelli GS, Henderson WR, Foster GE, Romer LM, Koehle MS, Sheel AW. Exercise-induced quadriceps muscle fatigue in men and women: effects of arterial oxygen content and respiratory muscle work. J Physiol. 2017;595(15):5227–44.

Dominelli PB, Ripoll JG, Cross TJ, Baker SE, Wiggins CC, Welch BT, Joyner MJ. Sex differences in large conducting airway anatomy. J Appl Physiol. 2018;125(3):960–5.

Dominelli PB, Molgat-Seon Y, Sheel AW. Sex differences in the pulmonary system influence the integrative response to exercise. Exerc Sport Sci Rev. 2019;47(3):142–50.

Dominelli PB, Molgat-Seon Y. Sex, gender and the pulmonary physiology of exercise. Eur Respir Rev. 2022;31(163): 210074.

Dombovy ML, Bonekat HW, Williams TJ, Staats BA. Exercise performance and ventilatory response in the menstrual cycle. Med Sci Sports Exerc. 1987;19(2):111–7.

Duffin J. Measuring the respiratory chemoreflexes in humans. Respir Physiol Neurobiol. 2011;177(2):71–9.

Duffin J, Mohan RM, Vasiliou P, Stephenson R, Mahamed S. A model of the chemoreflex control of breathing in humans: model parameters measurement. Respir Physiol. 2000;120(1):13–26.

Duke JW, Beasley KM, Speros JP, Elliott JE, Laurie SS, Goodman RD, Futral E, Hawn JA, Lovering AT. Impaired pulmonary gas exchange efficiency, but normal pulmonary artery pressure increases, with hypoxia in men and women with a patent foramen ovale. Exp Physiol. 2020;105(9):1648–59.

Duke JW, Elliott JE, Laurie SS, Beasley KM, Mangum TS, Hawn JA, Gladstone IM, Lovering AT. Pulmonary gas exchange efficiency during exercise breathing normoxic and hypoxic gas in adults born very preterm with low diffusion capacity. J Appl Physiol. 2014;117(5):473–81.

Dutton K, Blanksby BA, Morton AR. CO_2 sensitivity changes during the menstrual cycle. J Appl Physiol. 1989;67(2):517–22.

Elliott JE, Laurie SS, Kern JP, Beasley KM, Goodman RD, Kayser B, Subudhi AW, Roach RC, Lovering AT. AltitudeOmics: impaired pulmonary gas exchange efficiency and blunted ventilatory acclimatization in humans with patent foramen ovale after 16 days at 5,260 m. J Appl Physiol. 2015;118(9):1100–12.

Freemas JA, Baranauskas MN, Constantini K, Constantini N, Greenshields JT, Mickleborough TD, Raglin JS, Schlader ZJ. Exercise performance is impaired during the midluteal phase of the menstrual cycle. Med Sci Sports Exerc. 2020;53(2):442–52.

García-Martínez D, Bastir M, Torres-Tamayo N, O'Higgins P, Torres-Sánchez I, García-Río F, Heuzé Y. Three-dimensional analysis of sexual dimorphism in ribcage kinematics of modern humans. Am J Phys Anthropol. 2019;169(2):348–55.

García-Martínez D, Torres-Tamayo N, Torres-Sanchez I, García-Río F, Bastir M. Morphological and functional implications of sexual dimorphism in the human skeletal thorax. Am J Phys Anthropol. 2016;161(3):467–77.

Guenette JA, Diep TT, Koehle MS, Foster GE, Richards JC, Sheel AW. Acute hypoxic ventilatory response and exercise-induced arterial hypoxemia in men and women. Respir Physiol Neurobiol. 2004;143(1):37–48.

Guenette JA, Witt JD, McKenzie DC, Road JD, Sheel AW. Respiratory mechanics during exercise in endurance-trained men and women. J Physiol. 2007;581(3):1309–22.

Guenette JA, Querido JS, Eves ND, Chua R, Sheel AW. Sex differences in the resistive and elastic work of breathing during exercise in endurance-trained athletes. Am J Physiol Regul Integr Comp Physiol. 2009;297(1):R166–75.

Hackney AC, Curley CS, Nicklas BJ. Physiological responses to submaximal exercise at the mid-follicular, ovulatory and mid-luteal phases of the menstrual cycle. Scand J Med Sci Sports. 1991;1(2):94–8.

Harms CA, Stager JM. Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. J Appl Physiol. 1995;79(2):575–80.

Harms CA, McClaran SR, Nickele GA, Pegelow DF, Dempsey JA. Exercise-induced arterial hypoxaemia in healthy young women. J Physiol. 1998;507(2):619–28.

Hirshman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. J Appl Physiol. 1975;38(6):1095–8.
Hopkins SR, Barker RC, Brutsaert TD, Gavin TP, Entin P, Olfert IM, Veisel S, Wagner PD. Pulmonary gas exchange during exercise in women: effects of exercise type and work increment. J Appl Physiol. 2000;89(2):721–30.
Jensen D, Wolfe LA, O'Donnell DE, Davies GAL. Chemoreflex control of breathing during wakefulness in healthy men and women. J Appl Physiol. 2004;98(3):822–8.
Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest. 1999;116(2):488–503.
Jordan AS, Catcheside PG, Orr RS, O'Donoghue FJ, Saunders NA, McEvoy RD. Ventilatory decline after hypoxia and hypercapnia is not different between healthy young men and women. J Appl Physiol. 2000;88(1):3–9.
Kimura H, Tatsumi K, Kunitomo F, Okita S, Tojima H, Kouchiyama S, Masuyama S, Shinozaki T, Mikami M, Watanabe S, Ishikawa Y, Honda Y, Kuriyama T. Obese patients with sleep apnea syndrome treated by progesterone. Tohoku J Exp Med. 1988;156(Suppl):151–7.
Lebrun CM. Effect of the different phases of the menstrual cycle and oral contraceptives on athletic performance. Sports Med. 1993;16(6):400–30.
Lebrun CM, Petit MA, McKenzie DC, Taunton JE, Prior JC. Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomised controlled trial. Br J Sports Med. 2003;37(4):315–20.
Loeppky JA, Scotto P, Charlton GC, Gates L, Icenogle M, Roach RC. Ventilation is greater in women than men, but the increase during acute altitude hypoxia is the same. Respir Physiol. 2001;125(3):225–37.
LoMauro A, Aliverti A. Sex differences in respiratory function. Breathe. 2018; 14(2): 131–140.
Lovering AT, Stickland MK, Amann M, O'Brien MJ, Hokanson JS, Eldridge MW. Effect of a patent foramen ovale on pulmonary gas exchange efficiency at rest and during exercise. J Appl Physiol. 2011;110(5):1354–61.
Lovering AT, Elliott JE, Davis JT. Physiological impact of patent foramen ovale on pulmonary gas exchange, ventilatory acclimatization, and thermoregulation. J Appl Physiol. 2016;121(2):512–7.
Lovering AT, Laurie SS, Elliott JE, Beasley KM, Yang X, Gust CE, Mangum TS, Goodman RD, Hawn JA, Gladstone IM. Normal pulmonary gas exchange efficiency and absence of exercise-induced arterial hypoxemia in adults with bronchopulmonary dysplasia. J Appl Physiol. 2013;115(7):1050–6.
MacNutt MJ, De Souza MJ, Tomczak SE, Homer JL, Sheel AW. Resting and exercise ventilatory chemosensitivity across the menstrual cycle. J Appl Physiol. 2012;112(5):737–47.
Mann LM, Granger EA, Chan JS, Yu A, Molgat-Seon Y, Dominelli PB. Minimizing airflow turbulence in women lowers the work of breathing to levels similar to men. J Appl Physiol. 2020;129(2):410–8.
Martin BJ, Sparks KE, Zwillich CW, Weil JV. Low exercise ventilation in endurance athletes. Med Sci Sports Exerc. 1978;11(2):181–5.
Mateika JH, Mendello C, Obeid D, Badr MS. Peripheral chemoreflex responsiveness is increased at elevated levels of carbon dioxide after episodic hypoxia in awake humans. J Appl Physiol. 2003;96(3):1197–205.
Matsuo H, Katayama K, Ishida K, Muramatsu T, Miyamura M. Effect of menstrual cycle and gender on ventilatory and heart rate responses at the onset of exercise. Eur J Appl Physiol. 2003;90(1–2):100–8.
Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
Mitchell RA, Schaeffer MR, Ramsook AH, Wilkie SS, Guenette JA. Sex differences in respiratory muscle activation patterns during high-intensity exercise in healthy humans. Respir Physiol Neurobiol. 2018;247:57–60.

Molgat-Seon Y, Dominelli PB, Ramsook AH, Schaeffer MR, Romer LM, Road JD, Guenette JA, Sheel AW. Effects of age and sex on inspiratory muscle activation patterns during exercise. Med Sci Sports Exerc. 2018a;50(9):1882–91.

Molgat-Seon Y, Dominelli PB, Ramsook AH, Schaeffer MR, Sereacki SM, Foster GE, Romer LM, Road JD, Guenette JA, Sheel AW. The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. J Appl Physiol. 2018b;124(4):1092–106.

Molgat-Seon Y, Peters CM, Sheel AW. Sex differences in the human respiratory system and their impact on resting pulmonary function and the integrative response to exercise. Curr Opin Physiol. 2018c;6:21–7.

Molgat-Seon Y, Ramsook AH, Peters CM, Schaeffer MR, Dominelli PB, Romer LM, Road JD, Guenette JA, Sheel AW. Manipulation of mechanical ventilatory constraint during moderate intensity exercise does not influence dyspnoea in healthy older men and women. J Physiol. 2019;597(5):1383–99.

Moore LG, Huang SY, McCullough RE, Sampson JB, Maher JT, Weil JV, Grover RF, Alexander JK, Reeves JT. Variable inhibition by falling CO_2 of hypoxic ventilatory response in humans. J Appl Physiol. 1984;56(1):207–10.

Mortola JP, Saiki C. Ventilatory response to hypoxia in rats: gender differences. Respir Physiol. 1996;106(1):21–34.

Nettlefold L, Jensen D, Janssen I, Wolfe LA. Ventilatory control and acid–base regulation across the menstrual cycle in oral contraceptive users. Respir Physiol Neurobiol. 2007;158(1):51–8.

Olfert IM, Balouch J, Kleinsasser A, Knapp A, Wagner H, Wagner PD, Hopkins SR. Does gender affect human pulmonary gas exchange during exercise? J Physiol. 2004;557(Pt 2):529–41.

Otis AB. The work of breathing. In: Fenn WO, Rahn H, editors. Handbook of physiology. Washington, DC; American Physiological Society: 1964.

Peters CM, Molgat-Seon Y, Dominelli PB, Lee AMD, Lane P, Lam S, Sheel AW. Fiber optic endoscopic optical coherence tomography (OCT) to assess human airways: the relationship between anatomy and physiological function during dynamic exercise. Physiol Rep. 2020;9(1): e14657.

Peters CM, Leahy MG, Hohert G, Lane P, Lam S, Sin DD, McKenzie DC, Sheel AW. Airway luminal area and the resistive work of breathing during exercise in healthy young females and males. J Appl Physiol. 2021;131(6):1750–61.

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JK, Ip MS, Zheng J, Stocks J. ERS global lung function initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40(6):1324–1343.

Rebuck AS, Kangalee M, Pengelly LD, Campbell EJ. Correlation of ventilatory responses to hypoxia and hypercapnia. J Appl Physiol. 1973;35(2):173–7.

Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Pickett CK, Bender PR, Moore LG. Combined effects of female hormones and metabolic rate on ventilatory drives in women. J Appl Physiol. 1989;66(2):808–13.

Regensteiner JG, McCullough RG, McCullough RE, Pickett CK, Moore LG. Combined effects of female hormones and exercise on hypoxic ventilatory response. Respir Physiol. 1990;82(1):107–14.

Sajkov D, Neill A, Saunders NA, McEvoy RD. Comparison of effects of sustained isocapnic hypoxia on ventilation in men and women. J Appl Physiol. 1997;83(2):599–607.

Sarton E, Teppema L, Dahan A. Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop. Anesthesiology. 1999;90(5):1329–38.

Schoene RB, Robertson HT, Pierson DJ, Peterson AP. Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(6):1300–5.

Sébert P. Heart rate and breathing pattern: interactions and sex differences. Eur J Appl Physiol Occup Physiol. 1983;50(3):421–8.

Sheel AW, Guenette JA, Yuan R, Holy L, Mayo JR, McWilliams AM, Lam S, Coxson HO. Evidence for dysanapsis using computed tomographic imaging of the airways in older ex-smokers. J Appl Physiol. 2009;107(5):1622–8.

Sheel AW, Romer LM. Ventilation and respiratory mechanics. Compr Physiol. 2012; 2(2):1093–1142.

Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. J Appl Physiol Respir Environ Exerc Physiol. 1978;44(6):939–44.

Skatrud JB, Dempsey JA, Bhansali P, Irvin C. Determinants of chronic carbon dioxide retention and its correction in humans. J Clin Invest. 1980;65(4):813–21.

Slatkovska L, Jensen D, Davies GAL, Wolfe LA. Phasic menstrual cycle effects on the control of breathing in healthy women. Respir Physiol Neurobiol. 2006;154(3):379–88.

Smekal G, von Duvillard SP, Frigo P, Tegelhofer T, Pokan R, Hofmann P, Tschan H, Baron R, Wonisch M, Renezeder K, Bachl N. Menstrual cycle: no effect on exercise cardiorespiratory variables or blood lactate concentration. Med Sci Sports Exerc. 2007;39(7):1098–106.

Takano N. Reflex hypoxic drive to respiration during the menstrual cycle. Respir Physiol. 1984;56(2):229–35.

Takano N, Sakai A, Iida Y. Analysis of alveolar PCO_2 control during the menstrual cycle. Pflugers Arch. 1981;390(1):56–62.

Tatsumi K, Hannhart B, Pickett CK, Weil JV, Moore LG. Influences of gender and sex hormones on hypoxic ventilatory response in cats. J Appl Physiol. 1991;71(5):1746–51.

Tatsumi K, Pickett CK, Jacoby CR, Weil JV, Moore LG. Role of endogenous female hormones in hypoxic chemosensitivity. J Appl Physiol. 1997;83(5):1706–10.

Tatsumi K, Kimura H, Kunitomo F, Kuriyama T, Watanabe S, Honda Y. Sleep arterial oxygen desaturation and chemical control of breathing during wakefulness in COPD. Chest. 1986;90(1):68–73.

Torres-Tamayo N, García-Martínez D, Zlolniski SL, Torres-Sánchez I, García-Río F, Bastir M. 3D analysis of sexual dimorphism in size, shape and breathing kinematics of human lungs. J Anat. 2018;232(2):227–37.

Townsend NE, Gore CJ, Hahn AG, McKenna MJ, Aughey RJ, Clark SA, Kinsman T, Hawley JA, Chow C-M. Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes. J Appl Physiol. 2002;93(4):1498–505.

Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. J Clin Invest. 1970;49(6):1061–72.

White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW. Sexual influence on the control of breathing. J Appl Physiol Respir Environ Exerc Physiol. 1983;54(4):874–9.

Wilkie SS, Dominelli PB, Sporer BC, Koehle MS, Sheel AW. Heliox breathing equally influences respiratory mechanics and cycling performance in trained males and females. J Appl Physiol. 2015;118(3):255–64.

Williams TJ, Krahenbuhl GS. Menstrual cycle phase and running economy. Med Sci Sports Exerc. 1997;29(12):160–1618.

Chapter 5
Sex Hormones and Environmental Factors Affecting Exercise

Megan M. Wenner and Nina S. Stachenfeld

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 many of 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 in women compared to men, 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, 17β-estradiol (referred to as just estradiol herein) 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. 5.1; also, please see Chap. 1 of the book). 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. 5.1). 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. 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, and collapsing men and women into one group should be avoided when possible even when they appear similar on other variables. More powerful ways to address changing hormone exposure in women are to focus on the research question and determine if subjects need to be tested in more than one phase of the cycle to answer the research question. If this is not feasible, then the decision about when to test the subjects should be based not on where hormone exposure is lowest, but where the most important effects are expected to be found. For example, if it is already known that powerful fluid regulatory effects are apparent in the mid-luteal phase, then this might be the more interesting phase in which to test women rather than the early-follicular phase, where such effects are likely to be missed. These considerations apply to studies that examine sex differences as well as those studies examining outcome variables due to interventions within women.

Hormonal contraceptives [usually combinations of different types of estrogens and progestins (see Chap. 1 in this book)] 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

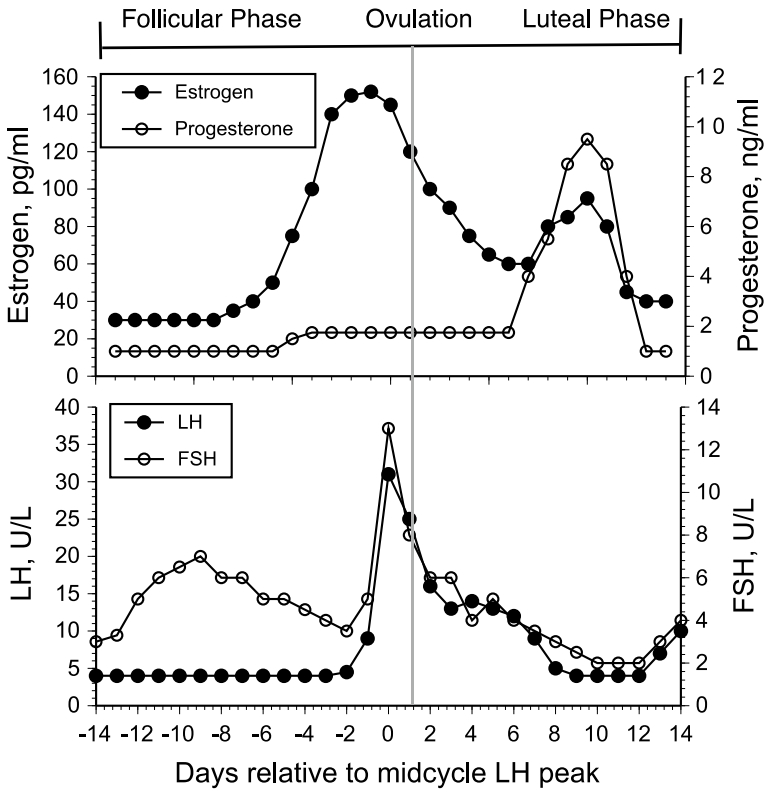

Fig. 5.1 Changes in 17β-estradiol (top) and progesterone (bottom) across the menstrual cycle (Stachenfeld et al. 2008, Copyright 2008 The American Physiological Society, used with permission)

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 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 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 where women are 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 gonadotropin-releasing hormone (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 follicle-stimulating hormone (FSH) stimulation and related steroidogenesis, followed by low or undetectable estrogen and progesterone concentrations within 7–14 days (Heritage et al. 1980). Additionally, Ganirelix and cetrorelix are synthetic decapeptides that compete with receptor binding, so function as competitive receptor antagonists, inducing rapid, reversible suppression of gonadotropin secretion and suppress estrogens and progesterone production by 36–48 h of administration (Oberye et al. 1999a). When hormones are suppressed, estrogens, progestogens, or androgens (or combinations) can be administered in a controlled fashion to test the hypothesis of interest.

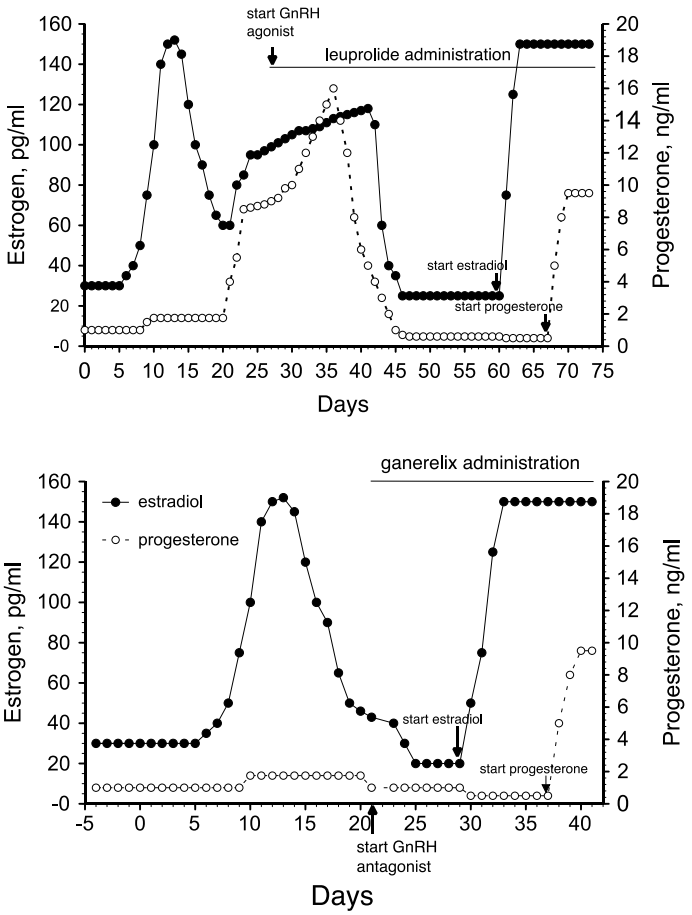

Fig. 5.2 Changes in 17β-estradiol and progesterone during treatment with a gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate) beginning on day 25 of a normal menstrual cycle, followed by treatment with two 17β-estradiol patches (0.1 mg) and oral progesterone (200 mg/day) (left). Changes 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)

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 and 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 the National Institutes of Health (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 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. Recent new requirements from NIH include the consideration of sex as a biological variable in all human and animal research, although this has not yet extended to research in cells. This has been changing as data indicate the impact of chromosomes on the functioning of all cells, indicating the importance of determining and reporting the sex of cells whenever possible.

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. 5.3). 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. 5.3). 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 physiological responses of sodium and water retention by the kidney (Fig. 5.3). 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)

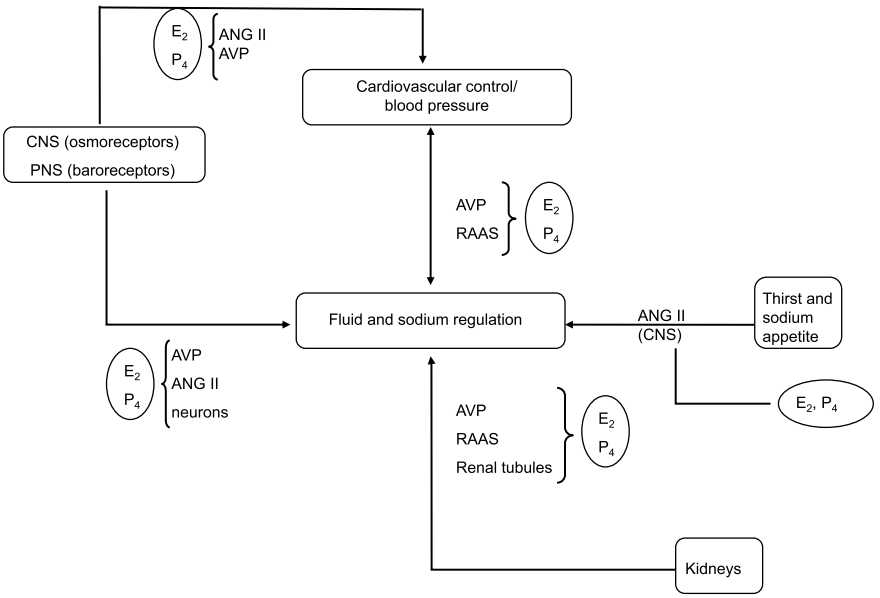

Fig. 5.3 Schematic to illustrate the complex control of fluid and sodium balance and the multiple ways in which estradiol (E2) and progesterone (P4) may influence these processes. AVP indicates arginine vasopressin; ANG II, angiotensin II; CNS, central nervous system; PNS, peripheral nervous system; RAAS, renin-angiotensin-aldosterone system (Stachenfeld 2008, used with permission)

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; 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.5.4). 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, which are also sensitive to changes in plasma volume during exercise, drinking or dehydration (Fig. 5.3).

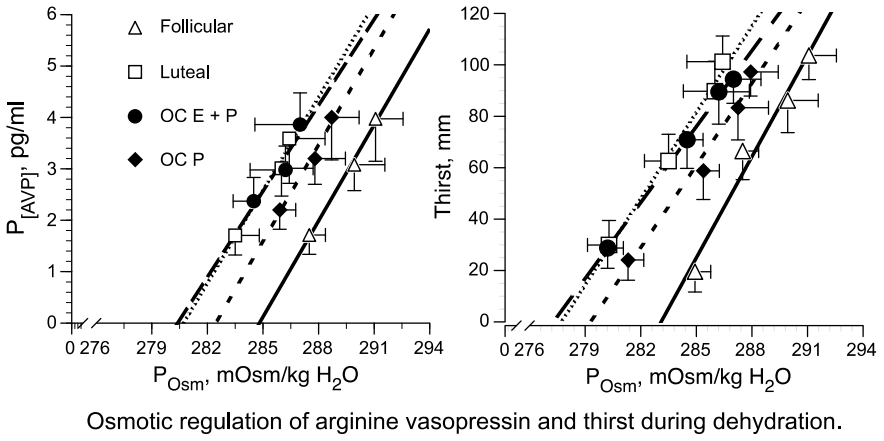

Fig. 5.4 Plasma arginine vasopressin (AVP) concentration and thirst sensation as a function of plasma osmolality (P_{Osm}) during 120 min of hypertonic (3.0% NaCl) saline infusion the early-follicular and mid-luteal phases of the menstrual cycle, and during combined (ethinyl estradiol + progestin, OC-E+P) 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 et al. 1999, 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 powerfull 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. 5.4) 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 (Heritage et al. 1980; Sar and Stumpf 1980) and there are sex differences in the activity and size in these nuclei (Ishunina et al. 2000). Resting P_{Osm} is greater in men than in women (in the early-follicular phase) (Stachenfeld et al. 2001; Claybaugh et al. 2000), although men have greater AVP sensitivity and blood pressure responses to hypertonic saline infusion (Stachenfeld et al. 1997). 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. 1999) 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 younger women. 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. 1999). A more recent paper, however, showed little impact of the menstrual cycle, estrogen, progesterone or E:P ratio on copeptin, a molecule usually highly correlated with AVP, and one sensitive to changes in plasma osmolality (Giersch et al. 2021).

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, to cool 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 and Stachenfeld 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. 5.5). 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. 5.5) 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 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 and Stachenfeld 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 smaller 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

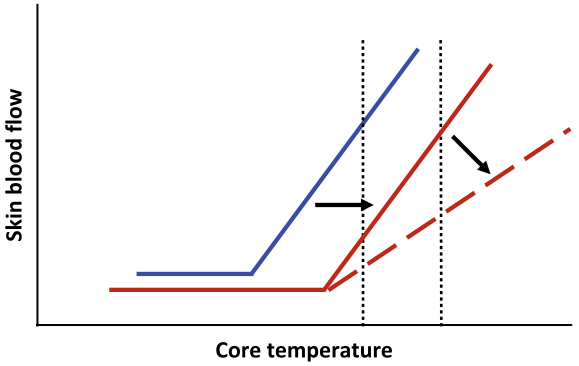

Fig. 5.5 Schematic example of graphs used in analysis of thermoregulatory effector mechanisms (primarily sweating and cutaneous vasodilation), showing the relevant effector as a function of core body temperature. As core temperature increases, a point is reached (the threshold) at which the heat dissipation 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 et al. 2014, Copyright 2014 The American Physiological Society, used with permission)

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*), 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, the slower sweating rates in women in the hot wet environment may convey an advantage. Also of interest is a study demonstrating a number of sex-specific miRNA following running exercise, suggesting that not all differences between men and women are due to differences in body size and hormone exposure. It is unclear whether these miRNA affects are specific to thermoregulatory targets (Hicks et al. 2018).

Sex Hormone Effects Within Women During Exercise

Thermoregulation in humans is keeping body temperature constant despite changes to the environment. During heat exposure and exercise, sympathetic cholinergic nerves in the skin cause sweating via eccrine sweat glands resulting in sweat evaporation. These responses are controlled through centers in the hypothalamus sensitive to estrogen and progesterone, and effects of sex hormones are also seen in the periphery in skin blood flow and sweating (Charkoudian and Stachenfeld 2015). Further, as described above, sex hormones (specifically estrogens and progesterone) can impact fluid and electrolyte regulation. These hormones can also alter thermoregulatory mechanisms (Sims et al. 2007). Early studies conducted in women in different phases of 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 VO2 peak for 40 min) under each hormonal condition. We showed a change in resting core temperature 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). For a given 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. Conversely, the lower sweating rates during OC-P were associated with a significant plasma volume contraction (~3%) that occurred with OC-P (Stachenfeld 2008). Throughout exercise, sweating sensitivity as represented by slopes of the relationship between sweat rate and core temperature was unaffected by hormone condition. Furthermore, core temperature was higher during the mid-luteal compared to the early-follicular phase of the menstrual cycle (Fig. 5.6). However, the addition of estrogen to progestin-only pills *prevented* the rightward shift in core temperature. Further, the onset of sweating occurred at a lower core temperature with the addition of estrogen to progestin pills.

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 does 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.

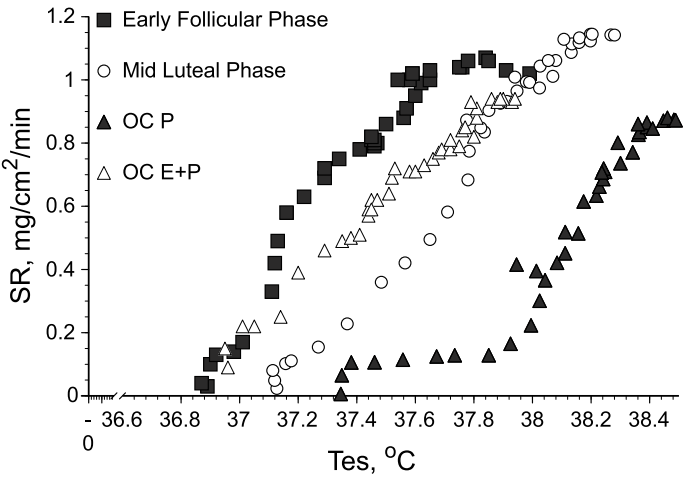

Fig. 5.6 Sweating rate (SR) as a function of core (esophageal) temperature during 40 min of exercise in the heat in young, healthy women during the early-follicular and mid-luteal phases of the menstrual cycle and during combined (ethinyl estradiol + progestin, OC-E+P) and progestin-only (OC-P) hormonal 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 (Data are based on Stachenfeld et al. 2000, Copyright 2000. The American Physiological Society, used with permission)

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, 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, estradiol 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 and colleagues (Araki et al. 1981) measured sweating responses to exercise in a hot environment in trained and untrained women during the same phase of the 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). This brings up the earlier point that when possible, testing at multiple phases of the menstrual cycle is key to truly testing hypotheses, or choosing the correct phase in which to test is key to answer the research question.

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

Menopause 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 thermoregulation. During the menopausal transition, women often experience symptoms such as vaginal dryness, hot flashes, and night sweats.

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, similar to what is observed in young women.

Although the mechanisms controlling skin blood flow and sweating during postmenopausal vasomotor symptoms (VMS) have 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, and anecdotal compliance is low. 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 (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. Consideration of the research question and hypothesis is key to deciding which phase of the cycle to test women, and whether women taking oral contraceptives can be included. 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. For the latter, because chromosomes can be altered in the formation of cell lines, confirmation of the sex of these cells should be made or fresh cells used when possible (Vallabhajosyula et al. 2020).

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 for 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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References

Almond CSD, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston marathon. N Engl J Med. 2005;352:1550–6.

Araki T, Matsushita K, Umeno K, Tsujino A, Toda Y. Effect of physical training on exercise-induced sweating in women. J Appl Physiol. 1981;51(6):1526–32.

Armstrong L, Casa D, Millard-Stafford M, Moran D, Pyne S, Roberts W. American college of sports medicine position stand. Exertional heat illness during competition. Med Sci Sports Exerc. 2007;39:556–72. https://doi.org/10.1249/MSS.0b013e31802fa199

Barontini M, Garcia-Rudaz MC, Veldhuis JD. Mechanisms of hypothalamic-pituitary-gonadal disruption in polycystic ovarian syndrome. Arch Med Res. 2001;32:544–52. https://doi.org/10.1016/S0188-4409(01)00325-3

Boschitsch E, Mayerhofer S, Magometschnigg D. Hypertension in women: the role of progesterone and aldosterone. Climacteric. 2010;13(4):307–13. https://doi.org/10.3109/13697131003624649

Brooks EM, Morgan AL, Pierzga JM, Wladkowski SL, Gorman JT, Derr JA, et al. Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. J Appl Physiol. 1997;83(2):477–84.

Brooks-Asplund EM, Cannon JG, Kenney WL. Influence of hormone replacement therapy and aspirin on temperature regulation in postmenopausal women. Am J Physiol. 2000;279:R839–48.

Byrne C, Lee JK, Chew SA, Lim CL, Tan EY. Continuous thermoregulatory responses to mass-participation distance running in heat. Med Sci Sports Exerc. 2006;38(5):803–10. https://doi.org/10.1249/01.mss.0000218134.74238.6a

Calzone WL, Silva C, Keefe DL, Stachenfeld NS. Progesterone does not alter osmotic regulation of AVP. Am J Physiol Regul Integr Comp Physiol. 2001;281:R2011–20.

Charkoudian N, Johnson J. Altered reflex control of cutaneous circulation by female sex steroids is independent of prostaglandins. Am J Physiol. 1999a;276:H1634–40.

Charkoudian N, Johnson JM. Reflex control of cutaneous vasoconstrictor system is reset by exogenous female reproductive hormones. J Appl Physiol. 1999b;87:381–5.

Charkoudian N, Stachenfeld N. Reproductive hormone influences on thermoregulation in women. Compr Physiol. 2014;4(2):793–804. https://doi.org/10.1002/cphy.c130029

Charkoudian N, Stachenfeld N. Sex hormone effects on autonomic mechanisms of thermoregulation in humans. Auton Neurosci. 2015;196:75–80. https://doi.org/10.1016/j.autneu.2015.11.004

Claybaugh JR, Sato AK, Crosswhite LK, Hassell LH. Effects of time of day, gender, and menstrual cycle phase on the human response to oral water load. Am J Physiol. 2000;279:R966–73.

Creinin MD, Lippman JS, Eder SE, Godwin AM, Olson W. The effect of extending the pill-free interval on follicular activity: triphasic norgestimate/35 μg ethinyl estradiol versus monophasic levonorgestrel/20 μg ethinyl estradiol. Contraception. 2002;66:147–52. https://doi.org/10.1016/S0010-7824(02)00344-X

D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise carbohydrate metabolism by estrogen and progesterone in women. A J Physiol Endocrinol Metab. 2002;283(5):E1046–55. https://doi.org/10.1152/ajpendo.00271.2002

Day DS, Gozansky WS, Van Pelt RE, Schwartz RS, Kohrt WM. Sex hormone suppression reduces resting energy expenditure and β-adrenergic support of resting energy expenditure. J Clin Endocrinol Metab. 2005;90(6):3312–7. https://doi.org/10.1210/jc.2004-1344

Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030. https://doi.org/10.1210/er.2011-1034

Diamanti-Kandarakis E, Christakou C, Marinakis E. Phenotypes and environmental factors: their influence in PCOS. Curr Pharm Des. 2012;18(3):270–82. https://doi.org/10.2174/138161212799040457

Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91(1):48–53. https://doi.org/10.1210/jc.2005-1329

Fortney SM, Wenger CB, Bove JR, Nadel ER. Effects of plasma volume on forearm venous and cardiac stroke volumes during exercise. J Appl Physiol. 1983;55:884–90.

Gagnon D, Kenny GP. Does sex have an independent effect on thermoeffector responses during exercise in the heat? J Physiol. 2012a;590(Pt 23):5963–73. https://doi.org/10.1113/jphysiol.2012.240739

Gagnon D, Kenny GP. Sex differences in thermoeffector responses during exercise at fixed requirements for heat loss. J Appl Physiol. 2012b;113(5):746–57. https://doi.org/10.1152/japplphysiol.00637.2012

Giersch GEW, Charkoudian N, Morrissey MC, Butler Cody R, Colburn AT, Caldwell AR, Kavouras SA, Casa DJ. Estrogen to progesterone ratio and fluid regulatory responses to varying degrees and methods of dehydration. Front Sports Active Living. 2021;3. https://doi.org/10.3389/fspor.2021.722305

Hapgood JP, Africander D, Louw R, Ray RM, Rohwer JM. Potency of progestogens used in hormonal therapy: toward understanding differential actions. J Steroid Biochem Mol Biol. 2014;142:39–47. https://doi.org/10.1016/j.jsbmb.2013.08.001

Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97(4):1159–68.

Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2011;17(2):171–83. https://doi.org/10.1093/humupd/dmq045

Heritage AS, Stumpf WE, Sar M, Grant LD. Brainstem catecholamine neurons are target sites for sex steroid hormones. Science. 1980;207:1377–9. https://doi.org/10.1126/science.7355296

Hertig BA, Sargent 2nd F. Acclimatization of women during work in hot environments. Fed Proc. 1963;22:810–3.

Hicks SD, Paige J, Middleton FA, Omar P, Zofia G. Distance running alters peripheral microRNAs implicated in metabolism fluid balance and myosin regulation in a sex-specific manner. Physiol Genom. 50(8):658–667. https://doi.org/10.1152/physiolgenomics.00035.2018

Hubing KA, Wingo JE, Brothers RM, Del Coso J, Low DA, Crandall CG. Nitric oxide synthase inhibition attenuates cutaneous vasodilation during postmenopausal hot flash episodes. Menopause. 2010;17(5):978–82. https://doi.org/10.1097/gme.0b013e3181d674d6

Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;96(1):E48–56. https://doi.org/10.1210/jc.2010-0828

Ishunina TA, Kruijver FPM, Balesar R, Swaab DF. Differential expression of estrogen receptor α and ß immunoreactivity in the human supraoptic nucleaus in relation to sex and aging. J Clin Endocrinol Metab. 2000;85:3283–91.

Kenney WL, Anderson RK. Responses of older and younger women to exercise in dry and humid heat without fluid replacement. Med Sci Sports Exerc. 1988;20(2):155–60. https://doi.org/10.1249/00005768-198820020-00009

Kolka M, Stephenson L. Control of sweating during the human menstrual cycle. Eur J Appl Physiol. 1989;58:890–5. https://doi.org/10.1007/BF02332224

Kuwahara T, Inoue Y, Abe M, Sato Y, Kondo N. Effects of menstrual cycle and physical training on heat loss responses during dynamic exercise at moderate intensity in a temperate environment. Am J Physiol Regul Integr Comp Physiol. 2005a;288(5):R1347–53. https://doi.org/10.1152/ajpregu.00547.2004

Kuwahara T, Inoue Y, Taniguchi M, Ogura Y, Ueda H, Kondo N. Effects of physical training on heat loss responses of young women to passive heating in relation to menstrual cycle. Eur J Appl Physiol. 2005b;94(4):376–85. https://doi.org/10.1007/s00421-005-1329-0

Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med. 2001;111(8):607–13. https://doi.org/10.1016/S0002-9343(01)00948-2

Low D, Davis S, Keller D, Shibasaki M, Crandall C. Cutaneous and hemodynamic responses during symptomatic postmenopausal women. Menopause. 2008;15:290–5. https://doi.org/10.1097/gme.0b013e3180ca7cfa

Low DA, Hubing KA, Del Coso J, Crandall CG. Mechanisms of cutaneous vasodilation during the postmenopausal hot flash. Menopause. 2011;18(4):359–65. https://doi.org/10.1097/gme.0b013e3181f7a17a

Luoto R, Moilanen J, Heinonen R, Mikkola T, Raitanen J, Tomas E, et al. Effect of aerobic training on hot flushes and quality of life—a randomized controlled trial. Ann Med. 2012;44(6):616–26.

Moran LJ, Brinkworth G, Noakes M, Norman RJ. Effects of lifestyle modification in polycystic ovarian syndrome. Reprod Biomed Online. 2006;12(5):569–78. https://doi.org/10.1016/S1472-6483(10)61182-0

Nadel ER, Fortney SM, Wenger CB. Effect of hydration state on circulatory and thermal regulations. J Appl Physiol. 1980;49:715–21.

Oberye JJL, Mannaerts BMJL, Huisman JAM, Timmer CJ. Pharmacokinetic and Pharmacodynamic characteristics of ganirelix (Antagon/Orgalutran). Part II. Dose-proportionality and gonadotropin suppression after multiple doses of ganirelix in healthy female volunteers. Fertil Steril. 1999a;72(6):1006–12. https://doi.org/10.1016/S0015-0282(99)00414-8

Oberye JJL, Mannaerts BMJL, Huisman JAM, Timmer CJ. Pharmacokinetic and Pharmacodynamic characteristics of ganirelix (Antagon/Orgalutran). Part I. Absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. Fertil Steril. 1999b;72(6):1001–5. https://doi.org/10.1016/S0015-0282(99)00413-6

Roberts MF, Wenger CB, Stolwijk JA, Nadel ER. Skin blood flow and sweating changes following exercise training and heat acclimation. J Appl Physiol. 1977;43:133–7.

Rogers SM, Baker MA. Thermoregulation during exercise in women who are taking oral contraceptives. Eur J Appl Physiol. 1997;75:34–8. https://doi.org/10.1007/s004210050123

Rojas J, Chavez-Castillo M, Bermudez V. The role of metformin in metabolic disturbances during pregnancy: polycystic ovary syndrome and gestational diabetes mellitus. Int J Reprod Med. 2014;2014:797681.

Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev. 1974;54(1):75–159.

Sar M, Stumpf WE. Simultaneous localization of [3H]estradiol and neurophysin I or arginine vasopressin in hypothalamic neurons demonstrated by a combined technique of dry-mount autoradiography and immunohistochemistry. Neurosci Lett. 1980;17:179–84. https://doi.org/10.1016/0304-3940(80)90081-6

Sawka MN, Wenger CB. Physiological responses to acute exercise heat stress. In: Pandolf KB, Sawka MN, Gonzalez RR, editors. Human performance physiology and environmental medicine at terrestrial extremes. Indianapolis, IN: Benchmark; 1988. p. 97–151.

Sawka MN, Young AJ, Latzka WA, Neufer PD, Quigley MD, Pandolf KB. Human tolerance to heat strain during exercise: influence of hydration. J Appl Physiol. 1992;73:368–75.

Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, Stachenfeld NS. American College of Sports Medicine position stand. Exercise and fluid replacement. Med Sci Sports Exerc. 2007;39(2):377–90. https://doi.org/10.1249/mss.0b013e31802ca597

Schlaff WD, Lynch AM, Hughes HD, Cedars MI, Smith DL. Manipulation of the pill-free interval in oral conceptive pill users: the effect on follicular suppression. Am J Obstet Gynecol. 2004;190:943–51. https://doi.org/10.1016/j.ajog.2004.02.012

Shapiro Y, Pandolf KB, Avellini BA, Pimental NA, Goldman RF. Physiological responses of men and women to humid and dry heat. J Appl Physiol. 1980;49(1):1–8.

Shibasaki M, Davis SL, Cui J, Low DA, Keller DM, Durand S, et al. Neurally mediated vasoconstriction is capable of decreasing skin blood flow during orthostasis in the heat-stressed human. J Physiol. 2006;575(Pt 3):953–9.

Sims ST, Rehrer NJ, Bell ML, Cotter JD. Preexercise sodium loading aids fluid balance and endurance for women exercising in the heat. J Appl Physiol. 2007;103(2):534–41. https://doi.org/10.1152/japplphysiol.01203.2006

Speroff L, Glass RH, Kase NG. Steroid contraception clinical gynecological endocrinology and infertility. 4th ed. Baltimore: Williams & Wilkins; 1999. p. 873–9.

Stachenfeld NS. Sex hormone effects on body fluid regulation. Exerc Sport Sci Rev. 2008;36(3):152–9. https://doi.org/10.1097/JES.0b013e31817be928
Stachenfeld NS, Keefe DL. Estrogen effects on osmotic regulation of AVP and fluid balance. Am J Physiol. 2002;283:E711–21.
Stachenfeld NS, Taylor HS. Effects of estrogen and progesterone administration on extracellular fluid. J Appl Physiol. 2004;96:1011–8. https://doi.org/10.1152/japplphysiol.01032.2003
Stachenfeld NS, Taylor HS. Progesterone increases plasma and extracellular fluid volumes independent of estradiol. J Appl Physiol. 2005;98:1991–7. https://doi.org/10.1152/japplphysiol.00031.2005
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. https://doi.org/10.1152/japplphysiol.91211.2008
Stachenfeld NS, Mack GW, DiPietro L, Nadel ER. Mechanism for attenuated thirst in aging: role of central volume receptors. Am J Physiol. 1997;272:R148–57.
Stachenfeld NS, DiPietro L, Palter SF, Nadel ER. Estrogen influences osmotic secretion of AVP and body water balance in postmenopausal women. Am J Physiol. 1998;274:R187–95.
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.
Stachenfeld NS, Silva C, Keefe DL. Estrogen modifies the temperature effects of progesterone. J Appl Physiol. 2000;88:1643–9.
Stachenfeld NS, Keefe DL, Palter SF. Effects of estrogen and progesterone on transcapillary fluid dynamics. Am J Physiol. 2001a;281:R1319–29.
Stachenfeld NS, Splenser AE, Calzone WL, Taylor MP, Keefe DL. Sex differences in osmotic regulation of AVP and renal sodium handling. J Appl Physiol. 2001b;91:1893–901.
Stachenfeld NS, Yeckel CW, Taylor HS. Greater exercise sweating in obese women with polycystic ovary syndrome compared with obese controls. Med Sci Sports Exerc. 2010;42(9):1660–8. https://doi.org/10.1249/MSS.0b013e3181d8cf68
Stephenson LA, Kolka MA, Francesconi R, Gonzalez RR. Circadian variations in plasma renin activity, catecholamines and aldosterone during exercise in women. Eur J Appl Physiol. 1989;58:756–64. https://doi.org/10.1007/BF00637388
Stephenson LA, Kolka MA. Esophageal temperature threshold for sweating decreases before ovulation in premenopausal women. J Appl Physiol. 1999;86(1):22–8.
Tankersley CG, Nicholas WC, Deaver DR, Mikita D, Kenney WL. Estrogen replacement therapy in middle-aged women: thermoregulatory responses to exercise in the heat. J Appl Physiol. 1992;73(4):1238–45.
Tripathi A, Mack GW, Nadel ER. Cutaneous vascular reflexes during exercise in the heat. Med Sci Sports Exerc. 1990;22:796–803. https://doi.org/10.1249/00005768-199012000-00011
Tsilchorozidou T, Overton C, Conway GS. The pathophysiology of polycystic ovary syndrome. Clin Endocrinol. 2004;60:1–17. https://doi.org/10.1046/j.1365-2265.2003.01842.x
Vallabhajosyula S, Ponamgi SP, Shrivastava S, Sundaragiri PR, Miller VM. Reporting of sex as a variable in cardiovascular studies using cultured cells: a systematic review. FASEB J. 2020;34(7) 8778–8786. https://doi.org/10.1096/fj.202000122R
Wenner MM, Stachenfeld NS. Blood pressure and water regulation: understanding sex hormone effects within and between men and women. J Physiol. 2012;590(Pt 23):5949–61. https://doi.org/10.1113/jphysiol.2012.236752
Wenner MM, Taylor HS, Stachenfeld NS. Progesterone enhances adrenergic control of skin blood flow in women with high but not low orthostatic tolerance. J Physiol. 2011a;589.4(4):975–86. https://doi.org/10.1113/jphysiol.2010.194563
Wenner MM, Taylor HS, Stachenfeld N. Endothelin B receptor contribution to peripheral microvascular function in women with polycystic ovary syndrome. J Physiol. 2011b;589(19):4671–9. https://doi.org/10.1113/jphysiol.2011.216218

Wenner MM, Haddadin AS, Taylor HS, Stachenfeld NS. Mechanisms contributing to low orthostatic tolerance in women: the influence of oestradiol. J Physiol. 2013;591(9):2345–55. https://doi.org/10.1113/jphysiol.2012.247882

Wyndham CH, Morrison JF, Williams CG. Heat reactions of male and female Caucasians. J Appl Physiol. 1965;20(3):357–64.

Chapter 6
Sex Hormone Effects on the Nervous System and Their Impact on Muscle Strength and Motor Performance in Women

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Introduction

Understanding the integration of the nervous system and the endocrine system can be daunting. Both systems, by definition, have the ability to enact effects in the local tissues as well as have far-reaching effects across the human body. Furthermore, both systems are largely governed by homeostatic mechanisms which are consistently dynamic, moving either toward or away from the given homeostatic set point. This chapter attempts to tackle the complex interactions of these two systems. First, the neurological effects of sex hormones and their metabolites are examined at a basic level to determine if it is reasonable to expect that they change human behavior on a larger scale. Since sex hormones do not change in isolation (e.g., the menstrual cycle results in predictable changes in multiple hormones), we explore how the menstrual cycle modifies the motor nervous system in vivo. Next, the effect of the menstrual cycle on human motor behavior is considered. Finally, a number of caveats relating to the interpretation of present scientific knowledge in the area are addressed. By the end of this chapter, the reader should firmly grasp the non-reproductive effects of sex hormones on the nervous system at a mechanistic level; however, they will also be acutely aware that translating and/or leveraging the effects of sex hormones to alter motor behavior remains an extremely challenging task.

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Sex Hormones and Their Metabolites—A Dynamic Ecosystem

While "female sex hormones" are classically conceived as two classes of hormones, estrogens and progesterones, this may not fully reflect the dynamic biochemical metabolism of sex hormones as a whole. A more complex view, where primary sex hormones (testosterone, estradiol, and progesterone) are considered to simply be metabolic derivatives of cholesterol with numerous intermediaries, is a more encompassing, but still insufficient perspective (see Fig. 6.1).

It is not enough to acknowledge that sex hormones are chemically related, and the metabolic intermediaries between the primary sex hormones need to be recognized as hormones which may actively alter muscular strength or function. In both human and animal models, the production and clearance rates of these hormones are poorly understood and appear to be different between biologic compartments (e.g., brain areas, plasma, fat, peripheral nerve, and tendon) (Wang et al. 1997; Bixo et al. 1997; Morfin et al. 1992) and change across the lifespan (Payne and Jaffe 1975). The intermingled web of transitory sex hormones is difficult to untangle and isolate, but it is further complicated when one recognizes that the precursor cholesterol molecule exists in both a sulfonated and unsulfonated form, creating a parallel web of sex hormones and intermediaries that have distinctly different biologic properties. Indeed, the metabolism between sulfonated sex hormone intermediaries may be

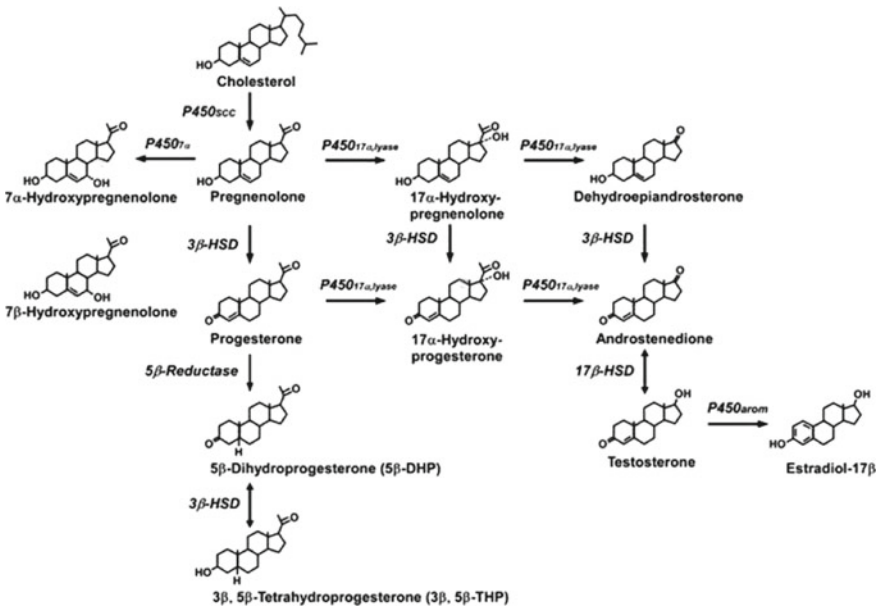

Fig. 6.1 General metabolic pathway for sex hormones in the brain (Tsutsui 2011). Image reproduced with the author's permission

slowed by as much as 40% compared to their non-sulfonated counterparts in humans (Neunzig et al. 2014). A slower conversion rate may create a longer time period in which sex hormones and their intermediaries can enact changes on the muscle tissue or nervous system. It should not be assumed that sulfonated and unsulfonated hormones exist in equal quantities, and it has been shown that their appearance is highly tissue dependent in humans (Morfin et al. 1992; Bixo et al. 1997) and life cycle dependent (Leowattana 2004). While there is no direct correlation between serum and brain levels of sex hormones in women, there is a general trend toward higher brain estradiol levels in the preoptic area, hypothalamus, and substantia nigra of women with high serum estradiol. There does not appear to be a similar trend for testosterone, and there is substantial variation across brain areas for both testosterone and estradiol (Bixo et al. 1997). The quantity of sulfonated and unsulfonated DHEA (Dehydroepiandrosterone) and pregnenolone in tendons and peripheral nerves also have substantial variance across the population; however, limited data suggest that unsulfonated pregnenolone and sulfonated DHEA predominate in peripheral nerves of women while muscle and tendon contain both sulfonated and unsulfonated types of pregnenolone and DHEA without any variant being dominant (Morfin et al. 1992). Finally, serum and cerebral spinal fluid levels of both sulfonated and unsulfonated forms of DHEA decrease after 18–25 years of age (Leowattana 2004; Guazzo et al. 1996).

It is necessary to be mindful of this highly complex and dynamic ecosystem when addressing whether sex hormones, the menstrual cycle, and hormonal contraceptives alter motor control in women. Our failure to fully comprehend the entire sex hormone ecosystem does not prohibit us from drawing conclusions on the effect of sex hormones on the nervous system, but it does urge a cautious interpretation of existing applied research.

Do Sex Hormones and/or the Menstrual Cycle Phases Affect the Nervous System?

Sex hormones are among a larger class of hormones called neuro-steroids, indicating that they exert their action at the level of the brain and are often times synthesized within the central nervous system itself (Stoffel-Wagner 2001). Sex hormones in the plasma can also easily traverse the blood–brain barrier due to their high lipid solubility (Stoffel-Wagner 2001) and other unknown mechanisms (Wang et al. 1997). Thus, there are at least two ways in which sex hormones and their metabolites may be introduced to the nervous system to enact effects on the motor system. This section explores the ways in which sex hormones and their metabolites exert inhibitory or excitatory effects on the nervous system and how they specifically alter the human motor nervous system.

General Effects on the Nervous System

Sex hormones and their intermediary metabolites have been shown to have profound effects on the nervous system at the cellular level. The general mechanisms of action for the most potent hormones will be discussed. To aid in the comprehension of the effects, their overall actions will be simplified as either net excitatory or inhibitory to the nervous system. For example, a molecule may be a Gamma-Aminobutyric Acid (GABA) receptor antagonist (blocker), but since GABA's effects are largely neural-inhibitory in nature, the net effect of a GABA antagonist is as an excitatory agent on the nervous system.

Pregnenolone is a first-order precursor to progesterone which has been shown to both enhance the action of GABA as well as directly activate the GABAA receptor in bovine preparations (Callachan et al. 1987). It is capable of both prolonging the temporal influx of chloride ions through the receptor's channel as well as directly opening the channel when pregnenolone levels are further elevated. Thus, unsulfonated pregnenolone has inhibitory effects on the nervous system. In contrast, pregnenolone-sulfate is a GABA receptor antagonist in rodent cell cultures (Mienville and Vicini 1989). Pregnenolone-sulfate decreases the frequency which the chloride channels open on the GABA receptor, decreasing the ability to inhibit neuron discharge (Mienville and Vicini 1989) and creating net excitatory effects on the nervous system.

The effects of pregnenolone and pregnenolone-sulfate create an interesting dichotomy for two chemically similar hormones that have extremely potent, but opposing, effects on the GABA receptor. Both of these hormones oscillate across the menstrual cycle (Wang et al. 1996), but they also are synthesized locally and have differing levels based on the tissue and location (Takase et al. 1999; Morfin et al. 1992).

Progesterone is also a neuro-steroid which can be synthesized within the nervous system as well as be introduced from plasma via the blood–brain barrier (Wang et al. 1997). Progesterone has a net inhibitory effect on the nervous system (Smith et al. 1987). While not as robust as pregnenolone, progesterone is able to increase the inhibitory response of the GABAA receptor up to 80% in the presence of GABA (Smith 1989). This net inhibitory effect has been shown in the rodent model where progesterone decreases cerebellum neuron discharge during treadmill locomotion (Smith et al. 1989).

Estradiol appears to play a broad role in both the development and maintenance of the central nervous system (McEwen and Alves 1999). This is evidenced by the wide array of brain structures which contain various densities of estrogen receptor isoforms (McEwen and Alves 1999). The long-term and developmental effects of estradiol have largely overshadowed the short-term transitory effects of estradiol which are the focus of this chapter and book as a whole. Recent work in rodents has indicated that estrogen receptors on GABA releasing (GABAergic) neurons may be the primary way in which estradiol creates a net excitatory effect on the nervous system (Schultz et al. 2009). Activation of estrogen receptor α on GABAergic neurons

attenuates the release of GABA. This mechanism explains how estradiol rapidly affects neurotransmitter pathways for both dopamine (Becker 1990; Xiao et al. 2003) and glutamate (Smith et al. 1988) in rodent models. This excitatory effect has been shown in vivo whereby estradiol administration increases neuronal discharge of the rat cerebellum during treadmill walking (Smith et al. 1989).

DHEA and DHEA-sulfate [DHEA(S)] have been shown to target multiple neuronal receptors (Spivak 1994; Monnet et al. 1995; Mellon and Griffin 2002) and modulate a number of neurotransmitter systems (Rhodes et al. 1996; Wolf and Kirschbaum 1999; Murray and Gillies 1997; Meyer et al. 2002) in animal models. Levels of DHEA(S) arising from the human adrenal cortex or adrenal gland (in fetal humans) fluctuate wildly across the human lifespan (Peretti and Forest 1978); however, there is evidence that DHEA(S) produced in the nervous system are unrelated to their counterparts in the periphery of animal models (Baulieu 1996; Baulieu and Robel 1998). Therefore, differential levels of peripheral DHEA(S) or the use of nutritional supplements purporting to affect DHEA(S) should have little effect on the nervous system. DHEA(S) has been shown to produce a net excitatory effect on the rodent nervous system primarily through its action on GABA and glutamate releasing neurons (Wolf and Kirschbaum 1999; Meyer et al. 2002; Dong et al. 2007), though also through actions on acetylcholine (Rhodes et al. 1996) and dopamine (Murray and Gillies 1997).

Sex hormones and their metabolites have clear effects on nervous system function; however, the net result of these many neuro-excitatory and inhibitory hormones is less certain. That the levels of these hormones change dynamically throughout the day, across the menstrual cycle, and vary across different regions of the nervous system further complicates the process of determining their effect on human performance. At the clinical level, it is typically more feasible to track how performance is modified as a function of external biological processes. Therefore, the remainder of this chapter will consider the holistic effect of the menstrual cycle on parameters of neuro-motor athletic performance.

Sex Hormone/Menstrual Cycle Phase Effects on Motor Control in Humans

There are two primary ways to examine the excitation of the motor system across the menstrual cycle: (1) direct stimulation of nervous tissue or (2) recording of single motor unit activity during voluntary contractions. Direct stimulation of the motor cortex and corticospinal tract (with transcranial magnetic stimulation) allows researchers to investigate the transmission of corticospinal excitation to motoneurons and the corticospinal control of spinal pathways. The corticospinal track is the primary tract involved with voluntary movement; however, it must be noted, that when assessing the changes in an EMG of a remote limb muscle, there are

influences to many segmental and supraspinal factors other than the direct corticomotoneuronal input (Pierrot-Deseilligny and Burke 2012). Nevertheless, transcranial magnetic stimulation allows researchers to noninvasively examine the excitatory/inhibitory environment of the entire tract, from brain to muscle cell depolarization. Corticospinal tract excitability is reported to be highest and inhibition lowest in the late-follicular phase compared to early-follicular and mid-luteal menstrual phases (Smith et al. 2002). Similarly, Ansdell et al. (2019) observed lower short-interval cortical inhibition (SICI) during the late-follicular phase compared to the mid-luteal phase (Fig. 6.2). Increased mid-luteal inhibition probably reflects potentiation of GABAA inhibition. On the other hand, acute exercise-induced changes in primary motor cortex excitability seem to be similar in men and women, with no apparent connection to female sex hormone concentrations and the menstrual cycle (El-Sayes et al. 2019). Albeit, not entirely convincing, El-Sayes et al.'s data to appear to qualitatively show that baseline cortical inhibition (SICI) is lower during late-follicular phase when directly contrasted to mid-luteal, which would be in agreement with Ansdell et al. (2019).

In addition to excitation at the cortical level, corticospinal excitation can be gauged at the spinal level via the Hoffmann reflex (H-reflex). Stimulation of a peripheral nerve with electricity activates a component of the monosynaptic reflex loop (H-reflex) and enables researchers to examine changes in neural transmission at the spinal level. One of the main factors affecting spinal excitability is presynaptic inhibition, which is modulated through GABAA interneurons. Since sex hormones interact with GABAA, the endogenous hormonal changes associated with the menstrual cycle may affect spinal excitability. Nevertheless, previous studies have suggested that H-reflexes, and thus spinal excitability, do not change across the menstrual cycle (Hoffman et al. 2008, 2018a). On the other hand, Hoffman et al. (2018b) found

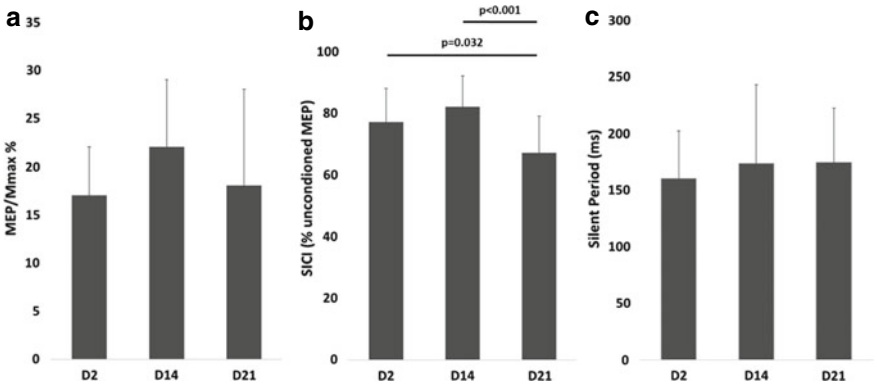

Fig. 6.2 Transcranial magnetic stimulation responses measured during different phases of the menstrual cycle (D2 = early follicular, D14 = late follicular, D21 = mid-luteal). **a** corticospinal excitability (MEP/Mmax %), **b** short-interval cortical inhibition (SICI), **c** cortical silent period. Data are presented as a mean ± SD. Significant differences in the SICI from the follicular phases (D2,D14) to the mid-luteal (D21) are denoted. (Figure produced from data Ansdell et al. 2019)

out that H-reflex amplitude (Hmax/Mmax ratio) did differ between men and women (women showed 18% higher H:M ratio), but this divergence was not due to menstrual cycle or changes in hormonal levels, since spinal level activity was assessed in both women and men at a point in time when naturally occurring levels of estradiol and progesterone were similar. When reviewing these studies, it is important to note that H-reflex was measured in a prone position. H-reflex, and thus spinal excitability, is a highly task-dependent phenomenon suggesting that more studies are needed focusing on active and dynamic conditions. Using the conditioning H-reflex test,

Hoffman et al. (2018a) observed decreased presynaptic inhibition during ovulation, when estrogen levels were relatively high, compared to menses, when estrogen levels were relatively low. Changes in presynaptic inhibition and estrogen correlated negatively, supporting the theory that increased estrogen levels attenuate GABA, leading to decreased presynaptic inhibition.

The summation of the stimulation research indicates that the corticospinal tract may be altered at the level of the brain or the spinal cord by the menstrual cycle and that movement generation may be facilitated in the late-follicular phase of the menstrual cycle. Recording of single motor unit discharges during voluntary exercise allows us to understand how the nervous system as a whole is able to generate movement. Preliminary results examining motor unit activity during the menstrual cycle indicate that discharge rates increase for some muscles (see Fig. 6.3), but not others, after ovulation (Tenan et al. 2013). The menstrual cycle creates evident modulations in motor activity which are observable via both stimulation and direct evaluation of motor neuron (motor unit) discharge. The following sections will explore how these modulations in the nervous system appear to manifest themselves as behavioral changes in muscle strength, endurance, and movement quality.

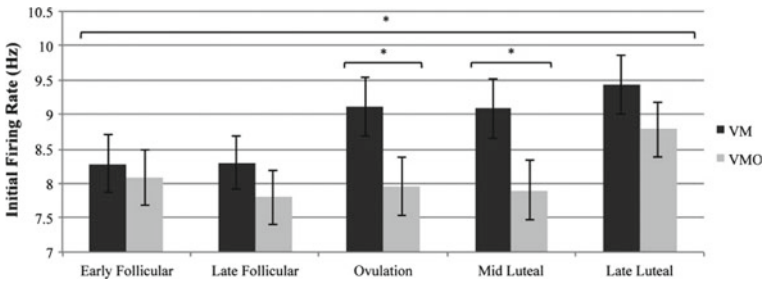

Fig. 6.3 Changes in motor unit discharge rate of the vastus medialis (VM) and vastus medialis oblique (VMO) across five phases of the menstrual cycle. While both muscles increase in discharge rate across the cycle, the timing of increases is different (Tenan et al. 2013)

Do Sex Hormones/Menstrual Cycle Phases Affect Muscle Strength?

The potential effect of sex hormones and the menstrual cycle on muscular strength has been an area of high interest and controversy for many years; however, a clear pattern is starting to emerge. There is an apparent diurnal effect of menstrual phase on muscular strength (Birch and Reilly 2002). During morning testing, maximal strength is lower in the luteal phase compared to the follicular phase, but testing in the afternoon suggests strength is augmented in the luteal phase. This diurnal effect may have confounded the numerous studies which did not control for time of day or simply kept time of day constant within participants. Research which focuses on the effect of whole menstrual phases has a tendency to show changes in maximal force (Phillips et al. 1996; Sarwar et al. 1996; Tenan et al. 2015; Birch and Reilly 2002), whereas, studies focused on specific hormones seldom see a clear effect (Elliott et al. 2003; Greeves et al. 1997), though there are notable exceptions to this generalization (Janse De Jonge et al. 2001; Kubo et al. 2009; Peltonen et al. 2022). The reasons for this discrepancy may be due to participant intraindividual variability, the timing of testing (within-day variability as well as between consecutive days) as well as intraindividual differences in tissue-specific sex hormone levels.

Generally, maximal force generation increases throughout the follicular phase; after ovulation, the ability to generate force decreases between 8 and 23% until returning to early-follicular levels just prior to menses (Phillips et al. 1996; Sarwar et al. 1996; Tenan et al. 2015). The biphasic pattern of maximal force generation appears to be relatively uniform with research support for both the upper extremity (Phillips et al. 1996; Sarwar et al. 1996), lower extremity (Sarwar et al. 1996; Tenan et al. 2015), and whole-body exercise (Birch and Reilly 2002). The increase in force generating ability may be a result of increased corticospinal tract excitability (Smith et al. 2002). The decrease in maximal force after ovulation corresponds to the increase in motor unit discharge at lower force levels (Tenan et al. 2013); this suggests that maximal forces may be lower in the luteal phase because maximal motor unit discharge is insufficient to generate the same level of force obtained in the follicular phase. This suggestion was also supported by more recent findings from Ansdell et al. (2019) where voluntary activation was observed to be lower in the luteal phase compared to the follicular phase. More recently, Peltonen et al. (2022) showed no differences in activation level between the menstrual cycle phases in eumenorrheic women. In addition, when more heterogeneous study designs were included in a meta-analysis examining changes in maximal force development across the menstrual cycle, it was concluded that there were no changes in maximal force generation (Blagrove et al. 2020). Importantly, the meta-analysis authors highlight that only a limited number of studies on this topic exist and several limitations were observed including small sample size, absence of hormonal measures, and weak control of confounding factors such as measurement time of the day and non-randomized order of the measurements (learning effect). Therefore, more research is

needed, especially regarding how the menstrual cycle affects force production during dynamic conditions.

For power-oriented athletes, it may be reasonable to check ovulatory status via urinary excretion of luteinizing hormone or basal body temperature tracking to determine if their athletic performance appears to be affected post-ovulation. Simple counting of days from menses to determine ovulation does not appear to be effective to examine strength changes (Dibrezzo et al. 1988; Tourville et al. 2016). While athlete monitoring to determine performance variability is advised, the clinician/coach should approach this training tactic with caution since the evidence is conflicting and there may be substantial intraindividual variability.

Do Sex Hormones/Menstrual Cycle Phases Affect Motor Performance?

The effect of sex hormones or the menstrual cycle on motor performance can be broadly classified into two categories: fine motor skill and gross motor skill. The neurologic pathways which characterize the two categories greatly overlap. Both incorporate levels of descending motor drive, integration of sensory information, and the actual feedback from sensory nerve endings in the muscle and joints as well as visual and auditory inputs. The present context is primarily concerned with changes in the behavioral outcome (e.g., dexterity goes up or down) as opposed trying to determine precisely why the behavioral outcome changes (e.g., differences in descending motor drive from the cortex, differential activation from the cerebellum, and differential perceptual visual inputs). Although the number of studies examining fine motor skill across the menstrual is small, they have generally all indicated that fine motor skill is increased in the mid-luteal phase of the menstrual cycle compared to the follicular phases (Hampson and Kimura 1988; Šimić et al. 2010; Zimmerman and Parlee 1973; Zoghi et al. 2015). Moreover, functional asymmetries (e.g., fine motor skill differences between left and right hand) appear to be decreased during the mid-luteal phase (Bayer and Hausmann 2012). In contrast, the quality of a gross motor task in both a normal and fatigued state appears to be lower in the mid-luteal phase (Tenan et al. 2015). The reason for this discrepancy is unclear. From a sporting perspective, the application of this work is also unclear since the majority of events incorporate both gross and fine motor control. Hormonal contraceptives may also exert effects on motor task performance. Limited cross-sectional research has suggested that oral hormonal contraceptives may decrease variability across the menstrual cycle, but taking oral hormonal contraceptives also creates systematic differences in vocal singing qualities and decreased steadiness in marksmanship (La et al. 2012, 2007; Hudgens et al. 1988) compared to women not on hormonal contraception. Before the "bench" science can be translated to the "real-world", more applied research is necessary. The translation of basic research into applied research

is further complicated by menstrual cycle irregularities and hormonal manipulation via contraceptive methods.

Caveats: The "Normal Menstrual Cycle" and Hormonal Contraception

The occurrence of amenorrhea (absence of menses) and oligomenorrhea (light or infrequent menses) has clear and evident physical manifestations which suggest an underlying hormonal disturbance. Less well characterized are the subtle menstrual cycle disturbances such as luteal phase defects or anovulation which also profoundly affect the hormonal profile of women in childbearing years. More than 50% of regularly exercising women exhibit some form of menstrual disturbance and half of them display no clinical abnormalities (i.e., appearance of normal menses but actually anovulatory or luteal phase defect) (De Souza et al. 2010). How menstrual cycle disturbances alter the nervous system is largely unknown. There are two perspectives from which menstrual disturbances can be viewed: (1) a lack of hormonal variation results in decreased motor performance variance or (2) a lack of expected hormonal variation causes an increase in performance variation. Perspective #1 is relatively easy to understand; if hormones do not cycle normally, then the effects of these hormones are unlikely to be observed. Perspective #2 is more counterintuitive; the normally cycling sex hormones, and resulting metabolites, have far-reaching effects and the time synchronization, and balance of hormones may be important to modulate motor performance. For instance, it is possible that the neuro-inhibitory effects of progesterone arising from ovulation are affected primarily at the peripheral level; this will not mitigate the neuro-inhibitory effects of progesterone in the central nervous system which is produced endogenously. It is also possible that the effects of sex hormones are tightly regulated and a decrease in circulating progesterone from ovulation simply results in an increase in progesterone produced by the nervous system locally. Both of these perspectives may be incorrect, but they relay the present lack of information regarding how disturbed menstrual patterns affect the nervous system. The sobering prevalence statistics about menstrual abnormalities suggest caution when assuming that an athlete, not on hormonal contraception, has a normal sex hormone profile.

Hormonal contraception can now be delivered systemically (oral contraceptive, injection, etc.) or locally (intrauterine device or ring). It is nearly completely unknown how these synthetic sex hormone analogues alter neurotransmitter function (Pletzer and Kerschbaum 2014), it is possible that hormonal contraception is neurologically inert and that their only neurologic effects are mediated by their effective decrease on endogenous production of bioactive sex hormones. However, it seems unlikely that the synthetic hormones, and their resulting metabolites, have no bioactive component on neurotransmitter systems when the endogenous analogues have profound effects. Devices delivering contraceptive hormones locally result in a decreased distribution

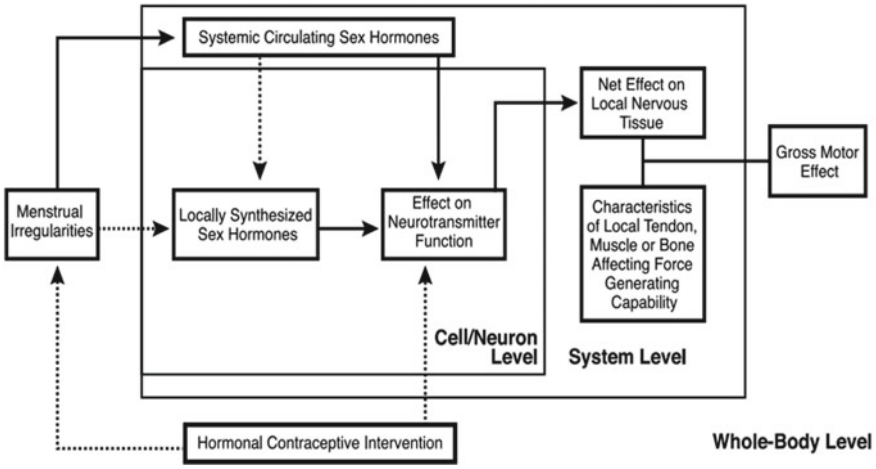

Fig. 6.4 General flowchart depicting how sex hormones modify motor behavior from the cellular to the whole-body level. Solid lines indicate known effects, and dashed lines indicate possible or probable effects

of the synthetic hormones (van den Heuvel et al. 2005), which may minimize any possible effects of synthetic hormones traversing the blood–brain barrier. It is also unknown if the use of hormonal contraceptives affects the production of sex hormones in the nervous system the way they do in the reproductive system.

With regard to hormonal contraceptives, there are a few studies suggesting no effect of oral contraceptives on motor control. Casey et al. (2014) showed no differences in stretch reflex fluctuation between eumenorrheic women and women using oral contraceptives. This was in line with modulation of spinal level activation (Hmax/Mmax ratio) between eumenorrheic women and women using oral contraceptives (Casey et. al. 2016). Similarly, Cueva et al. (2016) observed no changes in cortical excitability when comparing oral contraceptive phase to early-follicular phase. These results may indicate that oral contraceptives do not affect spinal level motor control. However, there is presently a lack of both basic and applied research showing either neurologic benefit or detriment as a result of hormonal contraceptive use (Fig. 6.4) and therefore more research is needed in future.

Conclusions

Where does the field of study go from here? There is irrefutable evidence that sex hormones and their metabolites alter the nervous system at a cellular level. It is also clear that many of these hormones can be produced within the nervous system itself and that the production of sex hormones from reproductive organs may only account for small change in the level of hormones in the nervous system. Moreover,

the amount of sex hormones in nervous tissue is not uniformly distributed, and it is unknown how menstrual cycle irregularities and hormonal contraception affect the nervous system. However, it should be noted that in most previous research, neural measurements have been completed in non-dynamic situations. Reflex responses will vary between conditions, and future research should be include examination of menstrual cycle/sex hormone concentrations on neuromuscular performance during dynamic tasks. All of this information points toward the idea that sex hormones may profoundly increase or decrease human performance but that (1) capturing these effects and leveraging them for athletic or rehabilitation gains is difficult, (2) intraindividual variability is likely extremely high, and (3) the complete underlying mechanisms which result in gains or losses are astronomically complex. Clinicians and researchers should be immediately wary of news outlets or individuals making blanket statements and claims such as "women shouldn't exercise before their period to avoid injury" or "athletic performance is decreased by taking birth control". Claims of this nature extend beyond what is scientifically known at this time and are typically made by individuals with ulterior motives and/or conflicts of interest (i.e., a potentially biased perspective). With the above warning in place, it is sensible for the coach or clinician to understand the menstrual status of their patient or client as this does have the potential to affect performance. Systematically track objective performance variation, the patient/client's perception of performance variation, and menstrual status. At the individual level, this information may be valuable in understanding the variability often observed in athletic performance or across an injury rehabilitation protocol.

References

Ansdell P, Brownstein CG, Skarabot J, Hicks KM, Simoes DC, Thomas K, Howatson G, Hunter SK, Goodall S. Menstrual cycle-associated modulations in neuromuscular function and fatigability of the knee extensors in eumenorrheic women. J Appl Physiol. 2019;126:1701–12.

Baulieu E. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res. 1996;52:1–32.

Baulieu E-E, Robel P. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. Proc Natl Acad Sci USA. 1998;95:4089–91.

Bayer U, Hausmann M. Menstrual cycle-related changes of functional cerebral asymmetries in fine motor coordination. Brain Cogn. 2012;79:34–8.

Becker JB. Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. Synapse. 1990;5:157–64.

Birch K, Reilly T. The diurnal rhythm in isometric muscular performance differs with eumenorrheic menstrual cycle phase. Chronobiol Int. 2002;19:731–42.

Bixo M, Andersson A, Winblad B, Purdy RH, Bäckström T. Progesterone, 5α-pregnane-3, 20-dione and 3α-hydroxy-5α-pregnane-20-one in specific regions of the human female brain in different endocrine states. Brain Res. 1997;764:173–8.

Balgrove RC, Bruinvels G, Pedlar CR. Variations in strength-related measures during the menstrual cycle in eumenorrheic women: a systematic review and meta-analysis. J Sci Med Sport. 2020;23(12):1220–7.

Callachan H, Cottrell GA, Hather NY, Lambert JJ, Nooney JM, Peters JA. Modulation of the GABAA receptor by progesterone metabolites. Proc R Soc Lond B Biol Sci. 1987;231:359–69.
Casey E, Hameed F, Dhaher YY. The muscle stretch reflex throughout the menstrual cycle. Med Sci Sports Exerc. 2014;46(3):600–9.
Casey E, Reese M, Okafor E, Chun D, Gagnon C, Nigl F, Dhaher YY. Influence of menstrual cycle and oral contraceptive phase on spinal excitability. PM&R. 2016;8(9):860–8.
Cueva AS, Galhardoni R, Cury RG, Parravano DC, Correa G, Araujo H, Cecilio SB, Raicher I, Toledo D, Silva V, Marcolin MA, Teixeira MJ, Ciampi de Andrade D. Normative data of cortical excitability measurements obtained by transcranial magnetic stimulation in healthy subjects. Neurophysiol Clin. 2016;46(1):43–51.
De Souza M, Toombs R, Scheid J, O'Donnell E, West S, Williams N. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. Hum Reprod. 2010;25:491–503
Dibrezzo R, Fort IL, Brown B. Dynamic strength and work variations during three stages of the menstrual cycle. J Orthop Sports Phys Ther. 1988;10:113–6.
Dong L-Y, Cheng Z-X, Fu Y-M, Wang Z-M, Zhu Y-H, Sun J-L, Dong Y, Zheng P. Neurosteroid dehydroepiandrosterone sulfate enhances spontaneous glutamate release in rat prelimbic cortex through activation of dopamine D1 and sigma-1 receptor. Neuropharmacology. 2007;52:966–74.
El-Sayes J, Turco CV, Skelly LE, Nicolini C, Fahnestock M, Gibala MJ, Nelson AJ. The effects of biological sex and ovarian hormones on exercise-induced neuroplasticity. Neuroscience. 2019;1(410):29–40.
Elliott KJ, Cable NT, Reilly T, Diver MJ. Effect of menstrual cycle phase on the concentration of bioavailable 17-beta oestradiol and testosterone and muscle strength. Clin Sci (lond). 2003;105:663–9.
Greeves JP, Cable NT, Luckas MJ, Reilly T, Biljan MM. Effects of acute changes in oestrogen on muscle function of the first dorsal interosseus muscle in humans. J Physiol. 1997;500(Pt 1):265–70.
Guazzo E, Kirkpatrick P, Goodyer I, Shiers H, Herbert J. Cortisol, dehydroepiandrosterone (DHEA), and DHEA sulfate in the cerebrospinal fluid of man: relation to blood levels and the effects of age. J Clin Endocrinol Metab. 1996;81:3951–60.
Hampson E, Kimura D. Reciprocal effects of hormonal fluctuations on human motor and perceptual-spatial skills. Behav Neurosci. 1988;102:456–9
Hoffman MA, Doeringer JR, Norcross MF, Johnson ST, Chappell PE. Presynaptic inhibition decreases when estrogen level rises. Scand J Med Sci Sports. 2018a;28(9):2009–15.
Hoffman M, Norcross M, Johnson S. The Hoffmann reflex is different in men and women. NeuroReport. 2018b;29(4):314–6.
Hoffman M, Harter RA, Hayes BT, Wojtys EM, Murtaugh P. The interrelationships among sex hormone concentrations, motoneuron excitability, and anterior tibial displacement in women and men. J Athl Train. 2008;43:364–72.
Hudgens GA, Fatkin LT, Billingsley PA, Mazurczak J. Hand steadiness: effects of sex, menstrual phase, oral contraceptives, practice, and handgun weight. Hum Factors. 1988;30:51–60.
Janse De Jonge XA, Boot CR, Thom JM, Ruell PA, Thompson MW. The influence of menstrual cycle phase on skeletal muscle contractile characteristics in humans. J Physiol. 2001;530:161–6.
Kubo K, Miyamoto M, Tanaka S, Maki A, Tsunoda N, Kanehisa H. Muscle and tendon properties during menstrual cycle. Int J Sports Med. 2009;30:139–43.
La FM, Ledger WL, Davidson JW, Howard DM, Jones GL. The effects of a third generation combined oral contraceptive pill on the classical singing voice. J Voice. 2007;21:754–61.
La FM, Sundberg J, Howard DM, Sa-Couto P, Freitas A. Effects of the menstrual cycle and oral contraception on singers' pitch control. J Speech Lang Hear Res. 2012;55:247–61.
Leowattana W. DHEAS as a new diagnostic tool. Clin Chim Acta. 2004;341:1–15.
McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev. 1999;20:279–307.

Mellon SH, Griffin LD. Neurosteroids: biochemistry and clinical significance. Trends Endocrinol Metab. 2002;13:35–43.
Meyer DA, Carta M, Partridge LD, Covey DF, Valenzuela CF. Neurosteroids enhance spontaneous glutamate release in Hippocampal neurons. Possible role of metabotropic sigma1-like receptors. J Biol Chem. 2002;277:28725–32.
Mienville J-M, Vicini S. Pregnenolone sulfate antagonizes GABA A receptor-mediated currents via a reduction of channel opening frequency. Brain Res. 1989;489:190–4.
Monnet FP, Mahé V, Robel P, Baulieu E-E. Neurosteroids, via sigma receptors, modulate the [3H] norepinephrine release evoked by N-methyl-D-aspartate in the rat hippocampus. Proc Natl Acad Sci U S A. 1995;92:3774–8.
Morfin R, Young J, Corpechot C, Egestad B, Sjövall J, Baulieu E-E. Neurosteroids: pregnenolone in human sciatic nerves. Proc Natl Acad Sci U S A. 1992;89:6790–3.
Murray H, Gillies G. Differential effects of neuroactive steroids on somatostatin and dopamine secretion from primary hypothalamic cell cultures. J Neuroendocrinol. 1997;9:287–95.
Neunzig J, Sánchez-Guijo A, Mosa A, Hartmann M, Geyer J, Wudy S, Bernhardt R. A steroidogenic pathway for sulfonated steroids: the metabolism of pregnenolone sulfate. J Steroid Biochem Mol Biol. 2014;144:324–33.
Payne AH, Jaffe RB. Androgen formation from pregnenolone sulfate by fetal, neonatal, prepubertal and adult human testes. J Clin Endocrinol Metab. 1975;40:102–7.
Peltonen H, Mikkonen-Taipale R, Uimonen T, Walker S, Hackney AC, Valtonen M, Kyröläinen H, Ihalainen JK. Power loading-induced fatigue is influenced by menstrual cycle phase. Med Sci Sports Exerc. 2022;accepted to publication.
Peretti ED, Forest MG. Pattern of plasma dehydroepiandrosterone sulfate levels in humans from birth to adulthood: evidence for testicular production*. J Clin Endocrinol Metab. 1978;47:572–7.
Phillips SK, Sanderson AG, Birch K, Bruce SA, Woledge RC. Changes in maximal voluntary force of human adductor pollicis muscle during the menstrual cycle. J Physiol. 1996;496(Pt 2):551–7.
Pierrot-Deseilligny E, Burke DC. The circuitry of the human spinal cord: spinal and corticospinal mechanisms of movement. 2nd ed. Cambridge: University Press; 2012. pp. 44, 58.
Pletzer B, Kerschbaum HH. 50 years of hormonal contraception—time to find out, what it does to our brain. Front Neurosci. 2014;8:1–6.
Rhodes ME, Li P-K, Flood JF, Johnson DA. Enhancement of hippocampal acetylcholine release by the neurosteroid dehydroepiandrosterone sulfate: an in vivo microdialysis study. Brain Res. 1996;733:284–6.
Sarwar R, Niclos BB, Rutherford OM. Changes in muscle strength, relaxation rate and fatiguability during the human menstrual cycle. J Physiol. 1996;493(Pt 1):267–72.
Schultz KN, Von Esenwein SA, Hu M, Bennett AL, Kennedy RT, Musatov S, Toran-Allerand CD, Kaplitt MG, Young LJ, Becker JB. Viral vector-mediated overexpression of estrogen receptor-alpha in striatum enhances the estradiol-induced motor activity in female rats and estradiol-modulated GABA release. J Neurosci. 2009;29:1897–903.
Šimić N, Tokić A, Peričić M. Performance of fine motor and spatial tasks during the menstrual cycle. Arh Hig Rada Toksikol. 2010;61:407–14.
Smith SS. Progesterone enhances inhibitory responses of cerebellar Purkinje cells mediated by the GABA A receptor subtype. Brain Res Bull. 1989;23:317–22.
Smith SS, Waterhouse BD, Chapin JK, Woodward DJ. Progesterone alters GABA and glutamate responsiveness: a possible mechanism for its anxiolytic action. Brain Res. 1987;400:353–9.
Smith SS, Waterhouse BD, Woodward DJ. Locally applied estrogens potentiate glutamate-evoked excitation of cerebellar Purkinje cells. Brain Res. 1988;475:272–82.
Smith SS, Woodward DJ, Chapin JK. Sex steroids modulate motor-correlated increases in cerebellar discharge. Brain Res. 1989;476:307–16.
Smith MJ, Adams LF, Schmidt PJ, Rubinow DR, Wassermann EM. Effects of ovarian hormones on human cortical excitability. Ann Neurol. 2002;51:599–603.
Spivak CE. Desensitization and noncompetitive blockade of GABAA receptors in ventral midbrain neurons by a neurosteroid dehydroepiandrosterone sulfate. Synapse. 1994;16:113–22.

Stoffel-Wagner B. Neurosteroid metabolism in the human brain. Eur J Endocrinol. 2001;145:669–79.

Takase M, Ukena K, Yamazaki T, Kominami S, Tsutsui K. Pregnenolone, pregnenolone sulfate, and cytochrome P450 side-chain cleavage enzyme in the amphibian brain and their seasonal changes. Endocrinology. 1999;140:1936–44.

Tenan MS, Peng Y-L, Hackney AC, Griffin L. Menstrual cycle mediates vastus medialis and vastus medialis oblique muscle activity. Med Sci Sports Exerc. 2013;45:2151–7.

Tenan M, Hackney AC, Griffin L. Maximal force and tremor changes across the menstrual cycle. Eur J Appl Physiol. 2015;116(1):153–60.

Tourville TW, Shultz SJ, Vacek PM, Knudsen EJ, Bernstein IM, Tourville KJ, Hardy DM, Johnson RJ, Slauterbeck JR, Beynnon BD. Evaluation of an algorithm to predict menstrual-cycle phase at the time of injury. J Athl Train. 2016;51:47–56.

Tsutsui K. Neurosteroid biosynthesis and function in the brain of domestic birds. Front Endocrinol. 2011;2:37.

van den Heuvel MW, van Bragt AJM, Alnabawy AKM, Kaptein MCJ. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception. 2005;72:168–74.

Wang M, Seippel L, Purdy RH, Bäckström T. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3, 20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. J Clin Endocrinol Metab. 1996;81:1076–82.

Wang M-D, Wahlström G, Bäckström T. The regional brain distribution of the neurosteroids pregnenolone and pregnenolone sulfate following intravenous infusion. J Steroid Biochem Mol Biol. 1997;62:299–306.

Wolf OT, Kirschbaum C. Actions of dehydroepiandrosterone and its sulfate in the central nervous system: effects on cognition and emotion in animals and humans. Brain Res Rev. 1999;30:264–88.

Xiao L, Jackson LR, Becker JB. The effect of estradiol in the striatum is blocked by ICI 182,780 but not tamoxifen: pharmacological and behavioral evidence. Neuroendocrinology. 2003;77:239–45.

Zimmerman E, Parlee MB. Behavioral changes associated with the menstrual cycle: an experimental Investigation1. J Appl Soc Psychol. 1973;3:335–44.

Zoghi M, Vaseghi B, Bastani A, Jaberzadeh S, Galea MP. The effects of Sex hormonal fluctuations during menstrual cycle on cortical excitability and manual dexterity (a pilot study). PLoS ONE. 2015;10: e0136081.

Chapter 7
Estrogen and Menopause: Muscle Maintenance, Repair, Function, and Health

Peter M. Tiidus

Introduction

Over the last 25–30 years, science has come to appreciate the wide-ranging and physiologically significant effects that estrogen has on skeletal muscle. Paradoxically, these important effects are often most discernable when they are lost, as happens following menopause in aging women. The acute and rapid reduction in muscle strength and mass, the ability of the muscle to effect post-injury repair and post-atrophy recovery of mass, and the metabolic and mitochondrial function alterations that all accompany menopause are greatly influenced by the steep drop in estrogen levels following menarche in aging women (Spangenburg et al. 2012; Tiidus et al. 2013).

This chapter primarily examines the effects of estrogen on skeletal muscle damage and repair mechanisms and also touches upon related physiological mechanisms associated with muscle mass and recovery from atrophy as well as muscle strength-related issues. It also summarizes some metabolic effects and the potential health implications of postmenopause estrogen loss and hormone replacement and how hormone replacement may counteract the negative effects of estrogen loss on skeletal muscle function. While the focus of the chapter is on the influence of estrogen and its postmenopausal loss on muscle function in older females, animal studies related to these issues are also cited as they often add corroboration and provide further evidence of for physiological mechanisms associated with the effects of estrogen on skeletal muscle function that are discerned from human studies.

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Muscle Damage

Some of the first studies that implicated estrogen in mitigating indices of exercise-induced muscle damage did so using rodents. In comparing male and female rats as well as ovariectomized female rats, with or without estrogen replacement, studies from the Bar laboratory in the 1980s and 1990s consistently found that estrogen attenuated muscle creatine kinase enzyme efflux following exercise or in vitro muscle contractions (Amelink et al. 1988, 1990). Measures of muscle creatine kinase and other specific enzyme efflux and blood levels of these enzymes are commonly used semiquantitative indicators of muscle membrane stability and in particular of muscle membrane damage and repair (Warren and Palubinskas 2008). It was postulated that estrogen acted to directly stabilize muscle membranes by influencing membrane fluidity and decreasing susceptibility to damage (Tiidus 1995). Subsequent research in our laboratory confirmed that estrogen reduced indices of muscle damage through non-receptor mediated mechanisms which could include membrane stabilization (Enns et al. 2008; Iqbal et al. 2008). Female rats also demonstrate a more stable muscle calcium homeostasis following exercise than male rats, suggesting greater membrane stability and less susceptibility to exercise-induced membrane disruption in females relative to male animals (Sonobe et al. 2010).

Studies that examined the effects of hormone replacement in older women have also demonstrated that the presence of estrogen will essentially eliminate a post-exercise rise in blood creatine kinase in those women who are long-term users of hormone replacement while the same muscular exercise-induced two to threefold increases in blood creatine kinase in those postmenopausal women who were not estrogen replaced (Dieli-Conwright et al. 2009a, b). This implies that estrogen in the form of hormone replacement will also provide protection against exercise-induced muscle damage in postmenopausal women.

Komulainen et al. (1999) reported sex-based differences in damage to muscle structural proteins (desmin, actin, dystrophin), fiber swelling, and necrosis following downhill running with male rodents exhibiting significantly more and earlier onset of post-exercise damage than females. The early post-exercise loss of the submembrane protein dystrophin which occurred in male but not female animals suggested that the higher estrogen levels in the females helped stabilize muscle membranes and diminish exercise-induced muscle disruption. Other markers of muscle damage such as activation of muscle lysosomal and calcium-activated proteases have also been demonstrated to be elevated following exercise in male and ovariectomized female rats, while normal female rats and ovariectomized female rats with estrogen replacement show little or no post-exercise increases in muscle protease activities (Komulainen et al. 1999; Enns and Tiidus 2008; Enns et al. 2008; Tiidus 2003). Markers of muscle oxidative damage following exercise or ischemia–reperfusion injury are also reduced by estrogen (Persky et al. 2000; Stupka and Tiidus 2001). This should be expected as estrogen has been reported to exhibit antioxidant properties (Tiidus 1995).

Taken together these findings from animal studies suggest that estrogen can have a significant influence on the amelioration of exercise-induced muscle damage. This can be of particular importance for postmenopausal women who may be more susceptible to exercise-induced muscle disruption as a result of their decline in circulating estrogen. Hormone replacement in postmenopausal females can restore circulating estrogen levels and therefore potentially restore the protective effects of estrogen on exercise-induced muscle damage. Dieli-Conwright et al. (2009a, b) compared the effects of eccentric muscle exercise in postmenopausal women who were or were not using hormone replacement. They measured markers of muscle damage such as serum creatine kinase activities and found significant attenuation of these indices of damage in the following exercise in those women using hormone replacement relative to those that were not, suggesting that the loss of estrogen in aging women made them more susceptible to exercise-induced muscle disruption.

Exposure to estrogen will also induce increased basal heat shock protein expression in skeletal muscles (Bombardier et al. 2009). Heat shock proteins (HSP) such as HSP70 are expressed when cells are stressed and serve to protect proteins and membranes from damage and assist in protein assembly (Noble et al. 2008). Ovariectomized female rats with estrogen replacement will express significantly more muscle HSP70 relative to those animals without estrogen. Exercise will typically increase HSP70 expression in male rats and ovariectomized female rats to levels achieved in unexercised normal female rats or ovariectomized females with estrogen replaced (Bombardier et al. 2009, 2013). Hence, it is possible that the increased expression of HSP70 exhibited in muscles exposed to estrogen may also act to limit exercise-induced muscle disruption and help maintain membrane integrity.

Muscle Inflammation

Muscle damage is followed by a well-documented sequence of events including increased muscle inflammation and leukocyte infiltration, subsequent activation and proliferation of muscle satellite cells and repair signaling, collagen synthesis, and consequent muscle repair (Tidball 2005). Estrogen has been reported to influence all of the above steps in the reaction to and consequent repair of skeletal muscle following injury (Tiidus et al. 2013). The first step in this process is the initiation of muscle inflammatory responses and infiltration of muscle by neutrophils and macrophages (Tiidus 1998).

The presence of estrogen has been repeatedly demonstrated to attenuate post-exercise and post-ischemia/reperfusion injury muscle neutrophil and macrophage infiltration in rodent models (Tiidus and Bombardier 1999; Tiidus et al. 2001; Stupka and Tiidus 2001; Iqbal et al. 2008). The provision of estrogen to male rats (Tiidus et al. 2001) or to ovariectomized female rats (Iqbal et al. 2008) will significantly reduce post-exercise muscle leukocytes (neutrophils and macrophages) infiltration relative to their unsupplemented cohorts. While the mechanisms by which estrogen may be able to attenuate post-exercise muscle leukocyte infiltration are not fully

known, it has been hypothesized that the potential membrane stabilizing effects of estrogen may attenuate some of the generations of and signaling by neutrophil and macrophage chemoattractants generated by exercise and subsequent muscle disruption and thereby reduce the adhesion and infiltration of these leukocytes into muscle following exercise (Tiidus 2003).

Indirect support for such a hypothesis has been shown in a study that used an estrogen receptor blocker to demonstrate the involvement or non-involvement of estrogen receptors in exercise-related muscular events (Enns et al. 2008). Blocking estrogenic receptors had no significant effect on the ability of estrogen to attenuate post-exercise muscle leukocyte infiltration in white *vastus* muscle (see Fig. 7.1) (Enns et al. 2008). This suggested that the mechanisms by which estrogen was able to attenuate post-exercise leukocyte infiltration were a non-receptor mediated process, hence the possibility that mechanisms associated with its possible direct effects on muscle membranes should be further investigated (Enns et al. 2008). Hormone replacement therapy in older females typically provides both estrogen and progesterone. However, animal-based studies have demonstrated that most of the anti-inflammatory effects of female sex hormones are mediated through estrogen with progesterone having relatively little influence on factors such as post-exercise muscle leukocyte infiltration (Iqbal et al. 2008).

The physiological consequences of the attenuation of muscle inflammatory responses following exercise, particularly the attenuation of muscle neutrophil and macrophage infiltration, are not certain. Inflammation and leukocyte infiltration are important obligatory responses to muscle damage which facilitate the breakdown, removal, and clearance of damaged components of the muscle, which is required to precede muscle repair (Tiidus 1998; Tidball 2005). Leukocyte and particularly macrophage infiltration have also been demonstrated to be important in signaling the activation of aspects of muscle repair such as muscle satellite cell proliferation (Hawke and Gerry 2001). However, inflammation and neutrophil infiltration following exercise has also been shown to induce further disruption and damage to components of muscle in conjunction with the removal of muscle damage debris (Tiidus 1998). Ideally, a fine balance of inflammation and repair signaling needs to be maintained in order to optimize muscle recovery. These seemingly paradoxical effects, of estrogen whereby it is able to achieve both a reduction in inflammation and augmentation of muscle repair indices, will be discussed in the next section.

The ubiquitous nature of estrogen suppression of post-damage muscle inflammation and leukocyte infiltration has recently been questioned by findings in a study by Le et al. (2018). This study noted that most previous studies, including those cited above, had used high or "supra-physiological" levels of estrogen that while within the range found in rodent pregnancy were generally higher than "normal" estrogen levels in rodent models. Contrary to previous studies noted above which found that "high" supra-physiological estrogen levels in rodents resulted in suppressed inflammation and muscle leukocyte infiltration, the Le et al. (2018) study noted that "normal" estrogen replacement levels resulted in higher leukocyte infiltration and inflammatory markers than low-estrogen levels in ovariectomized rodents. Le et al. (2018) suggested that the enhanced inflammation, as also noted above, leads to a greater rate

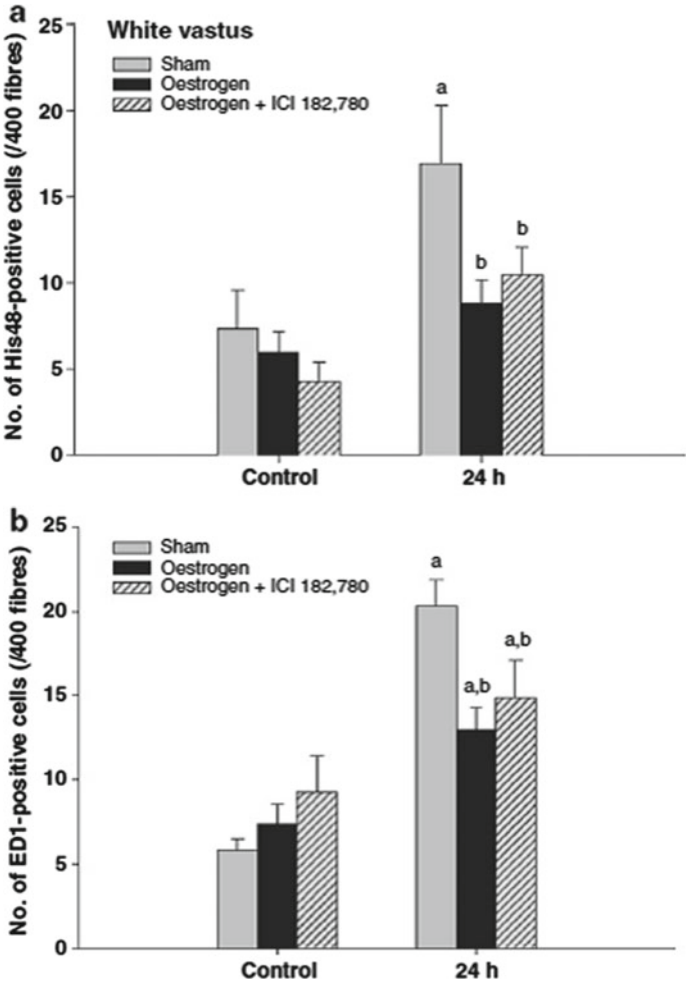

Fig. 7.1 From Enns et al. (2008) Effects of estrogen replacement, estrogen receptor blocker (ICI 182,780), and their combination on **a** neutrophil (His48 positive) and **b** macrophage (ED-1 positive) infiltration of skeletal muscle 24 h after downhill running exercise in ovariectomized female rats

of post-damage muscle recovery, as assessed by the rate of recovery of post-damage muscle force, due possibly to enhanced removal of damaged muscle components and activation of muscle repair processes.

Nevertheless, human studies have also generally demonstrated a reduction in inflammatory markers in postmenopausal females using hormone replacement containing estrogen at "normal" physiological levels (Tiidus et al. 2013). Dieli-Conwright et al. (2009a, b) examined two groups of postmenopausal females who were either taking hormone replacement or not before and after a bout of eccentric quadriceps muscle contractions designed to induce muscle disruption and soreness.

They found that following eccentric muscle exercise, postmenopausal women who were taking hormone replacement expressed little change in muscle mRNA levels of inflammation-related cytokines and interleukins such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8, and IL-15, while those women not on hormone replacement expressed five to tenfold increases in the messenger RNA (mRNA) of these inflammation and muscle turnover-related mediators. The provision of estrogen to young males also results in attenuated post-exercise muscle neutrophil infiltration (MacNeil et al. 2011). Thus, studies in humans have tended to corroborate some but not all, animal results demonstrating that estrogen will attenuate indices of post-exercise muscle inflammatory response. It is possible that the smaller inflammatory responses engendered by estrogen could result in a reduction in inflammation-induced secondary muscle damage and thereby attenuate the damaging effects of exercise and injury on overall muscle damage (Tiidus 1995; Enns and Tiidus 2010).

Muscle Satellite Cells and Muscle Repair

Estrogen has also been found to facilitate post-exercise muscle repair, particularly by enhancing the activation and proliferation of muscle satellite cells (Enns and Tiidus 2008). Adult muscle cells are post-mitotic and hence rely on muscle satellite cells, which are myogenic precursor cells, in order to hypertrophy and to effect repair (Hawke and Gerry 2001). Satellite cells are normally quiescent and reside in the periphery of muscle cells under the basal lamina. When stimulated by exercise or muscle damage, satellite cells become activated, proliferate, and can ultimately fuse with and/or donate their nuclei to muscle cells in order to optimize protein synthesis in response to hypertrophic or damage/repair signaling (Hawke and Gerry 2001). Muscle hypertrophy and muscle repair cannot occur to any great extent without activation and proliferation of satellite cells, and the rate of repair and hypertrophy is directly correlated with the degree of muscle satellite cell activation and proliferation (Yin et al. 2013).

Studies have repeatedly demonstrated that supplementation of ovariectomized female rodents as well as male rodents with estrogen will augment post-exercise muscle satellite cell activation and proliferation (Tiidus et al. 2005; Enns and Tiidus 2008; Enns et al. 2008; Mangan et al. 2014). Other animal models have also demonstrated positive effects of estrogen exposure on muscle satellite cell activation and proliferation (e.g., McFarland et al. 2013). Figure 7.2 illustrates such an effect in muscles of ovariectomized female rats with or without estrogen replacement sampled at 72 h following downhill running exercise (Enns and Tiidus 2008). These findings suggest that estrogen exposure could enhance muscle repair and/or hypertrophy-related mechanisms consequent to damaging exercise.

The mechanisms of how estrogen communicates with muscle satellite cells have not yet been fully elucidated. Nevertheless, it has been demonstrated that estrogen receptors in muscle appear to be critical to this effect. Both estrogen receptor-α and -β have been shown to be present in animal and human muscles, with greater

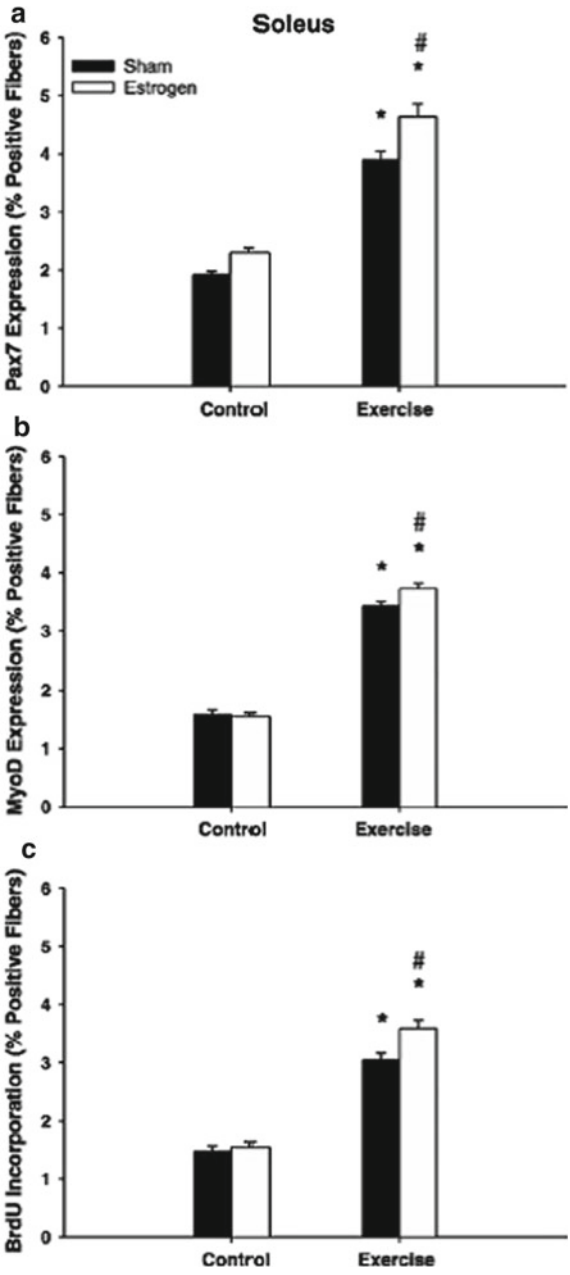

Fig. 7.2 From Enns and Tiidus (2008). Effects of estrogen supplementation on relative numbers of myofibers expressing total (Pax7; **a**), activated (MyoD; **b**), and proliferating (BrdU; **c**) satellite cell markers in rat soleus muscle 72 h following downhill running. Values are means ± SE; $n = 11$ rats per group. $^{*}P < 0.05$ compared with control. $\#P < 0.05$ compared with sham

receptor concentration typically found in type I than type II muscle fibers (Lemoine et al. 2003; Wiik et al. 2005). Blocking estrogen receptors not only completely negates the augmentation effect of estrogen on post-exercise muscle satellite cell activation and proliferation, but it also eliminates the ability of muscle satellite cells to respond at all to the exercise/damage stimuli (Enns et al. 2008). Results vary as to whether estrogen receptor-α or -β are the most critical to this effect (Thomas et al. 2010; Velders et al. 2012). Additionally, it appears that estrogen-dependent muscle satellite cell activation occurs via estrogen receptor communication with the phosphatidylinositide 3-kinase (PI3K) signaling pathway (Mangan et al. 2014). Similar to the effect of blocking estrogen receptors, blocking the PI3K signaling pathway will not only negate the augmentation effect of estrogen on post-exercise satellite cell activation, but it will also completely eliminate any positive muscle satellite cell response to exercise (Mangan et al. 2014).

Earlier in this chapter, it was noted that an optimal activation or balance of inflammation will enhance and optimize post-damage muscle repair. As previously noted, Le et al. (2018) had reported that modest or "normal" levels of post-ovariectomy estrogen replacement actually enhanced post-damage muscle leukocyte infiltration and suggested that enhanced inflammation stimulated and facilitated the enhanced post-damage muscle repair reported in the study. Paradoxically, the above studies which found an enhancement of muscle satellite activation suggesting enhanced muscle repair used a rodent model in which "supra-physiological" levels of estrogen likely suppressed inflammation. That enhanced muscle satellite cell activation still occurred, suggesting that either, as previously postulated, suppression of excess inflammation was important in enhancing muscle satellite activation or that enhanced muscle satellite cell activation was due to the activation of specific signaling pathways rather than direct inflammation-related pathways or facilitation. These issues have yet to be resolved but may be a possible explanation for this seeming paradox (Tiidus 2018).

As noted above, most of the studies examining the effects of estrogen on post-exercise muscle satellite cell activity and muscle repair have been conducted in animal models. While it has yet to be demonstrated that these specific benefits of estrogen on muscle repair mechanisms and satellite cell proliferation also operate in humans, particularly in postmenopausal females, other evidence, discussed later in this chapter, illustrates the benefits of estrogen on muscle mass and strength in older females, both of which rely in part on enhanced muscle satellite cell activation and proliferation. Hence, it is likely that the positive effects of estrogen on muscle satellite cell activity seen in animal models are also functional in aging female humans.

Muscle Mass and Recovery from Atrophy

Several rodent studies have demonstrated that skeletal muscle mass recovery following disuse atrophy is attenuated without the presence of estrogen (McClung et al. 2006; Brown et al. 2005; Sitnick et al. 2006). For example, McClung et al.

(2006) induced atrophy of hind-limb muscles of ovariectomized and intact rats by unweighting. When weight bearing was reinitiated after 10 days of atrophy, the muscles of the ovariectomized rats took twice as long (14 days) to recover pre-atrophy mass as those animals with normal estrogen levels (7 days). Non-functional collagen formation or fibrosis also significantly increased the recovering muscles of ovariectomized rats relative to the normal animals, which may have inhibited recovery (McClung et al. 2006).

The potential implications for older postmenopausal females of slower recovery from muscle loss such as might occur following inactivity due to injury or surgery suggest that loss of estrogen might contribute to a higher incidence and degree of functional decline related to greater muscle mass and strength loss and inhibited recovery. If hormone replacement was able to reverse these negative effects of estrogen loss on post-atrophy recovery of muscle mass, its potential to reduce and reverse the loss of muscle function and reduced mobility in elderly females could potentially be highly significant.

The effects of estrogen on muscle mass in postmenopausal females and its use in combination with resistance training in this population have, in most cases, demonstrated positive results (Enns and Tiidus 2010). A milestone study examining postmenopausal twins where one twin in each pair was taking hormone replacement and the other was not (Ronkainen et al. 2009) found greater overall muscle mass, less fat mass, and greater thigh muscle cross-sectional areas for those twins taking hormone replacement relative to those twins who were not. Other studies have also reported beneficial effects of hormone replacement on muscle mass in sedentary postmenopausal females as well as enhanced effects of resistance training on muscle mass gain relative to those older females not taking hormone replacement (Sipila et al. 2001; Taafe et al. 2005).

Postmenopausal hormone replacement also significantly augments a pro-anabolic signaling environment in the skeletal muscle of older females (Tiidus et al. 2013; Sipila et al. 2015). The anabolic PI3K/Akt (a serine/threonine kinase also known as protein kinase B [PKB]) signaling pathway has been implicated in animal studies as a means by which estrogen enhances muscle satellite cell activation and proliferation following exercise (Mangan et al. 2014). Human studies have also demonstrated the upregulation of this pathway by estrogen which consequently may provide an enhanced muscle anabolic signal for postmenopausal women taking hormone replacement (Sipila et al. 2015). Dieli-Conwright et al. (2009a, b) have also reported that postmenopausal women taking hormone replacement have significantly higher resting muscle mRNA levels of muscle a number of positive regulators of muscle hypertrophy such as myogenic differentiation protein D (MyoD), myogenic factor protein (Myf5), and myogenin and lower levels of negative muscle hypertrophy regulators such as myostatin than cohorts not taking estrogen replacement. Furthermore, although a single bout of resistance training enhances these pro-anabolic signaling pathways in all women, these exercise effects on muscle anabolic signaling are greatly augmented in those postmenopausal women who are taking hormone replacement (Dieli-Conwright et al. 2009a, b). These results suggest that in the presence of

estrogen, muscle in postmenopausal females is chronically exposed to greater pro-anabolic signaling and this signaling is further enhanced by exercise, particularly when estrogen is present (Dieli-Conwright et al. 2009a, b).

In summary, these findings suggest that estrogen in the form of hormone replacement will have significant positive effects in postmenopausal females for the maintenance of muscle mass, the recovery of muscle mass following atrophy, and the enhancement of exercise-induced muscle hypertrophy. These benefits have important implications for health and functional longevity in aging females.

Muscle Strength

In addition to enhanced or better maintained postmenopausal muscle size and the consequent increase in or better maintenance of muscle contractile protein content, it appears that additional effects of estrogen on other specific muscle contractile mechanisms may also act to further enhance muscle force production (Tiidus et al. 2013; Pollanen et al. 2015). Skelton et al. (1999) found that women taking hormone replacement exhibited increased adductor *pollicis* muscle strength relative to a matched group not taking hormone replacement. In a follow-up to the previously described postmenopausal female twin study which demonstrated greater lower body muscle power in the hormone-replaced twin (Ronkainen et al. 2009), Qaisar et al. (2013) reported that force relative to cross-sectional area in single muscle fibers was 25% greater in the twin taking hormone replacement relative to the non-hormone-replaced twin. In addition, a recent meta-analysis of literature comparing strength measures in postmenopausal hormone-replaced vs non-replaced women concluded that significant strength enhancement due to estrogen was evident in these populations (Greising et al. 2009). Postmenopausal women performing extended strength training while on hormone replacement also tend to increase muscle strength to a greater extent than matched cohorts, not on hormone replacement (Taafe et al. 2005; Perry et al. 2005).

Animal studies have also reported similar effects of estrogen removal and replacement on muscle strength. For example, ovariectomy in mice results in a 25% loss in tetanic muscle force, and this loss of force is restored by estrogen replacement (Moran et al. 2007). It has been suggested that these effects of estrogen in enhancing muscle contraction may be related to increases in the strong binding of myosin heads to actin during active contraction (Lowe et al. 2010). These suggestions have been directly verified by measures of active muscle stiffness during contraction (Greising et al. 2011). The mechanisms of how estrogen might be able to directly influence myosin binding and thus enhance muscle force production are currently under investigation. Possible mechanisms for this effect include the antioxidant properties of estrogen acting to maintain myosin structure during contraction (Lowe et al. 2010; Tiidus et al. 2013) and the possibility that estrogen could enhance myosin phosphorylation (Lai et al. 2016).

Myosin regulatory light chain phosphorylation induces potentiation of muscle force by increasing calcium sensitivity and myosin structure to allow for increased

strong binding during contraction (Vandenboom et al. 2013). Recently, estrogen has been shown to enhance myosin regulatory light chain phosphorylation in cultured muscle cells (Lai et al. 2016). In addition, older postmenopausal females, who lacked estrogen had 50% less contraction-induced myosin phosphorylation than age-matched males (Miller et al. 2013), suggesting that estrogen may be able to enhance myosin phosphorylation and thereby increase muscle force potentiation. As with inflammation and muscle repair, the level of estrogen replacement and the age of the animal models used in studies examining post-tetanic muscle myosin phosphorylation are important factors in demonstrating any possible estrogen influence on myosin phosphorylation and consequent enhancement of muscle force generation (Fillion et al. 2019).

The implications for the effects of estrogen on muscle strength in older females, as with its effects on muscle mass, also suggest that loss of estrogen could further exacerbate strength and muscle function loss in postmenopausal females.

Hormone Replacement, Health, and Exercise in Older Women

The above noted multifaceted beneficial effects of estrogen on muscle mass, strength, and repair mechanisms suggest that estrogen in the form of hormone replacement could have significant benefits for muscle function and consequent mobility, functionality, and independent living in postmenopausal women.

In addition to loss of muscle and bone mass, postmenopausal estrogen loss has been associated with an increase in fat mass, particularly visceral fat mass. It has been suggested that in rodent models, estrogen deficiency enhances the accumulation of adipocytes from bone marrow in subcutaneous fat deposits and may diminish brown fat-related metabolic uncoupling-related heat generation, resulting in enhanced energy expenditure and elevated metabolic rates (Gavin et al. 2018). Estrogen loss may also diminish spontaneous physical activity in rodents as well as humans (Gavin et al. 2018). Collectively, these estrogen loss-associated changes may contribute to the decreased energy expenditure and reductions in metabolic rates that contribute to weight gain typically seen in postmenopausal females (Gavin et al. 2018). These metabolic changes may be ameliorated with postmenopausal hormone replacement (Gavin et al. 2018).

A recent rodent study highlighted exercise as another important factor for potential health benefits that could apply to human females. Fritsch et al. (2021) reported that exercise was actually more effective than hormone replacement in preventing type 2 diabetes risk factors in ovariectomized rodents. This and other similar findings in rodent and human studies suggest that for females in which hormone replacement may be counter indicated or unwanted, exercise may serve as well or better in maintaining metabolic and muscle health following menopause (Gavin et al. 2018; Fritch et al. 2021).

Concerns regarding health issues with hormone replacement, primarily founded on results of the Women's Health Initiative (WHI) have contributed to a decline in hormone replacement prescriptions provided by physicians in subsequent years (Hondis et al. 2012).

Subsequent research has demonstrated that the health concerns related to hormone replacement suggested by the WHI study may have been overstated (Tiidus et al. 2013; Gurney et al. 2014). The average age of the women in the WHI study was 61 years, and therefore, most of the women had been postmenopausal for many years before initiating hormone replacement (Hondis et al. 2012). These were the cohorts who had significantly increased risks of coronary disease in the WHI study, while reanalysis of the WHI data demonstrated that younger women who started hormone replacement proximal to menopause onset actually decreased the risk of heart disease and other health risks (LaCroix et al. 2011). Two meta-analyses of more recent studies have also demonstrated that beginning hormone replacement proximal to menopause results in significantly decreased risk of overall mortality and cardiovascular risk factors in postmenopausal women, relative to women who were not hormone replaced (Schierbeck et al. 2012; Salpeter et al. 2009). Another comprehensive review of the related literature also concluded that hormone replacement is "generally safe and beneficial for women under 60 years of age" (Rozenberg et al. 2013).

A further example of the beneficial health effects of estrogen in postmenopausal women is a 10-year trial that followed 1000 recently postmenopausal women and concluded that those on hormone replacement had significantly reduced overall mortality and cardiovascular incidents without increased risk of cancer or other health threats, relative to the cohort not taking hormone replacement (Schierbeck et al. 2012). These studies all suggest that a "window of opportunity" exists where estrogen, as hormone replacement, if begun proximal to menopause will provide significant health benefits for most women and that it can be safely used for at least 10 years postmenopause (Schierbeck et al. 2012; Gurney et al. 2014). However, for women with pre-existing heart disease or those over 70 years of age use of hormone replacement may still be contraindicated (LaCroix et al. 2011; Rozenberg et al. 2013).

In addition to these health benefits, estrogen and hormone replacement in postmenopausal women has also been shown to maintain bone mass, reduce abdominal obesity, maintain insulin sensitivity, maintain mitochondrial and metabolic function, and enhance cognitive and neuro-regenerative functions (Spangenburg et al. 2012; Tiidus et al. 2013). Current recommendations for postmenopausal females experiencing negative menopausal symptoms suggest the utilization of low-dose oral or transdermal estradiol with progesterone for 3–5 years to ameliorate these symptoms (Pinkerton 2020). This would be followed by re-assessment and possibly tapering to discontinuation (Pinkerton 2020). This period of postmenopausal hormone replacement could serve to preserve the muscle and metabolic health benefits of estrogen in postmenopausal females for at least that length of time.

Rodent studies have also found that a delay in starting estrogen replacement, following ovariectomy, will negate the cardiovascular and neuro-regenerative benefits provided by estrogen in these tissues (Suzuki et al 2007). More specifically related to the topics covered in this chapter, Mangan et al. (2015) recently reported that the

previously described effects of estrogen in enhancing post-exercise muscle satellite cell activation and proliferation were also lost if estrogen replacement was delayed by 11 weeks (equivalent to several years delay the following menopause in humans) following ovariectomy in rats.

Hence, it appears that in addition to its beneficial effects on muscle mass, strength and regeneration, estrogen has significant health benefits for most, older women if replacement is started proximal to menopause. However, a significant delay in post-menopausal estrogen replacement following menopause will negate the beneficial effects that estrogen has on muscle and neural recovery from injury and also negate the health benefits associated with estrogen replacement (Suzuki et al. 2007; Mangan et al. 2015; Gurney et al. 2014).

Summary

In summary, the use of hormone replacement in postmenopausal women could be recommended as means to mitigate the loss of muscle force, mass, and function and to enhance muscle recovery following atrophy (as seen following immobilization with surgery or injury) in older women. Estrogen replacement could potentially help mitigate age-related declines in mobility and muscle strength and functionality that lead to frailty in older women. It is likely that regular vigorous resistance and aerobic exercise can also deliver many of the same benefits as estrogen to muscle and metabolic health and function in aging women (Tiidus et al. 2013). However, a number of studies have suggested that the effects of regular exercise on muscle mass in older women are further enhanced when they are on hormone replacement (Taafe et al. 2005) and that exercise may also help to negate some of the negative effects of postmenopausal estrogen loss on muscle function and overall health. The majority of older women do not regularly participate in resistance or aerobic exercise training. Therefore, timely postmenopausal return of estrogen in the form of hormone replacement with or without regular exercise accompaniment could be an important prophylactic in helping mitigate the age-related loss of muscle mass and function in aging females.

References

Amelink GJ, Kamp HH, Bar PR. Creatine kinase isoenzyme profiles after exercise in the rat: sex-linked differences in leakage of CK-MM. Pflugers Arch. 1988;412:417–21.

Amelink GJ, Koot RW, Erich WB, Van Gijn J, Bar PR. Sex-linked variation in creatine kinase release, and its dependence on oestradiol, can be demonstrated in an in vitro rat skeletal muscle preparation. Acta Physiol Scand. 1990;138:115–24.

Bombardier E, Vigna C, Iqbal S, Tiidus PM, Tupling AR. Effects of ovarian sex hormones and downhill running on fiber type-specific Hsp70 expression in rat soleus. J Appl Physiol. 2009;106:2009–15.

Bombardier E, Vigna C, Bloemberg D, Quadrilatero J, Tiidus PM, Tupling AR. The role of estrogen receptor-α in estrogen-mediated regulation of basal and exercise-induced Hsp70 and Hsp27 expression in rat soleus. Can J Physiol Pharmacol. 2013;91:823–9.

Brown M, Foley AM, Ferreira JA. Ovariectomy, hindlimb unweighting and recovery effects on skeletal muscle in adult rats. Aviat Space Environ Med. 2005;76:1012–8.

Dieli-Conwright CM, Specktor TM, Rice JC, Sattler FR, Schroder ET. Influence of hormone replacement therapy on eccentric exercise induced myogenic gene expression in postmenopausal women. J Appl Physiol. 2009a;107:1381–8.

Dieli-Conwright CM, Specktor TM, Rice JC, Schroder ET. Hormone therapy attenuates exercise-induced muscle damage in postmenopausal women. J Appl Physiol. 2009b;107:853–8.

Enns DL, Tiidus PM. Estrogen influences satellite cell activation and proliferation following downhill running in rats. J Appl Physiol. 2008;104:347–53.

Enns DL, Tiidus PM. The influence of estrogen on skeletal muscle: sex matters. Sports Med. 2010;40:41–58.

Enns DL, Iqbal S, Tiidus PM. Oestrogen receptors mediate oestrogen-induced increases in post-exercise rat skeletal muscle satellite cells. Acta Physiol. 2008;194:81–93.

Fillion M, Tiidus PM, Vandenboom R. Lack of influence of estrogen on myosin phosphorylation and post-tetanic potentiation in muscles from young adult C57BL mice. Can J Physiol Pharmacol. 2019;97–729–37.

Fritsch LJ, McCaulley SJ, Johnson CF, Lawson NJ, Gorres-Martens BK. Exercise prevents whole body type 2 diabetes risk factors better than estradiol replacement in rats. J Appl Physiol. 2021;131:1520–31.

Gavin KM, Korht WM, Klemm DJ, Melanson EL. Modulation of energy expenditure by estrogens and exercise in women. Exerc Sport Sci Rev. 2018;46:232–9.

Greising SM, Baltgalvis KA, Lowe DA, Warren GL. Hormone therapy and skeletal muscle strength: a meta-analysis. J Gerontol A Biol Sci Med Sci. 2009;64:1071–81.

Greising SM, Baltgalvis KA, Kosir AM, Moran AL, Warren GL, Lowe DA. Estradiol's beneficial effect on murine muscle function is independent of muscle activity. J Appl Physiol. 2011;110:109–15.

Gurney EP, Nachtagall MJ, Nachtagall LE, Naftolin F. The women's health initiative trial and related studies: 10 years later: a clinician's view. J Steroid Biochem Mol Biol. 2014;142:4–11.

Hawke TJ, Gerry DJ. Myogenic satellite cells: physiology to molecular biology. J Appl Physiol. 2001;91:534–51.

Hondis HN, Collins P, Mack WJ, Schierbeck LL. The timing hypothesis for coronary heart disease prevention and hormone therapy: past, present and future in perspective. Climeractic. 2012;15:217–28.

Iqbal S, Thomas A, Bunyan K, Tiidus PM. Progesterone and estrogen influence post-exercise skeletal muscle leukocyte infiltration in overiectomized female rats. Appl Physiol Nutr Metabol. 2008;33:1207–12.

Komulainen J, Koskinen S, Kalliokoski R, Takala T, Vihko V. Gender differences in skeletal muscle damage after eccentrically biased downhill running in rats. Acta Physiol Scand. 1999;165:57–63.

LaCroix AZ, Chiebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, Margolis KL, Stefanick ML, Brzyski R, Curb JD, Howard BV, Lewis CE, Wactawski-Wende J. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior historectomy. JAMA. 2011;305:1305–14.

Lai S, Collins BC, Colson BA, Kararigas G, Lowe DA. Estradiol modulates myosin regulatory light chain phosphorylation and contractility in skeletal muscle of female mice. Am J Physiol Endocinol Metab. 2016;310(9):E724–33.

Le G, Novolny SA, Mader TL, Greising SM, Chan SSK, Kyba M, Lowe DA, Warren GL. A moderate estradiol level enhances neutrophil number and activity in muscle after traumatic injury but strength recovery is accelerated. J Physiol. 2018;596:4665–80.

Lemoine S, Granier P, Tiffoche C. Effect of endurance training on oestrogen receptor alpha expression in different rat skeletal muscle type. Acta Physiol Scand. 2003;174:283–9.

Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. Exerc Sport Sci Rev. 2010;38:61–7.
MacNeil LG, Baker SK, Stevic I, Tarnopolsky MA. 17β-estradiol attenuates exercise-induced neutrophil infiltration in men. Am J Physiol Regul Integr Comp Physiol. 2011;300:R1443–51.
Mangan G, Bombardier E, Mitchell A, Quadrilatero J, Tiidus PM. Oestrogen-dependent satellite cell activation and proliferation following a running exercise occurs via the PI3K signalling pathway and not IGF-1. Acta Physiol. 2014;212:75–85.
Mangan G, Iqbal S, Hubbard A, Hamilton V, Bombardier E, Tiidus PM. Delay in post-ovariectomy estrogen-replacement negates estrogen-induced augmentation of post-exercise satellite cell proliferation. Can J Physiol Pharmacol. 2015;93:945–51.
McClung JM, Davis JM, Wilson MA, Goldsmith EC, Carson JA. Estrogen status and skeletal muscle recovery from disuse atrophy. J Appl Physiol. 2006;100:2012–3.
McFarland DC, Pesall JE, Coy CS, Velleman SG. Effects of 17β-estradiol on turkey myogenic satellite cell proliferation, differentiation, and expression of glypican-1, MyoD and myogenin. Comp Biochem Physiol A Mol Integr Physiol. 2013;164:556–71.
Miller MS, Bedrin NG, Callahan DM, Previs MJ, Jennings ME, Ades PA, Maughan DA, Palmer BM, Toth MJ. Age-related slowing of myosin actin cross-bridge kinetics is sex specific and predicts decrements in whole skeletal muscle performance in humans. J Appl Physiol. 2013;115:1004–14.
Moran AL, Nelson SA, Landisch RM, Warren GL, Lowe DA. Estradiol replacement reverses ovariectomy-induced muscle contractile and myosin dysfunction in mature female mice. J Appl Physiol. 2007;102:1387–93.
Noble EG, Milne KJ, Melling CWJ. Heat shock proteins and exercise: a primer. Appl Physiol Nutr Metab. 2008;33:1050–65.
Perry SK, Radke A, Bombardier E, Tiidus PM. Hormone replacement and strength training positively influence balance during gait in post-menopausal females: a pilot study. J Sports Sci Med. 2005;4:372–82.
Persky AM, Green PS, Stubley L, Howell CO, Zaulyanov L, Baseau GA, Simpkins JW. Protective effect of estrogens against oxidative damage to heart and skeletal muscle in vivo and in vitro. Proc Soc Exp Biol Med. 2000;223:59–66.
Pinkerton JV. Hormone therapy for postmenopausal women. N Engl J Med. 2020;382:446–53.
Pollanen E, Kangas R, Horttanainen M, Niskala P, Kaprio J, Butler-Browne G, Mouly V, Sipila S, Kovanen V. Intramuscular sex steroid hormones are associated with skeletal muscle strength and power in women with different hormonal status. Aging Cell. 2015;14:236–48.
Qaisar R, Renaud G, Hedstrom Y, Pollanen E, Ronkainen P, Kaprio J, Alen M, Sipila S, Artemenko K, Bergquist J, Kovanen V. Hormone replacement therapy improves contractile function and myonuclear organization of single muscle fibres from postmenopausal monozygotic female twin pairs. J Physiol. 2013;591:2333–44.
Ronkainen PHA, Kovanen V, Alen M, Pollanen E, Palonen EM, Ankarberg-Lindgren C, Hamalainen E, Trupeinen U, Kujula UM, Puolakka J, Kaprio J, Sipila S. Postmenopausal hormone replacement therapy modifies skeletal muscle composition and function: a study with monozygotic twin pairs. J Appl Physiol. 2009;107:25–33.
Rozenberg S, Vandromme J, Antoine C. Postmenopausal hormone therapy: risks and benefits. Nat Rev Endocrinol. 2013;9:216–27.
Salpeter SR, Cheng J, Thabene L, Buckley EE, Salpeter NS. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. Am J Med. 2009;122:1016–22.
Schierbeck LL, Rejnmark L, Torteng CL, Stigren L, Eiken P, Mosekilde L, Kober L, Jensen JEB. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. Br Med J. 2012;345: e6409.
Sipila S, Taafe DR, Cheng S, Puolakka J, Toivanen J, Suominen H. Effects of hormone replacement therapy and high-impact physical exercise on skeletal muscle in post-menopausal women: a randomized placebo-controlled study. Clin Sci. 2001;101:147–57.
Sipila S, Finni T, Kovanen V. Estrogen influences on neuromuscular function in postmenopausal women. Calcif Tissue Int. 2015;96:222–33.

Sitnick M, Foley AM, Brown M, Spangenburg EE. Ovariectomy prevents the recovery of atrophied gastrocnemius skeletal muscle mass. J Appl Physiol. 2006;100:286–93.
Skelton DA, Phillips SK, Bruce AS, Naylot CH, Woledge RC. Hormone replacement therapy increases isometric muscle strength of adductor pollicis in post-menopausal women. Clin Sci. 1999;96:257–364.
Sonobe T, Inagaki T, Sudo M, Poole DC, Kano Y. Sex differences in intracellular Ca^{2+} accumulation following eccentric contractions of rat skeletal muscle in vivo. Am J Physiol Regul Integr Comp Physiol. 2010;299:R1006–12.
Spangenburg EE, Geiger PC, Leinwand LA, Lowe DA. Regulation of physiological and metabolic function of muscle by female sex steroids. Med Sci Sports Exerc. 2012;44:1653–62.
Stupka N, Tiidus PM. Effects of ovariectomy and estrogen on ischemia-reperfusion injury in hindlimbs of female rats. J Appl Physiol. 2001;91:1828–35.
Suzuki S, Brown CM, Dela-Cruz CD, Yang E, Bridwell DA, Wise PM. Timing of estrogen therapy after ovariectomy dictates the efficacy of its neuroprotective and anti-inflammatory actions. Proc Natl Acad Sci U S A. 2007;104:6013–8.
Taafe DR, Siplia S, Cheng S, Puolakka J, Toivanen J, Suominen H. The effect of hormone replacement therapy and/or exercise n skeletal muscle attenuation in postmenopausal women: a yearlong intervention. Clin Physiol Funct Imaging. 2005;25:297–304.
Thomas A, Bunyan K, Tiidus PM. Oestrogen receptor-alpha activation augments post-exercise muscle myoblast proliferation. Acta Physiol. 2010;198:81–9.
Tidball JG. Inflammatory processes in muscle injury and repair. Am J Physiol Regul Integr Comp Physiol. 2005;288:R345–53.
Tiidus PM. Can estrogens diminish exercise induced muscle damage? Can J Appl Physiol. 1995;20:26–38.
Tiidus PM. Radical species in inflammation and overtraining. Can J Physiol Pharmacol. 1998;76:533–8.
Tiidus PM. Influence of estrogen and gender on muscle damage, inflammation and repair. Exerc Sport Sci Rev. 2003;31:40–4.
Tiidus PM. Oestrogen and a Goldilocks zone for post-damage muscle inflammation and repair? J Physiol. 2018;596:4563–4.
Tiidus PM, Bombardier E. Oestrogen attenuates myeloperoxidase activity in skeletal muscle of male rats. Acta Physiol Scand. 1999;166:85–90.
Tiidus PM, Holden D, Bombardier E, Zajchowski S, Enns D, Belcastro A. Estrogen effect on post-exercise skeletal muscle neutrophil infiltration and calpain activity. Can J Physiol Pharmacol. 2001;79:400–6.
Tiidus PM, Deller M, Liu XL. Estrogen influence on myogenic satellite cells following downhill running in male rats; a preliminary study. Acta Physiol Scand. 2005;184:67–72.
Tiidus PM, Lowe DA, Brown M. Estrogen replacement and skeletal muscle: mechanisms and population health. J Appl Physiol. 2013;115:569–78.
Vandenboom R, Gittings W, Smith IC, Grange RW, Stull JT. Myosin phosphorylation and force potentiation in skeletal muscle: evidence from animal models. J Muscle Res Cell Motil. 2013;34:317–32.
Velders M, Schleipen B, Fritzemeier KH, Zierau O, Diel P. Selective estrogen receptor-beta activation stimulates skeletal muscle growth and regeneration. FASEB J. 2012;26:1909–20.
Warren GL, Palubinskas LE. Human and animal experimental muscle injury models. In: Tiidus PM, editor. Muscle damage and repair. Champaign IL: Human Kinetics; 2008. p. 13–36.
Wiik A, Gustafsson T, Esbjornsson M, Johansson O, Ekman M, Sundberg CJ, Jansson E. Expression of oestrogen receptor α and β is higher in skeletal muscle of highly endurance-trained than moderately active men. Acta Physiol Scand. 2005;184:105–12.
Yin H, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. Physiol Rev. 2013;93:23–67.

Chapter 8
The Effect of Sex Hormones on Ligament Structure, Joint Stability and ACL Injury Risk

Sandra J. Shultz and Justin A. Fegley

Introduction

While more physically active males injure their anterior cruciate ligament (ACL) due to their greater exposure to high risk sport activity (Gianotti et al. 2009), high school and college age females are two to five times more likely to suffer a non-contact ACL injury compared to similarly trained males (Gornitzky et al. 2016; Hootman et al. 2007; Prodromos et al. 2007). This increased risk in females begins to develop around 12–13 years of age (Beck et al. 2017; Bloom et al. 2020; Shea et al. 2004), when females begin to markedly differ from males in hormone secretion and their physical characteristics such as body composition (McCarthy et al. 2013), lower extremity strength (Ervin et al. 2014), joint laxity (Shultz et al. 2008; Svenningsen et al. 1989), and hip and knee control during sport-related activity (Ford et al. 2010; Schmitz et al. 2009). As such, hormones have often been implicated in the ACL injury risk equation, because they underlie most of the sex differences in physical characteristics that emerge after puberty, and because they have the potential to impact collagen metabolism, ligament remodeling, and the structural integrity of the ACL in a way that may increase the potential for ligament failure. Before examining these hormone effects, the chapter first highlights the inherent complexity of studying sex hormone profiles in physically active females. We then focus primarily on what we know about the impact of sex hormones on collagen metabolism, ligament remodeling, and structural integrity of the ACL and how this may impact ACL injury risk. The impact of oral contraceptive hormones and the hormone relaxin is also discussed.

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Complexity of Studying Hormone Profiles in Physically Active Females

It is well known that hormone profiles in women change considerably over the course of the menstrual cycle. These changes are often described relative to a typical 28-day cycle where the follicular phase represents the first half of the cycle (days 1–14) and the luteal phase represents the latter half of the cycle (days 15–28), with ovulation occurring between days 10 and 14. The time of ovulation is then subsequently used to represent the time of peak estrogen concentrations and 7 days later the time of peak progesterone and the secondary peak in estrogen concentrations in the mid-luteal phase. These "typical" cycle events have commonly been used as a calendar framework for determining relative ACL injury risk and changes in relevant risk factors (e.g., laxity) across the menstrual cycle (e.g., Somerson et al. 2019). Most commonly, measurements are collected at three time points; one sample each to depict when both hormone concentrations are low (a day during menses), when estrogen rises unopposed near ovulation (days 10–14) and when both estrogen and progesterone are elevated during the luteal phase (day 21). While a serum or urine sample is sometimes obtained to confirm that the hormone milieu of interest was actually captured, more often than not cycle characteristics are assumed based on calendar days alone (Somerson et al. 2019).

Unfortunately, the sampling approaches described above are fraught with error given the large interindividual variability in hormone profiles among women. For example, Landgren et al. reported that while the mean follicular and luteal phase lengths in 68 women were 15 and 13 days, respectively, the actual length of the follicular and luteal phases ranged from 9 to 23 days and 8 to 17 days, respectively (Landgren et al. 1980). Shultz et al. (2004) reported similar findings when measuring daily serum sex hormone concentrations in 22 women who reported normal and consistent menstrual cycles lasting 28–32 days (Table 8.1). These data not only demonstrate the large variations in the timing of cycle events (cycle length, timing of ovulation, timing of the subsequent rises and peaks in estrogen and progesterone) but also in the peak concentration values obtained. Although testosterone concentrations are much lower in women than men, and as such their effects have received less attention than those of estrogen and progesterone, these concentrations also vary considerably among women.

The variations observed in the timing of specific cycle events (e.g., ovulation, day of peak concentrations) are not simply a function of different cycle lengths. This is exemplified in data obtained from four different women (unpublished) who each had a 28-day cycle length (Fig. 8.1). The red line in each graph indicates the day that the ovulation test strip tested positive for the surge in luteinizing hormone. Of the four women, only one actually ovulated within the typical 10–14-day window. Further, the timing of peak estradiol levels (blue line) is not consistent relative to the day of ovulation, occurring within one day in two women, but occurring 3–5 days later in two other women. Capturing the progesterone peak at day 21 was more consistent, but was entirely missed in one female. Hence, if one uses calendar days

Table 8.1 Variability in sex hormone profile characteristics in eumenorrheic females

Cycle characteristic	Range in values
Cycle length	24–36 days
Day of positive ovulation test	Day 9–20
Day of first estradiol peak near ovulation	Day 8–25
Day of progesterone rise (<2 ng/mL)	Day 11–27
Day of progesterone peak	Day 15–27
Peak estradiol concentration	86–295 pg/mL
Peak progesterone concentration	3.6–26.8 ng mL
Peak testosterone concentration	37–115 ng/mL

Data from Shultz et al. (2004). Data are representative of a single investigative study and are not intended to imply "clinical reference range" values

alone, the hormone milieu of interest may be missed in the majority of women, yielding inaccurate findings.

It is also important to note that when measuring a particular risk factor or documenting an injury at a particular time in the cycle, the hormone milieu at the time of

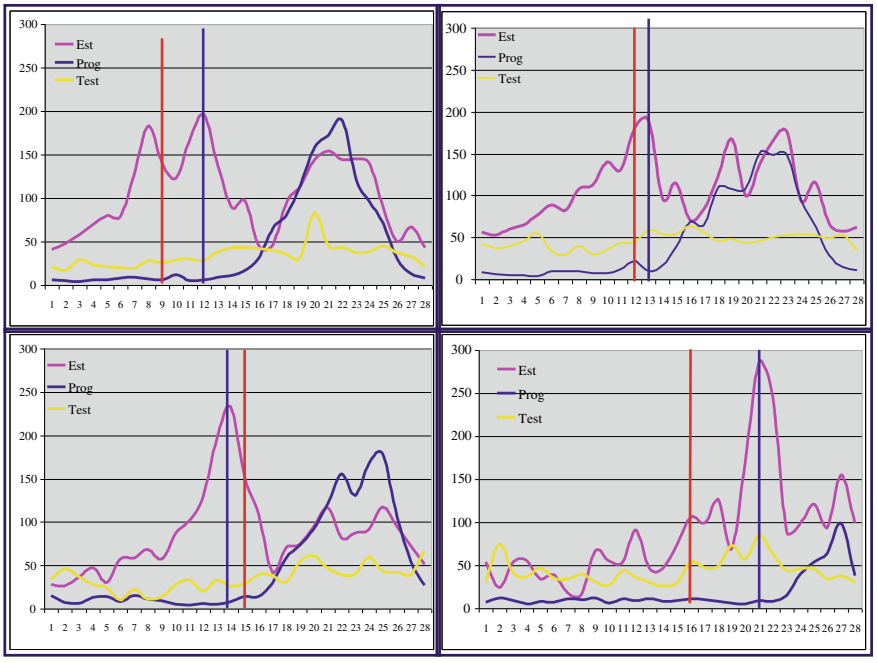

Fig. 8.1 Comparative timing of menstrual cycle events in four women who each had 28-day cycle lengths. Red bar indicates the day the ovulation test strip tested positive. Individual subject data (previously unpublished) derived from the study by Shultz et al. (2004)

risk factor measurement or injury may not be the most relevant. Research indicates that the impact of changing hormones on ligament tissue may occur at some time delay (Shultz et al. 2004), suggesting that the hormone milieu in the days preceding the day of testing or injury may be more relevant to the variables of interest than the hormone concentrations obtained on the day of testing.

Together, this variability suggests that using a particular day or range of days of the menstrual cycle to depict a particular hormone event in all women will introduce considerable error. As we proceed through this chapter, it is important to appreciate this variability among physically active females, and that the sampling techniques/research designs that have been used to examine hormone effects often do not adequately account for this variability.

Cycle Phase and Injury Risk

Because women are exposed to large variations in their hormone concentrations across the menstrual cycle, a number of studies have retrospectively examined whether ACL injury risk is disproportionately greater at certain times of the menstrual cycle (Adachi et al. 2008; Arendt et al. 2002; Beynnon et al. 2006; Myklebust et al. 1998, 2003; Slauterbeck et al. 2002; Wojtys et al. 1998, 2002). These retrospective studies generally report a greater number of injuries than expected during the follicular as compared to luteal phase (Table 8.2), and this has been confirmed by two recent meta-analyses (Herzberg et al 2017; Somerson et al 2019). However, among studies that identified the follicular phase as being of greater risk, some reported a greater proportion of injuries early in the follicular phase during the perimenstrual days when hormone levels are nearing or at their nadirs (Myklebust et al. 1998, 2003; Slauterbeck et al. 2002), while others reported a greater proportion of injuries late in follicular phase near the time of ovulation when estrogen begins to rapidly rise (Adachi et al. 2008; Wojtys et al. 1998, 2002). While the hormone profile surrounding these two times points is quite different, they are alike in that both time points represent transitional periods of the menstrual cycle when hormone concentrations are rapidly changing. However, the actual hormone milieu or phase at the time of injury may be very difficult to accurately characterize in these retrospective studies.

In the majority of these studies, cycle phase was determined based on calendar counting methods via subject self-recall of her menstrual cycle events over previous months. Unfortunately, these methods have been found to be quite inaccurate (Small et al. 2007; Wideman et al. 2013; Wojtys et al. 2002). Only three studies collected blood or urine samples to compliment calendar counting methods to better determine the hormone milieu at the time of injury. These samples were obtained within 2 h (Beynnon et al. 2006), 24 h (Wojtys et al. 2002), and 72 h (Slauterbeck et al. 2002) of the injury event. Despite this, it can be difficult to determine retrospectively from this single hormone sample what the hormone milieu may have been at the time of injury, as hormone concentrations can change substantially within hours near the time of menses and ovulation. The inaccuracy in ascertaining cycle phase at the time of an

Table 8.2 ACL injury risk and menstrual cycle phase

Study	Normalized day of the cycle																										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	Follicular phase (%)														Luteal phase (%)												
Myklebust et al. (1998) ($N = 17$)[a]	29							12							6							53					
Myklebust et al. (2003) ($N = 46$)[a]	50							26							11							13					
Wojtys et al. (1998) ($N = 28$)[a]	13									29					58												
Wojtys et al. (2002) ($N = 51$)[a,b]	23									43					34												
Adachi et al. (2008) ($N = 18$)[a]	11									73					17												
Arendt et al. (2002) ($N = 83$)[a]	64														36												
Beynnon et al. 2006 ($N = 46$)[a,b]	74														26												
Ruedl et al. 2009 ($N = 93$)[a]	57														43												
Slauterbeck et al. 2002 ($N = 37$)[a,b]	70														30												

Menstrual cycle phase determine by [a]Calendar counting or [b]Hormone assessment
With permission, from Sigward et al. (2008)

injury event from a single hormone sample was confirmed by Tourville et al. (2016). Specifically, retrospective classification of menstrual cycle phase using self-reported menstrual cycle questionnaire data and a single hormone sample taken at a random date after a mock injury was not able to accurately classify the cycle phase that the women were in at the time of injury.

Even if research advances were able to accurately determine the hormone milieu at the time of injury, there is much that remains unknown about the mechanisms that underlie the potential relationship between menstrual cycle phase and ACL injury. First, research has yet to identify how the time of injury occurrence aligns with the hormone changes responsible for the increased risk and therefore what hormone actions are most relevant to target in injury prevention efforts. Second, the specific mechanisms through which sex hormones are impacting soft tissues and the potential for ligament failure are largely unknown. While there is good evidence that sex hormones have the potential to exert substantial influence on collagen metabolism and the structural integrity of the ACL, understanding these mechanisms is complicated for several reasons. Beyond the known variability in the timing and magnitude of hormone concentration changes between women as previously described (see previous section), there are also variations in cycle characteristics within a given female from month to month, including the occurrence of anovulatory cycles (Lenton et al. 1983; Shultz et al. 2011b). Because not all women go on to injure their ACL, understanding how this intra- and interindividual variability affects risk may be critically important. There is also evidence of a time and dose-dependent effect by which soft tissues changes may occur in response to hormone concentration changes (Shultz et al. 2004; Yu et al. 2001), which complicates our ability to align the timing of injury occurrence to the hormone concentrations that may be responsible for that risk. Finally, it is unlikely that any effect is due to a single hormone, but rather represents a complex interaction among multiple hormones (Shultz et al. 2004; Yu et al. 2001; Dragoo et al. 2011a) and other relevant factors such as an individual's genotypic profile (Posthumus et al. 2009; Shultz et al. 2015) and exercise habits (Lee et al. 2004) that together may determine the extent to which a female is susceptible to injury. To address many of these challenges, prospective study designs that track a female's hormone profiles over several months would be required. Unfortunately, this approach is impractical given the relative infrequency in which these injuries occur.

Effect of Sex Hormones on Collagen Metabolism, Tissue Remodeling, and Mechanical Properties

Steroidal hormones have the potential to exert substantial influence on soft tissue structures composed of collagen, including the ACL. Tissues exposed to estradiol are reported to increase both collagen synthesis (Dyer et al. 1980; Hassager et al. 1990; Ho and Weissberger 1992; Hosokawa et al. 1981) and absorption (Dyer et al.

1980; Fischer 1973), indicating increased metabolic activity. Structural changes in tissue have also been observed in response to estrogen exposure, noting decreases in total collagen and protein content, and fiber diameter and density (Abubaker et al. 1996; Dubey et al. 1998; Hama et al. 1976). These tissue responses appear to be enhanced with exposure to both estrogen and progesterone (Abubaker et al. 1996; Dubey et al. 1998), but are diminished when the tissue is exposed to either progesterone or testosterone alone (Abubaker et al. 1996; Hama et al. 1976; Shikata et al. 1979). Although these findings are based on a variety of connective tissues and research models, the general consensus from the literature is that collagen structure and metabolism are greatly influenced by sex hormones.

These investigations, along with the identification of sex hormone receptors on the human ACL (Dragoo et al. 2003; Hamlet et al. 1997; Liu et al. 1996), have led to considerable interest in how sex hormones might modify the structural integrity of the ACL (Hamlet et al. 1997; Lee et al. 2015; Liu et al. 1996; Yu et al. 1997). Investigations include both animal and human models that have primarily examined the effects of estrogen (with or without progesterone) on collagen metabolism and the mechanical properties of the ACL.

Effect on Collagen Metabolism

The effect of estrogen on collagen metabolism of the ACL has primarily been examined in animal (Seneviratne et al. 2004; Liu et al. 1997) and human cell culture models (Yu et al. 1999, 2001), and more recently in engineered ligaments (Lee et al. 2015).

Yu et al. (1999, 2001) examined human ACL tissue in cell culture to prospectively evaluate the effects of both physiologic and supraphysiologic levels of 17β-estradiol (range 2.9–2500 pg/mL) and progesterone on cell proliferation and collagen synthesis in vitro. They observed progressive decreases in fibroblast proliferation and Type 1 procollagen synthesis as estradiol levels progressively increased, which eventually leveled off at supraphysiologic levels. Increasing levels of progesterone attenuated this inhibitory effect, and when estradiol levels were controlled, increasing progesterone levels actually resulted in dose-dependent increases in fibroblast proliferation and Type 1 procollagen synthesis. The second relevant finding is that these hormone effects were transient, with the most pronounced effects observed in the initial days after hormone exposure (days 1 and 3), which then began to attenuate within 7 days of exposure. Conversely, Lee et al. (2015) observed an *increase* in collagen production in engineered ligaments from human ACLs when exposed to low (5 pg/ml), medium (50 pg/ml), and high (500 pg/ml) physiological estrogen levels.

Results from animal model studies also reveal conflicting findings. Liu et al. (1997) prospectively examined female rabbit ACLs in cell culture after 2 weeks of exposure to control (0 pg/ml) physiologic (2.9, 25, and 250 pg/mL) and supraphysiologic (2500 and 25,000 pg/mL) concentrations of estradiol. A decrease in collagen synthesis and fibroblast proliferation was noted with increasing concentrations of estradiol,

starting with physiological levels of 25 pg/mL, compared to a control group with no exposure to estradiol. Conversely, Seneviratne et al. (2004) prospectively examined sheep ACL fibroblasts in cell culture 4 and 6 days after being subjected to somewhat similar incremental doses of estradiol [2.2 (control), 5, 15, 25, 250, and 2500 pg/mL], and found no difference in fibroblast proliferation and collagen synthesis at any concentration level.

Because of the limited and conflicting studies in this area, it is difficult to draw meaningful conclusions. Differences in the study designs, including the length and magnitude of estradiol exposure and the control group that was used, and how collagen production is measured, make it somewhat difficult to directly compare results between studies. Where Liu et al. (1997) used a control group that received no estradiol, and examined changes after 2 weeks of exposure, Seneviratne et al. (2004) compared their data to a control group receiving 2.2 pg/mL after 4 and 6 days following exposure. Yu et al. (1999) also compared their data to a control group that received no estradiol and was the only study to look at transient changes that occurred within days of exposure.

While these results are inconclusive as to directionality of impact, they do suggest the potential transient changes in estrogen and progesterone across the menstrual cycle may influence ACL metabolism and collagen synthesis in an interactive, dose-, and time-dependent manner.

Effect on Mechanical Properties

Estrogen effects on the ultimate mechanical properties of the ACL are equivocal and largely based on animal models, including rabbit (Slauterbeck et al. 1999; Hattori et al. 2010; Komatsuda et al. 2006), sheep (Strickland et al. 2003), and monkey (Wentorf et al. 2006), with more recent work using engineered ligaments from human ACLs (Lee et al. 2015). As with studies of collagen synthesis, a variety of methodologies and hormone concentrations have been utilized. Using a prospective, matched control design, Slauterbeck et al. (1999) examined the ultimate failure load on the ACL in ovariectomized rabbits with and without 30 days of exposure to estradiol concentrations consistent with pregnancy levels. While biomechanical testing revealed the estrogen-treated ACLs failed at a 10% lower load compared to control ACLs, these results were limited to supraphysiological levels of estradiol exposure. Komatsuda et al. (2006) examined mechanical properties in ovariectomized rabbits receiving different physiological [no (control), low and medium concentrations] or supraphysiologic levels (high concentrations) of estradiol over 5 weeks. Those administered high concentrations (supraphysiologic) demonstrated a decrease in ultimate tensile stress and linear stiffness compared to those administered medium (high physiologic) concentrations who had the highest values of all groups (but not significantly more than control or low concentration groups).

Studies investigating the effects of estrogen on mechanical properties at more physiological levels have not consistently demonstrated an effect (Hattori et al. 2010;

Lee et al. 2015; Strickland et al. 2003; Wentorf et al. 2006). In subsequent analyses of the work by Komatsuda et al. (2006), those administered medium concentrations of estradiol had less tissue elasticity than controls as measured by scanning acoustic microscopy (lower sound speed and attenuation) (Hattori et al. 2010). Strickland et al. (2003) examined the biomechanical properties of sheep knee ligaments 6 months following random assignment to sham-operated, ovariectomy, ovariectomy + estradiol implant, as well as low-dose and high-dose raloxifene (estrogen receptor agonist) groups. For this study, estradiol was administered at concentrations near 2 pg/ml, which was deemed similar to that experienced during the normal luteal phase of their estrus cycle. While the ultimate stress of the ram was greater than the ewes, they observed no difference in ligament strength (maximum force, stiffness, energy to failure) between groups. Similar findings were reported by Wentorf et al. (2006), who examined the mechanical properties of the ACLs and patellar tendons obtained from Cynomolgus macaque monkeys two years after they were divided into sham-operated and ovariectomized groups. They found no difference in any of the mechanical or material properties tested, including failure load, stiffness, elongation at failure, ultimate stress or strain, or energy at failure. A strength of the latter study is that monkeys were examined, who closely mirror the estrogen levels and cyclic variations of the human menstrual cycle (Goodman et al. 1977).

While these studies suggest that mechanical properties of the ACL may not be substantially altered after prolonged exposure to different physiological concentrations of estrogen (6 months to 2 years) (Strickland et al. 2003; Wentorf et al. 2006), the tissue may be more affected by acute changes (5 weeks) (Hattori et al. 2010; Yu et al. 2001). This was also demonstrated by Lee et al. (2015) who examined changes in both collagen production, collagen content, and mechanical properties in engineered ligaments derived from human female and male ACLs. While they observed increases in collagen production with low (5 pg/ml), medium (50 pg/ml), and high (500 pg/ml) physiological concentrations of estradiol for 14 days, they observed no change in the mechanical properties of the ACL. Only when they exposed the ligaments to the higher estrogen levels for a short time (500 pg/ml for 48 hours) did they observe a decrease in tensile strength and mechanical stiffness. Moreover, this change in mechanical properties was not attributable to a decrease in collagen, but rather due to inhibition of lysyl oxidase (LOX) activity, the primary enzyme that produces collagen cross-links. Appreciating the stable nature of collagen, this may provide a more plausible explanation for acute changes in ligament behavior that have been observed across the menstrual cycle (see next section).

Future studies should examine more acute, physiological changes in estradiol concentrations that more closely mimic what women experience and include sex hormones other than estrogen (either in combination or isolation), as estrogen alone may not be responsible for changes in ligament properties. Given the attenuating hormone effects on collagen metabolism over time described by Yu et al. (1999, 2001), and the cyclic variations that occur in sex hormones across the female menstrual cycle, examining both acute and chronic effects seems prudent. Work by Lee et al (2015) suggests we need to look beyond collagen content to factors that have the potential to change more transiently (e.g., collagen cross-links). Finally, more

studies using human models are recommended. While data from various animal studies have improved our understanding of the effects of estradiol on mechanical properties of the ligament, their clinical relevance to the human ACL is uncertain since non-primates have estrous cycles rather than menstrual cycles and therefore experience very different hormone profiles (Griffin et al. 2006).

Effect of Sex Hormones on Knee Joint Laxity

While direct biomechanical measurement of the mechanical properties of the ACL is not possible to obtain in vivo, indirect noninvasive clinical measures of knee joint behavior provide important insights into the structural integrity of the ACL and the biological processes that may mediate its structural integrity.

Sex Differences in Knee Laxity and ACL Injury Risk

Anterior knee laxity (the amount of anterior displacement of the tibia relative to the femur when an anterior directed load is applied to the posterior tibia) is often used to characterize an individual's ACL integrity, because the ACL acts as the primary restraint to this motion (Butler et al. 1980). Research has shown that ACLs that are smaller would be less volume, smaller cross sectional area (Wang et al 2016, 2021) and that are less dense (fewer collagen fibers per unit area) and have lower mechanical properties (less strain/stress at failure)(Chandrashekar et al. 2006; Hashemi et al. 2008) tend to be more lax. It is well documented that females have smaller ACLs (Cone et al. 2019) and greater anterior knee laxity compared males (Scerpella et al. 2005; Rozzi et al. 1999; Shultz et al. 2005; Beynnon et al. 2005; Uhorchak et al. 2003; Nguyen and Shultz 2007), and both smaller ACLs (Chaudhari et al. 2009; Whitney et al. 2014; Wang et al. 2020) and greater knee laxity (Uhorchak et al. 2003; Vacek et al. 2016) have been associated with a greater risk of ACL injury. In fact, two large multivariate studies have identified anterior knee laxity to be among the strongest independent predictors of ACL injury in females. In a prospective study of US military cadets, the risk of ACL injury was 2.7 times greater when females had AKL values $\geq$1 SD above the mean (Uhorchak et al. 2003). In a prospective cohort study with a nested, matched case–control analysis of high school and college aged athletes, anteroposterior knee laxity was a significant predictor in the final multivariate model along with greater body mass index (BMI = weight in kilograms/height in meters^2) and having a parent with history of ACL injury in females (Vacek et al 2016). Specifically, females with knee laxity values 1sd (2.7) and 2 sd (5.4 mm) above the mean had a 70 and 140% greater risk of suffering an ACL injury.

There are two likely mechanisms through which greater knee laxity is associated with a greater risk of ACL injury. One is a *biomechanical mechanism* where the

ACL acts as a passive restraint to control tibial motion during weight bearing tasks. Studies have shown that greater knee laxity is associated with greater anterior tibial translation of the tibia on the femur during the transition of the knee from non-weight bearing to weight bearing (Shultz et al. 2006b), a stiffer (less absorptive) landing upon ground contact that leads to greater knee extensor loads (Shultz et al. 2010b, 2013), and greater knee valgus motion and moments during landing (i.e., a more inward collapse of the knee) (Shultz and Schmitz 2009), all of which have the potential to increase loading of the ACL during weight bearing activities.

The second is a *biological mechanism*. Sex differences in ACL size and laxity are thought to be modulated by metabolic/remodeling processes that regulate the material properties of the ligament (Comerford et al. 2005; Chandrashekar et al. 2006). This is supported by animal studies, where greater laxity was associated with ligament biomarkers indicative of greater collagen turnover (Comerford et al. 2005; Quasnichka et al. 2005), more immature cross-links (Quasnichka et al. 2005), and lower failure loads (Comerford et al. 2005; Quasnichka et al. 2005; Wang et al. 2006). Given the potent effects of sex hormones on collagen metabolism and cross-links previously described, the changing sex hormone concentrations that females experience likely play a critical role in the biological processes that contribute to their greater magnitudes of knee laxity, thus their greater risk of ACL injury.

Sex Hormone Effects on Knee Laxity

Boys and girls have similar magnitudes of knee laxity prior to puberty. During maturation, knee laxity decreases in males to a greater extent than females (Ahmad et al. 2006; Shultz et al. 2008), and this results in greater average knee laxity values in females compared to males throughout adulthood (Scerpella et al. 2005; Rozzi et al. 1999; Shultz et al. 2005; Beynnon et al. 2005; Uhorchak et al. 2003; Nguyen and Shultz 2007). Additionally, females are unique in that they experience substantial changes in knee laxity across their menstrual cycle. Studies have largely concluded that knee laxity is generally greater in the peri-ovulatory days of the cycle and, to a lesser extent, in the mid-luteal days of the cycle compared to the days of menses (Herzberg et al 2017; Somerson et al. 2019). When sex hormones and knee laxity changes are tracked and compared daily across one complete menstrual cycle, knee laxity was observed to change on average 3–4 days following changes in sex hormone concentrations (Shultz et al. 2004). When this time delay was accounted for, changes in estradiol, progesterone, testosterone, and their interactions explained on average $63 \pm 7.7\%$ of the variance in knee laxity changes (compared to 5.4 and 26% when changes in estradiol alone or in combination with progesterone and testosterone were examined without accounting for this time delay) (Shultz et al. 2004). However, the magnitude of change in knee laxity was quite variable among the women studied (range 1.5–5.3 mm) and was found to be more pronounced in response to rising concentrations of estradiol and testosterone in women who had lower minimum estradiol and higher minimum progesterone concentrations at menses (a more androgenic

environment) (Shultz et al. 2006a). This individual variability in hormone profiles and knee laxity responsiveness is important for clinicians and scientists to understand, as it may expose some women to a greater risk of injury compared to others. For example, studies have shown that those who experience greater acute increases in knee laxity are more likely to move toward higher risk biomechanics when knee laxity is increased, including greater anterior tibial translation during the transition from non-weight bearing to weight bearing (Shultz et al. 2011a), greater knee stiffness upon landing (Shultz et al. 2013), and greater dynamic knee valgus movement and forces during landing and cutting maneuvers (Park et al. 2009b; Shultz et al. 2012a).

To further understand the mechanisms by which sex hormone changes may lead to knee laxity changes, Shultz et al. (2012b) completed a secondary analysis of their data by assaying serum markers of collagen production (CICP; C-terminal propeptide of collagen type I) and degradation (ICTP; carboxyterminal telopeptide of type I collagen) and insulin-like growth factor-I (IGF-I; a mediator of collagen production) (Malloy 2003). Their purpose was to determine if normal physiological changes in hormone concentrations across the menstrual cycle were sufficient to stimulate changes in collagen metabolism, and if these changes in collagen metabolism coincided with the changes in knee laxity observed. They also compared eumenorrheic females to females taking oral contraceptives (who were expected to maintain more stable hormone concentrations). Based on prior study findings (Hansen et al. 2008; Hansen et al. 2009; Wreje et al. 2000; Yu et al. 2001), it was expected that concentrations of CICP, ICTP, and IGF-I would generally be lower (i.e., collagen production and synthesis depressed) during days of the cycle when estradiol levels were elevated, and that greater suppression of collagen synthesis (greater decreases in CICP, ICTP, and IGF-I concentrations) would be associated with greater anterior knee laxity. Results revealed that serum levels of CICP and ICTP tended to be higher during the days of menses, then decreased during the peri-ovulatory and luteal days compared to menses while IGF-I values stayed relative stable (Shultz et al. 2012b). This decrease in CICP and ICTP was most pronounced in the initial days post-ovulation when estrogen was rising unopposed, and this effect began to attenuate in the early luteal phase once progesterone began to rise. When these data were compared to women taking oral contraceptives, eumenorrheic women generally had lower CICP and ICTP concentrations and tended to demonstrate more variability in these concentration changes across time compared to women on oral contraceptives. However, in both groups, decreasing CICP concentrations and increasing IGF-I concentrations predicted increasing anterior knee laxity across the cycle ($R^2 = 0.310$ and 0.400). While these results tend to support the findings from in vitro cell culture models that increasing estradiol concentrations have the potential to influence collagen synthesis and ligament integrity in a dose-dependent and negative manner, this study represents a fairly rudimentary step in attempting to understand these mechanisms. When markers of Type I collagen synthesis and degradation are measured in the serum, they represent changes from a variety of collagen tissue and do not directly represent the local environment of the knee (Hansen et al. 2008, 2009). Additionally, the temporal sequencing of these changes was not examined, which makes it difficult to ascertain

the sequencing of these events with the times in the cycle when ACL injury risk may be elevated (Renstrom et al. 2008). Further research examining these mechanisms is warranted.

Summary

It is clear that sex hormones have the potential to have a profound effect on collagen metabolism in a way that may impact the structural integrity of the ACL, which may impact both the functional stability of the knee and the resiliency of the ligament to external loading. There remains much we do not know about the mechanisms through which these hormone actions occur, the time dependency of these actions, or the hormone profiles that are most likely to contribute to an inferior collagen structure or a more lax ligament. It should also be noted that the majority of in vivo studies examining hormone effects on knee laxity and injury risk are limited to eumenorrheic females with "normal" cycles that are consistent month to month. Menstrual dysfunction in exercising females is common, and reported to be as high as 50% in some athletic populations (DeSouza et al. 2010; Thein-Nissenbaum et al. 2014; Tourville et al. 2016; Vescovi 2011), and current sampling techniques cannot distinguish between ovulatory and anovulatory cycles. Given the high prevalence of menstrual dysfunction, it is equally important to examine relationships between sex hormones, collagen metabolism, ligament behavior, and ACL injury risk in oligomenorrheic and amenorrheic females. In fact, limited research suggests that the risk for severe musculoskeletal injury may be somewhat higher in high school female athletes who experience menstrual cycle disturbances (i.e., those with nine or fewer cycles in previous year and those with primary amenorrhea) (Thein-Nissenbaum et al. 2012). Moreover, a large percentage of physically active females use oral contraceptives, which may also differentially exert their influence on ligament structures. The effect of oral contraceptive use will be covered in the next section.

Contraceptive Hormones

A large portion of physically active females use oral contraceptives (OC) for a variety of reasons. Research estimates that 8–14% of adolescents and 27–42% of collegiate females (and as high as 70% in collegiate soccer athletes) use birth control hormones of some kind (Agel et al. 2006; Beals and Manore 2002; Miller et al. 1999; Paulus et al. 2000; Thein-Nissenbaum et al. 2014). Because contraceptive hormones stabilize and lower endogenous sex hormone levels, it is often theorized that these stabilizing effects would have a protective effect against ACL injury. To date, however, there is limited evidence in the literature to support this. In two studies that included a control group to account for proportional population statistics, there was no evidence that OC users were at lower risk for ACL injury in female athletes (Agel et al. 2006; Ruedl et al. 2009). However, in more recent case–control studies using large national

insurance databases (De Froda et al. 2019; Gray et al. 2016; Rahr-Wagner et al. 2014), studies consistently observed a ~20% reduction in injuries in those using OCs. Two of these studies suggest this protective effect may change over time and may be most effective in the 15–19 year age group (Gray et al. 2016; De Froda et al. 2019). Gray et al. reported that ACL-reconstructed females who were 15–19 years of age were 18% *less* likely to use OC in the 12 months preceding the injury date than matched controls, while those who were 25–34 years of age were 15% *more* likely to use OCPs than matched controls. De Froda et al. reported that the overall reduction in ACL injury in the OCP group was largely driven by 15–19 year olds, where the risk reduction was 63%. While this may suggest that the duration of OCP use may modify its effect on ACL injury risk over time, these latter studies were not specific to sport participation and only represent those who underwent ACL reconstruction. Because athletes are more likely to use OCs and seek reconstructive surgery so that they can continue sport participation, this may have introduced a bias in the proportional use of OCPs in ACL-reconstructed cases versus control subjects. Thus, while these results may be promising, more research is needed to confirm a potential protective effect of OCPs.

Although contraceptive hormones stabilize and lower endogenous hormone levels (Clark et al. 2001; Coney and DelConte 1999; Henzyl 2001; London et al. 1992), and may also reduce relaxin concentrations (Nose-Ogura et al. 2017), they are also biologically active and able to exert their influence on soft tissue structures. It is often posited that contraceptive hormones provide a more stable, predictable hormone environment, yet this environment may differ widely depending on how the contraceptive hormone is administered. For example, dosing can be monophasic or triphasic, and therefore, concentrations may or may not vary over the 21 pill days of the cycle. The concentration of exogenous estradiol (ethinyl estradiol) and progesterone (progestogen) can also differ and can be as much as three to five times and one to two times higher, respectively, than normal, physiological endogenous levels (Burrows and Peters 2007). Also, while ethinyl estradiol is the only form of synthetic estrogen used in OCs, multiple progestogens are used (e.g., levonorgestrel, norethindrone, desogestrel, norgestimate, gestodene). Because the type, potency, and androgenicity of these progestogens may differ, the extent to which the progestogen counteracts the estrogenic effects may also differ (Burrows and Peters 2007).

These variations in oral contraceptive preparations may in part explain inconsistent findings when comparing the effects of OCs on collagen metabolism, tissue structure, and knee joint laxity. Wreje et al. (2000) compared serum markers of collagen synthesis and degradation prior to and following 2 months administration of an oral contraceptive that contained a progestogen with high androgenicity in healthy women. They reported lower concentrations of serum markers of collagen synthesis and degradation after OC administration as compared to pre-administration when measured during the luteal phase (Wreje et al. 2000). Hansen and colleagues compared local markers of tendon collagen synthesis and collagen fibril diameters during the luteal days of women on OCs (which contained high estradiol dosing and a progestogen with low androgenicity) compared to days of menses in eumenorrheic women (when hormones are at their nadirs). They observed reduced

markers of collagen synthesis and smaller tendon fibril diameters in women using OCs (Hansen et al. 2008, 2009). However, in subsequent analyses, they found no detrimental effects on tendon biomechanical properties, tendon fibril characteristics, or collagen cross-linking when comparing women who were long term users of OC versus non-OC users (Hansen et al. 2015). In other work comparing OCP versus eumenorrheic females across multiple days of the cycle, women on various types of OCs were reported to have *higher* concentrations of markers of both collagen synthesis and degradation (CICP and ICTP), and these differences were most pronounced when eumenorrheic women were at peak estradiol concentrations in the post-ovulatory/early luteal days of the cycle (Shultz et al. 2012b). Moreover, secondary correlational analyses suggested that the OCs that contained progestogens with greater androgenicity were more likely to be associated with decreases in IGF-I (marker of collagen production) and ICTP (marker of collagen degradation) concentrations than OCs that contained progestogens with lower androgenicity. In all three studies, IGF-I concentrations (a mediator of collagen production) were reported to be lower in women using oral contraceptives, particularly when comparisons were made in the luteal phase (Hansen et al. 2008, 2009; Shultz et al. 2012b; Wreje et al. 2000).

Limited studies have examined the effects of OCP use on knee laxity (Konopka et al. 2019). In studies comparing knee laxity in OC users and nonusers, one study observed no group differences in knee laxity (Pokorny et al. 2000) while another observed lower knee laxity in OC users (Martineau et al. 2004) when a single sample was measured on a random day during the cycle. When laxity changes were compared at different phases of the menstrual cycle, OC users were reported to have less anterior knee laxity than nonusers at all points, but this was most pronounced when knee laxity was increased in eumenorrheic women during ovulatory and luteal test days (Lee et al. 2014). When compared daily across the menstrual cycle, similar laxity values were observed for OC and eumenorrheic females across the majority of test days except for the early luteal phase (post-estrogen peak, before the rise in progesterone levels) when eumenorrheic females were found to increase their laxity values (Shultz et al. 2012b). In both studies (Lee et al. 2014; Shultz et al. 2012b), laxity values were more stable over time in women using OCs versus eumenorrheic women.

Summary

It is difficult to build a clear consensus of the effects of OC use on collagen metabolism knee laxity and ACL injury based on current literature because studies vary so much in the timing of sample(s) acquisition as well as in the type of OC administered (e.g., dosage of ethinyl estradiol and progestogen delivered, consistency of hormone concentrations over the cycle, and the androgenicity of progestogen). Because the patterns of variability in serum markers and knee laxity values are different across the cycle in OC users versus eumenorrheic females (Gorai et al. 1998; Shultz et al. 2012b), it is difficult to compare findings when serum samples are acquired at a single

random time point or at different phases of the cycle. Further, findings by Shultz et al. (2012b) suggest the need to control for dosage and periodicity of the estrogen, and the androgencity and potency of the progestins administered. A greater focus on the physically active female is also important. Addressing these limitations will help to further elucidate if OCs (or certain types of OCs) have a negative or positive effect on collagen metabolism, tissue integrity, and injury risk.

Relaxin

Although relaxin has been traditionally considered a pregnancy hormone responsible for relaxing pelvic ligaments in preparation for labor (Samuel et al. 2007), it is also detectable in the serum of non-pregnant females (Dragoo et al. 2011b; Johnson et al. 1993; Pehrsson et al. 2007; Stewart et al. 1990; Wolf et al. 2013b; Wreje et al. 1995). Relaxin is typically lower during the follicular phase, then rises by day 6 and peaks within 8–10 days following the LH surge at ovulation (Bryant et al. 1975; Johnson et al. 1993; Stewart et al. 1990; Wreje et al. 1995). However, actual levels can vary widely among females within this window both in magnitude and timing (Casey et al. 2018), with some having undetectable levels and others having unusually high levels that are similar to pregnancy concentrations (Dragoo et al. 2011b; Stewart et al. 1990). Additionally, some women are reported to have episodic peaks during the follicular phase (Bryant et al. 1975), while others have abnormally high values throughout the cycle (Bryant et al. 1975; Stewart et al. 1990). These interindividual variations in relaxin levels are likely in part due to large, interindividual variability in the timing and magnitude of sex steroid concentrations (Shultz et al. 2004, 2011b), as relaxin secretion and its impact on collagen metabolism are thought to be largely regulated by estradiol (Dragoo et al. 2011b; Konopka et al. 2016; Johnson et al. 1993; Wreje et al. 1995).

Relaxin and Collagen Metabolism

Relaxin is a member of the insulin superfamily of peptide hormones which initiate their actions by binding to receptors on the cell surface, utilizing cellular signaling pathways to further transmit messages, ultimately resulting in altered cellular function. Relaxin-2 is the predominant circulating form of relaxin in humans (Sherwood 2004). While it is difficult to study the effect of relaxin on collagen metabolism in human knee ligaments in situ, in vivo and in vitro animal studies and human cell culture studies suggest that relaxin administered at physiological levels can have a profound effect on soft tissue remodeling (ligament fibrocartilage, articular cartilage, tendon, and dermal). Specifically, circulating relaxin increases expression of relaxin receptors on target tissues (Kang et al. 2014), leading to dose-dependent increases in the expression of matrix metalloproteinases (MMPs) *for* collagenases (MMPs 1

and 13), gelatinases (MMP 2 and 9), and stromelysins (MMP 3) that break down fibrillar collagens, fibrocartilage, and extracellular matrix proteins (Konopka et al. 2016; Naqvi et al. 2005; Takano et al. 2009; Unemori and Amento 1990). Relaxin also decreases the expression of Type I, III, and IV collagen in a dose-dependent manner (Kang et al. 2014; Takano et al. 2009; Unemori and Amento 1990) and modestly reduces expression of tissue inhibitors (TIMPs) that regulate collagenase activity (Takano et al. 2009; Unemori and Amento 1990). These collagenolytic effects have also been shown in fibrotic and healing tissues where collagen synthesis and deposition (thus scar formation) were greatly reduced (Kang et al. 2014; Negishi et al. 2005). The net effect of this tissue remodeling is a less organized (Unemori et al. 1993) and less dense (both in fiber diameter and density) collagen structure (Naqvi et al. 2005; Unemori et al. 1993). Because these same tissue properties have been associated with a more lax (less stiff) and structurally weaker ligament in ACL animal models (Comerford et al. 2005; Dragoo et al. 2009; Fleming et al. 2011; Quasnichka et al. 2005; Hashem et al. 2006), these findings provide evidence of the potential for relaxin to alter ligament structure and function in ways that may contribute to greater ligament laxity and risk of ACL injury.

Because of the stability of collagen, the aforementioned changes are thought to result more from chronic exposure (Dragoo et al. 2011a; Konopka et al. 2016) and more likely explain the higher baseline laxity values and perhaps structural weakening of the female ACL over time. Yet there is evidence that relaxin may also contribute to acute elongations of the ligament by interrupting interfibrillar bonds, allowing the fibers to slip and reorient (Wood et al. 2003). This collagen sliding has been demonstrated in rat tail tendon where a fluorescent dye was used to label collagen fibers, and changes in fiber orientation were observed over 48 h while the tendon was under strain (Wood et al. 2003). Tendons treated with relaxin demonstrated significantly more creep than controls within 3 h of relaxin exposure (3% vs. 1% of tendon length), and this creep gradually increased over 48 h (10–12% vs. 1%). Hence, acute collagen fiber sliding provides a plausible explanation for the acute increases in knee laxity that are commonly observed in females during the luteal phase of the menstrual cycle (i.e., similar in timing to the rise in relaxin concentrations) (Shultz et al. 2004, 2010a; Deie et al. 2002; Heitz 1999). This would also be consistent with the findings of Lee et al. (2015) who observed inhibition of collagen cross-links with acute changes in estradiol exposure. This collagen fiber sliding may also explain why greater relaxin concentrations were associated with decreased tendon stiffness ($r^2 = 0.31$), but not changes in cross-sectional area, when human tendon force-elongation characteristics were examined across three times points in the menstrual cycle (Pearson et al. 2011).

Relaxin, Knee Laxity, and ACL Injury

Relaxin receptors have been identified on the human ACL (Dragoo et al. 2003; Faryniarz et al. 2006; Galey et al. 2003) and are therefore capable of directly impacting

ACL laxity and structural integrity. Relaxin receptors on the human ACL are reported to be more prevalent in females versus males (Dragoo et al. 2003; Faryniarz et al. 2006; Galey et al. 2003) and in younger versus older women (Galey et al. 2003). Since collagen is the main load bearing structure of the ACL, the acute and chronic effects of relaxin on collagen organization and content previously described suggest that higher serum relaxin concentrations may lead to clinically relevant increases in laxity and weakness of the ACL (Dragoo et al. 2003). This is supported by a prospective study of Division I female athletes where relaxin levels were threefold higher and more variable in those who suffered an ACL injury compared to non-injured controls (6.0 ± 8.1 vs. 1.8 ± 3.4 pg/mL) and where females with relaxin levels greater than 6.0 pg/mL were reported to be four times more likely to suffer an ACL injury (Dragoo et al. 2011a). While the authors theorized this increased risk was likely due to altered ligament laxity and strength (Dragoo et al. 2011a, 2012), laxity was not measured in these participants. The likelihood of greater knee laxity in these individuals is supported by an animal model where guinea pig ACLs treated with relaxin at pregnancy levels were 13% more lax and 36–49% weaker (Dragoo et al. 2009). Other retrospective work indirectly corroborates these findings, as both serum relaxin and knee laxity values were significantly higher in females with a history of ACL injury compared to uninjured controls (Arnold et al. 2002).

Few studies have examined associations between relaxin and joint laxity in eumenorrheic females, and results are inconclusive (Konopka et al. 2019). Three studies by one group of authors reported no significant correlations between serum relaxin levels and general joint laxity (Wolf et al. 2013a, b, 2014). However, they only sampled relaxin at one time point, and this was not timed with the mid-luteal phase when relaxin is known to be elevated (Anderson et al. 2019; Casey et al. 2018). It is unlikely that representative peak relaxin levels were obtained in many of these women, and this may explain the large proportion of females they reported with undetectable levels (58–80%). One study examined anterior knee laxity while obtaining weekly samples of serum relaxin and anterior knee laxity for 4 weeks in 57 collegiate non-pregnant females (eight of which were ACL injured) (Arnold et al. 2002). Both serum relaxin and anterior knee laxity were higher in ACL injured versus non-injured, but no significant within-day correlations were identified. One sample was obtained each week, and the timing of each sample relative to known hormone events was not controlled (Arnold et al. 2002). Once again, considering the relatively transient peak in relaxin (Johnson et al. 1993; Stewart et al. 1990; Wreje et al. 1995), it is unclear how accurately minimum and peak relaxin was captured in all females, thus the magnitude of change in relaxin these women experienced. It is also unknown whether the relaxin concentrations obtained on the day of laxity testing would sufficiently characterize the relationship between relaxin and either baseline or cyclic increases in laxity.

Prior studies have not controlled for circulating sex hormone concentrations. This may be important in clarifying relationships between relaxin, knee laxity, and injury risk, as sex hormones are reported to alter the effect of relaxin on collagen structure and metabolism (Dehghan et al. 2014a, b; Hashem et al. 2006; Naqvi et al. 2005) and circulating estradiol is considered a primary regulator of relaxin secretion

(Johnson et al. 1993; Konopka et al. 2016; Wreje et al. 1995). Konopka demonstrated that ACL cells obtained from human female donors that were treated with relaxin and primed with estrogen showed a greater increase in MMP1 and MMP3 expression and greater decreases in Type I and III collagen expression compared to those treated with estrogen alone. In ovariectomized rabbits, relaxin secretion increased when primed with estradiol, and total collagen content in knee articular and temporomandibular joint (TMJ) fibrocartilage decreased with administration of relaxin, estradiol, and relaxin+estradiol, while it was maintained with relaxin+progesterone or relaxin+estradiol+progesterone (Hashem et al. 2006). In rabbit cell cultures, MMP1 and MMP2 expression were 1.7-fold higher when relaxin and relaxin+estradiol were administered at normal physiological levels, and this was substantially greater than when estradiol was administered alone (Naqvi et al. 2005). In ovarectomized rats, relaxin+estrogen, and relaxin+progesterone resulted in a dose-dependent increase in relaxin protein and mRNA expression in medial collateral ligaments and patellar tendons (Dehghan et al. 2014a), while relaxin+testosterone downregulated this response and subsequently inhibited an increase in passive knee motion that was observed with relaxin administration alone (Dehghan et al. 2014a, b). Although relaxin and estrogen are strongly correlated within a day (Johnson et al. 1993; Wreje et al. 1995), and estrogen is thought to be the primary regulator of relaxin secretion (Johnson et al. 1993), their combined impact on collagen metabolism is unclear as some studies suggest that estrogen does not enhance or alter relaxin's effect on target tissue (Dehghan et al. 2014a, b; Hashem et al. 2006; Naqvi et al. 2005), while other works suggest it does (Konopka 2016). Because progesterone and testosterone are reported to modify relaxin expression in target tissues, it may be important to control for these hormone levels when examining associations between relaxin, knee laxity, and ACL injury risk. The potential for progesterone and testosterone to downregulate relaxin expression and subsequently inhibit an increase in passive knee motion (Dehghan et al. 2014a, b) may also explain in part the highly variable associations previously observed between sex hormone changes and knee laxity changes in eumenorrheic women (Shultz et al. 2004, 2006a).

Together, these findings support the need for future in vivo studies examining the relationship between relaxin, knee laxity, and ACL injury risk in normal menstruating females. Future work should consider: (1) timing the sampling of relaxin to known hormone events (i.e., rather than calendar days of the cycle), (2) ideally obtaining serial measures around the time that relaxin is known to be at its nadir and peak levels in order to fully capture an individual's relaxin profile, and (3) accounting for circulating sex hormone concentrations to control for their moderating effects when characterizing these relationships.

Summary and Future Directions

Greater knee joint laxity has consistently been associated with a greater risk of ACL injury. Females, who are at greater risk for ACL injury, have consistently

been shown to have greater and more variable knee laxity than males both in terms of absolute magnitude and in the cyclic increases and decreases they experience across their menstrual cycle. While greater laxity in vivo has been shown to have detrimental biomechanical effects on knee stability during sport activity, there is also strong evidence that greater knee laxity in females is also associated with a smaller, less dense, less organized, and structurally weaker ligament that in part results from metabolic and remodeling processes that influence ligament structural integrity. The factors that differentially regulate these processes in females versus males and cause one female to have more laxity than another are complex and remain poorly understood.

What is clear is that sex steroid hormones (both endogenous and exogenous) and relaxin likely play a role in these processes given their potential to exert tremendous influences on the metabolism and structural and mechanical properties of soft tissue structures. However, we are just beginning to understand the extent to which normal physiological variations in these hormones impact the structural and mechanical properties of the ACL in a way that renders it more susceptible to injury in vivo. This work is challenging because of the large variability in hormone profiles in physically active women, and the potential time dependency of the tissues responsiveness to hormones, which make it difficult to understand these relationships without prospectively tracking hormone concentrations and variables or outcomes of interest over time. Addressing this individual variability and time dependency in future study designs is critical if we are to better align the time of injury occurrence with acute changes in ACL structure and metabolism and understand how the rate of increase or time duration of elevated hormone concentrations impacts ligament integrity (Shultz et al. 2015). Unfortunately, the study designs commonly used in this area of research fall well short of the complexity of these issues. The scientific community must become more vigilant in verifying the hormonal milieu at the time of and prior to the time of injury or outcome measurement of interest. This will likely require multiple samples taken over repeated days to accurately characterize a female's hormone environment.

Moreover, it is becoming increasingly evident that there is no one hormone that acts independently to exert these effects, but rather there is likely a complex interaction among multiple hormones and other relevant factors such as exercise status and one's genetic makeup. It is also critical that we expand our study designs to women taking contraceptive hormones and those who experience menstrual dysfunction (amenhorreic, oligomenorrheic), given the high prevalence of these conditions in physically active females. Despite these challenges, this remains an important area of study if we are to fully elucidate the underlying mechanisms for the increased risk of ACL injury in females and develop the most effective intervention strategies to mitigate that risk.

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References

Abubaker AO, Hebda PC, Gunsolley JN. Effects of sex hormones on protein and collagen content of the temporomandibular joint disc of the rat. J Oral Maxillofac Surg. 1996;54:721–7.

Adachi N, Nawata K, Maeta M, Kurozawa Y. Relationship of the menstrual cycle phase to anterior cruciate ligament injuries in teenage female athletes. Arch Orthop Trauma Surg. 2008;128(5):473–8.

Ahmad CS, Clark AM, Heilmann N, Schoeb JS, Gardner TR, Levine WN. Effect of gender and maturity on quadriceps-to-hamstring strength ratio and anterior cruciate ligament laxity. Am J Sports Med. 34(3):370–74. https://doi.org/10.1177/0363546505280426.

Agel J, Bershadsky B, Arendt EA. Hormonal therapy: ACL and Ankle injury. Med Sci Sports Exerc. 2006;38(1):7–12.

Anderson T, Shultz Sandra J, Williams NI, Casey E, Kincaid Z, Lieberman JL, Wideman L. Capturing detectable relaxin concentrations in eumenorrheic non-pregnant women. Women Sport Phys Act J. 2019;27(1):30–36. https://doi.org/10.1123/wspaj.2018-0014.

Arendt EA, Bershadsky B, Agel J. Periodicity of noncontact anterior cruciate ligament injuries during the menstrual cycle. J Gend Specif Med. 2002;5(2):19–26.

Arnold C, VanBell C, Rogers V, Cooney T. The relationship between serum relaxin and knee joint laxity in female athletes. Orthopedics. 2002;25(6):669–73.

Beals KA, Manore ML. Disorders of the female athlete triad among collegiate athletes. Int J Sport Nutr Exerc Metab. 2002;12:281–92.

Beck NA, Lawrence JTR, Nordin JD, De For TA, Tompkins M. ACL tears in school-aged children and adolescents over 20 years. Pediatrics. 2017;139(3). https://doi.org/10.1542/peds.2016-1877.

Bethene ER, Fryar CD, Wang C-Y, Miller IM, Ogden CL. Strength and body weight in US children and adolescents. Pediatrics 2014;134(3):e782–e789. https://doi.org/10.1542/peds.2014-0794.

Bloom DA, Wolfert AJ, Michalowitz A, Jazrawi LM, Carter CW. ACL injuries aren't just for girls: the role of age in predicting pediatric ACL injury. Sports Health Multidiscipl Approach. 12(6) 559–563. https://doi.org/10.1177/1941738120935429.

Beynnon BD, Bernstein I, Belisle A, Brattbakk B, Devanny P, Risinger R, Durant D. The effect of estradiol and progesterone on knee and ankle joint laxity. Am J Sports Med. 2005;33(9):1298–304.

Beynnon BD, Johnson RJ, Braun S, Sargent M, Bernstein I, Skelly JM, Vacek PM. The relationship between menstrual cycle phase and anterior cruciate ligament injury: A case-control study of recreational alpine skiers. Am J Sports Med. 2006;34(5):757–64.

Beynnon BD, Vacek PM, Tourville TW, Sturnick DR, Gardner-Morse M, Holterman LA, Smith HC, Slauterbeck J, Hashemi J, Shultz SJ, Johnson RJ. Multivariate analysis of the risk factors for first-time non-contact ACL injury in high school college athletes; A prospective cohort study with a nested, matched case-control analysis. Am J Sports Med. 2016;44(6):1492–501.

Bryant GD, Panter ME, Stelmasiak T. Immunoreactive relaxin in human serum during the menstrual cycle. J Clin Endocrinol Metab. 1975;41(6):1065–9.

Burrows M, Peters CE. The influence of oral contraceptives on athletic performance in female athletes. Sports Med. 2007;37(7):557–74.

Butler DL, Noyes FR, Grood ES. Ligamentous restraints to anterior-posterior drawer in the human knee. J Bone Joint Surg. 1980;62-A(2):259–70.

Chandrashekar N, Mansour JM, Slauterbeck J, Hashemi J. Sex-based differences in the tensile properties of the human anterior cruciate ligament. J Biomech. 2006;39:2943–50.

Chaudhari AMW, Zelman EA, Flanigan DC, Kaeding CC, Nagaraja HN. Anterior cruciate ligament—injured subjects have smaller anterior cruciate ligaments than matched controls. Am J Sports Med. 2009;37(7):1282–1287. https://doi.org/10.1177/0363546509332256.

Clark MK, Sowers M, Levy BT, Tenhundfeld P. Magnitude and variability of sequential estradiol and progesterone concentrations in women using depot medroxyprogesterone acetate for contraception. Fertil Steril. 2001;75(5):871–7.

Comerford EJ, Tarlton JF, Innes JF, Johnson KA, Amis AA, Bailey AJ. Metabolism and composition of the canine anterior cruciate ligament relate to differences in knee joint mechanics and predisposition to ligament rupture. J Orthop Res. 2005;23:61–6.

Cone SG, Barnes RH, Howe D, Fordham LA., Fisher MB, Spang JT. Age- and sex-specific differences in ACL and ACL bundle size during adolescent growth. J Orthopaed Res. https://doi.org/10.1002/jor.25198.

Cone SG, Howe D, Fisher MB. Size and shape of the human anterior cruciate ligament and the impact of sex and skeletal growth. JBJS Rev. 2019;7(6):e8. https://doi.org/10.2106/JBJS.RVW.18.00145.

Coney P, DelConte A. The effects of ovarian activity of a monophasic oral contraceptive with 100 μg levonorgestrel and 20 μg ethinyl estradiol. Am J Obstet Gynecol. 1999;181(5):S53–8.

Csintalan RP, Inacio MC, Funahashi TT. Incidence rate of anterior cruciate ligament reconstructions. Perm J. 2008;12(3):17–21.

Dehghan F, Muniandy S, Yusof A, Salley N. Sex-steroid regulation of relaxin receptor isoforms (RXFP1 & RXFP2) expression in the patellar tendon and lateral collateral ligament of female WKY rats. Int J Med Sci. 2014a;11(2):180–91.

Dehghan F, Muniandy S, Yusof A, Salley N. Testosterone reduces knee passive range of motion and expression of relaxin receptor isoforms via 5α-Dihydrotestosterone and androgen receptor binding. Int J Mol Sci. 2014b;15:619–4634.

DeFroda SF, Bokshan SL, Worobey S, Ready L, Daniels AH, Owens BD. Oral contraceptives provide protection against anterior cruciate ligament tears: a national database study of 165748 female patients. Phys Sportsmed. 2019;47(4):416–420. https://doi.org/10.1080/00913847.2019.1600334.

Deie M, Sakamaki Y, Sumen Y, Urabe Y, Ikuta Y. Anterior knee laxity in young women varies with their menstrual cycle. Int Orthop. 2002;26:154–6.

DeSouza MJ, Toombs RJ, Scheid JL, O'Donnell EO, West SL, Williams NI. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. Hum Reprod. 2010;25(2):491–503.

Dragoo JL, Lee RS, Benhaim P, Finerman GAM, Hame SL. Relaxin receptors in the human female anterior cruciate ligament. Am J Sports Med. 2003;31(4):577–84.

Dragoo JL, Padrez K, Workman R, Lindsey DP. The effect of relaxin on the female anterior cruciate ligament: Analysis of mechanical properties in an animal model. Knee. 2009;16(1):69–72.

Dragoo JL, Castillo TN, Braun HJ, Ridley BA, Kennedy AC, Golish SR. Prospective correlation between serum relaxin concentration and anterior cruciate ligament tears among elite collegiate female athletes. Am J Sports Med. 2011a;39(10):2175–80.

Dragoo JL, Castillo TN, Korotkova TA, Kennedy AC, Kim HJ, Stewart DR. Trends in serum relaxin concentration among elite collegiate female athletes. Int J Womens Health. 2011b;3:19–24.

Dragoo JL, Braun HJ, Durham JL, Chen MR, Harris AH. Incidence and risk factors for injuries to the anterior cruciate ligament in National Collegiate Athletic Association football: data from the 2004–2005 through 2008–2009 National Collegiate Athletic Association Injury Surveillance System. Am J Sports Med. 2012;40(5):990–5. https://doi.org/10.1177/0363546512442336.

Dubey RK, Gillespie DG, Jackson EK, Keller PJ. 17B-Estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth. Hypertension. 1998;31(2):522–8.

Dyer R, Sodek J, Heersche JM. The effect of 17 B-Estradiol on collagen and noncollagenous protein synthesis in the uterus and some periodontal tissues. Endocrinology. 1980;107:1014–21.

Eiling W, Bryant AL, Petersen W, Murphy A, Hohmann E. Effects of menstrual cycle hormone fluctuations on musculoskeletal stiffness and knee joint laxity. Knee Surg Sports Traumatol Arthrosc. 2007;15(2):126–32.

Ellen C, Travis A, Laurie W, Frances FS, Sandra JS. Optimal paradigms for measuring peak serum relaxin in eumenorrheic active females. Reprod Med Int. 2018;1(2). https://doi.org/10.23937/rmi-2017/1710006.

Faryniarz DA, Bhargave M, Lajam C, Attia ET, Hannafin JA. Quantitation of estrogen receptors and relaxin binding in human anterior cruciate ligament fibroblasts. In Vitro Cell Dev Biol Anim. 2006;42:176–81.

Fischer GM. Comparison of collagen dynamics in different tissues under the influence of estradiol. Endocrinology. 1973;93:1216–8.

Fleming BC, Vajapeyam S, Connolly SA, Margarian EM, Murray MM. The use of magnetic resonance imaging to predict ACL graft structural properties. J Biomech. 2011;44:2843–6.

Flynn JM, Mackenzie W, Kolstad K, Sandifer E, Jawad AF, Galinat B. Objective evaluation of knee laxity in children. J Pediatr Orthop. 2000;20:259–63.

Ford KR, Shapiro R, Myer GD, VanDenBogert AJ, Hewett TE. Longitudinal sex differences during landing in knee abduction in young athletes. Med Sci Sports Exerc. 2010;42(10):1923–31.

Galey S, Konieczko EM, Arnold CA, Cooney TE. Immunohistological detection of relaxin binding in anterior cruciate ligaments. Orthopaedics. 2003;26(12):1201–4.

Gianotti SM, Marshall SW, HUme PA, Bunt L. Incidence of anterior cruciate ligament injury and other knee injuries: a national population-based study. J Sci Med Sport. 2009;12:622–7.

Goodman AL, Descalzi CD, Johnson DK, Hodgen GD. Composite pattern of circulating LH, FSH, estradiol, and progesterone during the menstrual cycle in cynomolgus monkeys. Proc Soc Exp Biol Med. 1977;155(4):479–81.

Gorai I, Taguchi Y, Chaki O, Kikuchi R, Nakayama M, Yang BC, Yokota S, Minaguchi H. Serum soluble interleukin-6 receptor and biochemical markers of bone metabolism show significant variations during the menstrual cycle. J Clin Endocrinol Metab. 1998;83(2):326–32.

Gray AM, Gugala Z, Baillargeon J. Effects of oral contraceptive use on anterior cruciate ligament injury epidemiology. Med Sci Sports Exerc. 2016;48(4):648–54.

Griffin LY, Albohm MJ, Arendt EA, Bahr E, Beynnon BD, DeMaio M, Dick RW, Engebretsen L, Garrett WE, Gilchrist J, Hannafin JA, Hewett TE, Huston LJ, Johnson RJ, Lephart SM, Ireland ML, Mandelbaum BR, Mann B, Marks PH, Marshall SW, Myklebust G, Noyes FR, Powers C, Shields C, Shultz SJ, Silvers H, Slauterbeck J, Taylor D, Teitz CC, Wojtys EM, Yu B. Update on ACL prevention: theoretical and practical guidelines. Am J Sports Med. 2006;34(9):1512–32.

Gornitzky AL, Lott A, Yellin JL, Fabricant PD, Lawrence JT, Ganley TJ. Sport-specific yearly risk and incidence of anterior cruciate ligament tears in high school athletes. Am J Sports Med. 2016;44(10):2716–2723. https://doi.org/10.1177/0363546515617742.

Hama H, Yamamuro T, Takeda T. Experimental studies on connective tissue of the capsular ligament. Influences of aging and sex hormones. Acta Orthop Scand. 1976;47:473–9.

Hamlet WP, Liu SH, Panossian V, Finerman GA. Primary immunolocalization of androgen target cells in the human anterior cruciate ligament. J Orthop Res. 1997;15(5):657–63.

Hansen M, Koskinen SO, Petersen SG, Doessing S, Frystyk J, Flyvbjerg A, Westh E, Magnusson SP, Kjaer M, Langberg H. Ethinyl oestradiol administration in women suppresses synthesis of collagen in tendon in response to exercise. J Physiol. 2008;586(12):3005–16.

Hansen M, Miller BF, Holm L, Doessing S, Petersen SG, Skovgaard D, Frystyk J, Flyvbjerg A, Koskinen S, Pingel J, Kjaer M, Langberg H. Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. J Appl Physiol. 2009;106:1435–43.

Hansen M, Couppe C, Hansen CSE, Skovgaard D, Kovanen V, Larsen J, Aagaard P, Magnussson SP, Kjaer M. Impact of oral contraceptive use and menstrual phases on patellar tendon morphology, biomechanical composition, and biomechanical properties in female athletes. J Appl Physiol. 2015;114:998–1008.

Hashem G, Zhang Q, Hayami T, Chen J, Wang W, Kapila S. Relaxin and B-estradiol modulate targeted matrix degradation in specific synovial joint fibrocartilages: progesterone prevents matrix loss. Arthritis Res Ther. 2006;8(4):R98.

Hashemi J, Chandrashekar N, Mansouri H, Slauterbeck J, Hardy DM. The human anterior cruciate ligament: sex differences in ultrastructure and correlation with biomechanical properties. J Orthop Res. 2008;26:945–50.

Hassager C, Jensen LT, Podenphant J, Riis BJ, Christiansen C. Collage synthesis in postmenopausal women during therapy with anabolic steroid or female sex hormones. Metabolism. 1990;39:1167–9.

Hattori K, Sano H, Komatsuda T, Saijo Y, Sugita T, Itoi E. Effect of estrogen on tissue elasticity of the ligament proper in rabbit anterior cruciate ligament: measurements using scanning acoustic microscopy. J Orthop Sci. 2010;15(584-588).

Heitz NA. Hormonal changes throughout the menstrual cycle and increased anterior cruciate ligament laxity in females. J Athl Train. 1999;343(2):144–9.

Henzyl MR. Norgestimate: from the laboratory to three clinical indications. J Reprod Med. 2001;46(7):647–61.

Herzberg SD, Motu'apuaka ML, Lambert W, Fu R, Brady J, Guise J-M. The effect of menstrual cycle and contraceptives on ACL injuries and laxity: a systematic review and meta-analysis. Orthopaed J Sports Med. 2017;5(7). https://doi.org/10.1177/2325967117718781.

Hewett TE, Zazulak BT, Myer GD. Effects of the menstrual cycle on anterior cruciate ligament injury risk. Am J Sports Med. 2007;35(4):659–68.

Ho KKY, Weissberger AJ. Impact of short-term estrogen administration on growth hormone secretion and action: distinct route-dependent effects on connective and bone tissue metabolism. J Bone Miner Res. 1992;7:821–7.

Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. J Athl Train. 2007;42(2):311–9.

Hosokawa M, Ishii M, Inoue K, Yao CS, Takeda T. Estrogen induces different responses in dermal and lung fibroblasts: special reference to collagen. Connect Tissue Res. 1981;9:115–20.

Hosseinzadeh S, Kiapour AM. Age-related changes in ACL morphology during skeletal growth and maturation are different between females and males. J Orthopaed Res. 39(4):841-849. https://doi.org/10.1002/jor.24748.

Johnson MR, Carter G, Grint C, Lightman SL. Relationship between ovarian steroids, gonadotropins and relaxin during the menstrual cycle. Acta Endocrinol. 1993;129(2):121–5.

Kang Y, Choi Y, Yun C, Park J, Suk K, Kim H, Park M, Lee B, Lee H, Moon S. Down-regulation of collagen synthesis and matrix metalloproteinase expression in myofibroblasts from Dupuytren nodule using adenovirus-mediated relaxin gene therapy. J Orthop Res. 2014;32(4):515–23.

Khowailed IA, Petrofsky JS, Lohman E, Daher N, Mohamed O. 17B-Estradiol induced effects on anterior cruciate ligament laxness and neuromuscular activation patterns in female runners. J Women Health. 2015;24(8):670–80.

Komatsuda T, Sugita T, Sano H, Kusakabe T, Watanuki M, Yohsizumi Y, Murakami T, Hashimoto M, Kokubub S. Does estrogen alter the mechanical properties of the anterior cruciate ligament. Acta Orthop Scand. 2006;77(6):973–80.

Konopka JA, De Baun MR, Chang W, Dragoo JL. The intracellular effect of relaxin on female anterior cruciate ligament cells. Am J Sports Med. 2016;44(9):2384–2392. https://doi.org/10.1177/0363546516646374.

Konopka JA, Hsue LJ, Dragoo JL. Effect of oral contraceptives on soft tissue injury risk soft tissue laxity and muscle strength: a systematic review of the literature. Orthop J Sports Med. 2019;7(3):232596711983106. https://doi.org/10.1177/2325967119831061

Landgren BM, Unden AL, Deczfalusy E. Hormonal profile of the cycle in 68 normal menstruating women. Acta Endocrinol. 1980;94:89–98.

Lee C, Liu X, Smith CL, Zhang X, Hsu H, Wang D, Luo ZP. The combined regulation of estrogen and cyclic tension on fibroblast biosynthesis derived from anterior cruciate ligament. Matrix Biol. 2004;23:323–9.

Lee H, Petrofsky JS, Daher N, Berk L, Laymon M. Differences in anterior cruciate ligament elasticity and force for knee flexion in women: oral contraceptive users versus non-oral contraceptive users. Eur J Appl Physiol. 2014;114:285–94.

Lenton EA, Lawrence GF, Coleman RA, Cooke ID. Individual variation in gonadotropin and steroid concentrations and in the lengths of the follicular and luteal phases in women with regular menstrual cycles. Clin Reprod Fertil. 1983;2:143–50.

Lee CA, Lee-Barthel A, Marquino L, Sandoval N, Marcotte GR, Baar K. Estrogen inhibits lysyl oxidase and decreases mechanical function in engineered ligaments. J Appl Physiol. 2015;118(10):1250–1257. https://doi.org/10.1152/japplphysiol.00823.2014.

Liu SH, Al-Shaikh RA, Panossian V, Finerman GM. Primary immunolocalization of estrogen and progesterone target cells in the human anterior cruciate ligament. J Orthop Res. 1996;14:526–33.

Liu SH, Al-Shaikh RA, Panossian V, Finerman GA, Lane JM. Estrogen affects the cellular metabolism of the anterior cruciate ligament. Am J Sports Med. 1997;25(5):704–9.

London RS, Chapdelaine A, Upmalis D, Olson W, Smith J. Comparative contraceptive efficacy and mechanism of action of the norgestimate-containing triphasic oral contraceptive. Acta Obstet Gynecol Scand. 1992;71:9–14.

Malloy T, Wang Y, Murrell GAC. The roles of growth factors in tendon and ligament healing. Sports Med. 2003;33(5):381–94.

Martineau PA, Al-Jassir F, Lenczner E, Burman ML. Effect of the oral contraceptive pill on ligamentous laxity. Clin J Sports Med. 2004;14:281–6.

McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2013;9(4):249–259. https://doi.org/10.1111/j.2047-6310.2013.00168.x.

Miller KE, Sabo DF, Farrell MP, Barnes GM, Melnick MJ. Sports, sexual behavior, contraceptive use, and pregnancy among female and male high school students: testing cultural resource theory. Sociol Sport J. 1999;16:366–87.

Myklebust G, Maehlum S, Holm I, Bahr R. A prospective cohort study of anterior cruciate ligament injuries in elite Norwegian team handball. Scan J Med Sci Sports. 1998;8:149–53.

Myklebust G, Engebretsen L, Braekken IH, Skjolberg A, Olsen OE, Bahr R. Prevention of anterior cruciate ligament injuries in female team handball players: a prospective intervention study over three seasons. Clin J Sports Med. 2003;13(2):71–8.

Naqvi T, Duong TT, Hashem G, Shiga M, Zhang Q, Kapila S. MMP induction by relaxin causes cartilage matrix degradation in target synovial joints: receptor profiles correlate with matrix turnover. Arthritis Res Ther. 2005;7(1):R1–11.

Negishi S, Li Y, Usas A, Fu F, Huard J. The effect of relaxin treatment on skeletal muscle injuries. Am J Sports Med. 2005;33(12):1816–24.

Nguyen AD, Shultz SJ. Sex differences in lower extremity posture. J Orthop Sports Phys Ther. 2007;37(7):389–98.

Nose-Ogura S, Yoshino O, Yamada-Nomoto K, Nakamura M, Harada M, Dohi M, Okuwaki T, Osuga Y, Kawahara T, Saito S. Oral contraceptive therapy reduces serum relaxin-2 in elite female athletes. J Obstet Gynaecol Res. 2017;43(3):530–535. https://doi.org/10.1111/jog.13226.

Park SK, Stefanyshyn DJ, Loitz-Ramage B, Hart DA, Ronsky JL. Changing hormone levels during the menstrual cycle affect knee laxity and stiffness in healthy female subjects. Am J Sports Med. 2009a;37(3):588–98. https://doi.org/10.1177/0363546508326713.

Park SK, Stefanyshyn DJ, Ramage B, Hart DA, Ronsky JL. Alterations in knee joint laxity during the menstrual cycle in healthy women leads to increases in joint loads during selected athletic movements. Am J Sports Med. 2009b;37(6):1169–77.

Paulus D, Saint-Remy A, Jeanjean M. Oral contraception and cardiovascular risk factors among adolescents. Contraception. 2000;62:113–6.

Pearson SJ, Burgess KE, Onambele GL. Serum relaxin levels affect the in vivo properties of some but not all tendons in normally menstruating young women. Exp Physiol. 2011;96(7):681–8.

Pehrsson M, Westberg L, Landen M, Ekman A. Stable serum levels of relaxin throughout the menstrual cycle: a preliminary comparison of women with premenstrual dysphoria and controls. Arch Womens Ment Health. 2007;10:147–53.

Pokorny MJ, Smith TD, Calus SA, Dennison EA. Self-reported oral contraceptive use and peripheral joint laxity. J Orthop Sports Phys Ther. 2000;30(11):683–92.

Posthumus M, September AV, O'Cuinneagain D, van der Merwe W, Schwellnus MP, Collins M. The COL5A1 gene is associated with increased risk of anterior cruciate ligament ruptures in a female participants. Am J Sports Med. 2009;37:2234–40.

Prodromos CC, Han Y, Rogowski J, Joyce B, Shi K. A meta-analysis of the incidence of anterior cruciate ligament tears as a function of gender, sport, and a knee injury-reduction regimen. Arthroscopy. 2007;23(12):1320–5. e1326.

Quasnichka HL, Anderson-MacKenzie JM, Tarlton JF, Sims TJ, Billingham ME, Bailey AJ. Cruciate ligament laxity and femoral intercondylar notch narrowing in early-stage knee osteoarthritis. Arthritis Rheum. 2005;52(10):3100–9. https://doi.org/10.1002/art.21340.

Rahr-Wagner L, Thillemann TM, Mehnert F, Pedersen AB, Lind M. Is the use of oral contraceptives associated with operatively treated anterior cruciate ligament injury? Am J Sports Med. 2014;42(12):2897–2905. https://doi.org/10.1177/0363546514557240.

Renstrom P, Ljungqvist A, Arendt E, Beynnon B, Fukubayashi T, Garrett W, Georgoulis T, Hewett TE, Johnson R, Krosshaug T, Mandelbaum B, Micheli L, Myklebust G, Roos E, Roos H, Schamasch P, Shultz S, Werner S, Wojtys E, Engebretsen L. Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. Br J Sports Med. 2008;42(6):394–412.

Rozzi SL, Lephart SM, Gear WS, Fu FH. Knee joint laxity and neuromuscular characteristics of male and female soccer and basketball players. Am J Sports Med. 1999;27(3):312–9.

Ruedl G, Ploner P, Linortner I, Schranz A, Fink C, Sommersacher R, Pocecco E, Nachbauer W, Burtscher M. Are oral contraceptive use and menstrual cycle phase related to anterior cruciate ligament injury risk in female recreational skiers? Knee Surg Sports Traumatol Arthrosc. 2009;17(9):1065–9.

Samuel CS, Lekgabe ED, Mookerjee I. The effects of relaxin on extracellular matrix remodeling in health and fibrotic disease. In: Agoulnik AI, editor. Relaxin and related peptides. Nottingham: Landes Bioscience and Springer Science+Business Media; 2007. p. 88–103.

Scerpella TA, Stayer TJ, Makhuli BZ. Ligamentous laxity and non-contact anterior cruciate ligament tears: a gender-based comparison. Orthopedics. 2005;28(7):656–60.

Schmitz RJ, Shultz SJ, Nguyen AD. Dynamic valgus alignment and functional strength in males and females during maturation. J Athl Train. 2009;44(1):26–32.

Seneviratne A, Attia E, Williams RJ, Rodeo SA, Hannafin JA. The effect of estrogen on ovine anterior cruciate ligament fibroblasts. Am J Sports Med. 2004;32(7):1613–8.

Shea KG, Pfeiffer R, Wang JH, Curtin M, Apel PJ. Anterior cruciate ligament injury in pediatric and adolescent soccer players: an analysis of insurance data. J Pediatr Orthop. 2004;24(6):623–8.

Sherwood OD. Relaxin's physiological roles and other diverse actions. Endocr Rev. 2004;25(2):205–34.

Shikata J, Sanda H, Yamamuro T, Takeda T. Experimental studies of the elastic fiber of the capsular ligament: influence of aging and sex hormones on the hip joint capsule of rats. Connect Tissue Res. 1979;7:21–7.

Shultz SJ, Schmitz RJ. Effects of transverse and frontal plane knee laxity on hip and knee neuromechanics during drop landings. Am J Sports Med. 2009;37(9):1821–30.

Shultz SJ, Schmitz RJ, Kulas AS, Labban JD, Wang H-M. Quadriceps muscle volume positively contributes to ACL volume. J Orthopaed Res. https://doi.org/10.1002/jor.24989.

Shultz SJ, Kirk SE, Johnson ML, Sander TC, Perrin DH. Relationship between sex hormones and anterior knee laxity across the menstrual cycle. Med Sci Sports Exerc. 2004;36(7):1165–74.

Shultz SJ, Kirk SE, Sander TC, Perrin DH. Sex differences in knee laxity change across the female menstrual cycle. J Sports Med Phys Fitness. 2005;45(4):594–603.

Shultz SJ, Gansneder BG, Sander TC, Kirk SE, Perrin DH. Absolute hormone levels predict the magnitude of change in knee laxity across the menstrual cycle. J Orthop Res. 2006a;24(2):124–31.

Shultz SJ, Shimokochi Y, Nguyen AD, Ambegaonkar JP, Schmitz RJ, Beynnon BD, Perrin DH. Nonweight-bearing anterior knee laxity is related to anterior tibial translation during transition from nonweight bearing to weight bearing. J Orthop Res. 2006b;24(3):516–23. https://doi.org/10.1002/jor.20040.

Shultz SJ, Nguyen A, Schmitz RJ. Differences in lower extremity anatomical and postural characteristics in males and females between maturation groups. J Orthop Sports Phys Ther. 2008;38(3):137–49.

Shultz SJ, Levine BJ, Nguyen AD, Kim HS, Montgomery MM, Perrin DH. A Comparison of cyclic variations in anterior knee laxity, genu recurvatum and general joint laxity across the menstrual cycle. J Orthop Res. 2010a;28:1411–7.

Shultz SJ, Schmitz RJ, Nguyen AD, Levine BJ. Joint laxity is related to lower extremity energetics during a drop jump landing. Med Sci Sports Exerc. 2010b;42(4):771–80. https://doi.org/10.1249/MSS.0b013e3181bbeaa6.

Shultz SJ, Schmitz RJ, Nguyen AD, Levine B, Kim H, Montgomery MM, Shimokochi Y, Beynnon BD, Perrin DH. Knee joint laxity and its cyclic variation influence tibiofemoral motion during weight acceptance. Med Sci Sports Exerc. 2011a;43(2):287–95. https://doi.org/10.1249/MSS.0b013e3181ed118d.

Shultz SJ, Wideman L, Montgomery MM, Levine BJ. Some sex hormone profiles are consistent over time in normal menstruating females: implications for sports injury epidemiology. Br J Sports Med. 2011b;45:735–42. https://doi.org/10.1136/bjsm.2009.064931.

Shultz SJ, Schmitz RJ, Kong Y, Dudley WN, Beynnon BD, Nguyen AD, Kim H, Montgomery MM. Cyclic variations in multiplanar knee laxity influence landing biomechanics. Med Sci Sports Exerc. 2012a;44(5):900–9. https://doi.org/10.1249/MSS.0b013e31823bfb25.

Shultz SJ, Wideman L, Montgomery MM, Beasley KN, Nindl BC. Changes in serum collagen markers, IGF-I and knee joint laxity across the menstrual cycle. J Orthop Res. 2012b;30:1405–12. https://doi.org/10.1002/jor.22093.

Shultz SJ, Schmitz RJ, Cone JR, Copple TJ, Montgomery MM, Pye ML, Tritsch AJ. Multiplanar knee laxity increases during a 90-min intermittent exercise protocol. Med Sci Sports Exerc. 2013;45(8):1553–61. https://doi.org/10.1249/MSS.0b013e31828cb94e.

Shultz SJ, Schmitz RJ, Benjaminse A, Collins M, Ford K, Kulas AS. ACL Research Retreat VII: An update on anterior cruciate ligament injury risk factor identification, screening, and prevention. J Athl Train. 2015;50(10):1076–93. https://doi.org/10.4085/1062-6050-50.10.06.

Sigward SM, Pollard CD and Shultz SJ. Risk factors for anterior cruciate ligament injury. Independent study course monograph 19.1.1. Series Title: Update on anterior cruciate ligament injuries. Orthopaedic Section, American Physical Therapy Association. 2008.

Slauterbeck J, Clevenger C, Lundberg W, Burchfield DM. Estrogen level alters the failure load of the rabbit anterior cruciate ligament. J Orthop Res. 1999;17:405–8.

Slauterbeck JR, Fuzie SF, Smith MP, Clark RJ, Xu KT, Starch DW, Hardy DM. The menstrual cycle, sex hormones, and anterior cruciate ligament injury. J Athl Train. 2002;37(3):275–80.

Small CM, Manatunga AK, Marcus M. Validity of Self-Reported Menstrual Cycle Length. Ann Epidemiol. 2007;17:163–70.

Stewart DR, Celniker AC, Taylor CA, Cragun JR, Overstreet JW, Lasley BL. Relaxin in the periimplantation period. J Clin Endocrinol Metab. 1990;70(6):1771–3.

Strickland SM, Belknap TW, Turner SA, Wright TM, Hannafin JA. Lack of hormonal influences on mechanical properties of sheep knee ligaments. Am J Sports Med. 2003;31(2):210–5.

Somerson JS, Isby IJ, Hagen MS, Kweon CY, Gee AO. The menstrual cycle may affect anterior knee laxity and the rate of anterior cruciate ligament rupture. JBJS Rev. 2019;7(9):e2. https://doi.org/10.2106/JBJS.RVW.18.00198.

Svenningsen S, Terjesen T, Auflem M, Berg V. Hip motion related to sex and age. Acta Orthop Scand. 1989;60(1):97–100.

Takano M, Yamaguchi M, Nakajima R, Fujita S, Kojima T, Kasai K. Effects of relaxin on collagen type I released by stretched human periodontal ligament cells. Orthod Craniofac Res. 2009;12:282–8.

Thein-Nissenbaum JM, Rauh MJ, Carr KE, Loud KJ, McGuine TA. Menstrual irregularity and musculoskeletal injury in female high school athletes. J Athl Train. 2012;47(1):74–82.

Thein-Nissenbaum JM, Carr KE, Hetzel S, Dennison E. Disordered eating, menstrual irregularity, and musculoskeletal injury in high school athletes: a comparison of oral contraceptive pill users and nonusers. Sports Health. 2014;6(4):313–20. https://doi.org/10.1177/1941738113498852.

Tourville T, Shultz SJ, Vacek P, Knudsen E, Bernstein I, Tourville K, Hardy DM, Slauterbeck J, Johnson R, Beynnon BD. Evaluation of an algorithm to predict menstrual cycle phase at the time of injury. J Athl Train. 2016;51(1):47–56.

Uhorchak JM, Scoville CR, Williams GN, Arciero RA, St Pierre P, Taylor DC. Risk factors associated with noncontact injury of the anterior cruciate ligament: a prospective four-year evaluation of 859 West Point cadets. Am J Sports Med. 2003;31(6):831–42.

Unemori EN, Amento EP. Relaxin modulates synthesis and secretion of procollagenase and collagen by human dermal fibroblasts. J Biol Chem. 1990;265(18):10681–5.

Unemori EN, Beck S, Lee WP, Xu Y, Siegel M, Keller G, Liggitt HD, Bauer EA, Amento EP. Human relaxin decreases collagen accumulation in vivo in two rodent models of fibrosis. J Invest Dermatol. 1993;101:280–5.

Vacek PM, Slauterbeck JR, Tourville TW, Sturnick DR, Holterman L-A, Smith HC, Shultz SJ, Johnson RJ, Tourville KJ, Beynnon BD. Multivariate analysis of the risk factors for first-time noncontact ACL injury in high school and college athletes. Am J Sports Med. 2016;44(6):1492–1501. https://doi.org/10.1177/0363546516634682.

Vescovi JD. The menstrual cycle and anterior cruciate ligament injury risk: Implications of menstrual cycle variability. Sports Med. 2011;41(2):91–101.

Wang VM, Banack TM, Tsai CW, Flatow EL, Jepsen KJ. Variability in tendon and knee joint biomechanics among inbred mouse strains. J Orthop Res. 2006;24:1200–7.

Wang H-M, Shultz SJ, Schmitz RJ. Association of anterior cruciate ligament width with anterior knee laxity. J Athletic Train 2016;51(6):460–465. https://doi.org/10.4085/1062-6050-51.7.07.

Wang H-M, Shultz SJ, Ross SE, Henson RA, Perrin DH, Schmitz RJ. ACL size and notch width between ACLR and healthy individuals: a pilot study. Sports Health Multidiscipl Approach. 2020;12(1):61–65. https://doi.org/10.1177/1941738119873631.

Wang H-M, Shultz SJ, Ross SE, Henson RA, Perrin DH, Schmitz RJ. Relationship of anterior cruciate ligament volume and T2* relaxation time to anterior knee laxity. Orthopaed J Sports Med 2021;9(2). https://doi.org/10.1177/2325967120979986.

Whitney DC, Sturnick DR, Vacek PM, DeSarno MJ, Gardner-Morse M, Tourville TW, Smith HC, Slauterbeck JR, Johnson RJ, Shultz SJ, Hashemi J, Beynnon BD. Relationship between the risk of suffering a first-time noncontact ACL injury and geometry of the femoral notch and ACL. Am J Sports Med. 2014;42(8):1796–1805. https://doi.org/10.1177/0363546514534182.

Wentorf FA, Sudoh K, Moses C, Arendt EA, Carlson C. The Effects of estrogen on material and mechanical properties of the intra- and extra-articular knee structures. Am J Sports Med. 2006;34(12):1948–52.

Wideman L, Montgomery MM, Levine BJ, Beynnon BD, Shultz SJ. Accuracy of calendar-based methods for assigning menstrual cycle phase in women. Sports Health Multidiscipl Approach. 2013;5(2):143–149. https://doi.org/10.1177/1941738112469930.

Wilmore JH, Costill DL. Physiology of sport and exercise. 2nd ed. Champaign: Human Kinetics; 1999.

Wojtys EM, Huston LJ, Lindenfeld TN, Hewett TE, Greenfield ML. Association between the menstrual cycle and anterior cruciate ligament injuries in female athletes. Am J Sports Med. 1998;26(5):614–9.

Wojtys EM, Huston LJ, Boynton MD, Spindler KP, Lindenfeld TN. The effect of the menstrual cycle on anterior cruciate ligament injuries in women as determined by hormone levels. Am J Sports Med. 2002;30(2):182–8.

Wolf JM, Cameron KL, Clifton KB, Owens BD. Serum relaxin levels in young athletic men are comparable with those in women. Orthopaedics. 2013a;36(2):128–31.

Wolf JM, Williams AE, Delaronde S, Leger R, Clifton KB, King KB. Relationship of serum relaxin to generalized and trapezial-metacarpal joint laxity. J Hand Surg Am. 2013b;38A:721–8.

Wolf JM, Scher DL, Etchill WE, Scott F, Williams AE, Delaronde S, King KB. Relationship of relaxin hormone and thumb carpometacarpal joint arthritis. Clin Orthop Relat Res. 2014;472(4):1130–7.

Wood ML, Luthin WN, Lester GE, Dahners LE. Tendon creep is potentiated by NKISK and relaxin which produce collagen fiber sliding. Iowa Orthop J. 2003;23:75–9.
Wreje U, Kristiansson P, Aberg H, Bystrom B, Schoultz B. Serum levels of relaxin during the menstrual cycle and oral contraceptive use. Gynecol Obstet Invest. 1995;39:197–200.
Wreje U, Brynhildsen J, Aberg H, Bystrom B, Hammar M, VonSchoultz B. Collagen metabolism markers as a reflection of bone and soft tissue turnover during the menstrual cycle and oral contraceptive use. Contraception. 2000;61:265–70.
Yu WD, Hatch JD, Panossian V, Finerman GA, Liu SH. Effects of estrogen on cellular growth and collagen synthesis of the human anterior cruciate ligament: an explanation for female athletic injury. In: 43rd Annual Meeting of the Orthopaedic Research Society, San Francisco, CA, February 9–13. Rider Dickerson, Inc; 1997. p. 397
Yu WD, Liu SH, Hatch JD, Panossian V, Finerman GA. Effect of estrogen on cellular metabolism of the human anterior cruciate ligament. Clin Orthop Relat Res. 1999;366:229–38.
Yu WD, Panossian V, Hatch JD, Liu SH, Finerman GA. Combined effects of estrogen and progesterone on the anterior cruciate ligament. Clin Orthop Relat Res. 2001;383:268–81.
Zazulak BT, Paterno M, Myer GD, Romani WA, Hewett TE. The effects of the menstrual cycle on anterior knee laxity. Sports Med. 2006;36(10):847–62.

Chapter 9
Sex Hormones and Endurance Exercise in Women: Physiological and Psychological Factors Affecting Performance

Clare Minahan and Surendran Sabapathy

Abbreviations

ATP	Adenosine triphosphate
CP	Critical power
d	Day(s)
DOMS	Delayed onset muscle soreness
HC	Hormonal contraception
h	Hour(s)
kJ	Kilojoule(s)
kg	Kilogram(s)
km	Kilometer(s)
[La-]	Lactate concentration
L	Liter(s)
MLSS	Maximal lactate steady-state
MC	Menstrual cycle
m	Meter(s)
mL	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
nMol	Nanomole(s)
%	Percent

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RPE	Rate of perceived exertion
s	Second(s)
VE	Minute expired ventilation
VO_2	Oxygen uptake
VO_{2peak}	Peak oxygen uptake
VCO_2	Carbon dioxide production
W	Watt(s)
yr	Year(s)

Introduction

Continuous, whole-body, dynamic exercise that is fueled predominately by the aerobic energy system is considered endurance exercise, with efforts/events lasting greater than 6 h deemed ultra-endurance exercise (Zaryski and Smith 2005). Endurance exercise includes efforts at intensities ranging from moderate to severe with the contribution of the aerobic energy system ranging from 50% to almost 100% (Burnley and Jones 2007). Ultimately, endurance exercise performance can only be resolved by event placings or time trials. However, due to the complexity of experimental control on event performances (e.g., environmental conditions) and variable female sex hormone profiles (e.g., fluctuating hormones across the menstrual cycle; MC), little data are available confirming or refuting a relationship between female sex hormones and endurance exercise performance. Nonetheless, endurance exercise performance can be predicted by measuring physiological characteristics such as peak oxygen uptake (VO_{2peak}), intensity domain thresholds, and exercise economy (Joyner 2017). While psychological determinants of endurance exercise performance are less well understood, characteristics such as achievement behavior, pain tolerance, and self-efficacy also play an important role (Cooke et al. 2011).

Optimization of performance in endurance events involves the integration of various biological systems, including the musculoskeletal, cardiovascular, respiratory, and nervous systems to defend homeostasis and sustain repeated muscle contractions. The female sex hormones, estrogen and progesterone, have been reported to affect the musculoskeletal (Enns and Tiidus 2010), nervous (McEwen and Alves 1999; Mercuro et al. 2000), respiratory (Harms 2006), and circulatory (Sarrel 1990) systems as well as immunological (Timmons et al. 2005; Larsen et al. 2020), thermoregulatory (Charkoudian and Stachenfeld 2014), and metabolic (Tarnopolsky et al. 2000; Weber and Schneider 2002) processes. Therefore, it is reasonable to propose that changes to the female sex hormone profile could affect endurance exercise performance as well as the rate and magnitude of changes to the physical and psychological characteristics associated with improved endurance exercise performance with training.

This chapter aims to present an overview of the physical and psychological characteristics used to predict endurance exercise performance and consider how female sex

hormones may influence these characteristics and performance outcomes. Given the paucity of data investigating the effect of female sex hormones on endurance exercise performance and endurance-type adaptations to training in women, this chapter is limited to interrogating the physical and psychological characteristics used to predict performance in endurance events, as well as the limiting factors for these characteristics. To that end, limiting factors related to societal influence on endurance exercise performance are not considered here.

Female Sex Hormone Profiles

To support theoretical relationships between female sex hormones and physical and psychological characteristics, two of the seven potential female sex hormone profiles of athletes are the focus of this chapter (see Table 9.1), including the MC phase in naturally-cycling women and women taking hormonal contraception (HC).

Effect of Female Sex Hormones on Endurance Exercise Events, Time Trials, and Field-Test Performances

At present, there is limited evidence to support the notion that female sex hormones affect endurance exercise performance in competitive events such as the Marathon, a 400-m swim, or 1-km track cycling. Nonetheless, examining the results of planned time trials among different female sex hormone profiles (i.e., MC phase, HC) provides the impetus to ask the question, "Do female sex hormones affect endurance exercise performance?".

Several studies have demonstrated poorer endurance exercise performances in the luteal compared with the follicular phase of the MC. For example, in a 1000-m time trial, Redman and Weatherby (2004) reported that rowing performance was enhanced during the early-follicular compared to the mid-luteal phase of the MC. Furthermore, Freemas et al. (2021) reported that fifteen recreationally active naturally-cycling women were 26 ± 36 s faster in an 8-km cycling time trial during the follicular (17.8 ± 1.7 min) compared with the mid-luteal (18.3 ± 2.0 min) phase of their MC. Finally, Campbell et al. (2001) reported that fasted subjects completed 4 kJ/kg of work 13% more quickly during a cycling time trial in the follicular phase compared with the luteal phase of the MC. This trend is mirrored in field tests of endurance exercise performance whereby female football athletes demonstrated that performance on the Yo-Yo Intermittent Endurance Test was lower during the mid-luteal (2833 ± 896 m) compared with the early-follicular (3288 ± 800 m) phase of the MC, as indicated by magnitude-based inferences suggesting a 39% probability of inferior performance during the mid-luteal phase (Julian et al. 2017). However, these findings are not categorical; others have either reported no difference in endurance

Table 9.1 Female sex hormone profiles

Profile	Description	Hormone profile
Menarche	First occurrence of a menstrual period in female adolescents	Variable levels of estrogen and progesterone for the first 2 yr from start
Eumenorrhea	Naturally-cycling women (i.e., no HC) with MC lengths of ≥ 21 d and ≤ 35 d and evidence of luteinizing hormone surge	Repeating pattern of fluctuating estrogen and progesterone across MC
Hormonal contraception	Presence of synthetic estrogen/progesterone via oral contraceptive pill, intrauterine device, injection, vaginal ring, implant, skin patch	Elevated concentrations of synthetic estrogen and/or progesterone with suppressed concentrations of endogenous estrogen and progesterone
Amenorrhea	Absence of ≥ 3 consecutive periods in previously eumenorrheic, non-pregnant, women	Suppressed concentrations of estrogen and progesterone
Menstrual disturbance	Perturbations of the eumenorrheic MC, such as anovulation and oligomenorrhea	Variable levels of estrogen and progesterone
Pregnancy	The gestation of a fetus inside the womb from conception to birth	Elevated concentrations of endogenous estrogen and progesterone
Menopause	Change in hormone profile (perimenopause) and complete cessation of menstruation for 12 months (menopause) in women aged 40–60 yr	Suppressed concentrations of estrogen and progesterone

Source Elliott-Sale et al. (2021)

exercise performance among phases of the MC (Nicklas et al. 1989; Oosthuyse et al. 2005; Forsyth and Reilly, 2008) or superior performance during exhaustive exercise in the luteal compared with the follicular phase of the MC (Jurkowski et al. 1981). Furthermore, differences in the performances of endurance exercise events in women taking HC compared with eumenorrheic women are not clear.

Defining the Predictors of Endurance Exercise Performance

While there is limited evidence suggesting that specific hormone profiles affect endurance exercise events and time trials, the variability in performances may be masked by environmental influences. Therefore, examining the effect of various hormone profiles on the predictors of endurance exercise performance under controlled laboratory conditions may provide important insight into the potential

of estrogen and progesterone to affect endurance exercise performance. Here, we define the predictors of endurance exercise performance and the factors that limit their potential to provide a clear framework with which to understand the effects of female sex hormones on endurance exercise performance. Then, we explore the effect, if any, of MC phase and the administration of HC on the defined physiological and psychological predictors of endurance exercise performance.

Peak Oxygen Uptake

The ability to take up, transport, and consume oxygen by the body provides the main energetic basis for sustained muscular activity, and the maximum or peak rate of oxygen uptake (VO_{2peak}) attained during dynamic exercise that engages a large muscle mass is a key determinant of endurance performance success (Joyner and Coyle 2008). VO_{2peak} is expressed in absolute terms as a function of time (i.e., L/min) or relative to body mass (mL/kg/min; Bassett and Howley 2000) and is typically measured in a laboratory setting during an incremental exercise test that concludes at volitional exhaustion in healthy individuals. The ability of the cardiorespiratory system to deliver oxygen to the exercising muscles and the ability of the muscles to uptake and utilize oxygen limits an individual's VO_{2peak}. Physiological limitations to the delivery and uptake of oxygen during exercise include pulmonary diffusion capacity, maximal cardiac output, the oxygen-carrying capacity of the blood, and skeletal muscle characteristics (Bassett and Howley 2000; Joyner and Coyle 2008).

It is widely accepted that a high VO_{2peak} is obligatory for endurance performance success (see, for example, Joyner and Coyle 2008), given that most endurance events are performed at an appreciable fraction of an individual's VO_{2peak}. Thus, a high VO_{2peak} enables an athlete to maintain a high power output (e.g., W or km/h) for a prolonged period of time. Nevertheless, a high rate of VO_2 is not the only prerequisite for endurance performance success. The energetic demand for a given rate of external work is also highly dependent on where this power output is situated within an individual's range of sustainable intensities that, in turn, are governed by key submaximal exercise thresholds and the attendant intensity domains that these thresholds demarcate (Burnley and Jones 2007).

Intensity Domain Thresholds

Exercise intensity domain thresholds demarcate the boundaries of moderate-, heavy-, and severe-intensity exercise. Exercise performed at an intensity below the point at which blood lactate concentration ($[La^-]$) begins to increase in the blood (i.e., lactate threshold) is considered "moderate-intensity" exercise, and metabolic steady-state is typically achieved within 2–3 min in healthy individuals when the power output is constant. Within the moderate-intensity exercise domain, the steady-state

VO_2 response increases linearly with power output and the oxygen cost of exercise (change in VO_2 for a given change in power output, or VO_2 gain) is relatively constant at 9–10 mL/min/W (Barstow et al. 1993). Thus, moderate-intensity exercise can be sustained for prolonged periods of time. Above the lactate threshold, a slow component of increasing VO_2 can be observed that is also accompanied by a rise in [La^-] (Poole et al. 1988). Power outputs above the lactate threshold, where these variables eventually stabilize, are considered "heavy-intensity" exercise. A key distinguishing characteristic of moderate- and heavy-intensity exercise is the higher oxygen and, consequently, ATP cost of exercise associated with the latter—the VO_2 gain exceeds 10 mL/min/W during heavy-intensity exercise (Barstow et al. 1993). Nevertheless, heavy-intensity exercise can be sustained for prolonged periods of time in well-trained individuals (Coyle et al. 1986). The upper limit of heavy-intensity exercise corresponds to the highest power output at which an elevated steady-state VO_2 and [La^-] can be sustained, i.e., maximal metabolic steady-state. By definition, exercise performed at an intensity beyond the maximal metabolic steady-state threshold is considered severe-intensity exercise and, if sustained, will rapidly drive VO_2 to peak values accompanied by an inexorable rise in [La^-] and fatigue or exhaustion (Burnley and Jones 2007). The maximal metabolic steady-state threshold is usually identified by measuring the maximal lactate steady-state (MLSS) exercise intensity and/or critical power, speed, or velocity (Jones et al. 2019). It is purported that discrete exercise intensity domains have clear implications for fatigue development and endurance exercise performance (Whipp and Ward 1992; Jones et al. 2011). Furthermore, Jones and colleagues have suggested that the lactate threshold is relevant for ultra-endurance and low-intensity endurance events while the maximal metabolic steady-state is more relevant to Olympic-distance endurance exercise events (Jones and Poole 2008; Jones and Vanhatalox 2017; Jones et al. 2019).

The lactate threshold is almost always determined during an incremental exercise test with step increases in power output occurring no less than 3 min apart. Alternatively, disproportionate changes in gas exchange indices such as VE and VCO_2 relative to VO_2 or power output (i.e., the ventilatory and gas exchange thresholds) during an incremental exercise test are commonly used as proxies for the lactate threshold (Poole et al. 2021). The MLSS is derived from four-to-five 30-min constant power output exercise bouts, where [La^-] is measured after every bout. The highest power output that does not result in a rise of [La^-] greater than 1 mmol/L between 10 and 30 min denotes MLSS (Jones and Doust 1998). On the other hand, critical power is defined as the highest sustainable power output derived from multiple exhaustive constant power output tests that are then to generate a hyperbolic power-duration curve: $t_{lim} = W'/(P–CP)$, where t_{lim} is the tolerable exercise duration, W' the curvature constant and CP is critical power (Moritani et al. 1981). More recently, a single, 3-min all-out test provides an expedited protocol to determine critical power (Vanhatalo et al. 2007).

The ability to sustain high rates of oxidative phosphorylation at a metabolic steady-state is dependent on the muscles' overall capacity to generate ATP without stimulating phosphofructokinase and driving carbohydrate turnover (i.e., glycolysis) with

a resulting increase in blood [La^-]. Thus, the dominant limiting factor of the lactate and metabolic steady-state thresholds is linked primarily to skeletal muscle characteristics including mitochondrial density and mitochondrial enzyme activity (Bassett and Howley 2000).

Exercise Economy

Exercise economy is the term given to express the VO_2 required to exercise at a given power output, i.e., the VO_2 gain. There is a strong association between economy and endurance exercise performance, with some researchers demonstrating that exercise economy largely explains the difference in endurance exercise performance outcomes in elite athletes with a similar VO_{2peak} (Shaw et al. 2015). Exercise economy can be determined by calculating the inverse relationship of the VO_2/power output relationship during continuous incremental exercise or by measuring steady-state VO_2 during a single submaximal, constant power output exercise bout. As mentioned earlier, a gradual increase in VO_2 that is apparent during heavy-intensity constant power output exercise (i.e., VO_2 "slow component") erodes exercise economy by increasing the oxygen required to fuel exercise despite the power output remaining unchanged.

There are numerous proposed physiological, biochemical, anthropometric, and biomechanical influences on exercise economy (Lundby et al. 2017). Several investigators have demonstrated that a greater dependence on type II muscle fibers is associated with higher VO_2 values measured during moderate- to heavy-intensity exercise (Hunter et al. 2001; Coyle et al. 1992; Lucia et al. 2002). Furthermore, higher rates of fat oxidation may lower exercise economy by requiring more oxygen at the same power output since less energy is released per liter of oxygen during fat oxidation when compared to glucose oxidation (Pate et al. 1992). Biomechanical factors appear to be a dominant factor that influence exercise economy in elite athletes including superior movement patterns (i.e., technique) and muscle recruitment patterns (Lucia et al. 2002), as well as the ability of the muscles and tendons to store and release elastic energy by increasing their stiffness (Barnes et al. 2014). Both elevated ventilation rate and core body temperature may also contribute to an increase in oxygen uptake during exercise, thus reducing exercise economy (Jones et al. 2011). Importantly, Lundby et al. (2017) explain that body weight is the primary determinant of exercise economy during running explaining 94% of the variability.

Achievement Behavior

The concept of achievement is associated with expectations of success or failure and can be measured in relation to one's peers or oneself. In endurance exercise events, achievement can be measured based on event placings and/or relative to personal

goals. We know that the achievement behavior of individuals may influence their athletic performance (McCormick et al. 2015; Wilmore 1968; Higgs 1972; Corbett et al. 2012; Peveler and Green 2010), and female and male athletes score higher on measures of achievement behavior than their non-athletic counterparts (Helmreich and Spence 1978). Many tools have been developed to investigate specific personality traits which may align with these psychological characteristics. In sports, the Sports Orientation Questionnaire (Gill and Deeter 1988) and the Sports Competition Trait Inventory (Fabian and Ross 1984) explore personal desires and standards to measure behavior related to sports performances. The questionnaires explore two main achievement behaviors: (i) Competitiveness and (ii) Mastery. Competitiveness relates to an individual's desire to win in interpersonal situations and/or gain rewards/incentives for superior performances over one's peers. In contrast, mastery relates to an individual's motivation to achieve competence at challenging tasks.

The associated mechanisms responsible for performance-enhancing psychological characteristics such as competitiveness and mastery are poorly understood. One theory that may drive competitiveness in some individuals is the hormonal response to an external stimulus such as an athletic event (Cooke et al. 2011). That is, in competitive environments, individuals with heightened competitiveness display a greater sympathetic response. This sympathetic reactivity in competitive individuals can drive an elevated cardiovascular response (Lee and Harley 2012) and an increase in muscle activity (Cooke et al. 2010; Voor et al. 1969). Whether these mechanisms augment endurance exercise performance directly is yet to be determined.

Pain Tolerance

The maximum level of perceived pain that someone can tolerate or the duration someone is willing to endure a given pain intensity can be described as "pain tolerance" and may be an important predictor of endurance exercise performance (Astokorki and Mauger 2017; Mauger 2014). Although pain is subjective, and the perception of pain is not always proportional to the size of the nociceptive signal, pain serves a protective function that signals tissue damage or a warning to disengage with the behavior that is causing it (Stevens et al. 2018). During endurance exercise, pain may arise as a consequence of the accumulation of deleterious metabolic by-products and heat stress (Wallace et al. 2017). Highly trained athletes demonstrate significantly enhanced pain tolerance and a dampened interpretation of thermal perception compared with non-athletic controls (for review see Stevens et al. 2018). Specific pain intensity and thermal discomfort rating scales as well as global ratings of perceived exertion (RPE) are typically used to assess the limiting factors of gpain to exercise tolerance (Borg 1998). RPE is suggested to signify overall effort and is a reflection of heart and breathing rates, muscle fatigue, perceived pain, temperature, and exertion.

Although improved pain inhibition would reduce the level of perceived pain experienced at a given exercise intensity, higher pain tolerance has been attributed predominantly to psychological adaptations (i.e., adaptive coping) rather than physiological adaptations in trained individuals (Astokorki and Mauger 2017). Nonetheless, some researchers have proposed actual desensitization of the nociceptors, resulting in a diminished signaling in response to exercise-induced pain. Endogenous opioids and stress hormones have been implicated as possible candidates contributing to pain-inhibition mechanisms (Micalos 2014).

Effect of Female Sex Hormones on the Predictors of Endurance Exercise Performance

Peak Oxygen Uptake

Numerous studies have investigated the effect of MC phase or HC on the physiological predictors of endurance exercise performance. These studies span almost 45 yr (e.g., Allsen et al. 1977; Rael et al. 2021), have been performed in almost every continent across the globe (e.g., Sunitha et al. 2013; Rael et al. 2021; Hackney et al. 1994; Castro et al. 2022; Oosthuyse et al. 2005; Joyce et al. 2013), are affiliated with world-top 10 and more moderately ranked research institutions (e.g., Gordon et al. 2018; Stone et al. 2021; Joyce et al. 2013), and performed with both robust and questionable experimental design (for review see McNulty et al. 2020). There appears to be a general consensus that MC phase does not affect VO_{2peak} (Jurkowski et al. 1981; Stephenson et al. 1982; Dombovy et al. 1987; Bemben et al. 1995; Beidleman et al. 1999; Casazza et al. 2003; Dean et al. 2003; Redman et al. 2003; Vaiksaar 2011; Smekal 2007; Janse de Jonge et al. 2012; Gordon et al. 2018; Lara et al. 2020), although this is not always the case—some studies have reported a lower VO_{2peak} measured in trained (Lebrun et al. 1995; De Souza et al. 1990) and untrained (Brutsaert et al. 2002) women during the luteal compared with follicular phase of the MC. Importantly, while most studies demonstrate no differences in VO_{2peak} among the phases of the MC, and some studies show higher VO_{2peak} values during the follicular phase, no study has reported higher VO_{2peak} values during the mid-luteal phase of the MC when compared with any other phase. Therefore, any influence of the MC on VO_{2peak} is likely to be related to elevated concentrations of estrogen in the late-follicular phase, elevated progesterone in the mid-luteal phase, or both.

It is worth noting some of the findings of the most methodologically sound studies as assessed by McNulty et al. (2020). For example, in a study by Janse de Jonge and colleagues (2012), VO_{2peak} was measured during the early-follicular (day 3–6) and the mid-luteal (day 19–25) phases of the MC. Daily oral temperature monitoring was used to predict the follicular and mid-luteal phases of the MC in twelve recreationally active women (40.0 ± 6.9 mL/kg/min). A resting blood sample was subsequently

analyzed for estradiol and progesterone concentration to verify MC phase. Furthermore, a progesterone concentration of greater than 16 nmol/L was required to confirm luteal-VO_2. No difference in VO_{2peak} between the follicular (2.5 ± 0.40 L/min) and mid-luteal (2.5 ± 0.43 L/min) phases of the MC was observed. Lebrun and colleagues (1995) measured VO_{2peak} during the early-follicular (days 3–8 of MC) and mid-luteal phase (4–9 d after predicted ovulation determined via a rise in basal body temperature of between 0.2–0.3 °C) of the MC in sixteen trained mixed-sport athletes (VO_{2peak} 53.7 ± 0.9 mL/kg/min). This study also utilized a strict MC phase confirmation with validation by measurement of estrogen and progesterone and confirmed the luteal phase of the MC with a progesterone concentration of greater than 16 nmol/L. In contrast to the study by Janse de Jonge et al. (2012), Lebrun et al. (1995) reported a difference (*nota bene,* $p = 0.06$) in the VO_{2peak} determined during the early-follicular (3.19 ± 0.09 L/min) compared to the mid-luteal (3.13 ± 0.08 L/min) phase of the MC. Despite the quality of these studies considered as high, their opposing findings could be attributed to differences in participant training status (trained versus recreationally active), exercise mode (cycle ergometry vs. treadmill running), and/or individual variability influencing the group mean average values. Despite Lebrun and colleagues stating in 1995 that, "*this study needs to be repeated with a large number of subjects, and at different phases of the menstrual cycle including the midcycle estrogen peak…*", no high-quality, large-scale study has been conducted to date, and therefore, the effect of MC on VO_{2peak} remains uncertain.

Two studies have dominated the narrative around the effect of HC on VO_{2peak} over the last 20 yr (Lebrun et al. 2003; Cazazza et al. 2002). This is due to the potential impact of their findings on female athletes and the nature of their experimental design. Lebrun et al. (2003) included MC phase confirmation with the determination of sex hormones, imposed a randomized, double-blind, placebo-control, and longitudinal experimental design where the VO_{2peak} of each participant was determined while naturally menstruating and after 6-wk administration of either a tri-phasic oral contraceptive or a placebo treatment. These authors reported that the change in VO_{2peak} determined after the administration of oral contraceptives in previously naturally menstruating women was 4.7% in the oral contraceptive group compared with a 1.5% improvement with placebo. Casazza et al. (2002) reported a significant decrease in both absolute (11%, L/min) and relative (13%, mL/kg/min) VO_{2peak} after, compared to before, 4 months of oral contraceptive administration. Numerous other studies support the notion that the administration of HC may reduce VO_{2peak} in women (Notelovitz et al. 1987; Bryner et al. 1996; Joyce et al. 2013). Nonetheless, others have reported no difference in VO_{2peak} between naturally menstruating women and women taking HC (Rebelo et al. 2010).

Intensity Domain Thresholds

It is widely accepted that the lactate threshold can vary between individuals, as well as before and after an exercise-training program, without differences occurring

in VO_{2peak} (Moquin et al. 2000). Furthermore, several studies demonstrate lower blood [La^-] at a given power output in the luteal- compared with the mid-follicular phase of the MC (De Souza et al. 1990; Dombovy et al. 1987; Jurkowski et al. 1981). Together with this, and the knowledge that female sex hormones can alter energy and substrate metabolism (Hackney 1999; Hackney et al. 1994), ventilation (Jurkowski et al. 1981), thermoregulation (Kolka and Stephenson 1997; Charkoudian et al. 2014; Minahan et al. 2017), and the catecholamine response to exercise (Sutton et al. 1980), examination of the intensity domain thresholds across the MC is warranted.

Numerous studies have shown that the lactate and/or ventilatory threshold is unaffected by MC phase (Stephenson et al. 1982; Dombovy et al. 1987; Redman et al. 2003; Gordon et al. 2018), although one study found that the ventilatory threshold occurred at a higher $\%VO_{2peak}$ during the early-follicular compared with the mid-luteal phase (Bemben et al. 1995). Bemben et al. (1995) examined the ventilatory threshold during incremental running in five eumenorrheic recreationally active women in the early-follicular (2–5 d), late-follicular (12–15 d), and mid-luteal phases of the MC, carefully predicted with body temperature measurements and subsequently verified with progesterone concentrations. Despite no differences in VO_{2peak}, the ventilatory threshold occurred at a significantly higher $\%VO_{2peak}$ in the early-follicular, compared with the mid-luteal, phase of the MC. No clear mechanistic explanation was provided by Bemben et al. (1995) to explain these findings. Interestingly, Dean et al. (2003) provide a sound rationale for why the lactate threshold could be higher in the mid-luteal, compared to the early-follicular, phase of the MC. Nonetheless, Dean et al. (2003) observed no significant difference in the VO_2 values corresponding to the lactate threshold measured during an incremental cycling test to exhaustion in ten naturally-menstruating women at three phases of the MC (early-follicular, mid-follicular, mid-luteal).

Few studies appear in the literature examining the effect of MC phase on maximal metabolic steady-state. In fact, no data are available examining the maximal lactate steady-state or critical power among MC phases. Nonetheless, a blood [La^-] of 4 mmol/L measured during an incremental exercise test has been used to calculate the power output or VO_2 value associated with the maximal metabolic steady-state. Forsyth and Reilly (2005) demonstrated a lower power output and lower VO_2 values associated with a blood [La-] of 4 mmol/L in the mid-follicular, compared with the mid-luteal, phase of the MC during rowing ergometry in twelve recreationally active naturally-menstruating women. However, Goldsmith and Glaister (2020) reported no effect of MC phase on treadmill speed achieved at a blood [La^-] of 4 mmol/L, and Smekal et al. (2007) did not report a difference in the power output or VO_2 associated with lactate turn-point two (Ribeiro et al. 1986).

There is little evidence to suggest that intensity domain thresholds are changed with the administration of HC. No studies have compared the maximal metabolic steady-state in women with and without HC and although both Casazza et al. (2002) and Lebrun et al. (2003) showed a decrease in VO_2 peak with HC administration, the lactate threshold was not reported in either study. Rebelo et al. (2010) examined the ventilatory threshold in active and sedentary naturally-cycling women and women taking HC; these authors demonstrated that HC does not affect the VO_2 achieved at

the ventilatory threshold. Joyce et al. (2013) examined the effect of a monophasic oral contraceptive on the VO_2 achieved at the ventilatory threshold reporting it was higher in naturally menstruating compared to women taking HC. However, when the ventilatory threshold was reported relative to VO_{2peak}, there were no differences between the two groups.

Exercise Economy

There is some suggestion that exercise economy is influenced by both MC phase and HC administration. Williams and Krahenbuhl (1997) investigated the economy during two, 6-min treadmill running bouts at 55 and 80% of VO_{2peak} in naturally-cycling trained runners. While running at 55% VO_{2peak} did not significantly alter exercise economy, running at 80% VO_{2peak} resulted in significantly higher VO_2 values (i.e., poorer economy) of 41.4 ± 0.8 mL/kg/min during the early-follicular versus 40.2 ± 0.5 mL/kg/min during the mid-luteal phase of the MC. Furthermore, by calculating the average VO_2 value of the last 30 s of each step of an incremental exercise test in trained female runners, Goldsmith and Glaister (2020) reported inferior exercise economy measured during the mid-luteal MC phase in trained naturally-menstruating runners. Specifically, VO_2 was increased from the early-follicular to the mid-luteal phase of the MC by 2.33 mL/kg/min, indicating that running economy is adversely affected in the mid-luteal phase of the MC. In contrast, Dokumacı and Hazır (2019) demonstrated that exercise economy was degraded during the follicular phase of the MC. These contrasting findings are most likely due to the differences in the calculation of exercise economy and the intensity at which exercise was performed.

It is possible that HC could have an effect on substrate utilization, thermoregulation, ventilation, and perhaps muscle/ligament stiffness; therefore, HC administration in exercise women as such could alter their exercise economy. Nonetheless, no difference in exercise economy between naturally menstruating women and women taking HC has been previously reported in recreationally active participants (Joyce et al. 2013). However, Giacomoni and Falgairette (2000) did find an effect of the HC on exercise economy, reporting that women taking an oral contraceptive demonstrated VO_2 values that were 3.0–5.8% lower than when they were not taking contraceptives.

Achievement Behavior

Achievement behavior is relevant to a broad variety of settings and individuals including salespeople, defense personnel, and athletes, for example. The body of research examining the effect of hormones on competitiveness and mastery is scarce and predominately explores testosterone as a key mechanism underlying an individual's concern with having an impact on and dominating others as well as the need for achievement and mastering challenging tasks (for reviews see Schultheiss 2007;

Stanton and Schultheiss 2009). Nonetheless, it is plausible that female sex hormones play a key role in a woman's dominance disposition suggesting that estrogen determines, in part, a woman's ability to derive reward from having a mental, emotional, or physical impact on other individuals (i.e., implicit power motivation; Stanton and Schultheiss 2007, 2009). Schultheiss, Stanton, and colleagues (Schultheiss et al. 2003; Stanton and Schultheiss 2007; Stanton and Edelstein 2009) demonstrate that basal concentrations of estrogen, as well as post-contest increases in estrogen (after an experimental contest), were positively associated with power motivation in women. The effect of female sex hormones on competitive behavior toward athletic competition is yet to be explicitly investigated. Nonetheless, given the relationship between estrogen and implicit power motivation in women, it could be suggested that MC phase might be related to a specific behavior in women during competitive endurance exercise events.

The effect of female sex hormones on achievement behavior has predominantly focused on "choices" and "risk taking" during economic challenges and rewards, not exercise performance. The mechanisms by which hormones affect behavior have been explained by neuro-endocrinological research examining how hormones alter brain activity and emotions. Indeed, estrogen has been reported to affect serotonin-binding sites in the brain associated with anticipation and receipt of reward (Fink et al. 1996; Bethea et al. 2002). Studies that have explored MC effects on competitive behavior (outside of intrasexual competition, i.e., individuals compete with members of their own sex for reproductively relevant resources) have shown that competitiveness among women is highest in the late-follicular phase, when estrogen concentrations are high (Eisenbruch and Roney 2016; Pearson and Schipper 2013) or when progesterone levels are relatively low (Buser 2012). Buser (2012) explains this finding by proposing that elevated progesterone may decrease anxiety and increase sedation.

Furthermore, it has been suggested that competitive behavior, expressed as risk-taking during competitive bidding in auctions, can be explained with an evolutionary hypothesis whereby female participants are predisposed by hormones to generally behave more riskily during the late-follicular phase of their MC (Pearson and Schipper 2013). Interestingly, McNamara et al (2022) reported that elite female athletes training for the 2020 Tokyo Olympic Games reported that their preference for the competition was during the second week of their MC (i.e., late-follicular phase) perhaps indicating heighten competitiveness during a high-estrogen/low progesterone hormone profile. Regarding competitive bidding activity, Pearson and Schipper (2013) report that women taking HCs make less advantageous competitive bidding decisions compared to naturally-cycling women. Collectively, these studies suggest that MC phase and HC use could be important for understanding competitive behavior during endurance exercise performances.

Pain Tolerance

It is difficult to provide an accurate explanation as to the mechanisms responsible for changes in pain sensation across the MC. It is plausible that hormonally induced opiate receptor desensitization could alter pain sensitivity across MC phase among women (for review see Iacovides et al. 2015). However, much of this evidence is based on clinical pain (e.g., migraine, arthritis) across the MC, not pain expressed as "perceived exertion" in response to an endurance exercise task. Nonetheless, it is interesting to note that in summarizing the literature, Iacovides et al. (2015) suggest that there is no obvious relationship between MC phase and various measures of clinical pain, e.g., the most severe incidence of headache occurs during menstruation while increased joint pain relating to arthritis occurs during the late-follicular phase of the MC. In contrast, Riley et al. suggest that for pressure stimulation, cold pressor pain, thermal heat stimulation, and ischemic muscle pain, a clear pattern emerges with the follicular phase of the MC associated with higher pain thresholds when compared with the luteal phase.

There is little evidence to support a difference in perceived "pain" (i.e., "exertion", expressed as RPE) measured during endurance exercise across the phases of the MC. For example, Rael et al. (2021) observed no difference in RPE measured during heavy-intensity interval running in twenty-one naturally-cycling endurance-trained females across three phases of the MC: early-follicular, late-follicular, and mid-luteal. This finding is common in other studies reporting no difference in RPE measured across the MC during running (De Souza et al. 1990; Beidleman et al. 1999; Sunderland and Nevillx 2003) and cycling (Stephenson et al. 1982; Bailey et al. 2000; Janse et al. 2012; Lara et al. 2019) in naturally-cycling women. Interestingly, Hackney et al. (1991) reported that "leg" RPE during cycling was 1–2 points greater during the late-follicular phase, but that there was no statistically significant change in global RPE across the MC. Furthermore, Gamberale et al. (1975) and Higgs and Robertson (1983) reported that RPE during maximal exercise was greater during the early-follicular compared with the mid-luteal phase of the MC. An estrogen-mediated change in localized blood flow is a plausible mechanism with which to base assertions about RPE changing across MC phases (Jurkowski et al. 1981; Hackney et al. 1991), but inconsistency in experimental findings renders this hypothesis currently unconfirmed.

Minahan et al. (2017) reported no difference in RPE values during heavy-intensity cycling in naturally-cycling women compared with women taking HC in temperate environmental conditions (22 °C). However, after repeating the cycling bout in hot conditions (35 °C), RPE for women taking HC was greater, resulting in higher RPE values compared to naturally-cycling women. These findings indicate that women taking HC found cycling in a hot environment more challenging compared with naturally-cycling women despite exercising at the same relative intensity, which could have important implications for endurance exercise performance (Crewe et al. 2008).

Self-efficacy refers to a belief in one's capabilities and represents an individual's belief as to what they are capable of doing, such as an athlete believing they can perform at their best or beat an opponent. Individuals possessing a strong sense of self-efficacy are likely to set higher goals concerning a particular task (Bandura and Locke 2003) and demonstrate higher levels of perseverance when challenged (Feltz et al. 2008). Self-efficacy is positively related to endurance exercise performance including triathlon (Burke and Jin 1996), distance running (Bueno et al. 2008), and swimming (Miller 1993). Interestingly, self-efficacy has been associated with improvements in pain tolerance and reductions in the perception of effort (i.e., lower RPE values) as it encourages continued engagement in the required task and coping mechanisms, respectively (Bandura 1997; Johnson et al. 2012; Peerdeman et al. 2016; Hutchinson et al. 2008). While there is some acknowledgment of a potential effect of MC phase on self-efficacy (Motl et al. 2007), we are unaware of any study that has deliberately examined if female sex hormone profiles alter self-efficacy and subsequently influence pain tolerance during endurance exercise.

Effect of Female Sex Hormones on the Physiological Limiting Factors of Endurance Exercise Performance

Pulmonary Diffusion

Pulmonary diffusion is dependent, in part, on pulmonary capillary blood volume as increased blood volume results in a greater surface area available for pulmonary diffusion. Elevated estrogen concentrations have been associated with increased fluid retention and consequently an increase in blood volume (Carlberg et al. 1984). Therefore, it is reasonable to suggest that phases of the MC characterized by elevated estrogen concentrations (i.e., late-follicular and mid-luteal) would be associated with both increased blood volume and higher rates of pulmonary diffusion. Sansores et al. (1995) investigated pulmonary diffusion capacity during the early-follicular, late-follicular, and mid-luteal phases of the MC in fourteen women. These authors demonstrated that resting pulmonary diffusion capacity was reduced during the early-follicular phase when compared to the late-follicular and mid-luteal phases. In agreement with Sansores et al. (1995), Smith et al. (2015) found that pulmonary diffusion capacity during heavy exercise was ~10% less in the early-follicular phase of the MC compared to the mid-luteal phase. Importantly, this finding is not universal (Seaton 1972; Bacon et al. 2005) and methodological missteps, such as the inclusion of women using HC included in the participant group (Smith et al. 2015), render the findings questionable. For a further detailed discussion, the reader is directed to the chapter by Duke et al. in this volume.

Cardiac Output

The maximal cardiac output is determined by the rate (i.e., heart rate) and volume (i.e., stroke volume) at which the heart pumps blood during maximal endurance exercise, and it is directly influenced by feedback from skeletal muscle afferents during exercise. There is mounting evidence to suggest that estrogen and/or progesterone may modify cardiovascular regulation during exercise (Ettinger et al. 1998; Minahan et al. 2018). In 1931, in the *American Journal of Physiology*, Arthur Grollman from the John Hopkins University, reported the cardiac output of one adult female subject every day for 22 d, observing no obvious pattern relating to MC phase (Grolman 1931). Fifty years later, Jurkowski et al. (1981) determined the cardiac output of women exercising at 40, 70, and 90% of VO_{2peak} 6–9 d after day one of menstruation (follicular) and 6–9 d after ovulation was detected (luteal). These authors observed no differences in heart rate, stroke volume, or cardiac output between the two phases of the MC. Despite potential interference of estrogen and/or progesterone on the skeletal muscle signal, there is little evidence to suggest that this interference manifests in changes to cardiac output during exercise.

Oxygen-Carrying Capacity

Red blood cell mass plays a primary role in determining the oxygen-carrying capacity of the blood. Due to blood loss associated with menstruation in the follicular phase of the MC, researchers have postulated that the oxygen-carrying capacity of the blood may be decreased as compared to the late-follicular and luteal phases of the MC. Nonetheless, the findings are mixed with a decrease (Vellar et al. 1974; Javaid et al. 2007; Jurkowski et al. 1981), an increase (Dombovy et al. 1987), or no difference (Claybaugh et al. 2000; Hackney et al. 1994; Lebrun et al. 1995; Keller et al. 2020) being reported. These discrepancies among studies are likely due to the methodology used to calculate red blood cell mass (i.e., hemoglobin concentration, hematocrit levels, hemoglobin mass) as well as the variations in participant hydration status and posture. Nonetheless, the effect of estrogen and progesterone on the oxygen-carrying capacity of the blood appears to be indirect by way of inducing blood loss during menstruation.

Keller et al. (2020) measured hemoglobin mass, red blood cell volume, plasma volume, and total blood volume to investigate the oxygen-carrying capacity of the blood in twenty-one women (naturally-cycling = 11; taking HC = 10). Given the reduced blood loss experienced during menstruation in women taking HC compared with naturally menstruating women, it could be proposed that a greater oxygen-carrying capacity would be observed in women taking HC. While these authors found no difference in hemoglobin, hematocrit, and serum ferritin concentrations between women using HC (specifically oral contraceptives) and naturally menstruating women, when normalized to body mass, hemoglobin mass was greater in the

women taking HC. Although oxygen-carrying capacity is a limiting factor of VO_{2peak}, the higher hemoglobin mass reported in women taking HC compared with naturally menstruating women does not translate to a higher VO_{2peak}.

Muscle Characteristics

Beyond substrate mobilization, provision, and utilization by muscle (see the chapters by Isacco and Boisseau as well as Vieira-Potter in this volume), it is unclear at this time if MC and HC directly influence skeletal muscle oxidative pathways downstream of substrate entry points that could, in turn, influence endurance exercise performance. However, there is evidence in rodent and murine models to suggest that estrogen and progesterone regulate or modulate elements of mitochondrial function that could impact exercise performance (Nagai 2016; Gigli and Bussman 2001). For example, Gigli and Bussman (2001) demonstrated that State 3 mitochondrial respiration following exercise was blunted in ovariectomized and estrous rats, accompanied by a reduced respiratory control ratio but preserved P/O_2 ratio, when compared to progesterone-treated ovariectomized rats. A recent review by Ikeda et al. (2019) summarizes the current state of knowledge regarding the influence of estrogen on skeletal muscle in animal models and presents a model of the role of estrogen in skeletal muscle and mitochondrial regulation in the context of exercise. To what extent these insights from animal models will translate to humans, and their impact on exercise performance remains to be determined.

Effect of Female Sex Hormones on Other Factors Affecting Endurance Exercise Performance

Numerous other factors that have been demonstrated to influence endurance performance in women could be affected by the female sex hormone profile. Here, we direct the reader to other chapters within the text that cover some of these factors in-depth and briefly touch on additional factors, guiding the reader to scientific literature supporting these relationships.

Previous research demonstrates that Marathon performance diminishes under hot environmental conditions in female athletes (El Helou et al. 2012). Put simply, the limiting factor for endurance exercise performance in the heat is an elevated core body temperature. Therefore, the regulation of core body temperature during endurance exercise in the heat is critical to maintaining power output and to reduce the risk of heat-related injury (Maughan 2010). There is evidence of changes to core body temperature across the MC in naturally-cycling women and with the administration of HC, as well as modification of thermoregulatory mechanisms (e.g., skin blood flow) in women taking HC compared to naturally menstruating women (Minahan

et al. 2017). Therefore, female sex hormones could indirectly affect endurance exercise performance by interfering with core body temperature and/or thermoregulation during exercise in the heat. Please see the chapter by Stachenfeld in this volume for a specific discussion on the effect of female sex hormones on thermoregulation in athletes.

Delayed onset muscle soreness (DOMS), caused by muscle-damaging eccentric or unaccustomed exercise, may adversely impact ventilatory and metabolic responses (Schneider et al. 2007), perceived exertion (Chen et al. 2007), and exercise economy (Joyce et al. 2014) during endurance exercise with some (Asp et al. 1998; Marcora and Bosio 2007; Joyce et al. 2014), but not all (Schneider et al. 2007) studies indicating a subsequent effect on performance. Interestingly, several studies (Joyce et al. 2014; Thompson et al. 1997; Savage and Clarkson 2002) suggest that the presence of HC may exacerbate, or negatively affect recovery from, muscle damage by suppressing endogenous estrogen. Furthermore, Joyce et al. (2014) demonstrated that muscle damage in response to severe eccentric exercise had a detrimental impact upon subsequent endurance exercise performance, but that this effect was blunted in naturally menstruating women when compared to women taking oral contraceptives. Therefore, female sex hormones could indirectly effect endurance exercise performance by altering DOMS after exercise causing muscle damage. Please refer to the chapter by Tiidus in this volume for specific discussion on the effect of female sex hormones on DOMS (see Chap. 7).

It is generally understood that enhanced glycogen storage and fat utilization during exercise may be beneficial to prolonged low-intensity endurance exercise performance and that this relationship has been demonstrated in trained female athletes (Walker et al. 2000). Therefore, any influence or manipulation of substrate utilization during exercise with MC phase or HC administration may affect endurance exercise performance. However, although there is evidence supporting a shift in substrate metabolism across the MC with increased fat oxidation occurring during the luteal phase compared with the follicular phase (Hackney et al. 2022; Willett et al. 2021; Zderic et al. 2001), there is no consistent evidence to suggest that the MC-related shift in substrate utilization has any effect on endurance exercise performance in female athletes. Please see the chapters by Isacco and Boisseau as well as Vieira-Potter in this volume for specific discussion on the effect of female sex hormones on substrate availability (see Chaps. 2 and 3).

In addition to peripheral oxygen delivery, cerebral blood flow may be a limiting factor to the predictors of endurance exercise performance by affecting motor neuron drive and subsequently motor output (Amann et al. 2006; Rasmussen et al. 2010; Nybo and Rasmussen 2007; Rupp and Perrey 2008). Considering that endogenous estrogen can enhance the bioavailability of nitric oxide, the female sex hormone profile may affect cerebral vascular tone (Iadecola et al. 1994) and thus cerebral oxygenation during exercise. Quinn et al. (2018) measured prefrontal tissue oxygenation using near-infrared spectroscopy demonstrating that cerebral oxygenation declined at a lower relative exercise intensity in women taking HC as compared to naturally-cycling women. Nonetheless, no difference in VO_{2peak} was determined between the two groups.

There is a positive relationship between body weight and energy expenditure during endurance exercise that is weight-bearing (e.g., running) and that which attracts significant resistive forces of gravity, e.g., mountain climbing (Olds et al. 1995). Haakonssen et al. (2016) provide evidence demonstrating a relationship between road cycling performance and body weight in female cyclists. While women anecdotally report changes in body weight throughout their MC, most of the scientific studies that measure body weight during different phases of the MC have found no significant change (Horvath et al. 1982; De Souza et al. 1990; Stachenfeld et al. 2000; Thompson et al. 2021). However, in one early study that measured body weight daily, the highest average body weight values were recorded in the late-luteal phase of the MC (Watson et al. 1965). This finding was supported by Pliner and Fleming (1983) who demonstrated an increase in mean body weight from 52.6 ± 5.4 kg during the follicular phase of the MC to 52.8 ± 5.6 kg during the luteal phase, with an increase in body weight observed in twenty-four of the thirty-four participants. In addition to MC phase, body weight changes with the administration of HC have been examined, with the most recent findings failing to identify a difference between naturally menstruating women and women taking HC (Thompson et al. 2021).

Effect of Female Sex Hormones on Other Factors Affecting Endurance Exercise Performance

To answer the question of whether female sex hormones affect the rate and/or magnitude of endurance-related adaptations to training, improvements in the predictors and limitations of endurance performance are compared between naturally menstruating women and women taking HC. Furthermore, we looked for evidence supporting phase-based training to enhance endurance-related adaptations to training.

After 4 wk of sprint-interval training, Schaumberg et al. (2017) found that improvements in VO_{2peak} were attenuated in women using HC (8.5%) compared to naturally menstruating women (13.0%). Interestingly, these authors observed a greater increase in cardiac output in naturally menstruating women (16.1%) when compared with women using HC (4.0%) after training, supporting the greater increase in VO_{2peak} observed in naturally menstruating women. Importantly, the hormonal contraceptives in the study by Schaumberg et al. (2017) were considered as a low-dose, combined oral contraceptive with a "second-" or "third-generation" progestin. Therefore, athletes, coaches, scientists, and performance staff should consider this before making conclusions about the effect of sprint-interval training on VO_{2peak} in women. Readers are directed to Schaumberg et al. (2017) for a discussion regarding the dampened effect of HC on cardiac output.

Mixed-type training programs including both endurance-type and strength-type exercises have not delineated the endurance-related adaptions to training observed in naturally menstruating women and women taking HC. Armstrong et al. (2005) evaluated adaptations to an 8-wk training program including heat acclimation (90 min/d, 3

d/wk) and physical training (including 4.6 km running performed at 60–85% VO_{2peak} and push-ups, 3 d/wk) in previously inactive women using HC or naturally menstruating. Both 4.6 km time trial performance (-24.7%) and VO_{2peak} (9.4%) were significantly improved after training. Nonetheless, no differences were observed between groups after the training program, suggesting that neither the suppression of endogenous hormones nor the elevation of synthetic hormones with the administration of HC influenced endurance-related adaptations to training when compared with naturally menstruating women. In addition, 10 wk of combined strength (2 sessions/wk) and endurance training (4 × 4-min running intervals > 70–90% of maximal heart rate and one 3 × 3 × 100-m all-out sprints, 2 session/wk) resulted in a similar magnitude of improvement in a 3000-m running time in physically-active women using monophasic oral contraceptives (3.5%) compared with naturally-cycling women (1.0%; Myllyaho et al. 2021).

Scientific evidence exists supporting phase-based training (i.e., prioritizing training around a specific phase of the MC) to obtain optimal strength gains in naturally-cycling women (Reis et al. 1995; Sung et al. 2014). However, evidence regarding phase-based training for the optimization of endurance-type adaptations is currently not available. Nonetheless, there is significant media attention and anecdotal accounts of how an individual's MC could be "used" to manipulate training prescription and ultimately enhance endurance-type adaptive responses (Rowan 2020). While there is no strong evidence demonstrating superior endurance-type adaptations to phase-based compared with traditionally periodized training in naturally-cycling women, there is perhaps a theoretical argument worth considering; that is, favorable hormonal milieu during certain phases of the menstrual cycle could lend themselves to specific adaptations. For example, the potential for increased levels of pain tolerance during the follicular phase of the MC could permit women to exercise at higher intensities, subsequently stimulating greater increases in the power output associated with their maximal metabolic steady-state. Furthermore, the reported shift toward increased fat oxidation during the late-follicular and mid-luteal phases of the MC could allow athletes to tolerate higher volumes of training, resulting in greater increases in exercise economy. Finally, the perception of elite female athletes that heightened performance is likely to be achieved during the second week of their MC (McNamara et al. 2022) may encourage improved quality of training (including higher volume, intensity, and improved motor patterns) and result in superior training adaptations when compared to other phases of the MC. These postulations require carefully considered scientific inquiry to elucidate their validity.

Summary

In summary, this chapter addressed the three main predictors of endurance exercise performance (peak oxygen uptake, intensity domain thresholds, and exercise economy), their interaction with varying female sex hormone profiles (MC phase,

HC), and the limiting factors that might be influenced by female sex hormones. While the intent was to focus on key "physiological" predictors and limiting factors of endurance exercise performance, some of the "psychological" factors relevant to such performance and related training were also explored.

Not surprisingly, there is limited or unclear information about the effect of female sex hormones on several areas covered in this chapter. Therefore, it is likely that the effect of female sex hormones on the physiological and psychological factors affecting endurance exercise performance/training needs to continue to remain an important area of research if sports science is to provide female athletes with the opportunity to reach their potential and optimize their endurance exercise performances.

References

Allsen P, Parsons P, Bryce G. Effect of the menstrual cycle on maximum oxygen uptake. The Phys Sports Med. 1977;5:53–5.

Amann M, Eldridge M, Lovering A, Stickland M, Pegelow D, Dempsey J. Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. J Physiol. 2006;575:937–52.

Armstrong L, Maresh C, Keith N, Elliott T, VanHeest J, Scheett T, Stoppani J, Judelson D, De Souza M. Heat acclimation and physical training adaptations of young women using different contraceptive hormones. Am J Physiol Endo Met. 2005;288:E868-875.

Asp S, Daugaard JR, Kristiansen S, Kiensand B, Richter EA. Exercise metabolism in human skeletal muscle exposed to prior eccentric exercise. J Physiol. 1998;509:305–13.

Astokorki A, Mauger A. Tolerance of exercise-induced pain at a fixed rating of perceived exertion predicts time trial cycling performance. Scand J Med Sci Sports. 2017;27:309–17.

Bacon C, Prior J, Abboud R, Oldham A, McKenzie D. Changes in pulmonary transfer factor with menstrual cycle phase. Resp Phys Neurobiol. 2005;146:195–203.

Bailey S, Zacher C, Mittleman K. Effect of menstrual cycle phase on carbohydrate supplementation during prolonged exercise to fatigue. J Appl Physiol. 2000;88:690–7.

Bandura A. Self-efficacy: the exercise of control. New York, NY: Freeman; 1997.

Bandura A, Locke E. Negative self-efficacy and goal effects revisited. J Appl Psych. 2003;88:87–99.

Barnes K, McGuigan M, Kilding A. Lower- body determinants of running economy in male and female distance runners. J Strength Cond Res. 2014;28:1289–97.

Barstow T, Casaburi R, Wasserman K. O2 uptake kinetics and the O2 deficit as related to exercise intensity and blood lactate. J Appl Physiol. 1993;75:755–62.

Bassett D, Howley E. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc. 2000;32:70–84.

Beidleman B, Rock P, Muza S, Fulco C, Forte V Jr, Cymerman A. Exercise Ve and physical performance at altitude are not affected by menstrual cycle phase. J Appl Physiol. 1999;86:1519–26.

Bemben D, Salm P, Salm A. Ventilatory and blood lactate responses to maximal treadmill exercise during the menstrual cycle. J Sports Med Phys Fitness. 1995;35:257–62.

Bethea C, Mirkes S, Su A, Michelson D. Effects of oral estrogen, raloxifene and arzoxifene on gene expression in serotonin neurons of macaques. Psychoneuroendocrinology. 2002;27:431–45.

Borg G. In: Borg's perceived exertion and pain scales. Champaign, IL,USA; Human Kinetics:1998. p 49.

Brutsaert T, Spielvogel H, Caceres E, Araoz M, Chatterton R, Vitzthum V. Effect of menstrual cycle phase on exercise performance of high-altitude native women at 3600 m. J Exper Biol. 2002;205:233–9.

Bryner R, Toffle R, Ullrich I, Yeater R. Effect of low dose oral contraceptives on exercise performance. Br J Sports Med. 1996;30:36–40.

Bueno J, Weinberg R, Fernández-Castro J, Capdevila L. Emotional and motivational mechanisms mediating the influence of goal setting on endurance athletes' performance. Psych Sport Exerc. 2008;9:786–99.

Burke S, Jin P. Predicting performance from a triathlon event. J Sport Behav. 1996;19:272–87.

Burnley M, Jones A. Oxygen uptake kinetics as a determinant of sports performance. Eur J Sport Sci. 2007;7:63–79.

Buser T. The impact of the menstrual cycle and hormonal contraceptives on competitiveness. J Eco Behav Org. 2012;1(83):1–10.

Campbell S, Angus D, Febbraio M. Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. Am J Physiol Endo Met. 2001;281:E817-825.

Carlberg K, Fregley M, Fahey M. Effects of chronic estrogen treatment on water exchange in rats. Am J Physiol Endocrinol Metab. 1984;247:E101–10.

Casazza GA, Suh SH, Miller BF, Brooks GA. Effects of oral contraceptives on peak exercise capacity. J Appl Physiol. 2002;93:1698–1702.

Castro E, Rael B, Romero-Parra N, Alfaro-Magallanes VM, Rojo-Tirado MA, García-de-Alcaraz A, Cupeiro R, Peinado AB. Influence of oral contraceptive phase on cardiorespiratory response to exercise in endurance-trained athletes. Eur J Contraception Repro Health Care. 2022; 18:1-9.

Casazza G, Suh S, Miller B, Navazio F, Brooks G. Effects of oral contraceptives on peak exercise capacity. J Appl Physiol. 2002;93:1698–702.

Corbett J, Barwood M, Ouzounoglou A, Thelwell R, Dicks M. Influence of competition on performance and pacing during cycling exercise. Med Sci Sports Exerc. 2012;44:509–15.

Charkoudian N, Stachenfeld NS. Reproductive hormone influences on thermoregulation in women. Compr Physiol. 2014;4:793–804.

Chen TC, Nosaka K, Tu J-H. Changes in running economy following downhill running. J Sports Sci. 2007;25:55–63.

Claybaugh JR, Sato AK, Crosswhite LK, Hassell LH. Effects of time of day, gender, and menstrual cycle phase on the human response to a water load. Am J Physiol Regul Integr Comp Physiol. 2000;279(3):R966–73.

Cooke A, Kavussanu M, McIntyre D, Ring C. Psychological, muscular and kinematic factors mediate performance under pressure. Psychophysiol. 2010;47:1109–11.

Cooke A, Kavussanu M, McIntyre D, Ring C. Effects of competition on endurance performance and the underlying psychological and physiological mechanisms. Bio Psyc. 2011;86:370–8.

Coyle E, Coggan A, Hemmert M, Ivy J. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. J Appl Physiol. 1986;61:165–72.

Coyle E, Sidossis L, Horowitz J, Beltz J. Cycling efficiency is related to the percentage of type I muscle fibers. Med Sci Sports Exerc. 1992;24:782–8.

Crewe H, Tucker R, Noakes TD. The rate of increase in rating of perceived exertion predicts the duration of exercise to fatigue at a fixed power output in different environmental conditions. Eur J Appl Physiol. 2008;103:569–77.

Dean T, Perreault L, Mazzeo R, Horton T. No effect of menstrual cycle phase on lactate threshold. J Appl Physiol. 2003;95:2537–43.

De Souza M, Maguire M, Rubin K. Effects of menstrual cycle phase and amenorrhea on exercise performance in runners. Med Sci Sports Exerc. 1990;22:575–80.

Dokumaci B, Hazir T. Effects of the menstrual cycle on running economy: oxygen cost versus caloric cost. Res Quart Exerc Sport. 2019;90:318–26.

Dombovy M, Bonekat H, Williams T, Staats B. Exercise performance and ventilatory response in the menstrual cycle. Med Sci Sports Exerc. 1987;19:111–7.

Eisenbruch A, Roney J. Conception risk and the ultimatum game: when fertility is high, women demand more. Personal Individ Differ. 2016;98:272–4.
El Helou N, Tafflet M, Berthelot G, Tolaini J, Marc A, Guillaume M, Hausswirth C, Toussaint JF. Impact of environmental parameters on marathon running performance. PLoS One. 2012; 7:e37407–10.1371.
Elliott-Sale KJ, Minahan CL, de Jonge XA, Ackerman KE, Sipilä S, Constantini NW, Lebrun CM, Hackney AC. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51(5):843–61.
Enns DL, Tiidus PM. The influence of estrogen on skeletal muscle. Sports Med. 2010;40:41–58.
Ettinger S, Silber D, Gray K, Smith M, Yang Q, Kunselman A, Sinoway L. Effects of the ovarian cycle on sympathetic neural outflow during static exercise. J Appl Physiol. 1998;85:2075–81.
Fabian L, Ross M. The development of the sports competition trait inventory. J Sport Behav. 1984;7(1):13.
Feltz D, Short S, Sullivan P. Self-efficacy in sport. Champaign, IL: Human Kinetics; 2008.
Fink G, Sumner B, Rosie R, Grace O, Quinn JP. Estrogen control of central neurotransmission: effect on mood, mental state, and memory. Cell Mol Neuro. 1996;16:325–44.
Forsyth JJ, Reilly T. The combined effect of time of day and menstrual cycle on lactate threshold. Med Sci Sports Exercise. 2005;37(12):2046–53.
Forsyth J, Reilly T. The effect of menstrual cycle on 2000-m rowing ergometry performance. Eur J Appl Physiol. 2008;8:351–357.
Freemas J, Baranauskas M, Constantini K, Constantini N, Greenshields J, Mickleborough T, Raglin J, Schlader Z. Exercise performance is impaired during the midluteal phase of the menstrual cycle. Med Sci Sports Exerc. 2021;53:442–52.
Gamberale F, Strindberg L, Wahlberg I. Female work capacity during the menstrual cycle: physiological and psychological reactions. Scand J Work Environ Heath. 1975;1:120–7.
Giacomoni M, Falgairette G. Decreased submaximal oxygen uptake during short duration oral contraceptive use: a randomized cross-over trial in premenopausal women. Ergonomics. 2000;43:1559–70.
Gigli I, Bussmann LE. Exercise and ovarian steroid hormones: their effects on mitochondrial respiration. Life Sci. 2001;68:1505–14.
Gill D, Deeter T. Development of the sport orientation questionnaire. Res Quart. 1988;59:191–202.
Goldsmith E, Glaister M. The effect of the menstrual cycle on running economy. J Sports Med Phys Fitness. 2020;60:610–7.
Gordon D, Scruton A, Barnes R, Baker J, Prado L, Merzbach V. The effects of menstrual cycle phase on the incidence of plateau at and associated cardiorespiratory dynamics. Clin Physiol Funct Imaging. 2018;38:689–98.
Grollman A. The effect of the menstrual cycle on the cardiac output, pulse rate, blood pressure, and oxygen consumption of a normal woman. Am J Physiol. 1931;96:1.
Haakonssen E, Barras M, Burke L, Jenkins D, Martin D. Body composition of female road and track endurance cyclists: normative values and typical changes. Eur J Sport Sci. 2016;16:645–53.
Hackney AC, Curley C, Nicklas B. Physiological responses to submaximal exercise at the mid-follicular, ovulatory and mid-luteal phases of the menstrual cycle. Scand J Med Sci Sports. 1991;1:94–8.
Hackney AC, McCracken-Compton M, Ainsworth B. Substrate responses to submaximal exercise in the midfollicular and midluteal phases of the menstrual cycle. Intern J Sport Nut. 1994;4:299–308.
Hackney AC. Influence of oestrogen on muscle glycogen utilization during exercise. Acta Physiol Scand. 1999;167:273.
Hackney AC, Koltun K, Williett H. Menstrual cycle hormonal changes: estradiol-β-17 and progesterone interactions on exercise fat oxidation. Endocrine. 2022;76:240–2.
Harms CA. Does gender affect pulmonary function and exercise capacity? Res Physiol Neuro. 2006;151:124–31.

Helmreich R, Spence J. The work and family orientation questionnaire: an objective instrument to assess components of achievement motivation and attitudes toward family and career. Cat Sel Doc Psychol. 1978;8:1677.
Higgs S. The effect of competition upon the endurance performance of college women. Int J Sport Psychol. 1972;3:128–40.
Higgs S, Robertson L. Cyclic variations in perceived exertion and physical work capacity in females. Can J Appl Sport Sci. 1983;6:191–6.
Horvath SM, Drinkwater BL. Thermoregulation and the menstrual cycle. Aviat Space Environ Med. 1982;53:790–479.
Hunter G, Newcomer B, Larson-Meyer D, Bamman M, Weinsier R. Muscle metabolic economy is inversely related to exercise intensity and type II myofiber distribution. Mus Nerve. 2001;24:654–61.
Hutchinson JC, Sherman T, Martinovic N, Tenenbaum G. The effect of manipulated self-efficacy on perceived and sustained effort. J Appl Sport Psychol. 2008;20:457–72.
Iacovides B, Alfaro-Magallanes V, Romero-Parra N, Castro EA, Cupeiro R, Janse de Jonge X, Wehrwein E, Peinado A, IronFEMME Study Group. Menstrual cycle phases influence on cardiorespiratory response to exercise in endurance-trained females. Intern J Enviro Res Pub Health. 2021; 18:860.
Iacovides S, Avidon I, Baker F. Does pain vary across the menstrual cycle? A review. Eur J Pain. 2015;19:1389–405.
Iadecola C, Pelligrino DA, Moskowitz MA, Lassen NA. Nitric oxide synthase inhibition and cerebrovascular regulation. J Cereb Blood Flow Metab. 1994;14:175–92.
Ikeda K, Horie-Inoue K, Inoue S. Functions of estrogen and estrogen receptor signaling on skeletal muscle. J Steroid Biochem Mol Biol. 2019;191: 105375.
Janse de Jonge XA. Effects of the menstrual cycle on exercise performance. Sports Med. 2003;33:833–51.
Janse de Jonge X, Thompson MW, Chuter VH, Silk LN, Thom JM. Exercise performance over the menstrual cycle in temperate and hot, humid conditions. Med Sci Sports Exerc. 2012; 44:2190–2198.
Javaid A, Hasan R, NaimT. A comparative study of bodyweight, hemoglobin concentration and hematocrit during follicular and luteal phases of menstrual cycle. J Med Sci. 2007;7:146–9.
Johnson MH, Stewart J, Humphries SA, Chamove AS. Marathon runners' reaction to potassium iontophoretic experimental pain: Pain tolerance, pain threshold, coping and self-efficacy. Eur J Pain. 2012;16:767–74.
Jones A, Burnley M, Black M, Poole D, Vanhatalo A. The maximal metabolic steady state: redefining the 'gold standard.' Physiol Rep. 2019;7: e14098.
Jones A, Doust J. The validity of the lactate minimum test for determination of the maximal lactate steady state. Med Sci Sports Exerc. 1998;30:1304–13.
Jones A, Grassi M, Christensen P, Krustrup P, Bangsbo J, Poole D. Slow component of VO2 kinetics: mechanistic bases and practical applications. Med Sci Sports Exerc. 2011;43:2046–62.
Jones A, Poole D. Physiological demands of endurance exercise. In: Maughan RJ, editor. Olympic textbook of science in sport, IOC. Oxford, UK; Blackwell: 2008. pp 43–55.
Jones A, Vanhatalo A. The 'critical power'concept: applications to sports performance with a focus onintermittent high-intensity exercise. Sports Med. 2017;47:65–78.
Joyce S, Sabapathy S, Bulmer A, Minahan C. Effect of long-term oral contraceptive use on determinants of endurance performance. J Stren Cond Res. 2013;27:1891–6.
Joyce S, Sabapathy S, Bulmer AC, Minahan C. The effect of prior eccentric exercise on heavy-intensity cycling: the role of gender and oral contraceptives. Eur J Appl Physiol. 2014;114:995–1003.
Joyner M. Physiological limits to endurance exercise performance: influence of sex. J Physiol. 2017;595:2949–54.
Joyner M, Coyle E. Endurance exercise performance: the physiology of champions. J Physiol. 2008;586:35–44.

Julian R, Hecksteden A, Fullagar H, Meyer T. The effects of menstrual cycle phase on physical performance in female soccer players. PLoS ONE. 2017;12: e0173951.
Jurkowski JE, Jones NL, Toews CJ, Sutton JR. Effects of menstrual cycle on blood lactate, O2 delivery, and performance during exercise. J Appl Physiol Respir Environ Exerc Physiol. 1981;51:1493–9.
Keller M, Harrison M, Lalande S. Impact of menstrual blood loss and oral contraceptive use on oxygen-carrying capacity. Med Sci Sports Exerc. 2020;52:1414–9.
Kolka MA, Stephenson LA. Resetting the thermoregulatory set-point by endogenous estradiol or progesterone in women. Ann New York Acad Sci. 1997;813(1):204-6.
Lara B, Ruiz-Moreno C, Salinero JJ, Del Coso J. Time course of tolerance to the performance benefits of caffeine. PLoS One. 2019;14(1):e0210275.
Lara B, Gutiérrez-Hellín J, García-Bataller A, Rodríguez-Fernández P, Romero-Moraleda B, Del Coso J. Ergogenic effects of caffeine on peak aerobic cycling power during the menstrual cycle. Eur J Nut. 2020;59:2525–34.
Larsen B, Cox A, Colbey C, Drew M, McGuire H, Fazekas de St Groth B, Hughes D, Vlahovich N, Waddington G, Burke L, Lundy B. Inflammation and oral contraceptive use in female athletes before the Rio Olympic Games. Front Physiol. 2020; 11:497.
Lebrun CM, McKenzie DC, Prior JC, Taunton JE. Effects of menstrual cycle phase on athletic performance. Med Sci Sports Exerc. 1995;27(3):437–44.
Lebrun C, Petit M, McKenzie D, Taunton J, Prior J. Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomised controlled trial. Br J Sports Med. 2003;37:315–20.
Lee J, Harley V. The male fight-flight response: a result of SRY regulation of catecholamines? BioEssays. 2012;34:454–7.
Lucia A, Hoyos J, Perez M, Santalla A, Chicharro JL. Inverse relationship between VO2max and economy/efficiency in world-class cyclists. Med Sci Sports Exerc. 2002;34:2079–84.
Lundby C, Montero D, Gehrig S, Andersson Hall U, Kaiser P, Boushel R, Meinild Lundby AK, Kirk N, Valdivieso P, Flück M, Secher NH. Physiological, biochemical, anthropometric, and biomechanical influences on exercise economy in humans. Scand J Med Sci Sports. 2017;27:1627–37.
Marcora SM, Bosio A. Effect of exercise-induced muscle damage on endurance running performance. Scand J Med Sci Sports. 2007;17:662–71.
Martin J, Gill D. The relationships among competitive orientation, sport-confidence, self-efficacy, anxiety, and performance. J Sport Exerc Psych. 1991;13:149–59.
Mauger A. Factors affecting the regulation of pacing: current perspectives. J Sports Med. 2014;5:209–14.
Maughan RJ. Distance running in hot environments: a thermal challenge to the elite runner. Scand J Med Sci Sports. 2010;20:95–102.
McCormick A, Meijen C, Marcora S. Psychological determinants of whole-body endurance performance. Sports Med. 2015;45:997–1015.
McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endo Rev. 1999;20:279–307.
McNamara A, Harris R, Minahan C. 'That time of the month' … for the biggest event of your career?! Perception of menstrual cycle on performance of Australian athletes training for the 2020 olympic and paralympic games. BMJ Open Sport Exerc Med. 2022;8: e001300.
McNulty K, Elliott-Sale K, Dolan E, Swinton P, Ansdell P, Goodall S, Thomas K, Hicks K. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. Sports Med. 2020;50:1813–27.
Mercuro G, Podda A, Pitzalis L, Zoncu S, Mascia M, Melis GB, Rosano GM. Evidence of a role of endogenous estrogen in the modulation of autonomic nervous system. Am J Cardio. 2000;85:787–9.
Micalos P. Perspectives on biochemical and neurosensory mechanisms for exercise-induced pain inhibition. Fatigue: Biomed, Health Behav. 2014; 2:219–230.

Miller M. Efficacy strength and performance in competitive swimmers of different skill levels. Intern J Sport Psych. 1993;24:284–96.
Minahan C, Melnikoff M, Quinn K, Larsen B. Response of women using oral contraception to exercise in the heat. Eur J Appl Physiol. 2017;117:1383–91.
Minahan C, O'Neill H, Sikkema N, Joyce S, Larsen B, Sabapathy S. Oral contraceptives augment the exercise pressor reflex during isometric handgrip exercise. Physiol Rep. 2018;6(5):e13629.
Moritani T, Nagata A, deVries H, Muro M. Critical power as a measure of physical work capacity and anaerobic threshold. Ergo. 1981;24:339–50.
Motl R, Gliottoni R, Scott J. Self-efficacy correlates with leg muscle pain during maximal and submaximal cycling exercise. J Pain. 2007;8:583–7.
Moquin A, Mazzeo RS. Effect of mild dehydration on the lactate threshold in women. Med Sci Sports Exerc. 2000;32:396–402.
Myllyaho M, Ihalainen J, Hackney AC, Valtonen M, Nummela A, Vaara E, Häkkinen K, Kyröläinen H, Taipale R. Hormonal contraceptive use does not affect strength, endurance, or body composition adaptations to combined strength and endurance training in women. J Stren Cond Res. 2021;35:449–57.
Nagai S, Ikeda K, Horie-Inoue K, Shiba S, Nagasawa S, Takeda S, Inoue S. Estrogen modulates exercise endurance along with mitochondrial uncoupling protein 3 downregulation in skeletal muscle of female mice. Biochem Biophys Res Comm. 2016;480:758–64.
Nicklas B, Hackney AC, Sharp R. The menstrual cycle and exercise: performance, muscle glycogen, and substrate responses. Intern J Sports Med. 1989;10:264–9.
Notelovitz M, Zauner C, McKenzie L, Suggs Y, Fields C, Kitchens C. The effect of low-dose oral contraceptives on cardiorespiratory function, coagulation, and lipids in exercising young women: a preliminary report. Am J Ob Gynecol. 1987;156:591–8.
Nybo L, Rasmussen P. Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. Exerc Sport Sci Rev. 2007;35:110–8.
Olds T, Norton K, Lowe E, Olive S, Reay F, Ly S. Modeling road-cycling performance. J Appl Physiol. 1995;78:1596–611.
Oosthuyse T, Bosch A, Jackson S. Cycling time trial performance during different phases of the menstrual cycle. Eur J Appl Physiol. 2005;94:268–76.
Pate R, Macera C, Bailey S, Bartoli W, Powell K. Physiological anthropometric and training correlates of running economy. Med Sci Sports Exerc. 1992;24:1128–33.
Pearson M, Schipper B. Menstrual cycle and competitive bidding. Games Eco Behav. 2013;1(78):1–20.
Peerdeman K, Van Laarhoven A, Peters M, Evers A. An integrative review of the influence of expectancies on pain. Front Psych. 2016;7:1270.
Peveler W, Green M. The effect of extrinsic factors on simulated 20-km time trial performance. J Stren Cond Res. 2010;24:3265–9.
Pliner P, Fleming AS. Food intake, body weight, and sweetness preferences over the menstrual cycle in humans. Physiol Behav. 1983;30:663–6.
Poole D, Ward S, Gardner G, Whipp B. Metabolic and respiratory profile of the upper limit for prolonged exercise in man. Ergo. 1988;31:1265–79.
Poole D, Rossiter H, Brooks G, Gladden L. The anaerobic threshold: 50+ years of controversy. J Physiol. 2021;599:737–67.
Quinn K, Billaut F, Bulmer A, Minahan C. Cerebral oxygenation declines but does not impair peak oxygen uptake during incremental cycling in women using oral contraceptives. Eur J Appl Physiol. 2018;118:2417–27.
Rael B, Alfaro-Magallanes VM, Romero-Parra N, Castro EA, Cupeiro R, Janse de Jonge XA, Wehrwein EA, Peinado AB, IronFEMME Study Group. Menstrual cycle phases influence on cardiorespiratory response to exercise in endurance-trained females. Int J Environ Res Public Health. 2021;18(3):860.

Rasmussen P, Nielsen J, Overgaard M, Krogh-Madsen R, Gjedde A, Secher N, Petersen N. Reduced muscle activation during exercise related to brain oxygenation and metabolism in humans. J Physiol. 2010;588:1985–95.

Rebelo A, Zuttin R, Verlengia R, Cesar M, de Sá M, da Silva E. Effect of low-dose combined oral contraceptive on aerobic capacity and anaerobic threshold level in active and sedentary young women. Contraception. 2010;81:309–15.

Redman L, Scroop G, Norman R. Impact of menstrual cycle phase on the exercise status of young, sedentary women. Eur J Appl Physiol. 2003;90:505–13.

Redman L, Weatherby RP. Measuring performance during the menstrual cycle: a model using oral contraceptives. Med Sci Sports Exerc. 2004;36:130–6.

Reis E, Frick U, Schmidtbleicher D. Frequency variations of strength training sessions triggered by the phases of the menstrual cycle. Int J Sports Med. 1995;16:545–50.

Ribeiro J, Hughes V, Fielding R, Holden W, Evans W, Knuttgen H. Metabolic and ventilatory responses to steady state exercise relative to lactate thresholds. Eur J Appl Physiol. 1986;55:215–521.

Riley J III, Robinson M, Wise E, Price D. A meta-analytic review of pain perception across the menstrual cycle. Pain. 1999;81:225–35.

Rowan K. Exclusive: chelsea become first club to tailor training to menstrual cycles. The Telegraph. 2020. Available from: https://www.telegraph.co.uk/football/2020/02/13/exclusive-chelsea-become-first-club-tailor-training-menstrual/.

Rupp T, Perrey S. Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. Eur J Appl Physiol. 2008;102:153–63.

Sansores R, Abboud R, Kennell C, Haynes N. The effect of menstruation on the pulmonary carbon monoxide diffusing capacity. Am J Res Crit Care Med. 1995;152:381–4.

Sarrel PM. Ovarian hormones and the circulation. Maturitas. 1990;12:287–98.

Schaumberg M, Jenkins D, Janse de Jonge X, Emmerton L, Skinner T. Oral contraceptive use dampens physiological adaptations to sprint interval training. Med Sci Sports Exerc. 2017; 49:717–727.

Savage K, Clarkson P. Oral contraceptive use and exercise-induced muscle damage and recovery. Contraception. 2002;66:67–71.

Schneider D, Berwick J, Sabapathy S, Minahan C. Delayed onset muscle soreness does not alter O2 uptake kinetics during heavy-intensity cycling in humans. Int J Sports Med. 2007;28:550–6.

Schultheiss O. A biobehavioral model of implicit power motivation arousal, reward and frustration. In: Harmon-Jones E, Winkielman P, editors. Social neuroscience: integrating biological and psychological explanations of social behavior. New York: Guilford; 2007. pp 176–196.

Schultheiss O, Dargel A, Rohde W. Implicit motives and gonadal steroid hormones: effects of menstrual cycle phase, oral contraceptive use, and relationship status. Hormones Behav. 2003;43:293–301.

Seaton A. Pulmonary capillary blood volume in women: normal values and the effect of oral contraceptives. Thorax. 1972;27:75–9.

Shaw A, Ingham S, Atkinson G, Folland J. The correlation between running economy and maximal oxygen uptake: cross-sectional and longitudinal relationships in highly trained distance runners. PLoS ONE. 2015;10: e0123101.

Smekal G, Von Duvillard S, Frigo P, Tegelhofer T, Pokan R, Hofmann P, Tschan H, Baron R, Wonisch M, Renezeder K, Bachl N. Menstrual cycle: no effect on exercise cardiorespiratory variables or blood lactate concentration. Med Sci Sports Exerc. 2007;39:1098–106.

Smith J, Brown K, Murphy J, Harms C. Does menstrual cycle phase affect lung diffusion capacity during exercise? Res Physiol Neuro. 2015;205:99–104.

Stachenfeld N, Silva C, Keefe D. Estrogen modifies the temperature effects of progesterone. J Appl Physiol. 2000;88:1643–9.

Stanton S, Edelstein R. The physiology of women's power motive: implicit power motivation is positively associated with estradiol levels in women. J Res Personality. 2009;43:1109–13.

Stanton S, Schultheiss O. Basal and dynamic associations between implicit power motivation and estradiol in women. Hor Behav. 2007;52:571–80.
Stanton S, Schultheiss O. The hormonal correlates of implicit power motivation. J Res Pers. 2009;43:942–60.
Stephenson L, Kolka M, Wilkerson J. Metabolic and thermoregulatory responses to exercise during the human menstrual cycle. Med Sci Sports Exerc. 1982;14:270–5.
Stevens C, Mauger A, Hassmen P, Taylor L. Endurance exercise performance in influenced by perceptions of pain ad temperature: theory, applications and safety considerations. Sport Med. 2018;48:525–37.
Stone T, Earley RL, Burnash SG, Wingo JE. Menstrual cycle effects on cardiovascular drift and maximal oxygen uptake during exercise heat stress. European J Appl Physiol. 2021;121:561–72.
Sunderland C, Nevill M. Effect of the menstrual cycle on performance of intermittent, high-intensity shuttle running in a hot environment. Eur J Appl Physiol. 2003;88:345–52.
Sung E, Han A, Hinrichs T, Vorgerd M, Manchado C, Platen P. Effects of follicular versus luteal phase-based strength training in young women. Springerplus. 2014;3:668.
Sunitha G, Ravi BN, Sudhir GK. Study of VO2max during phases of menstruation in young female athletes. J Evol Med Dental Sci. 2013; 2(23): 4070–4078.
Sutton JR, Jurkowski JE, Keane P, Walker WHC, Jones NL, Toews CJ. Plasma catecholamine, insulin, glucose and lactate responses to exercise in relation to the menstrual cycle. Med Sci Sports Exerc. 1980;12:83–4.
Tarnopolsky MA. Gender differences in metabolism; nutrition and supplements. J Sci Med Sport. 2000;3(3):287–98.
Tarnopolsky MA. Sex differences in exercise metabolism and the role of 17-beta estradiol. Med Sci Sports Exer. 2008;40:648–54.
Thompson H, Hyatt J, De Souza M, Clarkson P. The effects of oral contraceptives on delayed onset muscle soreness following exercise. Contraception. 1997;56:59–65.
Thompson BM, Hillebrandt HL, Sculley DV, Barba-Moreno L, Janse de Jonge XA. The acute effect of the menstrual cycle and oral contraceptive cycle on measures of body composition. Europ J Appl Physiol. 2021;121:3051–9.
Timmons BW, Hamadeh MJ, Devries MC, Tarnopolsky MA. Influence of gender, menstrual phase, and oral contraceptive use on immunological changes in response to prolonged cycling. J Appl Physiol. 2005;99:979–85.
Vaiksaar S, Jürimäe J, Mäestu J, Purge P, Kalytka S, Shakhlina L, et al. No effect of menstrual cycle phase and oral contraceptive use on endurance performance in rowers. J Strength Cond Res. 2011;25:1571–8.
Vanhatalo A, Doust J, Burnley M. Determination of critical power using a 3-minute all-out cycling test. Med Sci Sports Exerc. 2007;39:548–55.
Vellar OD. Changes in hemoglobin concentration and hematocrit during the menstrual cycle. I. A cross-sectional study. Acta Obstet Gynecol Scand. 1974;53(3):243–6.
Voor J, Lloyd A, Cole R. The influence of competition on the efficiency of an isometric muscle contraction. J Motor Behav. 1969;1:210–9.
Walker J, Heigenhauser G, Hultman E, Spriet L. Dietary carbohydrate, muscle glycogen content, and endurance performance in well-trained women. J Appl Physiol. 2000;88:2151–8.
Wallace P, McKinlay B, Coletta N, Vlaar J, Taber M, Wilson P, Cheung S. Effects of motivational self-talk on endurance and cognitive performance in the heat. Med Sci Sports Exerc. 2017;49:191–9.
Watson P, Robinson M. Variations in body-weight of young women during the menstrual cycle. Br J Nutr. 1965;19:237–48.
Weber CL, Schneider DA. Increases in maximal accumulated oxygen deficit after high-intensity interval training are not gender dependent. J Appl Physiol. 2002;92:1795–801.
Whipp J, Ward A. Gas exchange dynamics and the tolerance to muscular exercise: effects of fitness and training. Ann Physiol Anthro. 1992;11:207–14.

Willett HN, Koltun KJ, Hackney AC. Influence of menstrual cycle estradiol-β-17 fluctuations on energy substrate utilization-oxidation during aerobic, endurance exercise. Int J Environ Res Pub Health. 2021;18(13):7209.
Williams T, Krahenbuhl G. Menstrual cycle phase and running economy. Med Sci Sports Exerc. 1997;29:1609–18.
Wilmore JH. Influence of motivation on physical work capacity and performance. J Appl Physiol. 1968;24:459–63.
Zaryski C, Smith D. Training principles and issues for ultra-endurance athletes. Curr Sports Med Rep. 2005;4:165–70.
Zderic TW, Coggan AR, Ruby BC. Glucose kinetics and substrate oxidation during exercise in the follicular and luteal phases. J Appl Physiol. 2001;90:447–53.

Chapter 10
Sex Hormones, Menstrual Cycle, and Resistance Exercise

Yuki Nakamura and Katsuji Aizawa

Introduction

During a normal menstrual cycle, women are exposed to a continuously changing profile of female sex steroid hormones. Estrogen starts to increase halfway through the follicular phase and peaks just prior to ovulation. Estrogen and progesterone are both elevated during the middle of the luteal phase (Table 10.1) and have profound physiological effects (see earlier chapters in this book). To better understand the relationship between the menstrual cycle and resistance exercise in women, it is important to consider the hormonal fluctuations that occur throughout the menstrual cycle. This chapter attempts to address these points.

Estrogen receptors have been localized to skeletal muscle tissue as well as tendons and ligaments. Through these receptors, estrogen is thought to influence the turnover of skeletal muscle and connective tissue proteins at rest in the post-absorptive phase and enhance sensitivity to anabolic stimuli (Hansen and Kjaer 2014). In women, estradiol (the principal estrogen, see Chap. 1) functions as an antioxidant and membrane stabilizer during exercise, particularly exercise that induces high levels of oxidative stress, such as intense aerobic and resistance exercise. The protective role of estradiol appears to be a primary factor in mitigating muscle damage due to exercise stress and is evidenced by the smaller inflammatory response found in women (Fleck and Kraemer 2014; Enns and Tiidus 2010).

Interesting, women experience a rapid decline in muscle mass and strength around menopause when estrogen levels decline dramatically. These changes may at least partly be related to the hormonal changes during aging. The striking decline in muscle

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Table 10.1 Menstrual cycle phase with corresponding variations in basal body temperature and fluctuations of ovarian female sex hormones

Menstrual cycle phase (days of menstrual cycle[a])		Basal body temperature (BBT)	Estrogen concentration	Progesterone concentration
Follicular (1–13)	Early follicular (2–7)	Lower temperature	Low	Low
Ovulation (14)	Late follicular (9–13)	Lower temperature	High	Low
Luteal (15–28)	Mid-luteal (18–24)	Higher temperature	High	High

[a]Based on a 28-day cycle with ovulation occurring on day 14 (Janse de Jonge 2003)

strength during perimenopause and after menopause can be reversed with hormone replacement therapy (Jabbour et al. 2006).

In contrast, there is a paucity of data on the effects of progesterone on skeletal muscle, although progesterone is purported to be catabolic (Oosthuyse and Bosch 2010). Another difficulty in interpreting menstrual cycle research stems from the interaction between estrogen and progesterone. During the early follicular phase, estrogen and progesterone levels are both low, but in the late-follicular phase there are high estrogen concentrations and low progesterone concentrations. In the mid- luteal phase, levels of both estrogen and progesterone are high. To compare the increase in estrogen concentration relative to progesterone concentration, some studies have reported the estrogen/progesterone ratio in the luteal phase. This ratio may provide information about the opposing effects of estrogen and progesterone (Janse de Jonge 2003).

To understand the relationship between hormonal fluctuations during the menstrual cycle and exercise in women, researchers, athletes, and coaches should take physical and mental symptoms related to menstruation into account, not only the effects of sex hormones on skeletal muscles. Furthermore, dysmenorrhea (painful menstruation) and premenstrual syndrome (PMS) which can involve mood swings, tender breasts, food cravings, fatigue, irritability, and depression, are commonly seen in eumenorrheic women. These symptoms in turn may affect performance and physical and mental conditions for training and performance during the menstrual cycle phases.

Muscle Strength During the Menstrual Cycle

Several review articles on muscle strength during the menstrual cycle (Constantini et al. 2005; Janse de Jonge 2003; Lebrun 1994) have reported that some studies found greater strength in the follicular phase or in the ovulatory phase than in the luteal phase, whereas other studies have reported that strength was greater in the mid- luteal phase. A majority of studies could not find any changes in muscle strength over the

menstrual cycle. In particular, recent studies measuring estrogen and progesterone concentration in order to verify menstrual cycle phase have reported no changes over the menstrual cycle in isokinetic peak torque of knee extensors and flexors and maximum isometric strength of knee extensors (Bambaeichi et al. 2004), maximum voluntary isometric force of the first dorsal interosseous muscle (Elliott et al. 2003), or handgrip strength and isokinetic muscle strength of knee extensors (peak torque), muscle endurance, and one leg hop test (Fridén et al. 2003). Based on these results, although from a very limited number of studies, it can be concluded there is little or no difference in muscle strength at various times during the menstrual cycle. However, since there are many factors that can potentially influence exercise performance such as self-expectations, negative attitudes toward menstruation, and weight gain, the effect of the menstrual cycle on performance is probably very individual specific and much more research is needed.

Anabolic Hormones and Resistance Exercise in Women

Resistance exercise provides a potent stimulus for muscular adaptation. This process is mediated, at least in part, by acute and chronic hormonal responses to resistance training, including changes in testosterone, growth hormone (GH),dehydroepiandrosterone sulfate (DHEA-S), andinsulin-like growth factor I (IGF-I) (Consitt et al. 2002; Fleck and Kraemer 2014; Kahn et al. 2002; Kraemer and Ratamess 2005). This is true for both sexes. However, the resistance exercise-induced anabolic hormone changes are considerably different in men and women.

Testosterone, a major androgenic-anabolic hormone, exerts a significant influence on anabolic functions in the human body, especially in males. Blood serum testosterone concentration is acutely elevated immediately following heavy resistance exercise in men, although several factors such as muscle mass, exercise intensity and volume, nutrition intake, and training experience play a role in this response (Fleck and Kraemer 2014). At rest, women have a 10- to 40-fold lower blood concentrations of testosterone than men (Kraemer et al. 1991; Vingren et al. 2010). Previous studies have reported that concentrations of testosterone do not change acutely after resistance exercise in women (Kraemer et al. 1991, 1993; Staron et al. 1994; Häkkinen and Pakarinen 1995) (Fig. 10.1), but some other data challenges this construct in relation to other exercise forms (Lane et al. 2015).

Growth hormone (GH) appears to be involved in the growth of skeletal muscle and many other tissues in the body. It also appears to play a vital role in the body's adaptation to the stimulus of resistance training (Fleck and Kraemer 2014). The GH response to resistance training is quite similar between the sexes. A high-intensity and high-volume resistance exercise program with short rest periods has been shown to induce a post-exercise increase in GH in both men and women (Kraemer et al. 1991; Häkkinen and Pakarinen 1995) (Fig. 10.2).

Insulin-like growth factor-I (IGF- I) is a salient biomarker for monitoring health, fitness, and training status. It also reflects nutritional status as well (Fleck and

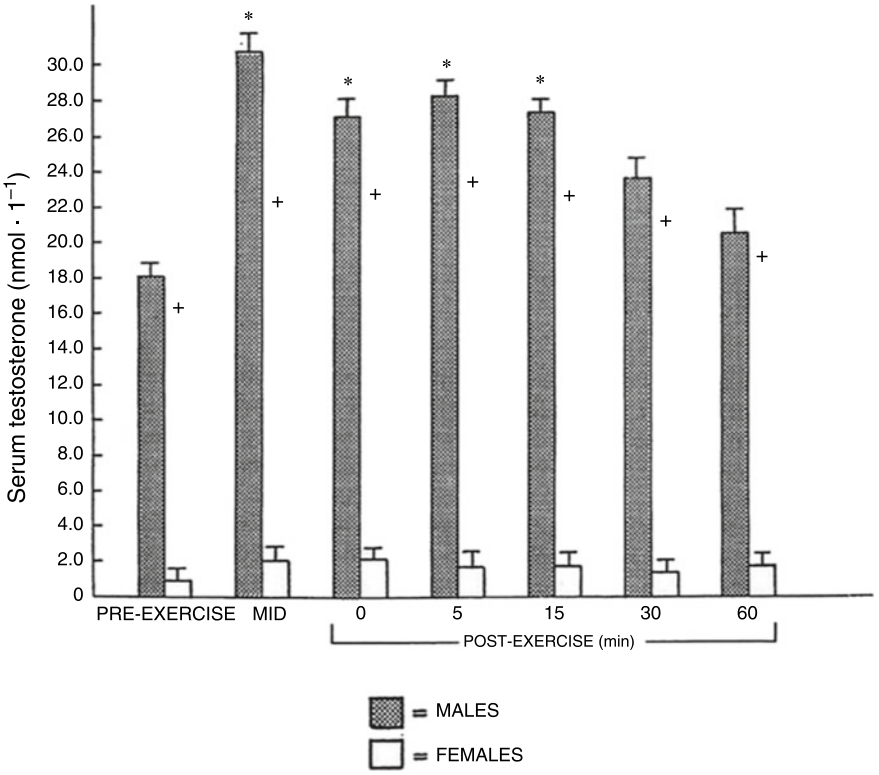

Fig. 10.1 Serum testosterone concentrations in men and women after the same resistance training session consisting of three sets of eight exercises at 10RM (ten repetition maximum) with 1 min of rest between sets and exercises (Kraemer et al. 1991). * Significantly different from pre-exercise value in the same sex; + significantly different from females at the same time point

Kraemer 2014). The acute response of IGF-I to resistance exercise remains unclear. Most studies have shown no change in IGF-I during or immediately following an acute bout of resistance exercise (Kraemer et al. 1993; Consitt et al. 2001), whereas a few studies have shown acute elevations during and following resistance exercise (Kraemer et al. 1991; Kraemer and Ratamess 2005). However, long-term studies in women have shown elevations in resting IGF-I, particularly during high-volume training (Marx et al. 2001; Koziris et al. 1999). Interestingly, researchers showed that GH and IGF-I appear to compensate for the attenuated testosterone response to signal muscle tissue growth in women and therefore may play a more central role in muscle hypertrophy than they do in men (Fleck and Kraemer 2014).

In women, about 90 % of circulating testosterone is derived from the metabolism of peripheral precursors, in particular from DHEA- S (Baulieu 1996; Labrie et al. 1997). DHEA-S is actually the predominant adrenal steroid hormone in both sexes. Regrettably, there is little information available on acute responses of DHEA-S to resistance exercise in women (Enea et al. 2011). Riechman et al. (2004) reported

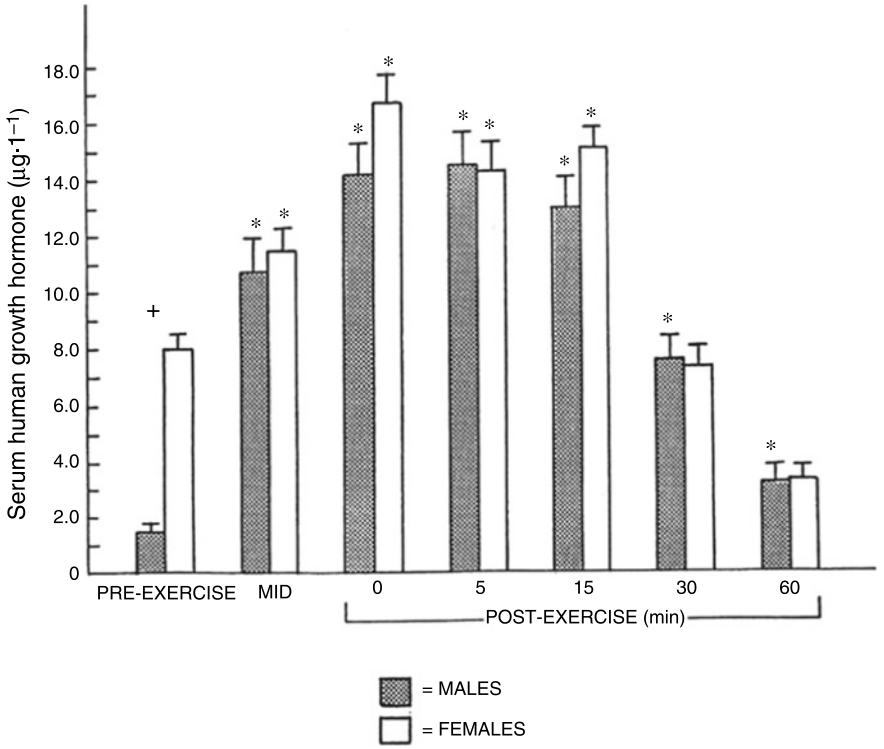

Fig. 10.2 Serum growth hormone concentrations in men and women after the same resistance training session consisting of three sets of eight exercises at 10RM with 1 min of rest between sets and exercises (Kraemer et al. 1991). * Significantly different from pre-exercise value in the same sex; + significantly different from females at the same time point

that acute resistance exercise increases blood DHEA-S levels in both men and women. Aizawa et al. (2003) have reported a dramatic increase in resting serum DHEA-S concentrations after 8 weeks of resistance training. Furthermore, Aizawa et al. (2006) demonstrated that serum DHEA-S levels are positively correlated with leg extensor power in female athletes, but not in male athletes (Fig. 10.3). These findings suggest that blood DHEA-S levels in female athletes may reflect training-induced adaptation and play an important role in muscular strength development. DHEA- S may also play a major biological role in women through its transformation into active androgens and estrogens (McMurray and Hackney 2000).

Thus, it is clear there are sex (gender) differences in basal anabolic hormone levels and responses to exercise. Nevertheless, women and men display similar relative changes in hypertrophy with resistance exercise. Although not discussed here, other hormones or mechanisms may also be responsive to resistance training and thus affect long-term adaptations to resistance training in women (see McMurray and Hackney 2000).

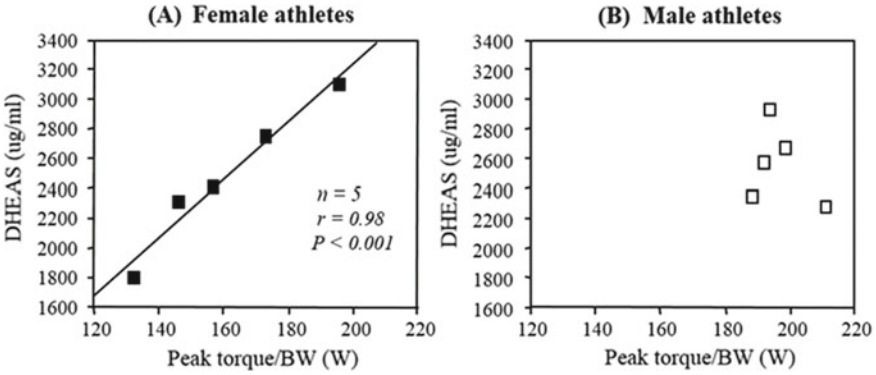

Fig. 10.3 Serum DHEA-S levels were positively correlated with leg extensor power (peak torque/body weight) in female athletes but not in males athletes (Aizawa et al. 2006)

Hormonal Responses to Resistance Exercise During Different Menstrual Cycle Phases

It has been suggested that many factors (e.g., sex, age, fitness level, nutritional status, exercise variables) influence hormonal responses to resistance exercise (Consitt et al. 2002; Kraemer and Ratamess 2005). When interpreting a woman's hormonal response to training, the potential effects of the menstrual cycle must be considered, because the hormonal responses to exercise are modified by the ovarian systems in women. Logically then understanding the potential effects of the menstrual cycle is vital for female athletes and their coaches.

Previous studies have reported that GH concentrations are higher in the peri-ovulatory phase than in the early-follicular phase (Faria et al. 1992; Ovesen et al. 1998). Kraemer et al. (1995) demonstrated that low-volume resistance exercise induces larger increases in estradiol, GH, and androstenedione in the mid- luteal phase than in the early- follicular phase, although they did not compare the responses within the same individuals. Nakamura et al. (2011) have investigated the effect of the menstrual cycle on ovarian and anabolic hormonal responses to acute resistance exercise in young women. Specifically in this work, eight eumenorrheic women and eight women with menstrual disorders including oligomenorrhea and amenorrhea were enrolled in the study. All subjects were recreationally active young women (18–30 years of age) and were not using oral contraceptives. The eumenorrheic women participated in two series of exercise sessions, one in the early-follicular phase (days 4–7 of the menstrual cycle) and one in the mid-luteal phase (7–10 days after ovulation). The women with menstrual disorders participated in a series of exercise session on an arbitrary day. All subjects performed three sets each of resistance exercises (i.e., lat pull-downs, leg curls, bench presses, leg extensions, and squats) at 75–80 % of the one-repetition maximum with 1 min of rest between sets. Blood samples were obtained before exercise and immediately, 30 and 60 min after exercise. The effects

of the menstrual cycle phase in eumenorrheic women are described in this section of the chapter, and the effects of menstrual status in women with menstrual disorders are described in the next section.

In the mid- luteal phase, serum estradiol and progesterone increased after exercise, but they did not change after exercise in the early- follicular phase (Fig. 10.4). Serum GH increased after exercise in both the early-follicular and mid-luteal phases. On the other hand, total secretion (area under the curve) of GH was increased significantly after exercise in the mid- luteal phase, but not in the early- follicular phase (Fig.10.5). Hornum et al. (1997) also demonstrated that total secretion of GH after a high-intensity cycling exercise was greater in the peri-ovulatory phase (estradiol levels were high) than in the follicular phase (estradiol levels were low). These findings indicate that menstrual cycle variations in circulating estradiol levels may affect exercise-induced GH secretion. Testosterone and IGF- I concentrations showed no significant increase in response to the resistance exercise protocols during either menstrual cycle phases (Fig. 10.5). These findings are consistent with previous studies (Consitt et al. 2001; Copeland et al. 2002; Häkkinen and Pakarinen 1995; Häkkinen et al. 2000; Kraemer et al. 1993). DHEA-S concentrations showed no significant increase immediately after resistance exercise in either menstrual cycle phases; however, there was a significant increase in DHEA- S 60 min after exercise in the early-follicular phase. Cortisol, a catabolic hormone, also did not increase after resistance exercise in either menstrual cycle phases (Fig. 10.5). Likewise, Häkkinen and Pakarinen (1995) reported no changes in cortisol levels after acute resistance exercise in women. Kraemer et al. (1998), however, found significant elevations in cortisol after acute resistance exercise in men and women. It is possible that these differences in the response of cortisol to exercise are affected by the training status of the subjects (Kraemer et al. 1998), daily hormonal fluctuation, or both factors interacting (Hackney and Viru 2008).

The findings from these studies suggest that anabolic hormone responses to resistance exercise (e.g., levels of ovarian hormones, GH) may be influenced by menstrual cycle phase and the hormonal changes associated with the phases.

Hormonal Responses to Resistance Exercise with Different Menstrual Cycle Status

Menstrual disorders such as oligomenorrhea and amenorrhea are functional disorders characterized by altered gonadotropin-releasing hormone pulsatility, loss of pulsatile gonadotropin secretion (FSH and LH), and, in turn, altered ovarian steroidogenesis (Meczekalski et al. 2000). These reproductive hormonal changes have the potential to impact of a variety of other hormones (McMurray and Hackney 2000). For example, Waters et al. (2001) reported that amenorrheic athletes had significantly lower (four to fivefold) GH responses to 50 min of submaximal exercise (70% maximal oxygen consumption) compared with eumenorrheic athletes.

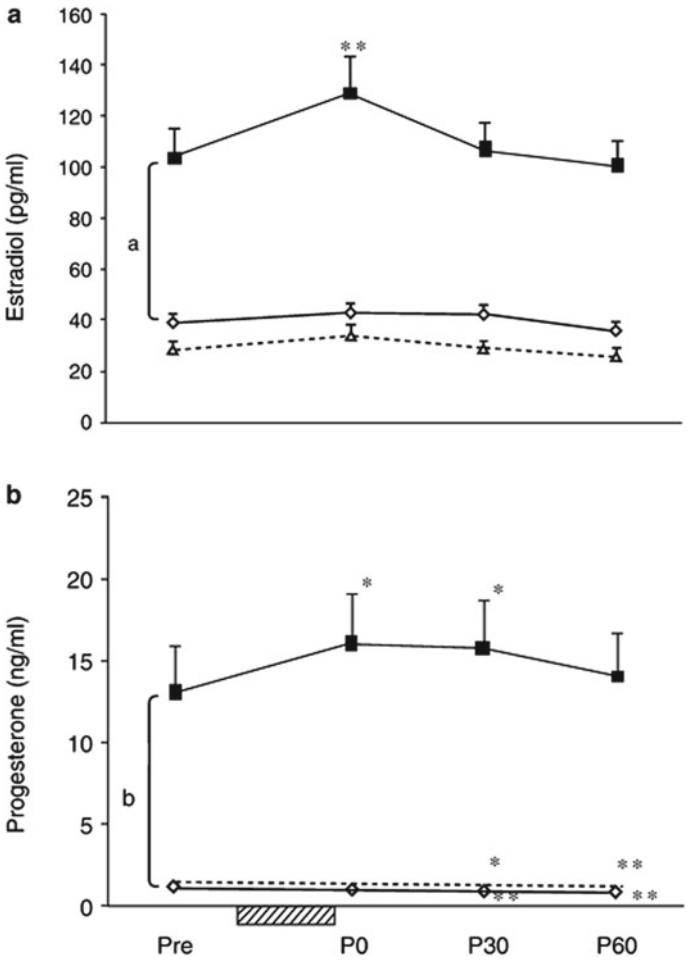

Fig. 10.4 Concentrations of ovarian hormones (estradiol and progesterone) before (Pre) and after resistance exercise: immediately after the end of the resistance exercise: (P0), 30 min after exercise. (P30) and 60 min after exercise (P60). In the mid- luteal phase, these hormones increased after exercise, but they did not change in the early-follicular phase and in women with menstrual disorders. Early-follicular phase:*diamond*, mid-luteal phase:*filled square*, women with menstrual disturbance:*triangle.* Data are expressed as means ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ versus Pre.$^{a}P < 0.001$,$^{b}P < 0.01$ between Pre in the early-follicular phase and Pre in the mid-luteal phase. The *hatched box* represents resistance exercise (Nakamura et al. 2011)

Yahiro et al. (1987) reported that serum testosterone levels increased in eumenorrheic runners, but not in amenorrheic runners, after acute treadmill exercise.

As mentioned in the preceding section, Nakamura et al. (2011) investigated changes in ovarian and anabolic hormones after acute resistance exercise in women with menstrual disorders including oligomenorrhea and amenorrhea. Serum estradiol and progesterone concentrations in these women with menstrual disorders did not

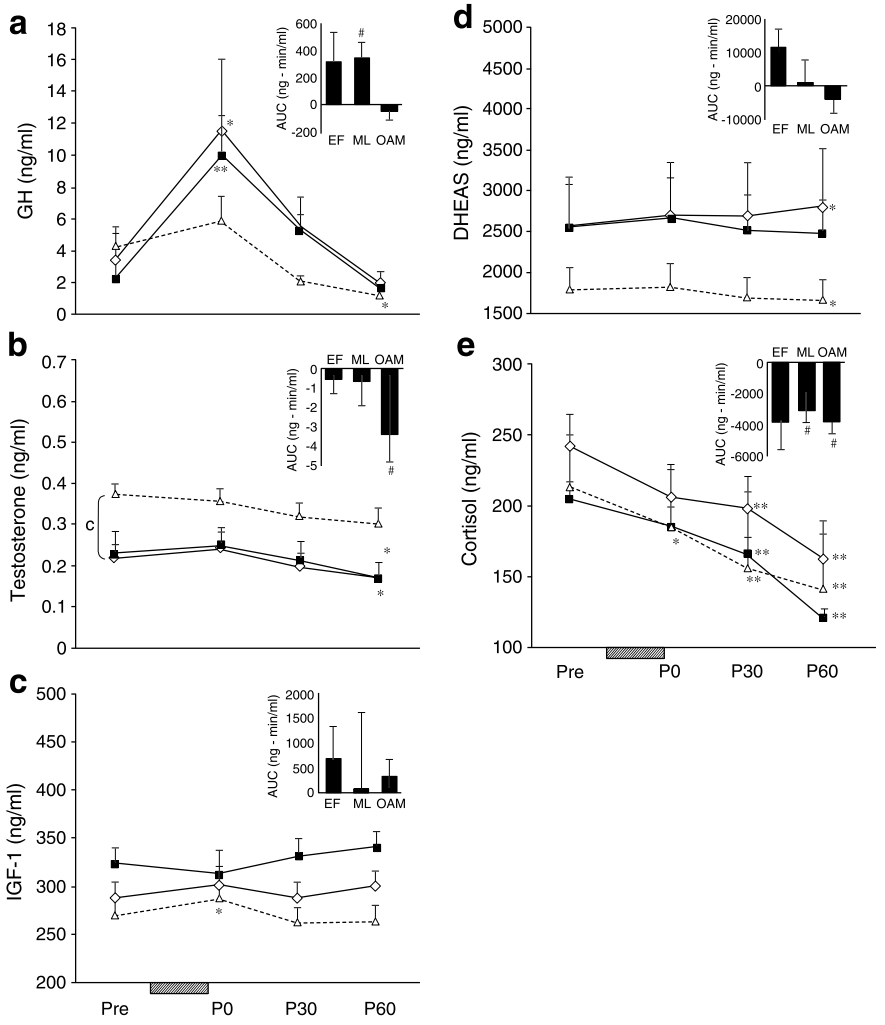

Fig. 10.5 Concentrations of anabolic hormones (GH, IGF-I, testosterone, and DHEA-S) and cortisol before (Pre) and after resistance exercise (immediately after the end of the resistance exercise (P0), 30 min after exercise (P30), and 60 min after exercise (P60). Early-follicular (EF): *diamond*, mid-luteal phase (ML): filled square, women with menstrual disturbance (OAM): triangle. Data in the *small upper panels* represent the area under the curve (AUC). Data are expressed as means ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ versus Pre.$^{c}P < 0.01$ between Pre in the early-follicular (EF) phase and Pre in women with menstrual disorders (MD). The *hatched box* represents resistance exercise.$^{\#}P < 0.05$ compared with zero (Nakamura et al. 2011)

increase after exercise (Fig. 10.4). Immediately after the end of resistance exercise, GH concentrations in eumenorrheic women increased significantly from pre-exercise levels, but this difference was not observed in women with menstrual disorders. However, a small, but statistically significantly higher increase in IGF- I in response to resistance exercise, was observed immediately after exercise in women with menstrual disorders. Testosterone and DHEA-S concentrations showed no significant increase in response to the resistance exercise protocols either, regardless of menstrual cycle status. However, total secretion (area under the curve) of testosterone was significantly lower in women with menstrual disorders. In addition, DHEA- S increased significantly 60 min after exercise in the early-follicular phase in eumenorrheic women, but it was decreased significantly in women with menstrual disorders. And finally no significant differences in cortisol levels were found within any menstrual cycle status (Fig. 10.5).

The neuroendocrine mechanisms of exercise-induced GH release are not fully understood; however, GH secretion is controlled by hypothalamic hormones. These hormones include GH-releasing hormone, which exerts positive feedback, and somatostatin, which exerts negative feedback, on GH secretion (Giustina and Veldhuis 1998; Jenkins 1999). It is possible that the attenuated GH secretion of these women in response to acute resistance exercise is related to a disturbance in hypothalamic–pituitary function, but the mechanism of these events is not well understood at this time.

Findings from previous studies have suggested that estradiol stimulates GH secretion because estrogen replacement therapy increases GH secretion in postmenopausal women and prepubertal girls with Turner syndrome (Kanaley et al. 2005; Mauras et al. 1990). In addition, Kraemer et al. (1998) and Kanaley et al. (2005) demonstrated that GH responses to endurance exercise are higher in postmenopausal women receiving hormone replacement therapy than those who were not. This effect of estrogen may be due to a combination of withdrawal of somatostatin's (also known as growth hormone-inhibiting hormone [GHIH]) inhibitory tone, amplification of endogenous GH-releasing hormone release or its pituitary actions, and recruitment of other mechanisms that stimulate GH release (Giustina and Veldhuis 1998).

Specific endocrine differences between eumenorrheic women and women with menstrual disorders include cyclic fluctuations of estrogen and progesterone which are controlled by the hypothalamic–pituitary–gonadal axis (see Chap. 1). Women with menstrual disorders can be estrogen deficient on a long-term basis. Insufficient estrogen and progesterone feedback disturbs hypothalamic–pituitary axis responses (De Crée 1998). Thus, differences in ovarian hormone secretion status, that is, differences in hypothalamic–pituitary function between women with menstrual disorders and eumenorrheic women, may influence the GH response to acute resistance exercise. However, there appears to be no available information on anabolic hormonal responses to resistance exercise in women with menstrual disorders. There is also little information available on acute responses of DHEA-S to resistance exercise in such women. Riechman et al. (2004) reported that acute resistance exercise increases blood DHEA-S levels. Exercise-induced increases in DHEA- S concentrations have been attributed to an increased rate of secretion from the adrenal cortex in response to

ACTH stimulation (Johnson et al. 1997). Meczekalski et al. (2000) investigated the hypothalamic–pituitary–adrenal axis in women with hypothalamic amenorrhea and reported that the ACTH response to corticotrophin-releasing hormone was significantly lower in amenorrheic women compared with healthy control women. Nakamura et al. (2011) reported DHEA-S levels were not significantly higher immediately after acute resistance exercise regardless of menstrual cycle status. Enea et al. (2009) reported short-term exercise does not induce increased adrenal steroid production in response to ACTH secretion. It is possible that a higher-volume resistance exercise program for a longer period could induce an increase in DHEA-S.

In summary, women with certain forms of menstrual disorders, associated with low estradiol and progesterone levels, appear to have an attenuated anabolic hormonal response to acute resistance exercise. However, there is extremely limited evidence on this topic and more research is needed.

Resistance Exercise-Induced Muscle Damage and Recovery During Different Menstrual Cycle Phases

As estrogen receptors have been localized to skeletal muscle tissue, variations in hormonal concentrations due to the menstrual cycle may influence resistance training outcomes. Haines et al. (2018) compared estrogen receptor activation and subsequent effects on myogenic-related genes in response to eccentric exercise in the mid-follicular phase (MF) and mid-luteal phase (ML). Skeletal muscle estradiol levels were not significantly impacted by either menstrual phase despite greater levels of serum estradiol during ML. This is consistent with data from rats showing no significant change in muscle estradiol levels following treadmill exercise at 30 m/min for 30 min (Aizawa et al. 2008). However, both skeletal muscle estrogen receptor-α (ER-α) mRNA and protein were significantly increased during MF. ER activation and subsequent expression of Myo-D mRNA occurred independent of the circulating estradiol levels. Furthermore, skeletal muscle cyclin D1 mRNA expression was increased by eccentric exercise to a much greater extent during MF and may play a role in ER activation during periods of lower circulating estradiol. These results suggests that greater potential for recovery and repair in MF following eccentric exercise.

It has been suggested that endogenous estrogen may be protective against exercise-induced muscle damage, and if so, it could be speculated that endogenous estrogen may play a role in enhancing recovery from exercise-induced muscle damage (Thompson et al. 2020). Despite the problem of combining oral contraceptives and menstrual cycle participants into one group, the results of Markofski et al. (2014) examining the effect of menstrual cycle phase on markers of exercise-induced muscle damage following acute high-volume eccentric exercise are very interesting. After high-volume eccentric exercise, creatine kinase (CK) was significantly lower and strength recovery was better at 96 hours post-session in the follicular phase than in the luteal phase (Fig. 10.6). Blood estrogen levels were significantly higher in the

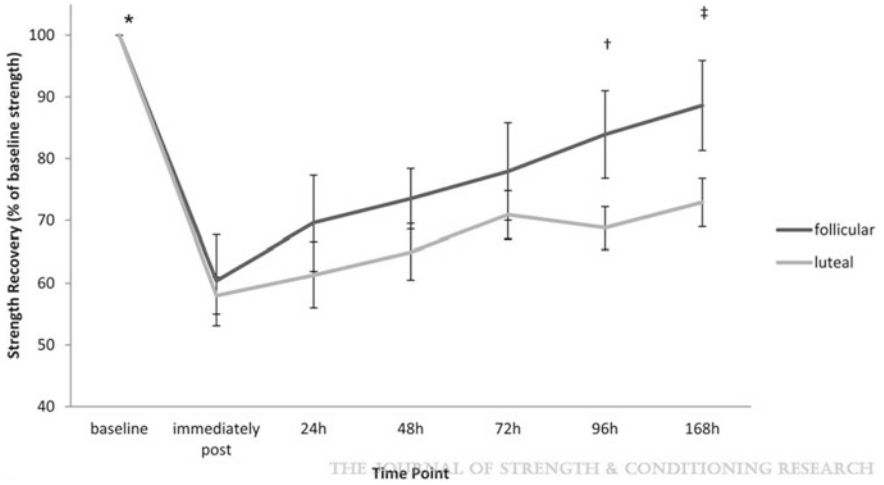

Fig. 10.6 Strength recovery over the period of 1 week after eccentric-biased extension exercises performed during the follicular and luteal phases (Markofski et al. 2014). A significant ($p < 0.0001$) main effect was present for time. * Strength was significantly higher than baseline at all other time points. † Follicular phase significantly ($p = 0.009$) higher strength than luteal phase. ‡ Follicular phase significantly ($p = 0.001$) higher strength than luteal phase

luteal phase than in the follicular phase; however, the effects of estrogen in skeletal muscle tissue are very complex. To understand the effects of estrogen on muscle damage, it will be necessary to consider the interactions between estrogen and ER and estrogen and progesterone.

Menstrual Cycle and Resistance Training Program

As discussed in this chapter, the responses of sex hormones and anabolic hormones to acute resistance exercise, as well as muscle damage and recovery are affected by hormonal fluctuations during the menstrual cycle, suggesting that menstrual cycle may influence exercise training-induced skeletal muscular adaptation. Thus, it would be possible that training programs for eumenorrheic women could be timed in accordance with the menstrual cycle for enhancing resistance training outcomes.

Recent studies have begun investigating the trainability of muscle strength with menstrual cycle-triggered training. Sung et al. (2014) compared the effects of two different menstrual cycle-based leg strength training programs (follicular phase-based training versus luteal phase-based training) on muscle volume and microscopic morphological parameters. The increase in maximum isometric force with follicular phase-based training was higher than with luteal phase-based training (Fig. 10.7), which was consistent with earlier findings of Reis et al. (1995). Follicular phase-based training was also associated with a higher increase in muscle diameter than

luteal phase-based training. Moreover, they found significant increases in fiber type II diameter and cell nuclei-to-fiber ratio after follicular phase-based training but not luteal phase-based training.

In contrast, Sakamaki-Sunaga et al. (2015) reported no major differences among different training frequencies for arm curls during menstrual cycle phases with regard to muscle hypertrophy and strength, but this study did not use hormone testing to confirm menstrual cycle phase. Another study investigated the effects of menstrual and oral contraceptive cycle on a high-frequency periodized leg resistance training in trained women (Wikström-Frisén et al. 2017). Significant increase in squat and countermovement jump, and peak torque values in hamstrings for follicular/early oral contraceptive cycle phase-based training group were observed, and significant increase in lean body mass of the legs. These results suggest that follicular phase-based training may be superior to both regular training and luteal phase-based training for developing strength and muscle mass in eumenorrheic women (Thompson et al. 2020).

On the other hand, many reproductive-aged women, including athletes, experience menstrual irregularities and amenorrhea. In addition, the use of oral contraceptives (OC) is becoming more common among both the general population and athletes. It is notable that women with menstrual disorders characterized by low estradiol and progesterone serum concentrations show an attenuated GH response to acute resistance exercise (Nakamura et al. 2011). Women who take OC also have significantly lower levels of circulating estrogen compared to eumenorrheic women throughout

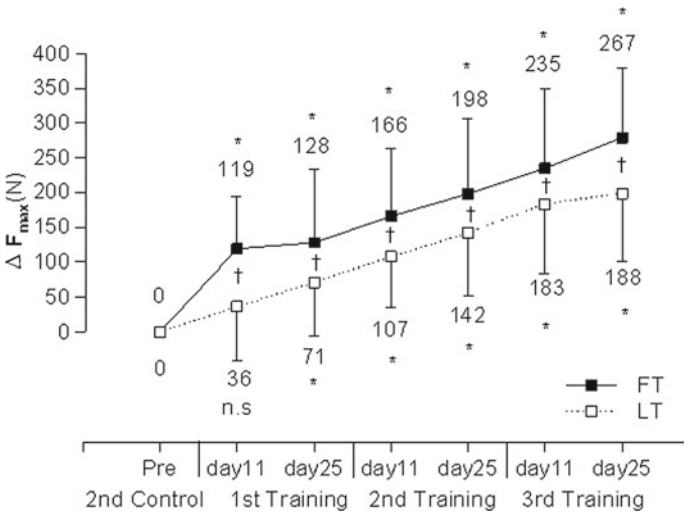

Fig. 10.7 Increase in the strength of maximum isometric knee extension (F_{max}) after two different menstrual cycle-based leg strength training programs were compared to each other (follicular phase-based- [FT] versus luteal phase-based training [LT]) (Sung et al. 2014). Pre: before training, control: control cycle, training: training cycle, day 11: analysis around day 11; day 25: analysis around day 25; *$P < 0.05$ compared to pre-training, †$P < 0.05$ FT versus LT

the menstrual cycle. Several studies reported a higher level of post-exercise CK in OC group than eumenorrheic group (Hicks et al. 2017; Minahan et al. 2015; Roth et al. 2001). These appear that endogenous estrogen may be protective against exercise-induced muscle damage, suggesting that recovery from exercise-induced muscle damage may be different between OC users and eumenorrheic women (Thompson et al. 2020). This may have implications for long-term adaptations to resistance training, but at this time there is no data available to clearly demonstrate these. Further studies are needed to demonstrate the short-term and long-term effects of changes in hormonal responses to resistance exercise on skeletal muscle by menstrual cycle status and OC use.

Conclusion

The fluctuations of sex steroid hormones have the potential influence muscle strength performance and response to resistance exercise in women. However, based on a number of studies investigating the effects of the menstrual cycle on muscle strength performance, it can be concluded there is little or perhaps no difference in muscle strength at various times during the menstrual cycle. On the other hand, though, there is very limited data about responses to resistance exercise in women as related to their sex hormone levels. A few studies do indicate that menstrual cycle phase and status variations affect exercise-induced secretion of some hormones and muscle damage and recovery. Therefore, there is a possibility of an effect on trainability of muscle strength to resistance training programs. But much more research work is needed on these topics. In addition, exercise performance and physiological response to exercise, resistance and otherwise, are probably very individual specific and influenced by many factors, and more research is also needed taking into account these individual specific factors.

References

Aizawa K, Akimoto T, Inoue H, et al. Resting serum DHEAS level increases after 8-week resistance training among young. Eur J Appl Physiol. 2003;90:575–80.

Aizawa K, Hayashi K, Mesaki N. Relationship of muscle strength with dehydroepiandrosterone sulfate (DHEAS), testosterone and insulin-like growth factor-I in male and female athletes. Adv Exerc Sports Physiol. 2006;12:29–34.

Aizawa K, Iemitsu M, Otsuki T, Maeda S, Miyauchi T, Mesaki N. Sex differences in steroidogenesis in skeletal muscle following a single bout of exercise in rats. J Appl Physiol. 2008;104(1):67–74.https://doi.org/10.1152/japplphysiol.00558.2007.

Bambaeichi E, Reilly T, Cable NT, et al. The isolated and combined effects of menstrual cycle phase and time-of-day on muscle strength of eumenorrheic females. Chronobiol Int. 2004;21:645–60.

Baulieu EE. Dehydroepiandrosterone (DHEA): a fountain of youth? J Clin Endocrinol Metab. 1996;81:3147–51.

Consitt LA, Copeland JL, Tremblay MS. Hormone responses to resistance vs. endurance exercise in premenopausal females. Can J Appl Physiol. 2001;26:574–87.
Consitt LA, Copeland JL, Tremblay MS. Endogenous anabolic hormone responses to endurance versus resistance exercise and training in women. Sports Med. 2002;32:1–22.
Constantini NW, Dubnov G, Lebrun CM. The menstrual cycle and sport performance. Clin Sports Med. 2005;24:e51–82.
Copeland JL, Consitt LA, Tremblay MS. Hormonal responses to endurance and resistance exercise in females aged 19–69 years. J Gerontol A Biol Sci Med Sci. 2002;57:B158–65.
De Crée C. Sex steroid metabolism and menstrual irregularities in the exercising female. A review. Sports Med. 1998;25:369–406.
Elliott KJ, Cable NT, Reilly T, et al. Effect of menstrual cycle phase on the concentration of bioavailable 17-beta oestradiol and testosterone and muscle strength. Clin Sci (Lond). 2003;105:663–9.
Enea C, Boisseau N, Ottavy M, et al. Effects of menstrual cycle, oral contraception, and training on exercise-induced changes in circulating DHEA-sulphate and testosterone in young women. Eur J Appl Physiol. 2009;106:365–73.https://doi.org/10.1007/s00421-009-1017-6.
Enea C, Boisseau N, Fargeas-Gluck MA. Circulating androgens in women: exercise-induced changes. Sports Med. 2011;41:1–15.https://doi.org/10.2165/11536920-000000000-00000.
Enns DL, Tiidus PM. The influence of estrogen on skeletal muscle: sex matters. Sports Med. 2010;40:41–58.https://doi.org/10.2165/11319760-000000000-00000.
Faria AC, Bekenstein LW, Booth Jr RA, et al. Pulsatile growth hormone release in normal women during the menstrual cycle. Clin Endocrinol (Oxf). 1992;36:591–6.
Fleck SJ, Kraemer WJ. Designing resistance training programs. 4th ed. Champaign, IL: Human Kinetics; 2014.
Fridén C, Hirschberg AL, Saartok T. Muscle strength and endurance do not significantly vary across 3 phases of the menstrual cycle in moderately active premenopausal women. Clin J Sport Med. 2003;13:238–41.
Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19:717–97.
Hackney AC, Viru A. Research methodology: endocrinologic measurements in exercise science and sports medicine. J Athl Train. 2008;43:631–9.
Häkkinen K, Pakarinen A. Acute hormonal responses to heavy resistance exercise in men and women at different ages. Int J Sports Med. 1995;16:507–13.
Häkkinen K, Pakarinen A, Kraemer WJ, et al. Basal concentrations and acute responses of serum hormones and strength development during heavy resistance training in middle-aged and elderly men and women. J Gerontol A Biol Sci Med Sci. 2000;55:B95–105.
Hansen M, Kjaer M. Influence of sex and estrogen on musculotendinous protein turnover at rest and after exercise. Exerc Sport Sci Rev. 2014;42:183–92.https://doi.org/10.1249/JES.0000000000000026.
Haines M, McKinley-Barnard SK, Andre TL, et al. Skeletal muscle estrogen receptor activation in response to eccentric exercise up-regulates myogenic-related gene expression independent of differing serum estradiol levels occurring during the human menstrual cycle. J Sports Sci Med. 2018;17:31-39.
Hicks KM, Onambélé-Pearson G, Winwood K, Morse CI. Oral contraceptive pill use and the susceptibility to markers of exercise-induced muscle damage. Eur J Appl Phys 2017;117(7):1393-1402.https://doi.org/10.1007/s00421-017-3629-6.
Hornum M, Cooper DM, Brasel JA, et al. Exercise-induced changes in circulating growth factors with cyclic variation in plasma estradiol in women. J Appl Physiol. 1997;82:1946–51.
Jabbour HN, Kelly RW, Fraser HM, et al. Endocrine regulation of menstruation. Endocr Rev. 2006;27:17–46.
Janse de Jonge XA. Effects of the menstrual cycle on exercise performance. Sports Med. 2003;33:833–51.
Jenkins PJ. Growth hormone and exercise. Clin Endocrinol (Oxf). 1999;50:683–9.

Johnson LG, Kraemer RR, Haltom R, et al. Effects of estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol responses to exercise in postmenopausal women. Fertil Steril. 1997;68:836–43.
Kahn SM, Hryb DJ, Nakhla AM, et al. Sex hormone-binding globulin is synthesized in target cells. J Endocrinol. 2002;175:113–20.
Kanaley JA, Giannopoulou I, Collier S, et al. Hormone-replacement therapy use, but not race, impacts the resting and exercise-induced GH response in postmenopausal women. Eur J Endocrinol. 2005;153:527–33.
Koziris LP, Hickson RC, Chatterton Jr RT, et al. Serum levels of total and free IGF-I and IGFBP-3 are increased and maintained in long-term training. J Appl Physiol. 1999;86:1436–42.
Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35:339–61.
Kraemer WJ, Gordon SE, Fleck SJ, et al. Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. Int J Sports Med. 1991;12:228–35.
Kraemer WJ, Fleck SJ, Dziados JE, et al. Changes in hormonal concentrations after different heavy-resistance exercise protocols in women. J Appl Physiol. 1993;75:594–604.
Kraemer RR, Heleniak RJ, Tryniecki JL, et al. Follicular and luteal phase hormonal responses to low-volume resistive exercise. Med Sci Sports Exerc. 1995;27:809–17.
Kraemer RR, Johnson LG, Haltom R, et al. Effects of hormone replacement on growth hormone and prolactin exercise responses in postmenopausal women. J Appl Physiol. 1998;84:703–8.
Labrie F, Belanger A, Cusan L, et al. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997;82:2396–402.
Lane AR, O'Leary CB, Hackney AC. Menstrual cycle phase effects free testosterone responses to prolonged aerobic exercise. Acta Physiol Hung. 2015;102(3):336–41.
Lebrun CM. The effect of the phase of the menstrual cycle and the birth control pill on athletic performance. Clin Sports Med. 1994;13:419–41.
Markofski MM, Braun William A. Influence of menstrual cycle on indices of contraction-induced muscle damage. J Strength Conditioning Res. 2014;28(9):2649–2656.https://doi.org/10.1519/JSC.0000000000000429.
Marx JO, Ratamess NA, Nindl BC, et al. Low-volume circuit versus high-volume periodized resistance training in women. Med Sci Sports Exerc. 2001;33:635–43.
Mauras N, Rogol AD, Veldhuis JD. Increased hGH production rate after low-dose estrogen therapy in prepubertal girls with Turner's syndrome. Pediatr Res. 1990;28:626–30.
McMurray RG, Hackney AC. Endocrine responses to exercise and training. In: Garrett W, Kirkendall DT, editors. Exercise and sport science. Philadelphia, PA: Lippincott, Williams & Wilkins; 2000. p. 135–61.
Meczekalski B, Tonetti A, Monteleone P, et al. Hypothalamic amenorrhea with normal body weight: ACTH, allopregnanolone and cortisol responses to corticotropin-releasing hormone test. Eur J Endocrinol. 2000;142:280–5.
Minahan C, Joyce S, Bulmer AC, Cronin N, Sabapathy S. The influence of estradiol on muscle damage and leg strength after intense eccentric exercise. Eur J Appl Phys. 2015;115(7):1493–1500.https://doi.org/10.1007/s00421-015-3133-9.
Nakamura Y, Aizawa K, Imai T, et al. Hormonal responses to resistance exercise during different menstrual cycle states. Med Sci Sports Exerc. 2011;43:967–73.https://doi.org/10.1249/MSS.0b013e3182019774.
Oosthuyse T, Bosch AN. The effect of the menstrual cycle on exercise metabolism: implications for exercise performance in eumenorrhoeic women. Sports Med. 2010;40:207–27.https://doi.org/10.2165/11317090-000000000-00000.
Ovesen P, Vahl N, Fisker S, et al. Increased pulsatile, but not basal, growth hormone secretion rates and plasma insulin-like growth factor I levels during the periovulatory interval in normal women. J Clin Endocrinol Metab. 1998;83:1662–7.

Reis E, Frick U, Schmidtbleicher D. Frequency variations of strength training sessions triggered by the phases of the menstrual cycle. Int J Sports Med. 1995;16:545–50.

Riechman SE, Fabian TJ, Kroboth PD, et al. Steroid sulfatase gene variation and DHEA responsiveness to resistance exercise in MERET. Physiol Genomics. 2004;17:300–6.

Roth SM, Gajdosik R, Ruby BC, Effects of circulating estradiol on exercise-induced creatine kinase activity. J Exerc Physiol 2001;4:10–7.

Sakamaki-Sunaga M, Min S, Kamemoto K, et al. Effects of menstrual phase-dependent resistance training frequency on muscular hypertrophy and strength. J Strength Cond Res. 2015;30(6):1727–34.

Staron RS, Karapondo DL, Kraemer WJ, et al. Skeletal muscle adaptations during early phase of heavy-resistance training in men and women. J Appl Physiol. 1994;76:1247–55.

Sung E, Han A, Hinrichs T, et al. Effects of follicular versus luteal phase-based strength training in young women. SpringerPlus. 2014;3:668.https://doi.org/10.1186/2193-1801-3-668.

Thompson B, Almarjawi A, Sculley D, Janse de Jonge X. The effect of the menstrual cycle and oral contraceptives on acute responses and chronic adaptations to resistance training: a systematic review of the literature. Sports Med. 2020;50(1):171–85.https://doi.org/10.1007/s40279-019-01219-1.

Vingren JL, Kraemer WJ, Ratamess NA, et al. Testosterone physiology in resistance exercise and training: the up-stream regulatory elements. Sports Med. 2010;40:1037–53.https://doi.org/10.2165/11536910000000000-00000.

Waters DL, Qualls CR, Dorin R, et al. Increased pulsatility, process irregularity, and nocturnal trough concentrations of growth hormone in amenorrheic compared to eumenorrheic athletes. J Clin Endocrinol Metab. 2001;86:1013–9.

Wikström-Frisén L, Boraxbekk CJ, Henriksson-Larsén K. Effects on power strength and lean body mass of menstrual/oral contraceptive cycle based resistance training. J Sports Med Phys Fitness. 2017;57(1–2).https://doi.org/10.23736/S0022-4707.16.05848-5.

Yahiro J, Glass AR, Fears WB, et al. Exaggerated gonadotropin response to luteinizing hormone-releasing hormone in amenorrheic runners. Am J Obstet Gynecol. 1987;156:586–91.

Chapter 11
The Effect of the Menstrual Cycle on Exercise and Sports Performance

Kirsty M. Hicks, Kelly McNulty, and Paul Ansdell

Abbreviations

FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
MVC	Maximal voluntary contraction
RER	Respiratory exchange ratio
$\dot{V}E$	Ventilatory rate
$\dot{V}O_2$	Volume of oxygen consumption
$\dot{V}CO_2$	Volume of carbon dioxide produced
$\dot{V}O_{2peak}$	Peak oxygen consumption

Introduction

Women's participation in sport and exercise is increasing, with full gender equivalence expected to be achieved for the first time in the history of the Olympic Games in Paris in 2024. Therefore, for women athletes and those working with them, it is important that any potential modulations, either positive or negative, in performance, training, and adaptation can be understood and optimized. Research-informed exercise prescription aims to achieve optimal performance for an individual or group of athletes, based on available evidence. However, despite the surge in women's sport and exercise participation and subsequently, financial investment, media coverage, and sponsorship deals, women remain underrepresented in the sport and exercise science literature (Cowley et al. 2021). Consequently, it is not uncommon for the

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understanding and prescription of exercise to be based on data from men, which is concerning given the known differences between men and women and their physiological responses to exercise (Ansdell et al. 2020). Indeed, the most notable biological sex difference is the menstrual cycle; during which, there are significant fluctuations in endogenous sex hormones; namely estrogen and progesterone. As this chapter outlines, understanding the effects of variable concentrations of estrogen and progesterone is important, as they potentially exert an influence on the underpinning components of exercise performance (i.e., cardiovascular function, respiratory function, substrate metabolism, and neuro-muscular function). Performance can be quantified in various ways; however, for the purpose of this chapter, exercise performance was defined as force/torque production, power output, time to exhaustion, and time to completion.

In light of the above, the specific aims of this chapter are as follows:

(1) to describe the fluctuations in sex hormones that underpin the menstrual cycle;
(2) to discuss physiological mechanisms that might affect exercise performance across the menstrual cycle;
(3) to summarize the literature regarding the impact of the menstrual cycle on exercise performance;
(4) to provide practical implications and future recommendations for women athletes, and those working with them.

The Menstrual Cycle

A menstrual cycle lasts between 21 and 35 days, with an average cycle length commonly being reported as 28 days. The primary purpose of the menstrual cycle is to prepare a woman's body for reproduction, which is broadly achieved through naturally occurring changes in circulating endogenous hormones and structural changes to the endometrial lining. The menstrual cycle is regulated by hormones released by the hypothalamus (gonadotropin-releasing hormone, GnRH), pituitary gland (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and the ovaries (estrogen and progesterone). Often, the concentrations and/or ratio of these hormones are used to separate the menstrual cycle into specific phases. Due to complexities within applied practice and research, for simplicity the menstrual cycle is often divided into two phases: (1) the follicular phase (from day 1 of menses to ovulation) and (2) the luteal phase (post-ovulation to the start of the following menses). However, this two-phase division is an oversimplification, as it does not capture all time points whereby circulating concentrations of estrogen and progesterone, and the ratios between the two, vary substantially. To achieve this, the menstrual cycle can more accurately be separated into four phases (Elliott-Sale et al. 2021): (1) the early-follicular phase, the onset of bleeding to day five, during which estrogen and progesterone are low; (2) the late-follicular phase, < 26 h pre-ovulation, whereby estrogen peaks but progesterone remains low (< 6.4 nmol·L^{-1}); (3) ovulation, 24–36 h after a positive ovulation test, when estrogen is high and progesterone is still low (< 6.4 nmol·L^{-1}); and

(4) the mid-luteal phase, occurring seven to nine days after a positive ovulation test, during which both estrogen and progesterone are high. Importantly, these time points allow for three key hormone ratios (low:low, high:low, and high:high) of estrogen and progesterone to be investigated. To achieve a consensus on the taxonomy used to describe these time points, and the criteria for each menstrual cycle phase, the interested reader is directed to the work of Elliott-Sale et al. (2021).

It is important to note that the menstrual cycle can be subject to internal (i.e., anovulatory, oligomenorrhea, amenorrhea) and external (i.e., hormonal contraceptive use) modulations, adding further complexity to the support provided to, and research conducted on, women athletes. Internal permutations could be indicative of menstrual dysfunction and should be discussed with appropriate medical professionals (Davison et al. (2022). External manipulation, however, is common, with almost half of the women athletic population studied using hormonal contraceptives (Martin et al. 2018). Hormonal contraceptives downregulate fluctuations in endogenous sex hormones resulting in a significantly different hormonal profile compared to that of the naturally occurring menstrual cycle. Therefore, given the varying hormonal statuses of women athletes, it is pertinent to understand how both internal and external modulations of the menstrual cycle affect exercise performance. While Elliott-Sale and Hicks (2018) discuss external modulations of the menstrual cycle and exercise performance, the current chapter focuses on the internal modulations of endogenous hormones and exercise performance.

The Menstrual Cycle and Physiological Function

Sex hormone receptors mediate the biological and physiological processes of estrogen and progesterone. In addition to the reproductive system, estrogen (ERα and ERβ) and progesterone (hPR-A and hPR-B) receptors are expressed within a multitude of tissues and organs, including musculoskeletal tissues such as bone, ligaments, and tendons, as well as the cardiovascular, respiratory, and central nervous systems. The expression of sex hormone receptors is of importance as the functions of the aforementioned physiological systems are fundamental to exercise performance. Constantini et al. (2005) compiled a network of components of exercise performance, where the effect of the menstrual cycle might exert its influence; this interaction commonly provides the rationale for subsequent implications on strength, aerobic and anaerobic performance. However, in addition to physiology, exercise performance is a multifaceted process (e.g., motivation, competition, etc.) with many external and internal nuances; thus, it is not surprising that the research investigating the effects of the menstrual cycle on exercise performance remains equivocal. This section discusses the proposed influence of the menstrual cycle on key physiological systems involved in exercise performance.

Mechanisms Potentially Altering Strength Performance Across the Menstrual Cycle

Force generation, commonly referred to as strength, is not only a determinant of sporting performance, but is altered by exercise in the form of fatigue, muscle damage, and recovery. The ability to produce force is a sequence of chemical and protein interactions from the propagation of nervous system impulses along the motor pathway to the contractile proteins within the skeletal muscle (Dulhunty 2006). As detailed below, estrogen and progesterone exert their influences at several segments of the motor pathway, making it difficult to isolate the individual mechanisms underpinning potential influences on strength.

Beginning within the motor cortex, estrogen and progesterone are both neurosteroids with contrasting impacts; estrogen increases cortical excitability (Smith et al. 1999), whereaBembens progesterone enhances cortical inhibition (Smith et al. 1999). More recently, Ansdell et al. (2019) demonstrated the link between hormone-induced changes in excitability and voluntary activation of the knee extensors. Specifically, around ovulation (day 14 of the menstrual cycle) the neuro-excitatory effects of high-estrogen concentrations were observed alongside an increased voluntary activation of the knee extensors. Furthermore, during the mid-luteal phase, cortical inhibition was increased, alongside a concomitant decrease in voluntary activation, highlighting the neuro-inhibitory effect of progesterone. Thus, the hormonal influence on central nervous system function might influence muscle function. At the other end of the motor pathway, previous work has proposed that changes in motor unit firing rates across the menstrual cycle might be a potential mechanism which underpins changes in maximal strength (Tenan et al. 2016). Tenan et al. (2013) reported greater motor unit discharge rates at recruitment (~10%) in the latter half of the menstrual cycle, which taken together with the findings of Ansdell et al. (2019) could suggest that the changes in pre-synaptic properties (i.e., cortical excitability) modulate post-synaptic output (i.e., motor unit discharge rate) within the motor pathway.

In addition to influences within the central nervous system, estrogen has been reported to improve strength due to its effects on the binding of calcium and troponin C and contractile proteins, such as myosin. Myosin consists of two heavy chains and two pairs of light chains. These pairs are known as the essential light chain and the regulatory light chain and are both pertinent to muscle contractions; the former is considered to act as a structural stabilizer, whereas the latter acts as a lever arm which results in the movement of myosin and force production (Rayment et al. 1993). Estrogen has also been reported to modulate phosphorylation of the regulatory light chain (Lai et al. 2016); this has functional consequences, as phosphorylation of the regulatory light chain erects the essential light chain from the thick filament, positioning the myosin heads for optimal actin-myosin interaction (Levine et al. 1996). The influence of estrogen on contractile proteins during active muscle contractions is suggested to promote a stronger binding of the myosin head to actin, thus enhancing force production (Lowe et al. 2010). These suggestions are supported by a reduction in the fraction of strong-binding myosin during active

contractions occurring to the same extent as maximal isometric tetanic force loss in ovariectomized mice (Moran et al. 2006). Whereas estrogen replacement reversed decrements in maximal isometric tetanic force and increased the fraction of strong-binding myosin during active contractions (Moran et al. 2007). Additionally, in six pairs of postmenopausal monozygotic female human twins, active stiffness, a marker of the number of strongly attached cross-bridges, in type IIa muscle fibers was higher in the female twin receiving hormone replacement therapy compared to the female twin not using hormone replacement therapy (Qaisar et al. 2013). Therefore, it is suggested that estrogen might enhance strength performance by improving the intrinsic quality of contractile function (Lowe et al. 2010) but any potential effects might be fiber-type dependent (Qaisar et al. 2013). Although the body of evidence is predominantly within animal studies or in vitro settings, estrogen's influence on the function of myosin could be speculated to underpin the potential influence of estrogen on muscle strength (Collins et al. 2019). Although the role of progesterone has been recognized, possibly by acting synergistically with estrogen (Greeves 2000), the mechanistic effect of progesterone on muscle function remains relatively understudied and further research is required (Kim et al. 2016). Nonetheless, it is evident that estrogen, however, might influence components of muscle strength but whether this translates to changes in measures of strength performance is unclear.

Measures of Strength Performance Across the Menstrual Cycle

Within the body of literature, there is a substantial divide between research that supports (e.g., (Rodrigues et al. 2019; Sarwar et al. 1996; Tenan et al. 2016) and refutes (e.g., (Ansdell et al. 2019; Elliott et al. 2003; Janse De Jonge et al. 2001)) an effect of the menstrual cycle on measures of strength performance in humans. Sarwar et al. (1996) reported both quadricep and handgrip strength (maximal voluntary contraction; MVC) to be higher "mid-cycle" (unconfirmed ovulatory phase), compared to the early- and mid-follicular and mid- and late luteal phases of the menstrual cycle. In agreement, Bambaeichi et al. (2004) reported greater knee extensor MVC at confirmed ovulation compared to the early- and late-follicular and mid- and late luteal phases of the menstrual cycle. Although both Sarwar et al. (1996) and Bambaeichi et al. (2004) speculated that elevated estrogen levels at ovulation were conducive to strength performance, neither study subsequently verified sex hormone concentrations. A study that did address this was Janse De Jonge et al. (2001), who utilized calendar-based counting, and changes in basal body temperature, as well as serum hormone analysis and progesterone thresholds (>16 nmol.l^{-1}) to identify and verify the early-follicular, late-follicular, and mid-luteal phases of the cycle. Confident that testing occurred at distinctly different ratios of estrogen to progesterone, Janse De Jonge et al. (2001) concluded that both voluntary and electrically evoked quadriceps strength and handgrip strength did not alter across

the menstrual cycle. Likewise, using the advocated "three-step" methodological recommendation to confirm phases (Janse De Jonge et al. 2019) for menstrual cycle research, Fridén et al. (2003) and Ekenros et al. (2013) reported no differences in handgrip strength between the early-follicular, ovulatory, and mid-luteal phases of the menstrual cycle. Interestingly, however, Ekenros et al. (2013) reported knee extensor MVC to be greater in the mid-luteal phase of the menstrual cycle, a finding that contradicts earlier research such as Sarwar et al. (1996). The inconclusive effects of the menstrual cycle on strength performance could reflect high heterogeneity in study design and quality (McNulty et al. 2020). Furthermore, studies use a variety of strength measures (e.g., dynamic and isometric contractions in the upper and lower limbs), participants of differing training status (e.g., recreational to elite), and menstrual phases, making it difficult to draw direct comparisons between this literature.

Mechanisms Potentially Altering Endurance Performance Across the Menstrual Cycle

Endurance exercise requires the integration of several physiological systems and processes such as substrate metabolism, musculoskeletal function, and the cardiovascular and respiratory systems. Endogenous hormones, such as estrogen and progesterone, have been suggested to exert their influence on nearly all of these physiological mechanisms. To that end, estrogen is a vasodilator, which increases blood flow to the heart and muscles through vasodilation of the coronary, brachial arteries, and the peripheral microvascular beds (Adkisson et al. 2010; Traupe et al. 2007). Adkisson et al. (2010) partly attributed improved central hemodynamic and reactivity of peripheral vascularity during the late-follicular phase of the menstrual cycle due to an estrogen-mediated increase in nitric oxide (NO) bioavailability. Although vasodilation of the feeder arteries to the working muscle could promote greater oxygen delivery to that working muscle, the ability to capitalize on this response is still partly dependent on oxygen extraction (Wagner 2000).

Earlier in the oxygen transport pathway, hormone-mediated effects are evident. For example, Smith et al. (2015) reported an increase in lung diffusion capacity during the mid-follicular compared to the early-follicular phase of the menstrual cycle. The increase in diffusion capacity is attributed to the concurrent increase in capillary blood volume, which was speculated to be a result of estrogen increasing water retention during the luteal phase of the menstrual cycle (Smith et al. 2015). However, this study included tri-phasic oral contraceptive users within their cohort and reported no significant differences in the hormone concentrations between phases; therefore, it is difficult to attribute Smith et al. (2015) findings to fluctuations in endogenous hormone changes alone. At rest, ventilatory rate ($\dot{V}E$) has been demonstrated to be greater in the luteal phase (MacNutt et al. 2012; Schoene et al. 1981), while during exercise, several studies have shown a greater ventilatory equivalent ($\dot{V}E/\dot{V}O_2$ and

$\dot{V}E/\dot{V}CO_2$, (Dombovy et al. 1987; Schoene et al. 1981)) in the luteal phase. As discussed by Janse De Jonge (2003), these changes are likely driven by the effects of progesterone on central respiratory drive, or indirectly through the increase in body temperature. However, it is important to note that conflicting literature exists demonstrating no effect of the menstrual cycle on minute ventilation, particularly at high intensities of exercise (Beidleman et al. 1999; Bemben et al. 1995; De Souza et al. 1990). Similarly, conflicting literature exists regarding the respiratory exchange ratio (RER, i.e., $\dot{V}CO_2/\dot{V}O_2$), which is influenced by substrate utilization (Dombovy et al. 1987; Hackney et al. 1994; Kanaley et al. 1992).

Substrate metabolism is a large contributor to endurance performance, and the ability to optimize fat metabolism is deemed preferable during moderate- and heavy-intensity exercise (i.e., especially of a prolonged duration). During endurance exercise, research has demonstrated that estrogen initiates a shift from carbohydrate utilization to fat oxidation (D'Eon et al. 2002; Hackney et al. 1991, 2022); however, these findings are not always consistent (Frandsen et al. 2020; Horton et al. 2002). The genomic and non-genomic mechanisms of estrogen on substrate utilization are complex; therefore, the interested reader is encouraged to read Oosthuyse and Bosch (2012) for more information. Although fat oxidation has been reported to be highest during ovulation (Hackney et al. 1991), the anti-estrogenic effect of progesterone must be taken into account when considering substrate utilization during the menstrual cycle (D'Eon et al. 2002; Hackney et al. 2022). For example, during submaximal exercise, D'Eon et al. (2002) demonstrated that the estrogenic reduction in carbohydrate oxidation and increase in fat oxidation was reversed when high levels of exogenous estrogen and progesterone were administered. Furthermore, Hackney et al. (2022) reported an "in vivo" shift toward fat metabolism from the follicular to luteal phase of the menstrual cycle during exercise. The magnitude of this shift was greater in those women with a smaller increase in progesterone relative to estrogen in the luteal phase (Hackney et al. 2022). As such, it is plausible that the inconsistencies in research to date investigating the effect of the menstrual cycle on substrate metabolism could be attributed to focusing on the absolute hormone concentrations rather than the ratio across the menstrual cycle (Hackney et al. 2022). Therefore, although the estrogenic effect on substrate metabolism might favor endurance performance, research must consider the estrogen-to-progesterone ratio to fully elucidate the potential mechanisms and impact on endurance performance. Although estrogen and progesterone might influence several of the physiological systems involved in endurance performance, the literature regarding such exercise performance is less clear.

Endurance Performance Across the Menstrual Cycle

Typically, endurance performance can be inferred using time to exhaustion tests or time to completion (i.e., time or distance trials). Time to exhaustion tests requires the athlete to maintain a constant power output or speed to the limit of tolerance,

with no controlled endpoint. Whereas time trial performance tests require athletes to complete a set distance or workload within the shortest time possible.

Research investigating the effect of the menstrual cycle on endurance performance is inconclusive, with studies supporting (e.g., (Bandyopadhyay and Dalui 2012; Campbell et al. 2001); Nicklas et al. 1989) or refuting (e.g., (Campbell et al. 2001; Janse De Jonge et al. 2012; Mattu et al. 2020; Redman et al. 2003)) an effect. Nicklas et al. (1989) had women cycle to exhaustion (70% VO_{2max}) at their mid-follicular and mid-luteal phases of the MC (hormonal confirmed). The mean luteal performance was nearly 13 min greater in duration ($p \leq 0.06$). Bandyopadhyay and Dalui (2012) investigated running time to exhaustion at 70% of heart rate maximum during the early-follicular, late-follicular, and mid-luteal phases of the menstrual cycle. Time to exhaustion was reduced during the early-follicular phase; however, no menstrual cycle phase verification method was used in this study. On the contrary, Mattu et al. (2020) reported no difference in cycling time to exhaustion, at 85% peak power output, between the mid-follicular and mid-luteal phases. These discrepancies could be attributed to the differences in exercise duration, ~ 31 min (Bandyopadhyay and Dalui 2012) and ~ 2.5 min (Mattu et al. 2020). With these trial durations implying that exercise was occurring in different intensity domains, the limiting factors to performance most likely differed. For instance, the short exercise duration reported by Mattu et al. (2020) was likely limited by substrate-level phosphorylation and the accumulation of fatiguing metabolites, rather than shifts in oxidative fuel sources. In another study, Campbell et al. (2001) reported that following 2 h of cycling at 70% of peak oxygen consumption ($\dot{V}O_{2peak}$), within a fasted state, maximal 4 kJ/kg body weight time trial performance (~ 24 to 28 min) was better within the follicular compared to the luteal phase of the menstrual cycle. Interestingly, when participants repeated the time trial exercise with carbohydrate supplementation, any phase difference noted was removed. Campbell et al. (2001) proposed that the potential effects of the menstrual cycle on endurance performance can be reduced with adequate ingestion of carbohydrates, which has partially been supported by Hulton et al. (2021) who concluded that carbohydrate consumption during endurance exercise (90 min at 60% $\dot{V}O_{2peak}$) curtails any metabolic variations incurred by the menstrual cycle. As it stands, the conflict between studies investigating the effects of the menstrual cycle on endurance performance could be partly explained by the different exercise durations, fueling practices, and specific phases of the menstrual cycle investigated. To fully elucidate the effect of fluctuating sex hormones on endurance performance, more studies are required to perform longer exhaustive exercise durations (e.g., triathlons, ultra-endurance events, marathons (Carmichael et al. 2021)), be more transparent with fueling protocols, and include the late-follicular/ovulation phase within their investigations.

Overall Effect of the Menstrual Cycle on Exercise Performance

Despite the recent surge in research attempting to establish the effect of the menstrual cycle on performance, a consensus by the scientific community has not been reached. Recently, several high-quality narrative (Carmichael et al. 2021) and systematic reviews (Blagrove et al. 2020, McNulty et al. 2020) have been conducted to identify, evaluate, and summarize the available empirical evidence. Indeed, McNulty et al. (2020) performed a systematic review and meta-analysis on 78 studies investigating the effects of the menstrual cycle on strength and endurance performance. The conclusions were that on average, exercise performance might be reduced by a trivial amount during the early-follicular phase compared with all other phases of the menstrual cycle. Exclusively investigating strength-related measures, Blagrove et al. (2020) agreed that the fluctuations in endogenous sex hormones across the menstrual cycle might have a small to trivial effect on strength performance. Furthermore, these reviews have unanimously agreed that the current quality of evidence in this area is low; e.g., McNulty et al. (2020) findings were based on 68% of their studies having a quality rating of "low" to "very low". Additionally, there was a large between-study variance (McNulty et al. 2020), which might reflect the notoriously low participant numbers and varied protocols often used within this research area (Blagrove et al. 2020). Together, these limitations should be heavily considered when interpreting a small or trivial effects noted. Therefore, future studies should address these methodological shortcomings to improve the quality and consistency of the evidence used by and given to women athletes and those working with them.

While it is evident that estrogen and progesterone can exert their influences on physiological systems which might underpin both strength and endurance performance, it is important to note that exercise performance is not exclusively determined by the integration of physiological function. In addition to factors such as motivation and environment, performance could be altered by the likes of cycle-related symptoms, athlete perceptions (e.g., the perceived effects of the menstrual cycle on performance and training), as well as lived experiences (e.g., menses/menstrual stigma) and changes in behavior (e.g., training habits, gym attire) associated with the menstrual cycle phases (Carmichael et al. 2021; Kolić et al. 2022, 2021). For instance, in a recent narrative review, Carmichael et al. (2021) reported that ~ 71 and ~ 65% of athletes felt their performance in training and competition, respectively, varied across the menstrual cycle. Although causation cannot be concluded, perceived variations in performance were attributed to menstrual cycle symptomologies, such as feelings of fatigue, lethargy, and menstrual pain (Carmichael et al. 2021). Therefore, to fully understand the impact of the menstrual cycle on exercise and performance, the impact of all facets of the menstrual cycle must be considered using a holistic approach (e.g., physiological, psychology, behavior, etc.), rather than the potential effects of endogenous hormones in isolation.

Practical Recommendations

Practically, the current evidence and the large intra- and inter-individual variations and experiences of the menstrual cycle do not warrant general guidance on exercise performance across the menstrual cycle. As such, scientific support for women athletes, regarding the mensural cycle, should be individualized to each female and their unique menstrual cycle characteristics and history. For example, this can be achieved through regular menstrual cycle screening, and as a minimum, consistent menstrual cycle tracking (e.g., menses and cycle length) for at least three months. Furthermore, consistent monitoring of the type, prevalence, frequency, and severity of symptoms (e.g., blood flow, discharge, breast soreness, fatigue, etc.) experienced during the menstrual cycle can help understand, manage, or exploit the impact of negative and positive symptoms, respectively. Additional insight can be provided by including perceptual and/or objective noteworthy changes in exercise performance experienced by athletes across their menstrual cycle. For more in-depth recommendations on how to monitor and interpret menstrual health within an exercise setting, please see other chapters in this volume (those developed by Bruinvels and Pedlar, and Mikkonen et al.) or see reference Davison et al. (2022). Overall, it is imperative that high-quality research on women is used to inform practice, generate critical discussion, and close the sports science gender gap, but the application should be shaped, examined, and adjusted (if required) to the individual athlete and their own individual experiences of the menstrual cycle to optimize long-term performance outcomes and goals.

References

Adkisson EJ, Casey DP, Beck DT, Gurovich AN, Martin JS, Braith RW. Central, peripheral and resistance arterial reactivity: fluctuates during the phases of the menstrual cycle. Exp Biol Med. 2010;235(1):111–8.

Ansdell P, Brownstein CG, Škarabot J, Hicks KM, Simoes DC, Thomas K, Goodall S. Menstrual cycle-associated modulations in neuromuscular function and fatigability of the knee extensors in eumenorrheic women. J Appl Physiol. 2019;126(6):1701–12.

Ansdell P, Thomas K, Hicks KM, Hunter SK, Howatson G, Goodall S. Physiological sex differences affect the integrative response to exercise: acute and chronic implications. Exp Physiol. 2020;105(12):2007–21.

Bambaeichi E, Reilly T, Cable N, Giacomoni M. The isolated and combined effects of menstrual cycle phase and time-of-day on muscle strength of eumenorrheic females. Chronobiol Int. 2004;21(4–5):645–60.

Bandyopadhyay A, Dalui R. Endurance capacity and cardiorespiratory responses in sedentary females during different phases of menstrual cycle. Kathmandu Univ Med J. 2012;10(4):25–9.

Beidleman BA, Rock PB, Muza SR, Fulco CS, Forte VA Jr, Cymerman A. Exercise V̇ e and physical performance at altitude are not affected by menstrual cycle phase. J Appl Physiol. 1999;86(5):1519–26.

Bemben D, Salm P, Salm A. Ventilatory and blood lactate responses to maximal treadmill exercise during the menstrual cycle. J Sports Med Phys Fitness. 1995;35(4):257–62.

Blagrove RC, Bruinvels G, Pedlar CR. Variations in strength-related measures during the menstrual cycle in eumenorrheic women: A systematic review and meta-analysis. J Sci Med Sport. 2020;23(12):1220–1227.

Campbell S, Angus D, Febbraio M. Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. Amer J Physiol-Endocrinol Metabolism. 2001;281(4):E817–25.

Carmichael MA, Thomson RL, Moran LJ, Wycherley TP. The impact of menstrual cycle phase on athlete's performance: a narrative review. Int J Environ Res Public Health. 2021;18(4):1667.

Collins BC, Laakkonen EK, Lowe DA. Aging of the musculoskeletal system: How the loss of estrogen impacts muscle strength. Bone. 2019;123:137–44.

Constantini NW, Dubnov G, Lebrun CM. The menstrual cycle and sport performance. Clin Sports Med. 2005;24(2):e51–82.

Cowley ES, Olenick AA, McNulty KL, Ross EZ. "Invisible sportswomen": the sex data gap in sport and exercise science research. Women in Sport and Phys Activity J. 2021;29(2):146–51.

D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise carbohydrate metabolism by estrogen and progesterone in women. Amer J Physiol-Endocrinol Metabolism. 2002;283(5):E1046–55.

Davison R, Smith PM, Hopker J, Price MJ, Hettinga F, Tew G, Bottoms L. Sport and exercise physiology testing guidelines: volume I-sport testing: the british association of sport and exercise sciences guide. Routledge; 2022.

De Souza MJ, Maguire MS, Rubin KR, Maresh CM. Effects of menstrual phase and amenorrhea on exercise performance in runners. Med Sci Sports Exerc. 1990;22(5):575–80.

Dombovy ML, Bonekat HW, Williams TJ, Staats BA. Exercise performance and ventilatory response in the menstrual cycle. Med Sci Sports Exerc. 1987;19(2):111–7.

Dulhunty A. Excitation–contraction coupling from the 1950s into the new millennium. Clin Exp Pharmacol Physiol. 2006;33(9):763–72.

Ekenros L, Hirschberg AL, Heijne A, Fridén C. Oral contraceptives do not affect muscle strength and hop performance in active women. Clin J Sport Med. 2013;23(3):202–7.

Elliott K, Cable N, Reilly T, Diver M. Effect of menstrual cycle phase on the concentration of bioavailable 17-β oestradiol and testosterone and muscle strength. Clin Sci. 2003;105(6):663–9.

Elliott-Sale KJ, Hicks KM. Hormonal-based contraception and the exercising female. The exercising female. Routledge;2018. p. 30–43.

Elliott-Sale KJ, Minahan CL, de Jonge XA, Ackerman KE, Sipilä S, Constantini NW, Hackney AC. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51(5):843–61.

Frandsen J, Pistoljevic N, Quesada JP, Amaro-Gahete FJ, Ritz C, Larsen S, Helge JW. Menstrual cycle phase does not affect whole body peak fat oxidation rate during a graded exercise test. J Appl Physiol. 2020;128(3):681–7.

Fridén C, Hirschberg AL, Saartok T. Muscle strength and endurance do not significantly vary across 3 phases of the menstrual cycle in moderately active premenopausal women. Clin J Sport Med. 2003;13(4):238–41.

Greeves J. Circamensal rhythmicity and muscle function: the role of reproductive hormones in the regulation of strength. Biol Rhythm Res. 2000;31(1):15–28.

Hackney AC, Curley C, Nicklas B. Physiological responses to submaximal exercise at the mid-follicular, ovulatory and mid-luteal phases of the menstrual cycle. Scand J Med Sci Sports. 1991;1(2):94–8.

Hackney AC, Koltun KJ, Williett HN. Menstrual cycle hormonal changes: estradiol-β-17 and progesterone interactions on exercise fat oxidation. Endocrine. 2022;76(1):240–2.

Hackney AC, McCracken-Compton MA, Ainsworth B. Substrate responses to submaximal exercise in the midfollicular and midluteal phases of the menstrual cycle. Int J Sport Nutr Exerc Metab. 1994;4(3):299–308.

Horton TJ, Miller EK, Glueck D, Tench K. No effect of menstrual cycle phase on glucose kinetics and fuel oxidation during moderate-intensity exercise. Amer J Physiol-Endocrinol Metabolism. 2002;282(4):E752–62.

Hulton A, Malone J, Campbell I, MacLaren D. The effect of the menstrual cycle and hyperglycaemia on hormonal and metabolic responses during exercise. Eur J Appl Physiol. 2021;121(11):2993–3003.

Janse De Jonge X. The effect of the menstrual cycle on exercise metabolism. Sports Med. 2003;33(11):833–51.

Janse De Jonge X, Boot C, Thom J, Ruell P, Thompson M. The influence of menstrual cycle phase on skeletal muscle contractile characteristics in humans. J Physiol. 2001;530(Pt 1):161.

Janse De Jonge X, Thompson B, Han A. Methodological recommendations for menstrual cycle research in sports and exercise. Med Sci Sports Exerc. 2019;51(12):2610–7. https://doi.org/10.1249/mss.0000000000002073.

Janse De Jonge XAK, Thompson MW, Chuter VH, Silk LN, Thom JM. Exercise performance over the menstrual cycle in temperate and hot, humid conditions. Med Sci Sports Exerc. 2012;44(11):2190–8. https://doi.org/10.1249/mss.0b013e3182656f13.

Kanaley J, Boileau R, Bahr J, Misner J, Nelson R. Substrate oxidation and GH responses to exercise are independent of menstrual phase and status. Med Sci Sports Exerc. 1992;24(8):873–80.

Kim YJ, Tamadon A, Park HT, Kim H, Ku S-Y. The role of sex steroid hormones in the pathophysiology and treatment of sarcopenia. Osteoporosis and Sarcopenia. 2016;2(3):140–55.

Kolić P, Thomas L, Morse CI, Hicks KM. Presentation of self, impression management and the period: a qualitative investigation of physically active women's experiences in sport and exercise. J Appl Sport Psychol. 2022;1–20.

Kolić PV, Sims DT, Hicks K, Thomas L, Morse CI. Physical activity and the menstrual cycle: a mixed-methods study of women's experiences. Women in Sport and Phys Activity J. 2021;29(1):47–58.

Lai S, Collins BC, Colson BA, Kararigas G, Lowe DA. Estradiol modulates myosin regulatory light chain phosphorylation and contractility in skeletal muscle of female mice. Am J Physiol Endocrinol Metab. 2016;310(9):E724-733. https://doi.org/10.1152/ajpendo.00439.2015.

Levine R, Kensler RW, Yang Z, Stull JT, Sweeney HL. Myosin light chain phosphorylation affects the structure of rabbit skeletal muscle thick filaments. Biophys J. 1996;71(2):898–907.

Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. Exerc Sport Sci Rev. 2010;38(2):61.

MacNutt MJ, De Souza MJ, Tomczak SE, Homer JL, Sheel AW. Resting and exercise ventilatory chemosensitivity across the menstrual cycle. J Appl Physiol. 2012;112(5):737–47.

Martin D, Sale C, Cooper SB, Elliott-Sale KJ. Period prevalence and perceived side effects of hormonal contraceptive use and the menstrual cycle in elite athletes. Int J Sports Physiol Perform. 2018;13(7):926–32.

Mattu AT, Iannetta D, MacInnis MJ, Doyle-Baker PK, Murias JM. Menstrual and oral contraceptive cycle phases do not affect submaximal and maximal exercise responses. Scand J Med Sci Sports. 2020;30(3):472–84.

McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, Hicks KM. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. Sports Med. 2020;50(10):1813–27.

Moran AL, Nelson SA, Landisch RM, Warren GL, Lowe DA. Estradiol replacement reverses ovariectomy-induced muscle contractile and myosin dysfunction in mature female mice. J Appl Physiol. 2007;102(4):1387–93.

Moran AL, Warren GL, Lowe DA. Removal of ovarian hormones from mature mice detrimentally affects muscle contractile function and myosin structural distribution. J Appl Physiol. 2006;100(2):548–59.

Oosthuyse T, Bosch AN. Oestrogen's regulation of fat metabolism during exercise and gender specific effects. Curr Opin Pharmacol. 2012;12(3):363–71.

Nicklas BJ, Hackney AC, Sharp RL. The menstrual cycle and exercise: performance, muscle glycogen, and substrate responses. Int J Sports Med. 1989;10(4):264–9.

Qaisar R, Renaud G, Hedstrom Y, Pöllänen E, Ronkainen P, Kaprio J, Bergquist J. Hormone replacement therapy improves contractile function and myonuclear organization of single muscle fibres from postmenopausal monozygotic female twin pairs. J Physiol. 2013;591(9):2333–44.

Rayment I, Holden HM, Whittaker M, Yohn CB, Lorenz M, Holmes KC, Milligan RA. Structure of the actin-myosin complex and its implications for muscle contraction. Science. 1993;261(5117):58–65.

Redman LM, Scroop GC, Norman RJ. Impact of menstrual cycle phase on the exercise status of young, sedentary women. Eur J Appl Physiol. 2003;90(5):505–13.

Rodrigues P, de Azevedo Correia M, Wharton L. Effect of menstrual cycle on muscle strength. J Exercise Physiol Online. 2019;22(5):89–96.

Sarwar R, Niclos BB, Rutherford O. Changes in muscle strength, relaxation rate and fatiguability during the human menstrual cycle. J Physiol. 1996;493(1):267–72.

Schoene RB, Robertson HT, Pierson DJ, Peterson AP. Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. J Appl Physiol. 1981;50(6):1300–5.

Smith JR, Brown KR, Murphy JD, Harms CA. Does menstrual cycle phase affect lung diffusion capacity during exercise? Respir Physiol Neurobiol. 2015;205:99–104.

Smith M, Keel J, Greenberg B, Adams L, Schmidt P, Rubinow D, Wassermann EM. Menstrual cycle effects on cortical excitability. Neurology. 1999;53(9):2069–2069.

Tenan MS, Hackney AC, Griffin L. Maximal force and tremor changes across the menstrual cycle. Eur J Appl Physiol. 2016;116(1):153–60.

Tenan MS, Peng Y-L, Hackney AC, Griffin L. Menstrual cycle mediates vastus medialis and vastus medialis oblique muscle activity. Med Sci Sports Exerc. 2013;45(11):2151–7.

Traupe T, Stettler CD, Li H, Haas E, Bhattacharya I, Minotti R, Barton M. Distinct roles of estrogen receptors α and β mediating acute vasodilation of epicardial coronary arteries. Hypertension. 2007;49(6):1364–70.

Wagner PD. New ideas on limitations to VO2max. Exerc Sport Sci Rev. 2000;28(1):10–4.

Chapter 12
Nutritional Strategies and Sex Hormone Interactions in Women

Nancy J. Rehrer, Rebecca T. McLay-Cooke, and Stacy T. Sims

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 carbohydrates and protein. The varying impact of manipulation will be highlighted with respect to the 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 hyponatremia. Hereafter, estrogen, as an antioxidant, is discussed and several more minor nutrients are highlighted that, due to specific action of estrogen (and/ or progesterone), 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 a similar activity. Evidence from metabolic studies conducted in animal and human populations indicates that both estrogen and progesterone have varying effects on carbohydrate, lipid, and protein metabolism. Specifically, the female sex hormones appear to influence 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), energy substrate utilization-oxidation (Willett et al. 2021), 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 have been 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 mainly limited to the manipulation of carbohydrate and protein intake and predominantly concerning endurance exercise.

Habitual Diets

Energy Requirements

The energy requirements of female athletes will vary according to the amount of physical activity undertaken, age, occupation, health status, and basal metabolic rate of the individual. However, based on evidence from research into the female athlete triad and relative energy deficiency in sport (RED-s) (Melin et al. 2019), it has been suggested that female athletes should aim for an energy availability of 45 kcal per kg fat-free mass per day throughout the menstrual cycle for optimal health and performance (Holtzman and Ackerman 2021).

A recent systematic review and meta-analysis found that the menstrual cycle exerted a small (∼ 0.33) and inconsistent (∼ 50% of studies) effect size increase in resting metabolic rate (RMR) during the luteal compared to follicular phase in women (not specifically athletes) (Benton et al. 2020). A small number of studies have investigated energy intake during different phases of the menstrual cycle with some reporting no difference (de Souza et al. 2018; Eck et al. 1997; Gorczyca et al. 2016), and others reporting an increase in energy intake in the luteal compared to follicular phase (Barr et al. 1995; Kammoun et al. 2017; Nowak et al. 2020). To date, only one study has investigated the influence of the menstrual cycle and hormonal contraceptive cycle phase (active versus inactive) on energy intake and energy availability in recreational athletes (Ihalainen et al. 2021). Measurements were obtained at four time points: bleeding, mid-follicular/active 1, ovulation/active 2, and mid-luteal/inactive. The findings suggest that on average, neither the menstrual cycle nor hormonal cycle phase alters ad libitum energy intake or energy availability in recreationally active athletes. However, the authors emphasized that large inter-individual differences were observed within the data so further investigation is warranted with a larger study population over multiple cycles. Until such research is conducted, it is as yet unclear whether physically active women have increased energy requirements in the luteal phase of the menstrual cycle due to a potential small increase in RMR. Additional research on female athletes is also needed to assess the effect of the menstrual cycle phase and hormonal contraceptive use on appetite regulation, gastrointestinal symptoms, and food cravings, all of which have the potential to affect habitual energy intake (Krishnan et al. 2016).

Protein Requirements

Observations from several studies conducted in healthy non-athletic females point to a decrease in plasma amino acids during the luteal compared to the follicular phase of the menstrual cycle (Faustmann et al. 2018; Kriengsinyos et al. 2004; Sawai et al. 2020; Wallace et al. 2010). This difference may be reflective of greater utilization in this phase attributed to increased cell cycle progression and growth, and the associated endometrial protein biosynthesis required for endometrial thickening to prepare the uterus for pregnancy (Brennan and Gibbons 2020; Draper et al. 2018). Increased nitrogen utilization and excretion in healthy non-athletic females (Calloway and Kurzer 1982) and increased protein catabolism at rest (Lariviere et al. 1994) and during prolonged exercise (Bailey et al. 2000; Lamont et al. 1987) have been observed in the luteal compared to the follicular phase of the menstrual cycle. It appears higher circulating levels of progesterone or a reduced estrogen: progesterone (E:P) ratio are responsible for the increased catabolism of protein in the luteal phase (Kriengsinyos et al. 2004). Therefore, the greater E:P ratio of the follicular phase may have a "protein-sparing" effect (Moore et al. 2021). It is possible that 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). It is, therefore, plausible that the protein requirements of female athletes may be increased during

the luteal phase of the menstrual cycle when levels of estrogen and progesterone are elevated.

Recently, Mercer and colleagues (2020) conducted a systematic literature review aimed at determining the protein requirements of premenopausal female athletes and identifying if menstrual cycle phase and/or hormonal contraceptive use influences protein requirements. Unfortunately, most of the studies included in this review failed to report the menstrual cycle phase (Campbell et al. 2018; Pihoker et al. 2019; Taylor et al. 2016; Tinsley et al. 2019; West et al. 2012; Wilborn et al. 2016, 2013) or have grouped users and non-users of hormonal contraceptives together (Brown et al. 2018; Rowlands and Wadsworth 2011; Roy et al. 2002). To date, three studies investigating protein requirements of female athletes have attempted to document the menstrual cycle phase (Houltham and Rowlands 2014; Malowany et al. 2019; Wooding et al. 2017). Using the nitrogen balance method, the estimated average requirement (EAR) of protein for trained female endurance athletes was reported to be 1.63 g kg^{-1} d^{-1} (Houltham and Rowlands 2014), equating to a recommended dietary intake (RDI) of 2.02 g kg^{-1} d^{-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. The protein EAR for recreationally active resistance-trained female athletes completing a single whole-body resistance training session during the luteal phase was estimated to be 1.49 g kg^{-1} d^{-1} (Malowany et al. 2019) (calculated RDI 1.85 g kg^{-1} d^{-1}) (Mercer et al. 2020) using the indicator of amino acid oxidation (IAAO) technique. The IAAO method was also used by Wooding and colleagues (Wooding et al. 2017) who determined a luteal phase protein EAR of 1.41 g kg^{-1} d^{-1} (calculated RDI 1.75 g kg^{-1} d^{-1}) (Mercer et al. 2020) for competitive female athletes completing intermittent exercise (shuttle test). The protein requirements presented in these studies are within the upper RDI range of general protein recommendations for all athletes (1.2–2.0 g kg^{-1} d^{-1}) (Thomas et al. 2016) and provide a starting point for planning protein intakes of female athletes. However, due to the disparate nature of these studies and the inability to be able to make comparisons both within and between studies, the impact of the menstrual cycle phase and hormonal contraceptive use on the protein requirements of female athletes remains unclear at this time and further research is warranted.

Carbohydrate Requirements

In a recent review, Moore and colleagues (2021) attempted to compile carbohydrate recommendations for female athletes. Daily carbohydrate requirements are presented based on the intensity and duration of exercise (light = 4 g kg^{-1} d^{-1}; moderate = 4–6 g kg^{-1} d^{-1}; high = 6–8 g kg^{-1} d^{-1}; very high = 8–12 g kg^{-1} d^{-1}) but also include sex-specific considerations relating to menstrual cycle phase (Moore et al. 2021). Specifically, female athletes should consider the menstrual cycle phase firstly in relation to the potential effects of individualized physical and mental symptoms on the ability to achieve daily carbohydrate targets; secondly, additional carbohydrates

may be required in the follicular phase to overcome reduced muscle glycogen storage (Hackney 1990; McLay et al. 2007; Nicklas et al. 1989); and finally, there should be some consideration of menstrual cycle phase concerning appetite regulation and food cravings on habitual absolute carbohydrate intake (Moore et al. 2021). Studies investigating the menstrual cycle phase or hormonal contraceptive use relative to carbohydrate requirements are mainly limited to endurance exercise trials. Future studies should aim to explore the impact of hormonal variation on the glycogen requirements of female athletes in "real-world" training or competition settings.

Fat Requirements

Females oxidize proportionately more lipids than men at all exercise intensities (Cheneviere et al. 2011; Devries 2016) due to the effects of estrogen, and females have greater intramuscular triglyceride stores and differences in type I muscle fibers (Rossi 2017). Therefore, consuming a high-fat diet may offer a performance advantage for female endurance athletes. However, 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 2021). As a consequence, research in this area that incorporates fluctuations in ovarian hormones is non-existent.

Nutrient Intake in the days Before Exercise

Results of early research suggested the 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 eumenorrheic female athletes (Nicklas et al. 1989). Carbohydrate loading is a performance-enhancement strategy often used by endurance athletes before a competition to increase muscle glycogen stores in an effort to improve performance in events lasting longer than 90 min (Sedlock 2008). Modern versions of the approach involve combining a high dietary carbohydrate intake and exercise taper for several days before competition (Sedlock 2008). Only a small number of studies have attempted to explore this relationship by investigating the impact of a modified carbohydrate loading regime before exercise in females under a variety of hormonal influences. Carbohydrate loading (8.4–9 g kg body weight^{-1} d^{-1}) has been shown to increase muscle glycogen concentration in the mid-follicular phase of the menstrual cycle (Paul et al. 2001; Tarnopolsky et al. 2001; McLay et al. 2007). In contrast, following carbohydrate loading during the mid-luteal 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, 2005; Hawley et al. 1997; Burke et al. 2000; Tarnopolsky et al. 2001) 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 estradiol/levonorgestrel) showed increased muscle glycogen concentration following carbohydrate loading in both the mid-follicular and mid-luteal phases (James et al. 2001). However, unlike a normal natural menstrual cycle where resting levels of both estradiol and progesterone are higher during the mid-luteal than mid-follicular 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 mid-luteal phase could be interpreted in the same way as the mid-follicular phase results from this study, potentially adding to the evidence that carbohydrate loading in the mid-follicular 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 using different forms of hormonal contraception.

Although the lower level of muscle glycogen storage in the mid-follicular 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 (maximal oxygen uptake), measured during the mid-luteal 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 mid-luteal phase (McLay et al. 2007).

As with research conducted using male participants, there are many 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 before 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 the 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) occurs only when the estrogen to progesterone ratio (E:P) is elevated sufficiently in the luteal compared to follicular phase and the magnitude of the increase in estrogen 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 carbohydrates (CHO) ($\geq$ 8 g kg body weight^{-1} d^{-1}) needed for carbohydrate loading can be difficult for women whose habitual energy intakes are < 2000 kcal d^{-1} (8400 kJ d^{-1}) (Tarnopolsky et al. 1995; Wismann and

Willoughby 2006; Sedlock 2008), as this dosage 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

The menstrual cycle phase appears to influence glucose kinetics during exercise due to the ability of estrogen 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 the 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 for endogenous glucose production (Suh et al. 2002; Oosthuyse and Bosch 2010). Eumenorrheic female athletes should, therefore, follow current recommendations to consume a pre-exercise meal or snack containing carbohydrates three to four hours 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 utilization 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 the 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 before 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; Bourdas et al. 2021). However, the majority of research has been conducted using trained male participants, and the findings generalized and applied to female athletes. This issue is highlighted in by a recent meta-analysis of carbohydrate solution intake during prolonged exercise over the past 45 years, in which only six out of the 96 studies reviewed were conducted in

females and only one examined the effect of the menstrual cycle phase (Bourdas et al. 2021).

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; Gui et al. 2017). Several studies have reported lower carbohydrate oxidation rates and higher fat oxidation rates in the luteal phase compared with the follicular phase (Hackney et al. 1991, 1994; Willett et al. 2021; Zderic et al. 2001). However, when exogenous glucose is provided during exercise to ovulatory females, the influence of the menstrual cycle phase on glucose kinetics is minimized as the demand for endogenous glucose production is reduced (Campbell et al. 2001; Hulton et al. 2021). Furthermore, the 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 the usage 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}) during 2 h of cycling at moderate intensity, with no further increases when the rate was increased to 1.5 g min^{-1} (90 g h^{-1}) (Wallis et al. 2007). To date, the impact of high rates (90 + g h^{-1}) of exogenous carbohydrate ingestion has not been assessed in different phases of the menstrual cycle or under hormonal contraceptive use. Athletes should be wary of gastrointestinal upset caused by high rates of carbohydrate ingestion during exercise that could potentially overwhelm the gut (Holtzman and Ackerman 2021). In addition, it is also unknown if the menstrual cycle phase and hormonal contraceptive use have an effect on carbohydrate oxidation rates when dual-source blends of carbohydrates are consumed during exercise. Finally, no studies have yet attempted to examine the ingestion of whole foods on exogenous carbohydrate rates at different time points during the menstrual cycle or when hormone contraceptives are used.

Current general recommendations for carbohydrate intake during exercise of < 75 min include the provision of small amounts of carbohydrate, including mouth rinse (Thomas et al. 2016). This is another area that has received little research attention with respect to including female subjects and the fluctuations in ovarian hormones, with only apparently one study to date attempting to examine this area. Chryssanthopoulos and colleagues (2018) found carbohydrate mouth rinsing did not improve 60-min running performance in 5 postmenopausal and 10 eumenorrheic recreational runners tested in the follicular phase of the menstrual cycle.

In light of the limited data available, it would seem prudent to recommend that eumenorrheic female endurance athletes ingest carbohydrates at a rate of 60 g h^{-1} during moderate- to high-intensity exercise to offset menstrual cycle effects on glucose kinetics/exercise metabolism and to limit potential immune disturbances in the heat as well as protein catabolism. Considerable further research evidence

is required to elucidate whether menstrual cycle or hormone contraceptive specific recommendations for nutrient intake during exercise are warranted for female athletes outside of the current contemporary guidelines.

Nutrient Intake and Recovery from Exercise

Little is known about how extensively fluctuations in ovarian hormones may impact 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 four days prior, muscle glycogen repletion is reduced in the follicular phase compared to the luteal phase in moderately trained eumenorrheic women consuming a diet containing 56% of energy intake from carbohydrates (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 carbohydrates consumed in the hours after depleting exercise using both untrained (Kuipers et al. 1989) and endurance-trained (Tarnopolsky et al. 1997) participants.

A recent meta-analysis concluded that muscle glycogen synthesis rates are enhanced when carbohydrate and protein are co-ingested after exercise compared with carbohydrate alone only when the added energy of protein is in addition to, not in place of, carbohydrate (Margolis et al. 2021). However, all of the studies included in this review were conducted on male subjects with only 4/22 including females.

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). To date, these effects have not been tested during different phases of the menstrual cycle and studies investigating exogenous hormone users are rare, and the methods of hormonal contraceptive use are variable. For example, Flynn and colleagues (2020) recently reported similar rates of muscle glycogen resynthesis in recreationally active males and females using supplemental hormone prescriptions (triphasic, norethindrone, and ethyl estradiol oral pills) or time-release (intrauterine device) birth control when 1.6 g kg^{-1} of carbohydrate was ingested immediately and 2-h post-completion of a 90-min cycling protocol.

Based on these rather limited data, eumenorrheic women should aim to consume carbohydrates (1.2 g kg^{-1} h) as soon as possible following glycogen-depleting exercise, particularly during the follicular phase of the menstrual cycle, to maximize glycogen replenishment. This may be especially important if the next training session or event is likely to occur in < 8 h.

Research into the role of dietary protein ingested after exercise on recovery processes and subsequent performance in females is lacking. In contrast to research

in males, high protein feeding immediately after and for two 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 of the menstrual cycle, and as noted previously, protein catabolism appears to be increased in the luteal phase compared to the follicular and early follicular phases (Bailey et al. 2000; Kriengsinyos et al. 2004; Lamont et al. 1987; Lariviere et al. 1994), and this may have influenced the results of this study.

Current post-exercise recovery guidelines include the intake of high-quality protein as soon after exercise as possible to initiate muscle protein remodeling and repair, and to replenish any exercise-induced amino acid oxidative losses (Kerksick et al. 2017), ingested in an amount relative to the body weight of the individual (Moore 2019). Although these recommendations have not been systematically tested across different phases of the menstrual cycle or under conditions of hormonal contraceptive use, current evidence suggests that it is unlikely that acute post-exercise protein requirements to support muscle protein repair and remodeling would differ between the sexes or across the menstrual cycle (Moore 2019; Moore et al. 2021). Evidence for this potential lack of difference includes stimulation of myofibrillar protein synthesis after resistance exercise being unaffected by the menstrual cycle phase (Miller et al. 2006) and the observation of similar exercise-induced muscle protein synthesis in young men and women (Dreyer et al. 2010). As a consequence, Moore and colleagues (2021) have suggested the following post-exercise protein guidelines for female athletes undertaking resistance training: 0.3 g kg^{-1}; mixed training, e.g., team sports characterized by high-intensity intermittent exercise: 0.4 g kg^{-1}; and endurance training: 0.5 g kg^{-1}. The higher dose for endurance training athletes represents the additional need to replenish amino acid oxidative losses, while the higher dose for mixed training represents activity that includes both aerobic and resistive components (Moore et al. 2021).

Exercise-induced muscle damage (EIMD), specifically delayed onset muscle soreness (DOMS) and strength loss, is affected by hormone fluctuations during the menstrual cycle (Romero-Parra et al. 2020). This meta-analysis showed lower DOMS and strength loss differences between pre-exercise and post-exercise in the mid-luteal phase when estrogen and progesterone are high compared to the early-follicular phase. In addition, exercise-induced muscle damage (EIMD) has been shown to negatively affect functional performance for several days in female athletes tested in the luteal phase (Keane et al. 2015). There is some evidence, from research conducted on males, that the consumption of protein and the simultaneous ingestion of carbohydrates and protein offer protection against exercise-induced muscle damage (Howatson and van Someren 2008). Only a small number of studies have been conducted using endurance-trained, resistance-trained, and team sport female athletes and the post-exercise ingestion of whey protein versus casein protein (Wilborn et al. 2013), whey versus soy protein (Tara et al. 2013), carbohydrate versus carbohydrate/protein (Green et al. 2008), and whey protein versus maltodextrin (Taylor et al. 2016) on perceptions of muscle damage, strength, and biomarkers of muscle damage and inflammation. Unfortunately, none of these studies accounted for the menstrual cycle phase or hormonal contraceptive use (Köhne et al. 2016), so

the impact of post-exercise protein or carbohydrate/protein ingestion on EIMD in varying hormonal environments remains unclear.

In order to support muscle protein remodeling and repair, replenish any exercise-induced amino acid oxidative losses, offset the potential increased protein catabolism, and protect against exercise-induced muscle damage, eumenorrheic women should focus on consuming protein, coupled with carbohydrates, to replenish muscle glycogen stores during the post-exercise recovery period across the menstrual cycle.

Although speculative and open to adjustment and revision as more information becomes available, some broad recommendations regarding the manipulation of energy and macronutrient intake with sex hormone interactions can be garnered from the currently available research. These recommendations are summarized in Table 12.1.

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. 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. 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. Future research is needed to overcome earlier study design issues (e.g., type of oral contraceptive used, misidentification of menstrual cycle phase, and diverse participant characteristics), and investigators should be guided by recently published recommendations for conducting research in female athletes (Elliott-Sale et al. 2020).

Despite the need for continued, well-controlled, and informative research in this area, it is pleasing to note that several recent publications (Helm et al. 2021; Holtzman and Ackerman 2021; Moore et al. 2021; Rocha-Rodrigues et al. 2021; Rossi 2017) covering nutrition specifically for female athletes have acknowledged the potential impact of a changing hormonal environment and even attempted to incorporate menstrual cycle and hormonal contraceptive specific guidelines where possible.

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 2011; 2012), 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

Table 12.1 Potential macronutrient manipulations recommended for female athletes in relation to fluctuations in ovarian hormones

	Nutritional strategy	Target	Recommendation	Rationale
Habitual diet	Energy availability (EA) Protein requirement Carbohydrate requirement	Female athletes Eumenorrheic, endurance resistance and intermittent exercise-trained Eumenorrheic	EA > 45 kcal kgFFM^{-1} d^{-1} across all phases of the menstrual cycle Protein intake: 1.75–2.02 g kg^{-1} d^{-1} Aim for the higher end of the recommendation during the LP CHO intake is based on intensity and duration of exercise with greater emphasis on intake in FP	Based on data from the female athlete triad and RED-S research A higher intake may be required in the LP due to increased protein catabolism at rest and during exercise and to account for increased utilization associated with endometrial protein biosynthesis To overcome lower muscle glycogen storage in FP
Days before exercise	Modified CHO loading	Eumenorrheic—FP[a], endurance exercise > 90 min	Increase energy intake by up to 30% to achieve CHO intake > 8 g kg^{-1} d^{-1} on CHO loading days	To overcome lower muscle glycogen storage in FP
Hours before exercise	Pre-exercise feeding	Eumenorrheic—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	Eumenorrheic, endurance	CHO intake: 60 g h^{-1} during prolonged exercise	To reduce demand on endogenous glucose production. Limit potential immune disturbance and protein catabolism

(continued)

Table 12.1 (continued)

	Nutritional strategy	Target	Recommendation	Rationale
Recovery after exercise	CHO CHO + protein	Eumenorrheic—FP[a], endurance Eumenorrheic, endurance, resistance training, other activities that induce muscle damage	Ingestion of CHO (1.2 g kg^{-1}.h) as soon as practical following prolonged glycogen-depleting exercise Co-ingestion of protein (0.3–0.5 g kg) and CHO during the recovery period	To overcome potentially reduced muscle glycogen resynthesis in FP To support muscle protein remodeling and repair To replenish any exercise-induced amino acid oxidative losses To offset an increase in protein catabolism in the LP To protect against EIMD in the EFP

CHO carbohydrate, *EFP* early follicular phase, *EIMD* exercise-induced muscle damage, *FP* follicular phase, *LP* luteal phase, *OC* oral contraceptive, *RED-S* relative energy deficiency in sport

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

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 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 period than men; consequently, women have been more frequently diagnosed as heat intolerant compared with men (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 estrogen levels are increasing. However, PV falls by as much as 8% during the mid-luteal phase when both estrogen and progesterone levels are elevated. Progesterone and estrogen 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. 2001a, 1999, 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 thermoregulatory effect of progesterone (Kolka and Stephenson 1997a, b), which may also account for core temperature being elevated throughout the 28-d OC cycle relative to that in the natural menstrual cycle (Stachenfeld et al. 2000). Estrogen also functions in vasodilation via modulation of prostacyclin and nitric oxide release (Charkoudian and Johnson 1997, Charkoudian et al. 1999, Hiroshoren et al. 2002, Houghton et al. 2005). Moreover, plasma volume has been found to differ significantly in the two phases at higher ambient temperatures, as estrogen enhances aldosterone-mediated sodium absorption in the renal tubules and increases nitric oxide-mediated vasodilation (Houghton et al. 2005, Kang et al. 2001, Salazar Llinas 1996).

Charkoudian and Johnson (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 estrogen 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 estrogen and progestins found in oral contraceptive pills have similar influences on

the cutaneous vascular response to heat stress. Charkoudian and Johnson (Charkoudian and Johnson 1999) investigated the effect of oral contraceptives on cutaneous vascular control during heat stress, expecting to find 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 mid-luteal phase of the menstrual cycle. Moreover, central influences of estrogen and progesterone on hypothalamic thermoregulatory centers 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 hypervolemia—originally developed to help offset the 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^+ L^{-1}), with moderate osmolality (253 mOsm kg^{-1}), is effective in inducing hyperhydration and hypervolemia 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; Greenleaf et al. 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 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 (Eijsvogels et al. 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 estrogens 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 synthesized (Ishunina and Swaab 1999; Sar and Stumpf 1980). Stachenfeld and colleagues demonstrated an estrogen-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)).

Thermoregulatory and cardiovascular capacity may be impaired at lower relative magnitudes of exercise-induced dehydration in females compared with males. Females have, on average, lower absolute total water volume as compared with males (~ 31 versus ~ 44 L) (Ritz et al. 2008) even when expressed as a proportion of body mass (~ 49% versus 58%) (Driscoll et al. 2020). It has been suggested that the lower body water in females vs. males results in a larger proportion of a female's total body water lost during exercise-induced dehydration, yet equivalent losses of plasma volume between the sexes under similar exercise conditions (Logan-Sprenger et al. 2012, 2013) representing sex differences in the compartmentalization of fluids. Thus, with less total body water and blood volume in conjunction with a lower proportion of total body water (Retzlaff et al. 1969; Bhave and Neilson 2011) distributed to the extracellular compartment, as compared to males, females have less absolute and relative fluid available to lose via sweating making the physiological consequences of fluid loss more severe.

Exercise-associated hyponatremia (EAH) refers to a clinically relevant reduction in the serum, plasma, or blood sodium concentration during or up to 24 h after physical activity (Huang et al. 2019). 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 hyponatremia in women, the differential effects of female sex hormones on sodium handling likely play a role.

Menopause, Aging, and Hydration

Independent of menopause, aging in itself has important effects on fluid balance. Aging 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 hyponatremia (Rosner et al. 2013; Stachenfeld 2014). Moreover, rehydration is a slower process with aging, primarily due to slower kidney function and hormonal responses to sodium and water flux. Estrogen-based hormone replacement therapy results in increased basal plasma osmolality, plasma volume expansion, and an earlier osmotic threshold for arginine vasopressin release (e.g., 280 versus 285 mOsmol/kg 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 estrogens induce a reduction in sodium excretion (Stachenfeld et al. 1998, 2001b), eliciting a slight reduction in the hyponatremic risk.

Summary

Drinking fluids with a higher sodium concentration than in regular sports drinks, before exercise, can elicit a transient hypovolemic 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 comparison with men, the repercussions of exercise-induced mild dehydration may occur at a lower magnitude of dehydration, thus making the physiological consequences of fluid loss more severe. In women susceptible to EAH, more fluid is retained, and more sodium is lost, when both estradiol 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 hyponatremia when both estrogen and progesterone are elevated, such as during pregnancy, while taking oral contraceptives, during the luteal phase of the menstrual cycle, and in perimenopausal athletes.

Estrogen and Antioxidants

Estrogen has wide-ranging metabolic effects impacting 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 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. 12.1).

Reactive oxygen species (ROS), although integral in the immune response and signaling pathways, can result in lipid peroxidation, cellular and mitochondrial membrane and DNA damage as well as protein and low-density lipoprotein (LDL)

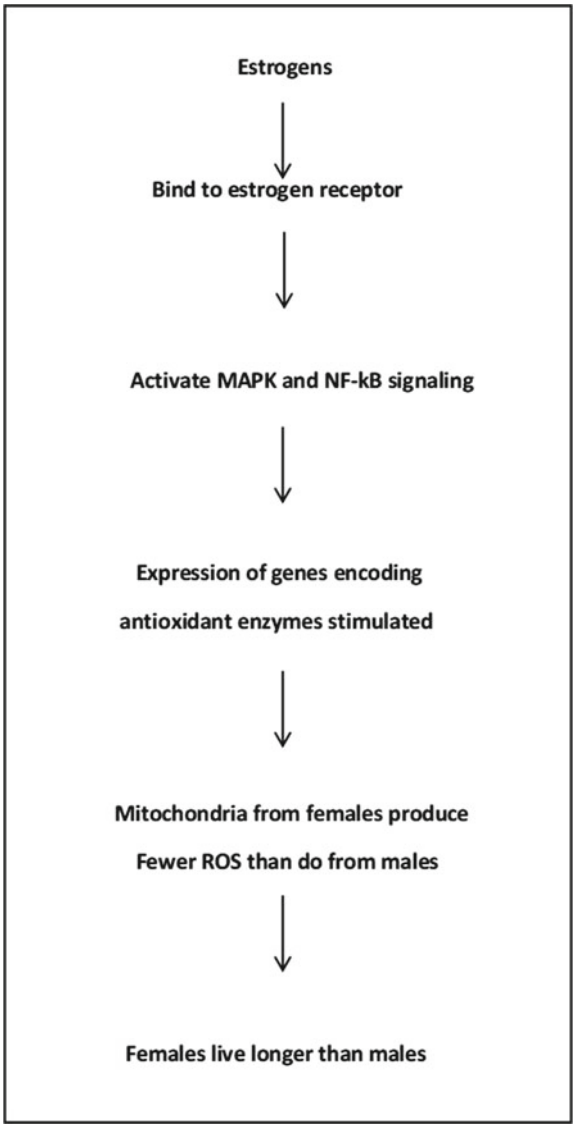

Fig. 12.1 The theoretical relationship between estrogen ROS (reactive oxygen species) and longevity of females (Adapted from Viña et al. (2005))

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 ovariectomized females (Baeza et al. 2011), and reinstated with estradiol supplementation (Stupka and Tiidus 2001), as in menopausal women reinstated with estrogens and progestins (Tranquilli et al. 1995) as well as in pharmacologically induced menopausal women (Borrás et al. 2021). Most human studies have been done in postmenopausal women, or models thereof, with and without hormone replacement therapy or in amenorrheic in contrast to eumenorrheic (Ayres et al. 1998) (Massafra et al. 1996). With the increase in lipid peroxidation and associated potential membrane damage with lack of estrogen in females, a case might be made for increased vitamin E supplementation in postmenopausal or amenorrheic women engaged in strenuous exercise regimens. However, Akova et al. (2001) observed a greater effect of endogenous estrogen levels on post-exercise damage than vitamin E, with no synergistic effect (see Fig. 12.2 for an overview of major endogenous antioxidant systems and the role of vitamins C and E.)

Differences across the menstrual cycle are less well studied and findings are not all consistent especially regarding the responses of varying measures of oxidative stress and antioxidant systems. 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 estrogen concentration but reduced thiobarbituric acid reactive substances (Tbars) (indicating

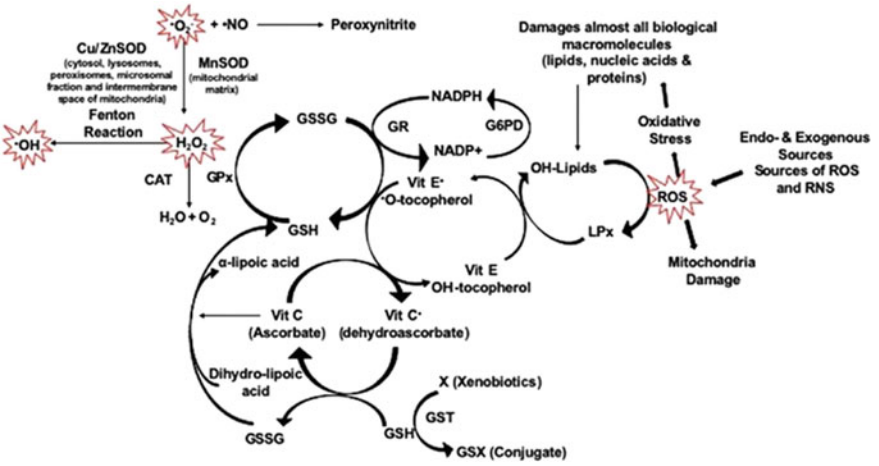

Fig. 12.2 Overview of endogenous reactive oxygen species (ROS) generation and antioxidant systems (From Chainy and Sahoo (2020))

lipid peroxidation) in response to exercise in the late-follicular compared to mid-luteal phases, and total superoxide dismutase activity greatest after exercise in the luteal phase.

However, Cornelli et al. (2013) monitored oxidative stress (hydroperoxides) every three days over the menstrual cycle and found that the greatest oxidative stress was at the estrogen peak, decreasing through the progestin (luteal) phase until the end of the cycle. They concluded that estrogen itself was not an antioxidant, but rather a pro-oxidant, like exercise, such that, in response, antioxidant systems were upregulated. There is, however, considerable conflicting evidence, supporting estrogen's role as an antioxidant. The varying models, species, methodologies, and timing of measurement may explain some of the contradictions 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 analyzing vitamin C (ascorbic acid) and its oxidized state (dehydroascorbic acid) across the menstrual cycle demonstrated that ascorbic acid concentration and total antioxidant plasma status were greatest during ovulation when estrogen peaks and in the mid-luteal phase, with dehydroascorbic acid greatest at menstruation and the mid-follicular phases (Michos et al. 2006). From this study, it is concluded that in eumenorrheic women antioxidant responses are modulated in concert with estrogen 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 ischemia/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 E supplementation was not (Kushi et al. 1996).

Furthermore, antioxidant vitamin supplementation can reduce adaptations to endurance training, including mitochondrial biogenesis (Gomez-Cabrera et al. 2008), as well as hinder the cellular adaptation to become more oxidant resistant, including upregulation of endogenous antioxidant systems (For a review of the topic 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 carbohydrate diets across the menstrual cycle (Klapcinska et al. 2002). Several antioxidant enzyme systems were improved on the low carbohydrate 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 hem iron consumed on the low carbohydrate diet (Klapcinska et al. 2002), although changes in the fatty acid composition of the diet or other nutrients cannot be discounted.

Diamanti-Kandarakis et al. (2017) describe how nutrition can impact oxidative stress in women, effects of estrogen, and how this can be linked with several metabolic disease states as well as fertility and other hormonal disorders (see Fig. 12.3). They also highlight the "yin-yang" of pro-oxidants (ROS) and antioxidants, indicating that their balance is necessary for healthy physiological function as ROS act as signaling molecules for myriad adaptations.

There are insufficient data to support supplementation with a specific antioxidant, not only can it reduce exercise-induced adaptations, but it is also less likely to provide a health, recovery, or performance edge than are antioxidant compounds provided in a matrix of nutritional components found in whole foods.

Further research is warranted to assess the positive or negative effects of antioxidant-rich foods and vitamin supplementation systematically, particularly in women during specific phases of the menstrual cycle while heavily training, and in those with low circulating sex hormones.

Polyphenols

Polyphenols are phytochemicals that can be categorized into four groups: phenolics, flavonoids, stilbenes, and lignans. Eating a diet rich in fruits and vegetables is associated with a reduction in several disease states in which chronic low-grade inflammation is a hallmark. Many flavonoids provided in particular foods alone or in combination with other nutrients have antioxidant and anti-inflammatory properties. Flavonoids include flavanols (e.g., quercetin), flavones, flavanols (e.g., catechins), anthocyanidins, flavanones, and isoflavones. For a review and meta-analysis of flavonoids on tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), two, predominantly pro-inflammatory cytokines, see Peluso et al. (2013). With respect to the training athlete, a more recent meta-analysis (27 studies, $n = 568$; 100 females) evaluated the effect of flavonoid-containing polyphenol ingestion on recovery after exercise-induced muscle damage. Polyphenol sources were tart cherry, tea extracts, pomegranate, quercetin, lemon verbena, black currant, cacao, and mixed fruit anthocyanin juice. They showed a significant beneficial impact on muscle soreness and increased strength (Carey et al. 2021).

Importantly, flavonoids have particular relevance to female athletes. A few are highlighted below. This is by no means a comprehensive review of flavonoid sources or other polyphenols and possible health, performance, or recovery attributes.

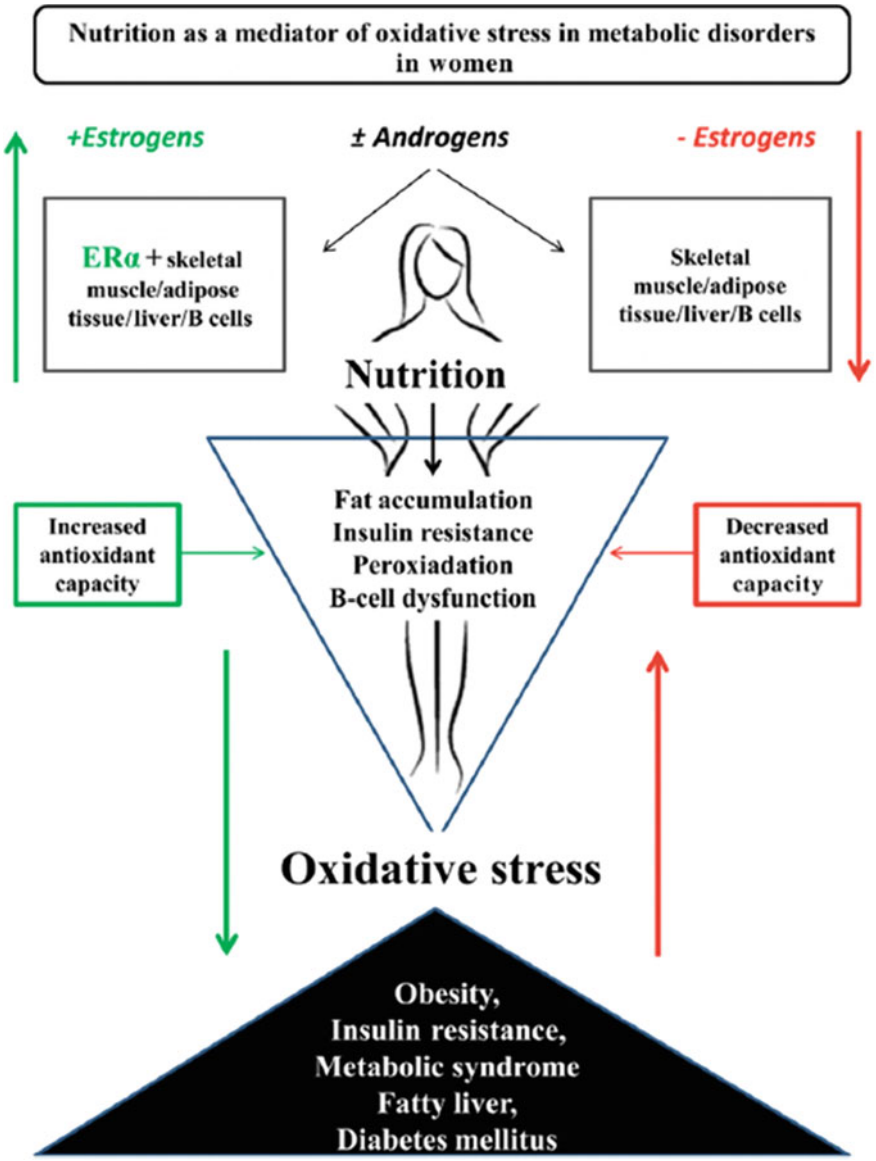

Fig. 12.3 Putative nutritional effects on oxidative stress and metabolic disorders in women . (Adapted from Diamanti-Kandarakis et al. (2017))

Soy and Isoflavones

Soy is the predominant dietary source of isoflavones, one of several classes of phytoestrogens (estrogen mimickers derived from plants that can bind to estrogen 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 estrogen-like functionality, it may promote breast cancer and some indications that there may be interference with certain breast cancer chemotherapy (Anandhi Senthilkumar et al. 2018). Thus, those at risk or diagnosed have been advised to avoid phytoestrogens. Results are far from consistent with some showing reduced cancer risk with high, long-term, isoflavone ingestion (Sak 2017).

In premenopausal women, soy phytoestrogens (45 mg isoflavones) have been observed to reduce mid-cycle surges in FSH and LH and increase estrogen in the follicular phase with one month of daily supplementation (Cassidy et al. 1994). However, the follicular phase and menstrual cycle were lengthened, and the progestin peak was 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) soy isoflavones were given for one year and no alteration in menstrual cycle length or hormone levels was observed (Maskarinec et al. 2002).

In a crossover study with young, eumenorrheic women receiving soy (52 mg isoflavones) or placebo "cookies" daily for one menstrual cycle, in addition to greater progesterone concentration three days before ovulation, the ratio of a marker of bone resorption/bone formation was higher at the mid-luteal phase (Zittermann et al. 2004). Whether this response would be observed with longer-term dietary intakes in young women and whether 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 that 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 estrogen receptors. 17-β-estradiol 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 estrogen, 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/day) was consumed 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 one 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 signaling and endogenous antioxidant systems, in this growing segment of the population.

(Blue-)Berries and Anthocyanins

Many berries contain a variety of polyphenols, in particular anthocyanins, that give them their red, blue, and purplish colors. Berry polyphenols have a range of effects ranging from anti-inflammatory, antioxidant to immunomodulatory, some of which are conferred by effects on and of the gut microbiota. For a review of berry polyphenols and their functionality, see Pap et al. (2021). Some studies with women are highlighted below.

In one well-controlled study, in recreationally (resistance and aerobically) trained females, responses to an exercise bout designed to elicit muscle damage were evaluated with blueberry supplementation (3 × 200 g) over the day, before and after exercise. This was compared with an iso-caloric dextrose drink containing vitamins C and E, with similar antioxidant capacity (ORAC) but no polyphenols (McLeay et al. 2012). Quicker recovery in peak isometric tension with the blueberry beverage was observed. McAnulty et al. (2014) observed increased natural killer cells and reduced arterial stiffness in 18- to 50-y-old men and (postmenopausal) women with 6 weeks of an equivalent of ~ 250 g of blueberries/day. It was speculated that nitric oxide (NO) half-life or production was increased. If and how these changes could account for the difference in functionality observed by McLeay et al. remains uncertain.

In contrast to the observations of McLeay et al (2012), a study in untrained older (60 + y) men and women, in which a supplement that provided an equivalent of ~ 250 g of blueberries/day versus a maltodextrin placebo, no differences in creatine kinase, inflammatory cytokines (including TNFα and IL-6), cytokine receptors, or other inflammatory signaling molecules were observed (Demczar et al. 2017). Since results were not reported for men and women separately, and the sample size may have not provided the power to detect a difference, we do not know whether sex differences may explain the varied results or whether age, training history, and dosage were critical factors.

A study in active females also found some indication of increased recovery (functional and subjective) following exercise designed to elicit muscle damage, with four days of daily supplementation with tart cherries (equivalent to 90 whole cherries), although differences in enzymatic measures of muscle damage were not observed (Brown et al. 2019). For a review on anthocyanin-containing foods and performance see Cook and Willems (2019), bearing in mind most of this work has been conducted in males.

Green Tea and Catechins

There are five main catechins in green tea, the most important of which is epigallocatechin gallate, which upregulates antioxidant enzyme systems and (potentially) modulates metabolism via SIRT1 and PGC-1α signaling pathways. In a meta-analysis of varying flavonoids, (green) tea (extract) consumption was found to be associated with decreased inflammatory cytokines IL-6 and TNFα (Peluso et al. 2013). A study of overweight, young women compared responses to an acute exercise bout with a green tea supplement or a placebo before and after 10 weeks of high-intensity training (Ghasemi et al. 2020). Training with a green tea supplement resulted in a significantly greater response in SIRT1 and PGC-1$^{\alpha}$ at rest and after an acute bout of exercise than either training or green tea supplement alone did (Ghasemi et al. 2020).

Other Polyphenol-Rich Foods and Diets

Beer contains some flavonoids and other phenolic compounds. There is some limited evidence that the polyphenols from hops and beer may help alleviate symptoms of menopause but this remains speculative (Sandoval-Ramírez et al. 2017). A systematic review was recently conducted to evaluate any cardiovascular health benefits of polyphenols in postmenopausal women (Sánchez-Martínez et al. 2021). They found variable and small effects and concluded that more study was necessary to draw firm conclusions.

Zeng et al. (2021) recently reviewed research in which the effects of a varying whole food (polyphenol-rich) on exercise-induced reactive oxygen species (ROS) were evaluated. The studies varied widely not only in the foods evaluated and experimental design but in outcome measures. These included indicators of oxidation (e.g., MDA), and to a lesser extent direct measurement of ROS, antioxidant activity, and/or inflammatory markers. The majority of studies were conducted in men, a few solely in women, and a number with both sexes. The majority reported some positive effects on exercise-induced oxidative stress with a variety of polyphenol-rich foods. The authors acknowledged that the "biological actions of the antioxidant properties from an antioxidant-rich diet are complex" and that some conflicting results may be due to varying phenolic and antioxidant composition and bioavailability thereof. There is little evidence to evaluate whether women respond differently and if menstrual phase hormones, or lack thereof, influence the response.

Fish Oil

It has been proposed that enhancement of endothelial nitric oxide (NO) production and downregulation of acute-phase cytokines by estrogen 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 IL-1 and IL-6 and may have a positive effect on endothelial NO production. Estrogen 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 double-blind, crossover study daily fish oil tablet (80 mg eicosatetraenoic acid and 120 mg docosahexaenoic acid), consumption for three months reduced premenstrual pain and ibuprofen use (Rahbar et al. 2012). Others have found similar results in combination with vitamin B12 supplementation (Deutch et al. 2000). In a review of the efficacy of treatment for dysmenorrhea, the use of fish oil was concluded to be "possibly effective", the 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 has little to no known negative effects and may prove efficacious, for those with PMS and in postmenopausal or amenorrheic women.

There may be other benefits, particularly to the older athlete. In one study with omega-3 (fish oil) supplementation conducted in older (65 + y), males and females, 16-week supplementation reduced mitochondrial ROS production, increased postabsorptive mitochondrial and sarcoplasmic protein synthesis, and post-resistance exercise mitochondrial and myofibrillar protein synthesis (Lalia et al. 2017). It is theorized that inflammation in older individuals may be, at least in part, responsible for the sarcopenia observed with aging due to inflammation and if inflammation can be reduced net protein synthesis can ensue. These results are tentative as there was no control group. Lewis et al. (2020) conducted a systematic review of randomized placebo-controlled trials on the effects of fish oil supplementation in athletes. Unfortunately, the majority were conducted with males only and no data report female responses. Results were inconsistent with some showing enhanced recovery, reduced inflammatory cytokines, enhanced antioxidant enzyme activities, enhanced cardiovascular function and oxygen kinetics (cycling), and enhanced cognitive function, but also increased lipid peroxidation. It was noted that this increased post-exercise lipid peroxidation could be alleviated if fish oil is consumed with antioxidant nutrients, e.g., polyphenols and/or vitamins (Lewis et al. 2020).

One cautionary note regarding fish or fish oil supplements, where the source of the fish and purity is uncertain, is the possibility that mercury levels could pose health risks if consumed regularly. However, it appears that supplements may pose no more of a risk of mercury toxicity than the regular consumption of fish (Foran et al. 2003; Hightower and Moore 2003), in which the levels of mercury, and other potential accumulated toxins, vary by type of fish, geographical location (Buck et al. 2019) and, to a lesser extent, cooking (Mieiro et al. 2016).

Vitamin D and 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 theorized 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, estrogen 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 estrogen in amenorrheic 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 the resumption of menstruation (Drinkwater et al. 1986) are evidence hereof. Additionally, the role vitamin D plays in immunity is gaining increased recognition. The suggested optimal

circulating level of vitamin D for athletes (75 nmol/L) is well above the deficiency cut-off of (<30 nmol/L) (He et al. 2016).

Pre- and Probiotics

Prebiotics are, to humans, non-digestible carbohydrates (fiber) that can feed and be metabolized by our gut microbiota. Probiotics are live bacterial cultures ingested to enhance endogenous gut microbes and health. Both can impact human health and metabolism. Effects of exercise on the microbiota and conversely, the microbiota on exercise, are of growing interest. (For review, see Claus et al. (2021).)

Although the long-term impact of probiotic supplementation on the microbial composition, without continued supplementation, is unlikely, several probiotic supplementation studies have been done on athletes. Few show significant performance effects, although some do show anti-inflammatory effects, cognitive/mood effects, and a few, enhancement in VO_{2max}. (For review see Marttinen et al. (2020)). A few studies have been conducted solely in females. One study in young adult, competitive, female swimmers supplemented for six weeks, during off-season training, with 4 g of 1×10^9 colony forming units (CFU)/g of a *Bifidobacterium longum* strain showed no effect on performance or immune function, but subjective stress-recovery improved (Carbuhn et al. 2018). However, in a group of moderately active, young females, two weeks of probiotic yogurt (450 g) taken daily decreased indicators of lipid peroxidation and some inflammatory factors and increased some antioxidant enzymes (Mazani et al. 2018). Unfortunately, the composition of the probiotic yogurt is not described.

In another study in distance runners, over 12 weeks, daily ingestion of a multi-strain *Bifidobacterium, Lactobacillus, Lactococcus spp.* supplement (2 g per day of 2.5×10^9 CFU/g) resulted in a decrease in the inflammatory cytokine, TNFα, in females (Smarkusz-Zarzecka et al. 2020). A study in triathletes (sex not specified) also observed lower exercise-induced increase in inflammatory cytokines (including TNFα, IL-6) after exercise with four weeks of *Lactobacillus plantarum sp.* (3×10^{10} CFU/day) supplementation (Huang et al. 2019). Additionally, post-competition creatine kinase increase was less with the probiotic supplementation.

A healthy microbiome appears to be important for bone health. (For a review of the role of the microbiota and bone health see Behera et al. (2020)). In "germ-free" rodents, bone growth is less than that of those that have typical bacterial colonization (Yan et al. 2016). In this study, systemic IGF-1 was also observed to be lower in germ-free rodents, which is known to play a role in bone remodeling.

Prebiotics (fiber-rich foods) can enhance the gut microbiota composition and the production of short-chain fatty acids, which can increase the absorption of calcium by decreasing the gut pH. A healthy microbiota is also important for intestinal wall integrity. A recent study of prebiotic supplementation (12 weeks) in 29 female athletes from various sports found a reduction in a marker of bone resorption (Ishizu et al. 2021); however, this study lacked a control group, and thus, conclusions are tentative.

There is some evidence that probiotic supplementation may help with maintaining bone mineral density in postmenopausal women. Although the data suggest that the microbiome can be important for bone health and remodeling, more data are needed (Yu et al. 2021).

Adjustments to one's diet can have profound effects on the gut microbiota and its function to optimize health and potential performance. For dietary recommendations for athletes to sustain healthy microbiota, see the article by Hughes and Holscher (2021).

Branched Chain Amino Acids (BCAA)

There appears to be an effect of estrogen 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). In ovariectomized female rats essential amino acid-BCAA mix supplementation reduced the dysmetabolism typically associated with a reduction in estrogen (body mass gain and fatty liver) (Della Torre et al. 2021). This may have particular relevance for postmenopausal and amenorrheic women, particularly those who train regularly. However, as the majority of this work has been conducted in animals, it is unclear to what extent this applies to women, and if so, whether there may be a menstrual cycle effect such that when estrogen is low should protein (and especially BCAA) 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 estrogen improved nitrogen balance during endurance exercise training (Hamadeh et al. 2005). 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.

Nutrients Versus Diet

It is tempting to search for a "magic bullet", specific nutrient or food, to supplement the diet with for a given outcome. Adherence is easier than modifying the whole diet; likewise, research interventions are easier. But nutrients in whole foods with a complement of identified and as yet unidentified elements and compounds confer greater health and adaptation to exercise than isolated essential nutrients, e.g., vitamins. One diet that has been gaining attention is the Mediterranean Diet. This dietary pattern is predominantly plant-based, rich in fruit and vegetables, with olive oil, (whole) grains, pulses, seeds, and nuts. Some dairy products (especially cheese and yogurt), eggs, fish, and small amounts of meat are eaten, along with regular,

low-moderate wine consumed with meals (Willett et al. 1995). Initially, epidemiological data indicated that those consuming such a diet, on average, lived longer and had reduced cardiovascular risk (Keys et al. 1986; Panagiotakos et al. 2006). Although randomized controlled trials are far from conclusive, there is enough evidence that this dietary pattern is recommended for postmenopausal women, in particular, providing a high level of polyphenols, other micro-nutrients, fiber and mono-unsaturated (oleic) fat, moderate protein, and low saturated fat (Cano et al. 2020; Barrea et al. 2021; Pugliese et al. 2020).

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 have focused on those with the most significant effects while acknowledging that more female-specific data are needed to draw strong conclusions. We have summarized how macronutrient intake may be modified in line with needs especially as influenced by the menstrual cycle phase in Table 12.2. Although specific foods and components of foods may have particular attributes that may be important for women at specific times (e.g., menopause), it is acknowledged that supplementation with a single (micro-) nutrient does not confer the health benefits that a varied, healthy diet, e.g., the Mediterranean Diet, does.

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, making specific recommendations for females is often based on male responses. We, as researchers that have undertaken intervention studies with females in varying phases of the

Table 12.2 Summary of practical applications of nutrients with respect to female sex hormone alterations

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 estrogen-induced reduction in gluconeogenesis during endurance exercise (> 50% VO_2max)
Female athletes need to pay extra attention to recovery nutrition throughout the menstrual cycle to protect against EIMD in the follicular phase and offset protein catabolism in the luteal phase
Estrogen and progesterone affect the hormonal and neural control of thirst, sodium regulation, and fluid retention, increasing the risk of hyponatremia during the luteal phase of the menstrual cycle

(continued)

Table 12.2 (continued)

Practical applications
Hormone therapy for menopausal women lowers the threshold for osmotic AVP release, increased basal plasma volume expansion, and decreased urine output, resulting in greater fluid retention
Estrogen enhances antioxidant capacity in females and estrogen replacement in the menopausal state can upregulate antioxidant systems
Supplementing with *dietary sources* of antioxidants may be prudent in those with amenorrhea or in menopause but may still not compensate for lack of estrogen
Single nutrients, e.g., anti-oxidant vitamins, appear to not have the same health effects as a diet rich in these from food sources and may be counterproductive in terms of exercise adaptation
Fish oil (omega-3 fatty acid source) may aid in inflammatory disorders such as dysmenorrhea and those associated with menopause
Vitamin D and calcium play a role in fertility, possibly in dysmenorrhea as well as bone health; however, they cannot fully compensate for lack of estrogen
Branched-chain amino acid oxidation may be greater when estrogen is low; this may have dietary implications for in those with amenorrhea or in menopause, particularly when training regularly and or on low energy diets

menstrual cycle, realize 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.

References

Akova B, Surmen-Gur E, Gur H, Dirican M, Sarandol E, Kucukoglu S. Exercise-induced oxidative stress and muscle performance in healthy women: role of vitamin E supplementation and endogenous oestradiol. Eur J Appl Physiol. 2001;84:141–7.

Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, Duncan CN, Olson DP, Salerno AE, Newburger JW. Hyponatremia among runners in the Boston Marathon. N Engl J Med. 2005;352:1550–6.

Anandhi Senthilkumar H, Fata JE, Kennelly EJ. Phytoestrogens: the current state of research emphasizing breast pathophysiology. Phytother Res. 2018;32:1707–19.

Ayres S, Baer J, Ravi Subbiah MT. Exercised-induced increase in lipid peroxidation parameters in amenorrhelc female athletes. Fertil Steril. 1998;69:73–7.

Baer J, Taper L, Gwazdauskas F, Walberg J, Novascone M, Ritchey S, Thye F. Diet, hormonal, and metabolic factors affecting bone mineral density in adolescent amenorrheic and eumenorrheic female runners. J Sports Med Phys Fitness. 1992;32:51–8.

Baeza I, De Castro NM, Arranz L, Fdez-Tresguerres J, De La Fuente M. Ovariectomy causes immunosenescence and oxi-inflamm-ageing in peritoneal leukocytes of aged female mice similar to that in aged males. Biogerontology. 2011;12:227–38.

Bailey SP, Zacher CM, Mittleman KD. Effect of menstrual cycle phase on carbohydrate supplementation during prolonged exercise to fatigue. J Appl Physiol. 2000;88:690–7.

Barr SI, Janelle KC, Prior JC. Energy intakes are higher during the luteal phase of ovulatory menstrual cycles. Am J Clin Nutr. 1995;61:39–43.

Barrea L, Pugliese G, Laudisio D, Colao A, Savastano S, Muscogiuri G. Mediterranean diet as medical prescription in menopausal women with obesity: a practical guide for nutritionists. Crit Rev Food Sci Nutr. 2021;61:1201–11.

Behera J, Ison J, Tyagi SC, Tyagi N. The role of gut microbiota in bone homeostasis. Bone. 2020;135: 115317.

Benton MJ, Hutchins AM, Dawes JJ. Effect of menstrual cycle on resting metabolism: a systematic review and meta-analysis. PLoS ONE. 2020;15: e0236025.

Berger NJA, Campbell IT, Wlkerson DP, Jones AM. Influence of acute plasma volume expansion on Vo2 kineitics, Vo2peak, and performance during high-intensity cycle exercise. J Appl Phsyiol. 2006;101:707–14.

Bhave G, Neilson EG. Body Fluid Dynamics: Back to the Future. J Am Soc Nephrol. 2011;22:2166–81.

Bisson DL, Dunster GD, O'hare JP, Hampton D, Penney MD. Renal sodium retention does not occur during the luteal phase of the menstrual cycle in normal women. Br J Obstet Gynaecol. 1992;99**:**247–52.

Blakesmith SJ, Lyons-Wall PM, George C, Joannou GE, Petocz P, Samman S. Effects of supplementation with purified red clover (Trifolium pratense) isoflavones on plasma lipids and insulin resistance in healthy premenopausal women. Br J Nutr. 2003;89:467–74.

Borrás C, Ferrando M, Inglés M, Gambini J, Lopez-Grueso R, Edo R, Mas-Bargues C, Pellicer A, Viña J. Estrogen replacement therapy induces antioxidant and longevity-related genes in women after medically induced menopause. Oxid Med Cell Longev. 2021.

Bourdas DI, Souglis A, Zacharakis ED, Geladas ND, Travlos AK. Meta-analysis of carbohydrate solution intake during prolonged exercise in adults: from the last 45+ years' perspective. Nutrients. 2021;13:4223.

Brennan L, Gibbons H. Sex matters: a focus on the impact of biological sex on metabolomic profiles and dietary interventions. Proc Nutr Soc. 2020;79:205–9.

Broad E, Cox G. What is the optimal composition of an athlete's diet? Eur J Sport Sci. 2008;8:57–65.

Brown MA, Stevenson EJ, Howatson G. Whey protein hydrolysate supplementation accelerates recovery from exercise-induced muscle damage in females. Appl Physiol Nutr Metab. 2018;43:324–30.

Brown MA, Stevenson EJ, Howatson G. Montmorency tart cherry (*Prunus cerasus L.*) supplementation accelerates recovery from exercise-induced muscle damage in females. Eur J Sport Sci. 2019;19:95–102.

Buck DG, Evers DC, Adams E, Digangi J, Beeler B, Samánek J, Petrlik J, Turnquist MA, Speranskaya O, Regan K, Johnson S. A global-scale assessment of fish mercury concentrations and the identification of biological hotspots. Sci Total Environ. 2019;687:956–66.

Burke L, Hawley J, Schabort E, St Clair Gibson A, Mujika I, Noakes T. Carbohydrate loading failed to improve 100 km cycling performance in a placebo-controlled trial. J Appl Physiol. 2000;88:1284–90.

Burke LM. Ketogenic low-CHO, high-fat diet: the future of elite endurance sport? J Physiol. 2021;599:819–43.

Calloway DH, Kurzer MS. Menstrual cycle and protein requirements of women. J Nutr. 1982;112:356–66.

Campbell BI, Aguilar D, Conlin L, Vargas A, Schoenfeld BJ, Corson A, Gai C, Best S, Galvan E, Couvillion K. Effects of high versus low protein intake on body composition and maximal strength in aspiring female physique athletes engaging in an 8-week resistance training program. Int J Sport Nutr Exerc Metab. 2018;28:580–5.

Campbell MJ, Woodside JV, Honour JW, Morton MS, Leathem AJ. Effect of red clover-derived isoflavone supplementation on insulin-like growth factor, lipid and antioxidant status in healthy female volunteers: a pilot study. Eur J Clin Nutr. 2004;58:173–9.

Campbell S, Angus D, Febbraio M. Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. Am J Physiol Endocrinol Metab. 2001;281:E817–25.

Campbell S, Febbraio M. Effect of ovarian hormones on mitochondrial enzyme activity in fat oxidation patheay of skeletal muscle. Am J Physiol Endocrinol Metab. 2001;281:E803–8.
Campbell S, Febbraio M. Effect of ovarian hormones on GLUT4 expression and contraction-stimulated glucose uptake. Am J Physiol Endocrinol Metab. 2002;282:E1139–46.
Cano A, Marshall S, Zolfaroli I, Bitzer J, Ceausu I, Chedraui P, Durmusoglu F, Erkkola R, Goulis DG, Hirschberg AL, Kiesel L, Lopes P, Pines A, Van Trotsenburg M, Lambrinoudaki I, Rees M. The Mediterranean diet and menopausal health: an EMAS position statement. Maturitas. 2020;139:90–7.
Carbuhn AF, Reynolds SM, Campbell CW, Bradford LA, Deckert JA, Kreutzer A, Fry AC. Effects of probiotic (Bifidobacterium longum 35624) supplementation on exercise performance, immune modulation, and cognitive outlook in Division I female swimmers. Sports. 2018;6:116.
Carey CC, Lucey A, Doyle L. Flavonoid containing polyphenol consumption and recovery from exercise-induced muscle damage: a systematic review and meta-analysis. Sports Med. 2021;51:1293–316.
Casazza G, Jacobs K, Suh S-H, Miller B, Horning M, Brooks G. Menstrual cycle phase and oral contraceptive effects on triglyceride mobilisation during exercise. J Appl Physiol. 2004;97:302–9.
Cassidy A, Bingham S, Setchell KD. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr. 1994;60:333–40.
Cederroth CR, Nef S. Soy, phytoestrogens and metabolism: a review. Mol Cell Endocrinol. 2009;304:30–42.
Cermak N, Van Loon L. The use of carbohydrates during exercise as an ergogenic aid. Sports Med. 2013;43:1139–55.
Chainy GBN, Sahoo DK. Hormones and oxidative stress: an overview. Free Radical Res. 2020;54:1–26.
Charkoudian N, Johnson JM. Modification of active cutaneous vasodilation by oral contraceptive hormones. J Appl Physiol. 1997;83:2012–8.
Charkoudian N, Johnson JM. Reflex control of cutaneous vasoconstrictor system is reset by exogenous female reproductive hormones. J Appl Physiol. 1999;87:381–5.
Charkoudian N, Stachenfeld NS. Reproductive hormone influences on thermoregulation in women. Compr Physiol. 2011;4:793–804.
Charkoudian N, Stephens DP, Pirkle KC, Kosiba WA, Johnson JM. Influence of female reproductive hormones on local thermal control of skin blood flow. J Appl Physiol. 1999;87:1719–23.
Cheneviere X, Borrani F, Sangsue D, Gojanovic B, Malatesta D. Gender differences in whole-body fat oxidation kinetics during exercise. Appl Physiol Nutr Metab. 2011;36:88–95.
Chryssanthopoulos C, Ziaras C, Oosthuyse T, Lambropoulos I, Giorgios PP, Zacharogiannis E, Philippou A, Maridaki M. Carbohydrate mouth rinse does not affect performance during a 60-min running race in women. J Sports Sci. 2018;36**:**824–33.
Chung SC, Goldfarb AH, Jamurtas AZ, Hegde SS, Lee J. Effect of exercise during the follicular and luteal phases on indices of oxidative stress in healthy women. Med Sci Sports Exerc. 1999;31:409–13.
Clauss M, Gérard P, Mosca A, Leclerc M. Interplay between exercise and gut microbiome in the context of human health and performance. Front Nutr. 2021;8:637010–637010.
Cook MD, Willems MET. Dietary anthocyanins: a review of the exercise performance effects and related physiological responses. Int J Sport Nutr Exerc Metab. 2019;29:322–30.
Cornelli U, Belcaro G, Cesarone MR, Finco A. Analysis of oxidative stress during the menstrual cycle. Reprod Biol Endocrinol. 2013;11:74.
Correia-Oliveira C, Bertuzzi R, Dal'molin Kiss M, Lima-Silva A. Strategies of dietary carbohydrate manipulation and their effects of performance in cycling time trials. Sports Med. 2013;43:707–19.
D'eon T, Sharoff C, Chipkin S, Grow D, Ruby B, Braun B. Regulation of exericse carbohydrate metabolism by estrogen and progesterone in women. Am J Physiol Endocrinol Metab. 2002;283:E1046–55.

De Souza LB, Martins KA, Cordeiro MM, Rodrigues YDS, Rafacho BPM, Bomfim RA. Do food intake and food cravings change during the menstrual cycle of young women? Rev Bras Ginecol Obstet. 2018;40:686–92.

Della Torre S, Benedusi V, Pepe G, Meda C, Rizzi N, Uhlenhaut NH, Maggi A. Dietary essential amino acids restore liver metabolism in ovariectomized mice via hepatic estrogen receptor α. Nat Commun. 2021;12:6883.

Demczar C, Behrens C, Baltz L, Georgescu V, Arminavage D, Brown J, Fussell D, Trate T, Mcanulty S, Mcanulty L. Six weeks of daily blueberry consumption does not alter aged skeletal muscle inflammation profile or inflammatory response to eccentric-exercise. J Aging Res Clin Pract. 2017;6:229–37.

Deutch B, Jørgensen EB, Hansen JC. Menstrual discomfort in Danish women reduced by dietary supplements of omega-3 PUFA and B 12 (fish oil or seal oil capsules). Nutr Res. 2000;20:621–31.

Devries M, Hamadeh M, Phillips S, Tarnopolsky M. Menstrual cycle phase and sex influence muscle glycogen utilization and glucose turnover during moderate-intensity endurance exercise. Am J Physiol Regul Integr Comp Physiol. 2006;291:R1120–8.

Devries MC. Sex-based differences in endurance exercise muscle metabolism: impact on exercise and nutritional strategies to optimize health and performance in women. Exp Physiol. 2016;101:243–9.

Diamanti-Kandarakis E, Papalou O, Kandaraki EA, Kassi G. Mechanisms in endocrinology: nutrition as a mediator of oxidative stress in metabolic and reproductive disorders in women. Eur J Endocrinol. 2017;176:R79–99.

Draper C, Duisters K, Weger B, Chakrabarti A, Harms A, Brennan L, Hankemeier T, Goulet L, Konz T, Martin F. Menstrual cycle rhythmicity: metabolic patterns in healthy women. Sci Rep. 2018;8:1–15.

Dreyer HC, Fujita S, Glynn EL, Drummond MJ, Volpi E, Rasmussen BB. Resistance exercise increases leg muscle protein synthesis and mTOR signalling independent of sex. Acta Physiol. 2010;199:71–81.

Drinkwater BL, Nilson K, Ott S, Chesnut CH. Bone mineral density after resumption of menses in amenorrheic athletes. JAMA. 1986;256:380–2.

Driscoll RL, Mccarthy DG, Palmer MS, Spriet LL. Mild dehydration impaired intermittent sprint performance and thermoregulation in females. Appl Physiol Nutr Metab. 2020;45:1045–8.

Druyan A, Makranz C, Moran D, Yanovich R, Epstein Y, Heled Y. Heat tolerance in women: reconsidering the criteria. Aviat Space Environ Med. 2012;83:58–60.

Eck LH, Bennett AG, Egan BM, Ray J, Mitchell CO, Smith MA, Klesges RC. Differences in macronutrient selections in users and nonusers of an oral contraceptive. Am J Clin Nutr. 1997;65:419–24.

Eijsvogels TMH, Scholten RR, Van Duijnhoven NTL, Thijssen DHJ, Hopman MTE. Sex difference in fluid balance responses during prolonged exercise. Scand J Med Sci Sports. 2013;23:198–206.

Elliott-Sale K, Ross E, Burden R, Hicks K. The BASES expert statement on conducting and implementing female athlete based research. Sport Exerc Sci**:**6–7.

Faustmann G, Meinitzer A, Magnes C, Tiran B, Obermayer-Pietsch B, Gruber H-J, Ribalta J, Rock E, Roob JM, Winklhofer-Roob BM. Progesterone-associated arginine decline at luteal phase of menstrual cycle and associations with related amino acids and nuclear factor kB activation. PLoS ONE. 2018;13: e0200489.

Flynn S, Rosales A, Hailes W, Ruby B. Males and females exhibit similar muscle glycogen recovery with varied recovery food sources. Eur J Appl Physiol. 2020;120:1131–42.

Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? Arch Pathol Lab Med. 2003;127:1603–5.

Fortney SM, Wenger CB, Bove JR, Nadel ER. Effect of hyperosmolality on control of blood flow and sweating. J Appl Physiol. 1984;57:1688–95.

Frey MaB, Riddle J, Charles JB, Bungo MW. Blood and urine responses to ingesting fluids of various salt and glucose-concentrations. J Clin Pharmacol. 1991;31**:**880–87.

Gagnon D, Jay O, Lemire B, Kenny GP. Sex-related differences in evaporative heat loss: the importance of metabolic heat production. Eur J Appl Physiol. 2008;104:821–9.
Gagnon D, Kenny GP. Sex modulates whole-body sudomotor thermosensitivity during exercise. J Physiol. 2011;589:6205–17.
Gagnon D, Kenny GP. Sex differences in thermoeffector responses during exercise at fixed requirements for heat loss. J Appl Physiol. 2012;113:746–57.
Ghasemi E, Afzalpour ME, Nayebifar S. Combined high-intensity interval training and green tea supplementation enhance metabolic and antioxidant status in response to acute exercise in overweight women. J Physiol Sci. 2020;70:31.
Gomez-Cabrera M-C, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo FV, Sastre J, Vina J. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. Am J Clin Nutr. 2008;87:142–9.
Gorczyca AM, Sjaarda LA, Mitchell EM, Perkins NJ, Schliep KC, Wactawski-Wende J, Mumford SL. Changes in macronutrient, micronutrient, and food group intakes throughout the menstrual cycle in healthy, premenopausal women. Eur J Nutr. 2016;55:1181–8.
Green MS, Corona BT, Doyle JA, Ingalls CP. Carbohydrate-protein drinks do not enhance recovery from exercise-induced muscle injury. Int J Sport Nutr Exerc Metab. 2008;18:1–18.
Greenleaf JE, Jackson CG, Geelen G, Keil LC, Hinghofer-Szalkay H, Whittam JH. Plasma volume expansion with oral fluids in hypohydrated men at rest and during exercise. Aviat Space Environ Med. 1998a;69:837–44.
Greenleaf JE, Looft-Wilson R, Wisherd JL, Jackson CG, Fung PP, Ertl AC, Barnes PR, Jensen CD, Whittam JH. Hypervolemia in men from fluid ingestion at rest and during exercise. Aviat Space Environ Med. 1998b;69:374–86.
Greenleaf JE, Looft-Wilson R, Wisherd JL, Mckenzie MA, Jensen CD, Whittam JH. Pre-Exercise hypervolemia and cycle ergometer endurance in men. Biol Sport. 1997;14:103–14.
Gui Z, Sun F, Si G, Chen Y. Effect of protein and carbohydrate solutions on running performance and cognitive function in female recreational runners. PLoS ONE. 2017;12: e0185982.
Hackney A. Effects of the menstrual cycle on resting muscle glycogen content. Horm Metab Res. 1990;22:647.
Hackney A, Curley C, Nicklas B. Physiological responses to submaximal exercise at the mid-follicular, ovulatory and mid-luteal phases of the menstrual cycle. Scand J Med Sci Sports. 1991;1:94–8.
Hackney AC, McCracken-Compton MA, Ainsworth B. Substrate responses to submaximal exercise in the midfollicular and midluteal phases of the menstrual cycle. Int J Sport Nutr Exerc Metab. 1994;4:299–308.
Hamadeh MJ, Devries MC, Tarnopolsky MA. Estrogen supplementation reduces whole body leucine and carbohydrate oxidation and increases lipid oxidation in men during endurance exercise. J Clin Endocrinol Metab. 2005;90:3592–9.
Hansen P, McCarthy T, Pasia E, Spina R, Gulve E. Effects of ovariectomy and exercise training on muscle GLUT-4 content and glucose metabolism in rats. J Appl Physiol. 1996;80:1605–11.
Hashimoto H, Ishijima T, Hayashida H, Suzuki K, Higuchi M. Menstrual cycle phase and carbohydrate ingestion alter immune response following endurance exercise and high intensity time trial performance test under hot conditions. J Int Soc Sports Nutr. 2014;11:39.
Hausswirth C, Le Meur Y. Physiological and nutritional aspects of post-exercise recovery: specific recommendations for female athletes. Sports Med. 2011;41:861–82.
Hawley J, Palmer G, Noakes T. Effects of 3 days of carbohydrate supplementation on muscle glycogen content and utilisation during a 1-h cycling performance. Eur J Appl Physiol Occup Physiol. 1997;75:407–12.
He C-S, Yong XHA, Walsh NP, Gleeson M. Is there an optimal vitamin D status for immunity in athletes and military personnel? Exerc Immunol Rev. 2016;22:42–64.
Helm MM, Mcginnis GR, Basu A. Impact of nutrition-based interventions on athletic performance during menstrual cycle phases: a review. Int J Environ Res Public Health. 2021;18:6294.

Hew-Butler T, Rosner MH, Fowkes-Godek S, Dugas JP, Hoffman MD, Lewis DP, Maughan RJ, Miller KC, Montain SJ, Rehrer NJ. Statement of the third international exercise-associated hyponatremia consensus development conference, Carlsbad, California, 2015. Clin J Sport Med. 2015;25:303–20.

Hightower JM, Moore D. Mercury levels in high-end consumers of fish. Environ Health Perspect. 2003;111:604.

Hiroshoren N, Tzoran I, Makrienko I, Edoute Y, Plawner MM, Itskovitz-Eldor J, Jacob G. Menstrual cycle effects on the neurohumoral and autonomic nervous systems regulating the cardiovascular system. J Clin Endocrinol Metab. 2002;87:1569–75.

Holtzman B, Ackerman KE. Recommendations and nutritional considerations for female athletes: health and performance. Sports Med. 2021;51:43–57.

Houghton BL, Holowatz LA, Minson CT. Influence of progestin bioactivity on cutaneous vascular responses to passive heating. Med Sci Sports Exerc. 2005;37**:**45–51; discussion 52.

Houltham S, Rowlands D. A snapshot of nitrogen balance in endurance-trained women. Appl Physiol Nutr Metab. 2014;39:219–25.

Howatson G, Van Someren K. The prevention and treatment of exercise-induced muscle damage. Sports Med. 2008;38:483–503.

Huang W-C, Wei C-C, Huang C-C, Chen W-L, Huang H-Y. The beneficial effects of *Lactobacillus plantarum* PS128 on high-intensity, exercise-induced oxidative stress, inflammation, and performance in triathletes. Nutrients. 2019;11:353.

Hughes RL, Holscher HD. Fueling gut microbes: a review of the interaction between diet, exercise, and the gut microbiota in athletes. Adv Nutr. 2021;12:2190–215.

Hulton A, Malone J, Campbell I, Maclaren D. The effect of the menstrual cycle and hyperglycaemia on hormonal and metabolic responses during exercise. Eur J Appl Physiol. 2021;121:2993–3003.

Ihalainen JK, Löfberg I, Kotkajuuri A, Kyröläinen H, Hackney AC, Taipale-Mikkonen RS. Influence of menstrual cycle or hormonal contraceptive phase on energy intake and metabolic hormones—a pilot study. Endocrines. 2021;2:79–90.

Ishizu T, Takai E, Torii S, Taguchi M. Prebiotic food intake may improve bone resorption in Japanese female athletes: a pilot study. Sports. 2021;9:82.

Ishunina TA, Swaab DF. Vasopressin and oxytocin neurons of the human supraoptic and paraventricular nucleus; size changes in relation to age and sex. J Clin Endocrinol Metab. 1999;84:4637–44.

James A, Lorraine M, Cullen D, Goodman C, Dawson B, Palmer T, Fournier P. Muscle glycogen supercompensation: absence of a gender-related difference. Eur J Appl Physiol. 2001;85:533–8.

Jeukendrup A. Nutrition for endurance sports: marathon, triathlon, and road cycling. J Sports Sci. 2011;29:S91–9.

Joo MH, Maehata E, Adachi T, Ishida A, Murai F, Mesaki N. The relationship between exercise-induced oxidative stress and the menstrual cycle. Eur J Appl Physiol. 2004;93:82–6.

Jukic AM, Steiner AZ, Baird DD. Association between serum 25-hydroxyvitamin D and ovarian reserve in premenopausal women. Menopause. 2015;22:312–6.

Kammoun I, Saâda WB, Sifaou A, Haouat E, Kandara H, Salem LB, Slama CB. Change in women's eating habits during the menstrual cycle. Ann Endocrinol. Paris:Elsevier; 2017. p. 33–37.

Kang AK, Duncan JA, Cattran DC, Floras JS, Lai V, Scholey JW, Miller JA. Effect of oral contraceptives on the renin angiotensin system and renal function. Am J Physiol Regul Integr Comp Physiol. 2001**:**R807–13.

Kawahata A. Sex differences in sweating. In: ITO S, Ogata H, Yoshimura H, editors. Essential problems in climatic physiology. Kyoto, Japan: Nankodo Publ.

Keane K, Salicki R, Goodall S, Thomas K, Howatson G. Muscle damage response in female collegiate athletes after repeated sprint activity. J Strength Cond Res. 2015;29:2802–7.

Kehrer JP. Free radicals as mediators of tissue injury and disease. Crit Rev Toxicol. 1993;23:21–48.

Kerksick CM, Arent S, Schoenfeld BJ, Stout JR, Campbell B, Wilborn CD, Taylor L, Kalman D, Smith-Ryan AE, Kreider RB. International society of sports nutrition position stand: nutrient timing. J Int Soc Sports Nutr. 2017;14:1–21.

Keys A, Mienotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, Kromhout D, Nedeljkovic S, Punsar S, Seccareccia F, Toshima H. The diet and 15-year death rate in the seven countries study. Am J Epidemiol. 1986;124:903–15.

Klapcinska B, Sadowska-Krepa E, Manowska B, Pilis W, Sobczak A, Danch A. Effects of a low carbohydrate diet and graded exercise during the follicular and luteal phases on the blood antioxidant status in healthy women. Eur J Appl Physiol. 2002;87:373–80.

Kobayashi R, Shimomura Y, Murakami T, Nakai N, Fujitsuka N, Otsuka M, Arakawa N, Popov KM, Harris RA. Gender difference in regulation of branched-chain amino acid catabolism. Biochem J. 1997;327:449–53.

Köhne JL, Ormsbee MJ, Mckune AJ. Supplementation strategies to reduce muscle damage and improve recovery following exercise in females: a systematic review. Sports. 2016;4:51.

Kolka MA, Stephenson LA. Effect of luteal phase elevation in core temperature on forearm blood flow during exercise. J Appl Physiol. 1997a;82:1079–83.

Kolka MA, Stephenson LA. Resetting the thermoregulatory set-point by endogenous estradiol or progesterone in women. Ann N Y Acad Sci. 1997b;813:204–6.

Kriengsinyos W, Wykes L, Goonewardene L, Ball R, Pencharz P. Phase of menstrual cycle affects lysine requirement in healthy women. Am J Physiol Endocrinol Metab. 2004;287:E489–96.

Krishnan S, Tryon RR, Horn WF, Welch L, Keim NL. Estradiol, SHBG and leptin interplay with food craving and intake across the menstrual cycle. Physiol Behav. 2016;165:304–12.

Kuipers H, Saris W, Brouns F, Keizer H, Ten Bosch C. Glycogen synthesis during exercise and rest with carbohydrate feeding in males and females. Int J Sports Med. 1989;10:S63–7.

Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med. 1996;334:1156–62.

Lalia AZ, Dasari S, Robinson MM, Abid H, Morse DM, Klaus KA, Lanza IR. Influence of omega-3 fatty acids on skeletal muscle protein metabolism and mitochondrial bioenergetics in older adults. Aging. 2017;9:1096–129.

Lamont L, Lemon P, Bruot B. Menstrual cycle and exercise effects on protein catabolism. Med Sci Sports Exerc. 1987;19:106–10.

Lariviere F, Moussalli R, Garrel D. Increased leucine flux and leucine oxidation during the luteal phase of the menstrual cycle in women. Am J Physiol Endocrinol Metab. 1994;267:E422–8.

Latour M, Shinoda M, Lavoie J-M. Metabolic effects of physical training in ovariectomized and hyperestrogenic rats. J Appl Physiol. 2001;90:235–41.

Lavoie J, Dionne N, Helie R, Brisson G. Menstrual cycle phase dissociation of blood glucose homeostasis during exercise. J Appl Physiol. 1987;62:1084–9.

Lewis NA, Daniels D, Calder PC, Castell LM, Pedlar CR. Are there benefits from the use of fish oil supplements in athletes? a systematic review. Adv Nutr. 2020;11:1300–14.

Logan-Sprenger HM, Heigenhauser GJF, Jones GL, Spriet LL. Increase in skeletal-muscle glycogenolysis and perceived exertion with progressive dehydration during cycling in hydrated men. Int J Sport Nutr Exerc Metab. 2013;23:220–9.

Logan-Sprenger HM, Heigenhauser GJF, Killian KJ, Spriet LL. Effects of dehydration during cycling on skeletal muscle metabolism in females. Med Sci Sports Exerc. 2012;44:1949–57.

Mack GW, Nadel ER. Body fluid balance during heat stress in humans. Compr physiol. Wiley.

Malowany JM, West DW, Williamson E, Volterman KA, Abou Sawan S, Mazzulla M, Moore DR. Protein to maximize whole-body anabolism in resistance-trained females after exercise. Med Sci Sports Exerc. 2019;51:798–804.

Margolis LM, Allen JT, Hatch-Mcchesney A, Pasiakos SM. Coingestion of carbohydrate and protein on muscle glycogen synthesis after exercise: a meta-analysis. Med Sci Sports Exerc. 2021;53:384.

Marttinen M, Ala-Jaakkola R, Laitila A, Lehtinen MJ. Gut microbiota, probiotics and physical performance in athletes and physically active individuals. Nutrients. 2020;12:2936.

Maskarinec G, Williams AE, Inouye JS, Stanczyk FZ, Franke AA. A randomized isoflavone intervention among premenopausal women. Cancer Epidemiol Biomarkers Prev. 2002;11:195–201.

Massafra C, Buonocore G, Gioia D, Sargentini I. Changes in the erythrocyte antioxidant enzyme system during transdermal estradiol therapy for secondary amenorrhea. Gynecol Endocrinol. 1996;10:155–8.

Matute M, Kalkhoff R. Sex steroid influence on hepatic glucoenogenesis and glycogen formation. Endocrinology. 1973;92:762–8.

Maughan RJ, Leiper JB, Shirreffs SM. Factors influencing the restoration of fluid and electrolyte balance after exercise in the heat. Br J Sports Med. 1997;31:175–82.

Maughan RJ, Shirreffs SM, Leiper JB. Errors in the estimation of hydration status from changes in body mass. J Sports Sci. 2007;25:797–804.

Mazani M, Nemati A, Amani M, Haedari K, Mogadam RA, Baghi AN. The effect of probiotic yoghurt consumption on oxidative stress and inflammatory factors in young females after exhaustive exercise. J Pak Med Assoc. 2018;68:1748–54.

McAnulty LS, Collier SR, Landram MJ, Whittaker DS, Isaacs SE, Klemka JM, Cheek SL, Arms JC, McAnulty SR. Six weeks daily ingestion of whole blueberry powder increases natural killer cell counts and reduces arterial stiffness in sedentary males and females. Nutr Res. 2014;34:577–84.

McCarty MF. Vascular nitric oxide, sex hormone replacement, and fish oil may help to prevent Alzheimer's disease by suppressing synthesis of acute-phase cytokines. Med Hypotheses. 1999;53:369–74.

McLay R, Thomson C, Williams S, Rehrer N. Carbohydrate loading and female endurance athletes: effects of menstrual-cycle phase. Int J Sport Nutr Exerc Metab. 2007;17:189–205.

McLeay Y, Barnes MJ, Mundel T, Hurst SM, Hurst RD, Stannard SR. Effect of New Zealand blueberry consumption on recovery from eccentric exercise-induced muscle damage. J Int Soc Sports Nutr. 2012;9:1–12.

Mee JA, Gibson OR, Doust J, Maxwell NS. A comparison of males and females' temporal patterning to short- and long-term heat acclimation. Scand J Med Sci Sports. 2015;25:250–8.

Mei J, Yeung SS, Kung AW. High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women. J Clin Endocrinol Metab. 2001;86:5217–21.

Melin AK, Heikura IA, Tenforde A, Mountjoy M. Energy availability in athletics: health, performance, and physique. Int J Sport Nutr Exerc Metab. 2019;29:152–64.

Mercer D, Convit L, Condo D, Carr AJ, Hamilton DL, Slater G, Snipe RM. Protein requirements of pre-menopausal female athletes: systematic literature review. Nutrients. 2020;12:3527.

Mestre-Alfaro A, Ferrer MD, Sureda A, Tauler P, Martinez E, Bibiloni MM, Micol V, Tur JA, Pons A. Phytoestrogens enhance antioxidant enzymes after swimming exercise and modulate sex hormone plasma levels in female swimmers. Eur J Appl Physiol. 2011;111:2281–94.

Michos C, Kiortsis DN, Evangelou A, Karkabounas S. Antioxidant protection during the menstrual cycle: the effects of estradiol on ascorbic-dehydroascorbic acid plasma levels and total antioxidant plasma status in eumenorrhoic women during the menstrual cycle. Acta Obstet Gynecol Scand. 2006;85:960–5.

Mieiro CL, Coelho JP, Dolbeth M, Pacheco M, Duarte AC, Pardal MA, Pereira ME. Fish and mercury: Influence of fish fillet culinary practices on human risk. Food Control. 2016;60:575–81.

Miller BF, Hansen M, Olesen JL, Flyvbjerg A, Schwarz P, Babraj JA, Smith K, Rennie MJ, Kjaer M. No effect of menstrual cycle on myofibrillar and connective tissue protein synthesis in contracting skeletal muscle. Am J Physiol Endocrinol Metab. 2006;290:E163–8.

Moore DR. Maximizing post-exercise anabolism: the case for relative protein intakes. Front Nutr. 2019;147.

Moore DR, Sygo J, Morton JP. Fuelling the female athlete: carbohydrate and protein recommendations. Eur J Sport Sci. 2021:1–13.

Moran DS, Shapiro Y, Laor A, Izraeli S, Pandolf KB. Can gender differences during exercise-heat stress be assessed by the physiological strain index? Am J Physiol Regul Integr Comp Physiol. 1999;276:R1798–804.

Moreira AC, Silva AM, Santos MS, Sardão VA. Phytoestrogens as alternative hormone replacement therapy in menopause: What is real, what is unknown. J Steroid Biochem Mol Biol. 2014;143:61–71.

Morrow C, Naumburg EH. Dysmenorrhea. Primary Care Clin Office Pract. 2009;36:19–32.

Nhan S, Anderson KE, Nagamani M, Grady JJ, Lu LJ. Effect of a soymilk supplement containing isoflavones on urinary F2 isoprostane levels in premenopausal women. Nutr Cancer. 2005;53:73–81.

Nicklas B, Hackney A, Sharp R. The menstrual cycle and exercise: performance, muscle glycogen, and substrate responses. Int J Sports Med. 1989;10:264–9.

Nowak J, Podsiadło A, Hudzik B, Jagielski P, Grochowska-Niedworok E, Gąsior M, Zubelewicz-Szkodzińska B. Food intake changes across the menstrual cycle: a preliminary study. Pielęgniarstwo i Zdrowie Publiczne. 2020;10.

Obayashi M, Shimomura Y, Nakai N, Jeoung NH, Nagasaki M, Murakami T, Sato Y, Harris RA. Estrogen controls branched-chain amino acid catabolism in female rats. J Nutr. 2004;134:2628–33.

Oian P, Tollan A, Fadnes HO, Noddeland H, Maltau JM. Transcapillary fluid dynamics during the menstrual cycle. Am J Obstet Gynecol. 1987;156:952–5.

Oosthuyse T, Bosch A. The effect of the menstrual cycle on exercise metabolism. Implications for exercise performance in eumenorrhoeic women. Sports Med. 2010;40:207–27.

Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis. 2006;16:559–68.

Pap N, Fidelis M, Azevedo L, Do Carmo MaV, Wang D, Mocan A, Pereira EPR, Xavier-Santos D, Sant'ana AS, Yang B, Granato D. Berry polyphenols and human health: evidence of antioxidant, anti-inflammatory, microbiota modulation, and cell-protecting effects. Curr Opin Food Sci. 2021;42:167–86.

Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. Front Neuroendocrinol. 2010;31:400–19.

Paul D, Mulroy S, Horner J, Jacobs K, Lamb D. Carbohydrate-loading during the follicular phase of the menstrual cycle: effects on muscle glycogen and exercise performance. Int J Sport Nutr Exerc Metab. 2001;11:430–41.

Peluso I, Raguzzini A, Serafini M. Effect of flavonoids on circulating levels of TNF-α and IL-6 in humans: a systematic review and meta-analysis. Mol Nutr Food Res. 2013;57:784–801.

Peternelj T-T, Coombes JS. Antioxidant supplementation during exercise training. Sports Med. 2011;41:1043–69.

Pihoker AA, Peterjohn AM, Trexler ET, Hirsch KR, Blue MNM, Anderson KC, Ryan ED, Smith-Ryan AE. The effects of nutrient timing on training adaptations in resistance-trained females. J Sci Med Sport. 2019;22:472–7.

Pitkin RM, Reynolds WA, Williams GA, Hargis GK. Calcium-regulating hormones during the menstrual cycle. J Clin Endocrinol Metab. 1978;47:626–32.

Pugliese G, Barrea L, Laudisio D, Aprano S, Castellucci B, Framondi L, Di Matteo R, Savastano S, Colao A, Muscogiuri G. Mediterranean diet as tool to manage obesity in menopause: a narrative review. Nutrition. 2020;79–80: 110991.

Rahbar N, Asgharzadeh N, Ghorbani R. Effect of omega-3 fatty acids on intensity of primary dysmenorrhea. Int J Gynaecol Obstet. 2012;117:45–7.

Rauch H, St Clair Gibson A, Lambert E, Noakes T. A signaling role for muscle glycogen in the regulation of pace during prolonged exercise. Br J Sports Med. 2005;39**:**34–38.

Rauch L, Rodger I, Wilson G, Belonje J, Dennis S, Noakes T, Hawley J. The effects of carbohydrate loading on muscle glycogen content and cycling performance. Int J Sport Nutr. 1995;5:25–36.

Rechichi C, Dawson B, Goodman C. Athletic performance and oral contraceptive. Int J Sport Physiol Perf. 2009;4:151–62.

Retzlaff JA, Tauxe WN, Kiely JM, Stroebel CF. Erythrocyte volume, plasma volume, and lean body mass in adult men and women. Blood. 1969;33:649–67.

Ritz P, Berrut G, Tack I, Arnaud M, Tichet J. Influence of gender and body composition on hydration and body water spaces. Clin Nutr. 2008;27:740–6.
Rocha-Rodrigues S, Sousa M, Lourenço Reis P, Leão C, Cardoso-Marinho B, Massada M, Afonso J. Bidirectional interactions between the menstrual cycle, exercise training, and macronutrient intake in women: a review. Nutrients. 2021;13.
Romero-Parra N, Alfaro-Magallanes VM, Rael B, Cupeiro R, Rojo-Tirado MA, Benito PJ, Peinado AB, Iron FSG. Indirect Markers of Muscle Damage Throughout the Menstrual Cycle. Int J Sports Physiol Perform. 2020;16:190–8.
Rosner MH, Bennett B, Hew-Butler T, Hoffman MD. Exercise-associated hyponatremia. In: Simon EE, editor Hyponatremia: evaluation and treatment. New York, NY: Springer New York.
Rossi KA. Nutritional aspects of the female athlete. Clin Sports Med. 2017;36:627–53.
Rowlands D, Wadsworth D. Effect of high-protein feeding on performance and nitrogen balance in female cyclists. Med Sci Sports Exerc. 2011;43:44–53.
Roy B, Luttmer K, Bosman M, Tarnopolsky M. The influence of post-exercise macronutrient intake on energy balance and protein metabolism in active females participating in endurance training. Int J Sport Nutr Exerc Metab. 2002;12:172–88.
Sak K. Epidemiological evidences on dietary flavonoids and breast cancer risk: a narrative review. Asian Pac J Cancer Prev: APJCP. 2017;18:2309–28.
Salazar FJ, Llinas MT. Role of nitric oxide in the control of sodium excretion. News Physiol Sci. 1996;11:62–7.
Sánchez-Martínez L, Periago M-J, García-Alonso J, García-Conesa M-T, González-Barrio R. A systematic review of the cardiometabolic benefits of plant products containing mixed phenolics and polyphenols in postmenopausal women: insufficient evidence for recommendations to this specific population. Nutrients. 2021;13.
Sandoval-Ramírez BA, Lamuela-Raventós M., Estruch R, Sasot G, Doménech M, Tresserra-Rimbau A. Beer polyphenols and menopause: effects and mechanisms—a review of current knowledge. Oxid Med Cell Longev. 2017;4749131.
Sar M, Stumpf W. Simultaneous localization of [3 H] estradiol and neurophysin I or arginine vasopressin in hypothalamic neurons demonstrated by a combined technique of dry-mount autoradiography and immunohistochemistry. Neurosci Lett. 1980;17:179–84.
Sawai A, Tsuzuki K, Yamauchi M, Kimura N, Tsushima T, Sugiyama K, Ota Y, Sawai S, Tochikubo O. The effects of estrogen and progesterone on plasma amino acids levels: evidence from change plasma amino acids levels during the menstrual cycle in women. Biol Rhythm Res. 2020;51:151–64.
Sedlock D. The latest on carbohydrate loading: a practical approach. Curr Sports Med Rep. 2008;7:209–13.
Sherman W, Costill D, Fink W, Miller J. The effect of exercise-diet manipulation on muscle glycogen and its subsequent utilisation during performance. Int J Sports Med. 1981;2:114–8.
Shimomura Y, Obayashi M, Murakami T, Harris RA. Regulation of branched-chain amino acid catabolism: nutritional and hormonal regulation of activity and expression of the branched-chain alpha-keto acid dehydrogenase kinase. Curr Opin Clin Nutr Metab Care. 2001;4:419–23.
Simpson LO. The etiopathogenesis of premenstrual syndrome as a consequence of altered blood rheology: a new hypothesis. Med Hypotheses. 1988;25:189–95.
Sims ST, Rehrer NJ, Bell ML, Cotter JD. Preexercise sodium loading aids fluid balance and endurance for women exercising in the heat. J Appl Physiol. 2007a;103:534–41.
Sims ST, Van Vliet L, Cotter JD, Rehrer NJ. Sodium loading aids fluid balance and reduces physiological strain of trained men exercising in the heat. Med Sci Sports Exerc. 2007b;39:123–30.
Sjödin B, Westing YH, Apple FS. Biochemical mechanisms for oxygen free radical formation during exercise. Sports Med. 1990;10:236–54.
Smarkusz-Zarzecka J, Ostrowska L, Leszczyńska J, Orywal K, Cwalina U, Pogodziński D. Analysis of the impact of a multi-strain probiotic on body composition and cardiorespiratory fitness in long-distance runners. Nutrients. 2020;12.

Stachenfeld NS. Hormonal changes during menopause and the impact on fluid regulation. Reprod Sci. 2014;21:555–61.
Stachenfeld NS, Dipietro L, Palter SF, Nadel ER. Estrogen influences osmotic secretion of AVP and body water balance in postmenopausal women. Am J Physiol Regul Integr Comp Physiol. 1998;274:R187–95.
Stachenfeld NS, Keefe DL. Estrogen effects on osmotic regulation of AVP and fluid balance. Am J Physiol Endocrinol Metab. 2002;283:E711–21.
Stachenfeld NS, Keefe DL, Palter SF. Estrogen and progesterone effects on transcapillary fluid dynamics. Am J Physiol Regul Integr Comp Physiol. 2001a;281:R1319–29.
Stachenfeld NS, Silva C, Keefe DL. Estrogen modifies the temperature effects of progesterone. J Appl Physiol. 2000;88:1643–9.
Stachenfeld NS, Silva C, Keefe DL, Kokoszka CA, Nadel ER. Effects of oral contraceptives on body fluid regulation. J Appl Physiol. 1999;87:1016–25.
Stachenfeld NS, Splenser AE, Calzone WL, Taylor MP, Keefe DL. Selected contribution: sex differences in osmotic regulation of AVP and renal sodium handling. J Appl Physiol. 2001b;91:1893–901.
Stephens DP, Bennett LA, Aoki K, Kosiba WA, Charkoudian N, Johnson JM. Sympathetic nonnoradrenergic cutaneous vasoconstriction in women is associated with reproductive hormone status. Am J Physiol Heart Circ Physiol. 2002;282:H264–72.
Stephenson LA, Kolka MA. Esophageal temperature threshold for sweating decreases before ovulation in premenopausal women. J Appl Physiol. 1999;86:22–8.
Stephenson LA, Kolka MA. Plasma volume during heat stress and exercise in women. Eur J Appl Physiol. 1988;57:373–81.
Stephenson LA, Kolka MA, Francesconi R, Gonzales RR. Circadian variations in plasma renin activity, catecholamines, and aldosterone during exercise in women. Eur J Appl Physiol. 1989;58:756–64.
Stumpf WE, Denny ME. Vitamin D (soltriol), light, and reproduction. Am J Obstet Gynecol. 1989;161:1375–84.
Stupka N, Tiidus PM. Effects of ovariectomy and estrogen on ischemia-reperfusion injury in hindlimbs of female rats. J Appl Physiol. 2001;91:1828–35.
Suh S-H, Casazza G, Horning M, Miller B, Brooks G. Luteal and follicular glucose fluxes during rest and exercise in 3-h postabsorptive women. J Appl Physiol. 2002;93:42–50.
Suh S-H, Casazza G, Horning M, Miller B, Brooks G. Effects of oral contraceptives on glucose flux and substrate oxidation rates during rest and exercise. J Appl Physiol. 2003;94:285–94.
Sun F-H, Wong S-S, Chen S-H, Poon T-C. Carbohydrate electrolyte solutions enhance endurance capacity in active females. Nutrients. 2015;7:3739–50.
Tara MK, Park JS, Mathison BD, Kimble LL, Chew BP. Whey protein but not soy protein supplementation alleviates exercise-induced lipid peroxidation in female endurance athletes. Open Nutr J. 2013;7:13–9.
Tarnopolsky M, Atkinson S, Phillips S, Macdougall J. Carbohydrate loading and metabolism during exercise in men and women. J Appl Physiol. 1995;75:2134–41.
Tarnopolsky M, Bosman M, Macdonald J, Vadeputte D, Martin J, Roy B. Post-exercise protein-carbohydrate and carbohydrate supplements increase muscle glycogen in men and women. J Appl Physiol. 1997;83:1877–83.
Tarnopolsky M, Zawada C, Richmond L, Carter S, Shearer J, Graham T, Phillips S. Gender differences in carbohydrate loading are related to energy intake. J Appl Physiol. 2001;91:225–30.
Taylor LW, Wilborn C, Roberts MD, White A, Dugan K. Eight weeks of pre- and postexercise whey protein supplementation increases lean body mass and improves performance in Division III collegiate female basketball players. Appl Physiol Nutr Metab. 2016;41:249–54.
Temesi J, Johnson N, Raymond J, Burdon C, O'connor H. Carbohydrate ingestion during endurance exercise improves performance in adults. J Nutr. 2011;141:890–7.
Thomas DT, Erdman KA, Burke LM. American college of sports medicine joint position statement. Nutrition and athletic performance. Med Sci Sports Exerc. 2016;48:543–68.

Thys-Jacobs S. Micronutrients and the premenstrual syndrome: the case for calcium. J Am Coll Nutr. 2000;19:220–7.

Thys-Jacobs S, Mcmahon D, Bilezikian JP. Cyclical changes in calcium metabolism across the menstrual cycle in women with premenstrual dysphoric disorder. J Clin Endocrinol Metab. 2007;92:2952–9.

Tinsley GM, Moore ML, Graybeal AJ, Paoli A, Kim Y, Gonzales JU, Harry JR, Vandusseldorp TA, Kennedy DN, Cruz MR. Time-restricted feeding plus resistance training in active females: a randomized trial. Am J Clin Nutr. 2019;110:628–40.

Tranquilli A, Mazzanti L, Cugini A, Cester N, Garzett G, Romanini C. Transdermal estradiol and medroxyprogesterone acetate in hormone replacement therapy are both antioxidants. Gynecol Endocrinol. 1995;9:137–41.

Van Pelt R, Gozansky W, Schwartz R, Kohrt W. Intravenous estrogens increase insulin clearance and action in postmenopausal women. Am J Physiol Endocrinol Metab. 2003;285:E311–7.

Verney EB. The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond B Biol Sci. 1947;135:25–106.

Vina, J., Borras, C., Gambini, J., Sastre, J. & Pallardo, F. V. 2005. Why females live longer than males: control of longevity by sex hormones. Sci of Aging Knowledge Environment, 2005**,** pe17.

Walker J, Heigenhauser G, Hultman E, Spriet L. Dietary carbohydrate, muscle glycogen content, and endurance performance in well-trained women. J Appl Physiol. 2000;88:2151–8.

Wallace M, Hashim YZ, Wingfield M, Culliton M, Mcauliffe F, Gibney MJ, Brennan L. Effects of menstrual cycle phase on metabolomic profiles in premenopausal women. Hum Reprod. 2010;25:949–56.

Wallis G, Yeo S, Blannin A, Jeukendrup A. Dose-response effects of ingested carbohydrate on exercise metabolism in women. Med Sci Sports Exerc. 2007;39:131–8.

West DW, Burd NA, Churchward-Venne TA, Camera DM, Mitchell CJ, Baker SK, Hawley JA, Coffey VG, Phillips SM. Sex-based comparisons of myofibrillar protein synthesis after resistance exercise in the fed state. J Appl Physiol. 1985;112**:**1805–13.

Wilborn CD, Outlaw JJ, Mumford PW, Urbina SL, Hayward S, Roberts MD, Taylor LW, Foster CA. A pilot study examining the effects of 8-week whey protein versus whey protein plus creatine supplementation on body composition and performance variables in resistance-trained women. Ann Nutr Metab. 2016;69:190–9.

Wilborn CD, Taylor LW, Outlaw J, Williams L, Campbell B, Foster CA, Smith-Ryan A, Urbina S, Hayward S. The effects of pre- and post-exercise whey versus casein protein consumption on body composition and performance measures in collegiate female athletes. J Sports Sci Med. 2013;12:74–9.

Willett HN, Koltun KJ, Hackney AC. Influence of menstrual cycle estradiol-β-17 fluctuations on energy substrate utilization-oxidation during aerobic, endurance exercise. Int J Environ Res Public Health. 2021;18.

Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995;61:1402S-1406S.

Wismann J, Willoughby D. Gender differences in carbohydrate metabolism and carbohydrate loading. J Int Soc Sports Nutr. 2006;31:28–34.

Wooding DJ, Packer JE, Kato H, West DWD, Courtney-Martin G, Pencharz PB, Moore DR. Increased protein requirements in female athletes after variable-intensity exercise. Med Sci Sports Exerc. 2017;49:2297–304.

Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, Sartor BR, Aliprantis AO, Charles JF. Gut microbiota induce IGF-1 and promote bone formation and growth. Proc Natl Acad Sci. 2016;113:E7554–63.

Yu J, Cao G, Yuan S, Luo C, Yu J, Cai M. Probiotic supplements and bone health in postmenopausal women: a meta-analysis of randomised controlled trials. BMJ Open. 2021;11: e041393.

Zderic T, Coggan A, Ruby B. Glucose kinetics and substrate oxidation during exercise in the follicular and luteal phases. J Appl Physiol. 2001;90:447–53.

Zeng Z, Centner C, Gollhofer A, König D. Effects of dietary strategies on exercise-induced oxidative stress: a narrative review of human studies. Antioxidants.2021; 10.

Zittermann A, Geppert J, Baier S, Zehn N, Gouni-Berthold I, Berthold HK, Reinsberg J, Stehle P. Short-term effects of high soy supplementation on sex hormones, bone markers, and lipid parameters in young female adults. Eur J Nutr. 2004;43:100–8.

Chapter 13
Tracking Health and Fitness Variables in Females: Menstrual Cycle Considerations

Georgie Bruinvels and Charles R. Pedlar

Introduction

The aim of this chapter is firstly to describe why and how to monitor the menstrual cycle in exercising females, and then to discuss how some internal and external factors may influence menstrual cycle patterns. Additionally, we discuss how some other variables that may be tracked can be influenced by the menstrual cycle. It is however beyond the scope of this chapter to discuss strategies to modify these responses or to go into great depth in any one area.

The tracking of health and fitness variables is a way to monitor athletic progress, reduce the risk of overtraining, illness, and injury, and ultimately help to guide performance optimization. The utility of tracking in the exercising population has been widely shown to be beneficial for monitoring readiness, overall wellness and fatigue, and response to exercise (Lee et al. 2017; Thorpe et al. 2017).

Tracking can take a variety of forms, many of which differ in terms of frequency (e.g., daily, weekly, monthly, per cycle, 3 monthly, etc.; Table 13.1); invasiveness; complexity; and financial cost. Examples in the athletic context include subjective daily wellness (perceived muscle soreness, mood, etc.); blood biomarkers; sleep; performance metrics (training volume, intensity, physiological responses); and menstrual cycle (MC) characteristics (e.g., cycle length, symptoms, bleeding patterns) in females. Many of these variables are interdependent (e.g., sensitive to the individual's combined mental and physical load, time zone shifts, life events, etc.); therefore, contextual information alongside tracking data is paramount. Furthermore, there is significant inter-individual variation in these variables; therefore, longitudinal

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Table 13.1 Tracking options are listed by the frequency in which the variable may be monitored

Frequency	Monitoring/Tracking variable
Daily	Sleep Heart rate, heart rate variability Exercise volume and intensity Menstrual cycle symptomology Wellness/readiness Reproductive hormones[a]
Weekly/Biweekly/Monthly/per cycle	Menstruation Point of care biomarkers that help to inform readiness Fitness testing measures (e.g., countermovement jump)
Quarterly	Blood biomarkers (collected from venous sampling) Fitness measures (e.g., physiological responses to exercise) Nutrition

[a] Specifically, this will likely be for a relatively short window of time; e.g., for 1–3 cycles—3 cycles would be optimal to establish an individualized normal

monitoring to understand and account for individual "normal" setpoints and variability will enable the detection of meaningful inter-individual deviations pointing to altered readiness for performance.

When interpreting monitoring data in eumenorrheic females, additional consideration is needed for the impact of cyclical fluctuating reproductive hormones. Being systemic in nature, variations in these hormones have been shown to impact multiple systems. For example, metabolic changes, cardiovascular function, thermoregulation, autonomic system, psychological, and neurological changes have all been observed. Accordingly, athletes have reported alterations in readiness to perform at certain time points in their MC (McNamara et al. 2022; Findlay et al. 2020; Armour et al. 2020).

Clearly hormonal contraception users following a fixed schedule of exogenous hormone consumption cannot use MC length as a marker of wellness or readiness, and in this, case variables other than MC length may be more appropriate.

Menstrual Cycle Phase, Length, and Symptom Tracking—Why and How?

Tracking health variables, such as MC length and symptoms, provides invaluable data that are inextricably linked to sustained high performance. Having a eumenorrheic (regular; cycle length of 21–35 days; Hacker et al. 2016) cycle is a positive indication that a female is in a good state of health. Irregular (oligomenorrhoea) or absent (amenorrhea) cycles, with no associated gynecological pathology, have been associated with adverse health outcomes such as cardiovascular disease (O'Donnell et al. 2011), illness and injury susceptibility (Cheng et al. 2021; Thein-Nissenbaum

et al. 2011; Shimizu et al. 2012), risk of depression and anxiety (Marcus et al. 2001), metabolic disturbances (Corbin 2013), type 2 diabetes (Solomon et al. 2001), and maladaptation to exercise training (Shufelt et al. 2017). Further, MC length can itself be a useful biomarker to track longitudinally, helping to characterize overall health and associated performance readiness (Campbell et al. 2021). Symptomology is also a useful sign, helping to inform overall readiness.

At an individual level, the physical act of cycle tracking enables eumenorrheic females to be prepared practically for the onset of menstruation (e.g., carrying sanitary products with them); in addition, clinically it can help with the identification of some menstrual dysfunctions, e.g., polycystic ovarian syndrome, where longer and more irregular cycles are more common. When cycles are tracked using biomarkers (e.g., hormones), further insight can be obtained as to whether cycles are ovulatory or whether there are other endocrinological abnormalities. When symptoms (both positive and negative) are tracked alongside cycles, individuals can learn more about themselves via pattern recognition and potentially optimize their wellness with simple lifestyle changes. When tracked longitudinally females can identify their individualized "normal" cycle length and symptom pattern, accordingly deviations from this "normal" can be used as a sign of a change and potentially a reduction in readiness for exercise or performance. A combination of too many stresses on the hypothalamic–pituitary–ovarian (HPO) axis can create a "perfect storm" which may manifest as increased symptoms or oligomenorrheic or amenorrheic states (Czajkowska et al. 2020). Deviations from the "normal" should be further investigated in order to find appropriate strategies to restore cycle regularity and/or reduce symptoms. Practitioners can use cycle tracking in this context, to provoke appropriate interdisciplinary support.

Menstrual cycle tracking can take different forms with substantial variation in the level of time commitment, complexity, cost, and invasiveness. These can be broadly broken down into those that are clinical/hormonal/biological and those that are practical/non-invasive (Table 13.2).

The most basic option involves manually recording the MC using a paper diary, capturing the following information: blood flow days, menstruation days, and intensity of flow. In parallel, symptoms at any time in the cycle can be logged. Several smartphone applications are available to facilitate this. Basal body temperature (BBT) can be measured, with the advantage of providing evidence of ovulation, since there is typically a 0.3–0.7 °C increase in BBT post-ovulation in response to the release of progesterone (Charjoudian and Stachenfeld 2016; Baker et al. 2020). A woman's temperature typically remains elevated for the majority of the luteal phase, usually declining a few days prior to the onset of menstruation. Urine testing for luteinizing hormone (and estrogen) can also be used to help identify ovulation since these hormones both dramatically rise immediately prior to ovulation. Longitudinal tracking using non-invasive testing methods enables the identification of trends and patterns over time. At least three cycles should be tracked before making inferences on data to accommodate intracycle variability.

Biomarker testing methods involving blood, urine, and saliva can be used to measure female hormones at different time points across the cycle. It is advisable to

Table 13.2 Menstrual cycle phase and length tracking options

	Cost	Frequency of collection	Markers tracked
Biomarkers			
• Blood—venous or capillary hormone monitoring	**	Daily—irregularly (alongside other biomarker testing)	Endogenous hormones
• Urine—hormone measures including ovulation tracking through LH	**		
• Saliva—typically daily sampling	*		
• Temperature—used to identify ovulation, ideally used alongside day-based counting	*		
Non-invasive			
• Day counting using pen and paper or a calendar	–	Daily	Menstrual bleed Flow days Symptoms Body temperature
• Menstrual bleed (and symptom) logging using a mobile phone application	–		
• Temperature monitoring using a wearable used alongside day counting	*		

* Denotes the likely cost of monitoring, – = minimal cost, ** = more costly

use non-invasive monitoring (Table 13.1) in parallel to allow for better interpretation. The purpose of biomarker testing will likely inform the optimal protocol for the frequency and duration of testing (e.g., daily for 3 cycles vs. one-off time points). Given that circulating hormone concentrations can change by over 100% in 24 h when measuring hormones for research purposes and to identify an individual's hormonal changes, it would be prudent to collect regular hormonal measures, at least every few days. This is particularly important at key time points where hormonal changes are proposed to happen as per the theoretical model. It is important to understand that hormones might not follow the established textbook MC model due to pre-analytical, analytical, inter-individual, and interday variability or error. If the goal is to identify whether an athlete is following an ovulatory cyclical hormonal pattern, a single measurement point mid-follicular and a second measurement point mid-luteal can provide this information; ideally, a means for identifying ovulation would be used in conjunction (see Vanheest et al. 2014). Given the invasiveness, practicalities, and costs associated with regular blood sampling, in some instances, this may be a more realistic protocol than daily sampling. Calendar-based methods should be used in conjunction, and it would be advisable to have established "individualized normal" MC characteristics through prior longitudinal tracking before testing.

Where more regular clinical tracking is used (e.g., daily saliva, urine, and capillary blood analysis), these results can be used to verify phases and days in the cycle.

Where significant symptomology is seen associated with certain days/times/phases of the cycle, monitoring and tracking can be used to understand the efficacy of an intervention.

The Use of Technology for Tracking the Menstrual Cycle

Over recent years, technology has developed to assist with MC tracking. Smartphone applications have been created to facilitate basic day-of-menstruation tracking and symptom logging. A number of different advanced wearables capture information such as body temperature and, in some cases, measures of cardiovascular strain (e.g., heart rate, heart rate variability, and respiratory rate). These can be used to predict MC length. As with all types of technology, there are strengths and limitations. Basic smartphone applications are typically free to use and easily accessible. They enable a user to evaluate historical trends and identify any abnormal patterns. Their accuracy of prediction will depend upon the accuracy of an algorithm. Accuracy can be improved by using a luteinizing hormone test to identify ovulation (via urine), and thus the transition into the luteal phase. This may not be sustainable every cycle due to cost and practicality.

Technology to measure basal body temperature is becoming increasingly available. A single measure of basal body temperature can be limited as it is susceptible to inaccuracies as a result of factors such as time of day and recent activity. The advent of wearables with continuous skin temperature monitoring alongside other physiological measures described above has created new opportunities for monitoring. Algorithms can predict ovulation/fertile windows and/or menstruation. While these offer huge potential, caution must be taken with use as they are subject to inaccuracies. Wrist skin temperature during sleep has limited sensitivity to predict ovulation or a higher fertility window (0.62–0.81 sensitivity; 54.9–90.0% of ovulatory cycles) depending on the device (Zhu et al. 2021; Goodale et al. 2019). These are reviewed in detail elsewhere (Baker et al. 2020). Nocturnal distal finger skin temperature also shows potential for identifying cycle characteristics (Maijala et al. 2019). Using a built-in algorithm, menstruation was predicted in a window of + 2 to + 4 days in 71.9% to 86.5% of participants, respectively, and ovulation was detected with a sensitivity of 83.3% (Maijala et al. 2019). While all of these results are promising, data have to be interpreted with caution as there is still a paucity of data using these wearables, and particularly in the case of predicting menstruation, predictive power will be significantly limited where cycles are anovulatory. It is also important to consider that technology companies can change these algorithms at any time.

To summarize, the use of new technology for menstrual cycle tracking and monitoring is an exciting area that could enable females to better predict cycle phases and adapt their behavior accordingly. However, due to the varying degree of accuracy of these technologies, there are clear limitations, and females should be made aware of these on initiation of use.

Factors Influencing Cycle Characteristics

There is a range of different factors that appear to be involved in MC regularity and the development of symptomology (see Fig. 13.1). When tracking reveals a deviation from an individual's historic "normal" cycle length or shows significant symptomology, these should be considered.

Menstrual History

Due to the immaturity of the HPO axis in the first 2–5 years post-menarche, anovulatory cycles are common in this window of time. As a result, cycle length variation is more likely. Similarly, cycles are more prone to length variation in the 2–5 years prior to menopause as a reflection of ovarian aging (Harlow and Ephross 1995). Therefore, if monitoring cycle length, factoring in the life stage could help inform understanding as to whether increased variation may be expected or abnormal for an individual. Age at menarche may also influence cycle variability and cycle length throughout reproductive life (Wesselink et al. 2016). Thus, in the exercising population, in conditions of primary amenorrhea or a delay to menarche due to early sport specialization or excess exercise pre-puberty (Frisch et al. 1981), future cycle characteristics may be affected. The changes in the hormonal milieu associated with breastfeeding will also likely cause changes in length and increased length variation (Najmabadi et al. 2020).

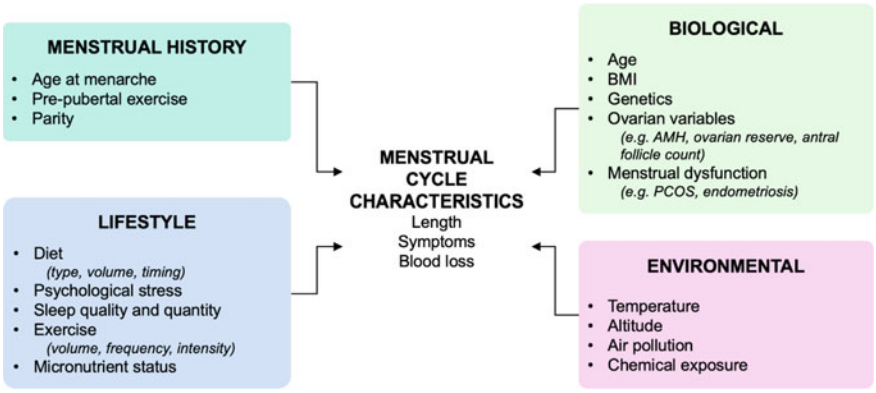

Fig. 13.1 Factors contributing to menstrual cycle characteristics. BMI = Body Mass Index; AMH = Anti-Müllerian Hormone; PCOS = Polycystic Ovary Syndrome

Lifestyle Factors

Diet

Where energy expenditure surpasses calorific intake over a period of time (prolonged energy deficit), significant disturbances in the HPO axis will ensue, and states of oligomenorrhoea and amenorrhea are inevitable (Loucks et al. 1988). While total calorific intake is highly relevant here, the macronutrient and potentially micronutrient distribution are also fundamental to maintaining a regular MC. The mechanism in which menstrual function is affected is associated with a reduction in luteinizing hormone pulsatility, therefore delaying ovulation and elongating the follicular phase. Further, being in an energy deficit, either by not fueling regularly and/or not fueling after exercise has also been shown to disrupt HPO-axis function (Fahrenholtz et al. 2018). This is covered in more detail elsewhere in the book. For females who exercise on a regular basis, the risk of under-fueling and/or insufficient timing or diet composition can be significant, particularly when training volume and/or intensity are increased or other environmental stressors are applied, monitoring MC length alongside this can be very useful as a sign that something is amiss.

Other literature points to dietary behaviors potentially impacting MC length and symptomology, for example, consumption of a Mediterranean diet is associated with a shorter MC length (Onieva-Zafra et al. 2020). Insufficient intake of certain micronutrients has been implicated in the incidence of irregular cycles and adverse symptomology; thus where irregularities are seen, full nutritional screening may be helpful. For example, iron, zinc, calcium, B vitamins, calcium, and magnesium have all been shown to be related to some extent to menstrual length and symptomology (Nasiadek et al. 2020; Ayre and Bauld, 1946; Livdans-Forret et al. 2007; Naz et al. 2020, Petkus et al. 2019).

Stress, Sleep, and Exercise

A literature review specifically reporting the effects of shift and night work on MC regularity found an association between night work and menstrual irregularity or increased MC variability (Lim et al. 2016); interestingly, one study specifically looked at alternating patterns of shift work and also found that, whether shifts were in the day or night, this resulted in increased MC length variability (Su et al. 2008). These findings could be translated into other contexts where irregular sleeping patterns are common such as elite sports.

Less than 6 h of sleep has been associated with an increased likelihood of an irregular MC length (Lim et al. 2016), and more pre-menstrual symptoms (Xing et al. 2020), while reported insomnia has also specifically been associated with reporting an irregular cycle length (Xing et al. 2020).

An association between chronic stress and hypothalamic hypogonadism has been observed; Nagma et al. (2015) found that high levels of stress were associated with

cycle length irregularities in university students. These findings are consistent with other research (Palm-Fischbacher and Ehlert 2014; Bae et al. 2018). This is hypothesized to be related to the interaction of the HPO axis with the hypothalamic–pituitary–adrenal (HPA) axis. Acute stress has also been found to exacerbate perimenstrual cycle symptomology (Gollenburg et al. 2010). Of note, females whose mothers were exposed to significant stress prenatally have been reported to have an increased sensitivity to the HPA axis (Ryterska et al. 2021). Early childhood experiences may also have a similar effect. Both of these could mean that some individuals are predisposed to changes in MC length characteristics (Pauli and Berga 2010; Bomba et al. 2014). Subtle menstrual disorders such as luteal phase defects, anovulatory cycles, or slight cycle length disturbances are relatively common in those who exercise (De Souza et al. 2010).

Environmental Factors

Pollutants and Endocrine-Disrupting Chemicals

A couple of recent studies have demonstrated that exposure to air pollution, particularly in the peripubertal transition and in early adulthood, is associated with increased time to menstrual regularity and earlier age at menarche (Mahalingaiah et al. 2018; Wronka and Kliś 2022). Further, exposure to pollutants such as particulate matter (less than 10 μm), sulfur dioxide, and nitrogen dioxide may also contribute to altered cycle length and increased cycle variability (Merklinger-Gruchala et al. 2017; Giorgis-Allemand et al. 2020). This is more probable if exposure to environmental toxicants occurs either during follicle recruitment or during corpus luteum activity (Hammer et al. 2020). For those who exercise outdoors and live in polluted areas, this is of particular relevance and it warrants further consideration.

Some small studies have found synthetic chemicals such as perfluoroalkyl substances to disrupt reproductive function and thus result in cycle length variation (Zhou et al. 2017). This is a relatively new research area that warrants consideration, particularly in certain sports where equipment is for example made using perfluoroalkyl substances (e.g., tennis rackets, ski wax, bicycles).

Exposure to high altitude has been shown to affect MC characteristics (Shaw et al. 2018). This is potentially linked to alterations in redox homeostasis and causes excess levels of reactive oxygen and nitrogen species, which can disrupt normal MC functioning, and it is feasible that the increases in the release of these, as which happens during hypoxic exposure, could disrupt menstrual function.

Biological Factors

Genetics

A number of mutations to the gene encoding the gonadotrophin-releasing hormone (GnRH) receptor have been associated with an increased likelihood of functional hypothalamic amenorrhea (Caronia et al. 2011; Roberts et al. 2020). This may also increase the individual sensitivity to "stressors" and thus predispose individuals to increased cycle length variation. For example, those who are homozygous for KA1, FGFR1, PROKR2, and GNRHR (i.e., gene mutations) are more susceptible to hypothalamic amenorrhea (Caronia et al. 2011; Roberts et al. 2020). Being heterozygous for these may also increase the likelihood of cycle length variation (Caronia et al. 2011; Roberts et al. 2020).

Body Mass Index (BMI)

Extreme BMI's = more irregular cycles and "atypical" cycle lengths. Research has pointed to an association between a high BMI and an increased likelihood of cycle length variability (Wei et al. 2009). Interestingly, there also appears to be a U-shaped relationship between BMI and MC-related symptoms, with those at the top and bottom end of the BMI spectrum being more likely to experience adverse symptomology (Ju et al. 2015).

Menstrual Dysfunction (MD)

Increases in MC length and more severe symptoms are associated with certain types of menstrual dysfunction. Polycystic ovarian syndrome for example is associated with longer cycles (Rosenfield and Ehrmann 2016), and endometriosis is typically associated with shorter and more painful cycles (Wei et al. 2016). With this in mind, where cycle irregularities and significant symptomology are observed, medical advice should be sought.

Summary

There is likely to be a synergistic effect from numerous contributory stressors, with some individuals being more sensitive to variation in MC length, and/or certain stressors that may affect symptomology.

How the Menstrual Cycle May Affect Other Metrics in the Female Athlete

As circulating ovarian hormones induce effects on other non-reproductive processes (e.g., respiratory, cardiovascular, and metabolic), there is potential for the changes through the cause of the MC to affect exercise performance readiness. It is well established that there can be significant inter- and intra-individual variation in physiological characteristics, blood biomarkers, readiness, etc., and endogenous hormonal changes across the MC could, in part, be responsible for these. The significant inter- and sometimes intra-individual variation in hormonal cycles poses a particular challenge here, while the substantial hormonal fluctuations mean that for really accurate interpretation, daily sampling is optimal.

Potential Impact of Changes in Endogenous Hormones on Blood Biomarkers

The cyclical changes in ovarian hormones have the potential to impact blood biomarkers, and thus, when interpreting these it would be advisable to measure reproductive hormones alongside and record the day of the MC where possible. Ideally, calendar-based tracking and historical cycle data should also be used to inform the analysis.

Inflammatory Markers and Markers of Oxidative Stress

Menstruation is often described as an inflammatory process, and many view the MC as a complex cycle of pro- and anti-inflammatory activity. The progesterone withdrawal that happens in the pre-menstrual phase releases the transcription factor NF-κB, which drives an essential inflammatory response, causing the infiltration of inflammatory mediators such as cyclo-oxygenase, cytokines, leukocytes, and matrix metalloproteinases, which create a hypoxic environment and cause the breakdown and shedding of the endometrial lining (Jabbour et al. 2006). This "perimenstrual" window is the time where MC-related symptoms are most commonly reported, and while the specific mechanisms behind each symptom type are not yet fully understood, a host of symptoms have been associated with the increase in biomarkers of inflammation markers (Bertone-Johnson et al. 2014). Other studies have shown there to be an increased release of biomarkers of inflammation in the perimenstrual window (Chaireti et al. 2016; Whitcomb et al. 2014), and cyclical variation in conditions that may be sensitive to inflammation (e.g., chronic fatigue or long COVID-19 have also been observed) (Davis et al. 2021; Sharp et al. 2021).

The cyclical hormonal changes have also been associated with changes in patterns of release of markers of oxidative stress; for example, toward the end of the luteal

phase there is an increase in production of lipid peroxidase, alongside a decrease in superoxide dismutase, which in part facilitates the breakdown of the endometrial lining (Gupta et al. 2012). However, not all research is conclusive here, and as with many studies in this area, this is likely due to the timepoints selected for sample collection, sample sizes, and individual variation (Bell and Bloomer 2010). Regardless, reactive oxygen species (ROS) and reactive nitrogen species are essential for some of the stages involved in the menstrual cycle; a certain amount of ROS is required for the development and maturation of follicles, for ovulation, and, for the development and function of the corpus luteum (Agarwal and Gupta 2006; Agarwal et al. 2005). Too much, however, is harmful (Agarwal and Gupta 2006).

While to our knowledge, this has not yet been studied experimentally if an increase in inflammatory biomarkers from an individualized normal is observed, an extra focus on good recovery and anti-inflammatory nutrition could be applied, but studies to validate this approach are warranted.

Regarding other biomarkers, see Table 13.3 for more on how the MC may affect such markers.

How the Menstrual Cycle May Affect Markers of Readiness and Wellness

Sleep

There are receptors for estrogen and progesterone in the hypothalamus, distributed via the central nervous system, locus coeruleus, and the dorsal raphe nucleus, all of which are involved in the regulation of sleep (Shughrue et al. 1997; Curran-Rauhut and Petersen 2002). Changes in ovarian hormones through the MC have been shown to influence sleep (Driver et al. 1996), but more research is needed to better understand the specific mechanisms, and as with many areas there appears to be significant inter-individual variation. It has been established that the sleep and wake-promoting areas of the central nervous system are sensitive to estrogen; thus, as ovarian hormones fluctuate through the cycle, this could affect sleep latency, quality, and quantity, and there is some evidence to suggest that ovarian hormones can specifically affect sleep architecture (Baker et al. 2019; Baker and Lee, 2018). Some studies have specifically captured subjective "sleep disruption" as a commonly reported MC symptom, and this is typically reported during the late luteal phase, in the pre-menstrual window, and during menstruation where estrogen and progesterone levels rapidly change (Baker and Driver 2004; Bruinvels et al. 2021).

Experimental studies specifically monitoring sleep throughout the entirety of the MC are relatively sparse. When studied in cross-section, most researchers have shown sleep efficiency and sleep latency to be stable across the MC (Driver et al. 1996; Baker et al. 2007), but in the luteal phase, a decrease in rapid eye movement sleep (Mong et al. 2011), an increase in slow-wave sleep (Baker et al. 2002), and earlier REM

Table 13.3 The influence of the menstrual cycle on selected biomarker groups

Biomarker group	Effect of the menstrual cycle
Inflammatory markers	An increased release of biomarkers of inflammation in the perimenstrual window has been observed in response to progesterone withdrawal (Chaireti et al. 2016; Whitcomb et al. 2014). Further, in response to a controlled endurance exercise bout, creatine kinase and interleukin-6 levels at both 24 and 72 h post-exercise have been found to be greater in the mid-follicular phase when sex hormones are low (Hackney et al. 2019), with possible implications for recovery duration
Oxidative stress markers	Markers of oxidative stress have been found to vary in line with hormonal changes; for example, toward the end of the luteal phase, there is an increase in production of lipid peroxidase, alongside a decrease in superoxide dismutase, which in part facilitates the breakdown of the endometrial lining (Gupta et al. 2012)
Markers of cardiovascular health	Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and a number of associated lipid and lipoprotein ratios have been shown to change when comparing the follicular and luteal phases (Saxena et al. 2012; Vashishta et al. 2017; Olean-Oliveira et al. 2022). Leptin concentrations have been reported to be higher in the luteal phase when compared to the follicular phase, and adiponectin levels are lower (Wyskida et al. 2017; Rafique et al. 2018)
Immune markers	Higher numbers of circulating neutrophils, lymphocytes, and monocytes have been observed during the luteal phase (Timmons et al. 2005). In the perimenstrual window, an upregulation in macrophages, neutrophils, granular lymphocytes eosinophils, and mast cells in endometrial tissue have all been observed when compared to the follicular and luteal phases; this triggers the inflammatory cascade (Berbic and Fraser 2013). This inflammatory cascade may be further increased with some menstrual dysfunctions
Iron status markers	Some research has found hemoglobin concentration, transferrin saturation, serum ferritin, serum iron, total iron-binding capacity, mean corpuscular volume, and albumin all appear to fluctuate and show significant variation between menstruation and at least one other identified time point in the MC (follicular, mid-luteal, and late luteal). More recently, iron and hepcidin have been shown to change during and just after menstruation when compared to other time points (Angeli et al. 2016), and a reduction in iron status markers during menstruation (Barba-Moreno et al. 2022)

(continued)

Table 13.3 (continued)

Biomarker group	Effect of the menstrual cycle
Red cell markers	One study specifically looking at how red cell indices may change at three different time points during the menstrual cycle concluded hemoglobin, hematocrit, and red cell count to be stable, but the percentage of reticulocytes significantly decreased in the follicular phase when compared to measurements taken during the ovulatory and luteal phases (Mullen et al. 2020)

onset have been observed (Lee et al. 1990). These findings are not however universal, with some studies finding no changes (Chuong et al. 1997; Baker et al. 2019). One study using actigraphy did observe a decline in sleep efficiency and total sleep time in the week before the onset of menstruation (Zheng et al. 2015). Most likely due to the inconvenience and expense of polysomnography (PSG), the gold standard means for evaluating sleep, most studies using this technique have only compared a couple of specific time points within the MC (e.g., mid-follicular versus mid-luteal phase). One study ($n = 9$) by Driver (1996) however did evaluate electroencephalogram (EEG) activity every other night for the duration of an MC, finding no changes in slow-wave sleep or slow-wave activity; however, sleep spindle activity did significantly increase in the luteal phase. This finding has been corroborated by other more recent studies (Baker et al. 2007; Baker et al. 2012, Genzel et al. 2012) and while the mechanism for this is not understood, it is hypothesized to be associated with progesterone acting on GABA-A receptors.

Menstrual cycle symptoms and the need to change sanitary products may also result in a disruption to sleep. A study in collegiate female athletes found an increased sleep latency and a reduction in total sleep duration and quality associated with MC symptoms and concerns over sanitary products during the night (Koikawa et al. 2020). With this in mind, it would be sensible to work on symptom management and raise awareness around available sanitary protection overnight. More studies are needed to better understand the within-day variation in sleep metrics. Where sleep latency, duration, and quality are reduced, sleep strategies could be used to reduce disruption and sleep could even be banked in advance in preparation for noticeably disrupted timepoints. In summary, there is an argument for monitoring sleep across the menstrual cycle. The various methods available for sleep monitoring are beyond the scope of this chapter.

Heart Rate, Respiratory Rate, and Heart Rate Variability

Attributed to the cyclical changes in ovarian hormones, the majority of research has found heart rate at rest to increase during the luteal phase when compared to the follicular phase (Tenan et al. 2014; McKinley et al. 2009). This is thought associated with an increase in body temperature, which may affect cardiovascular strain. Some

studies have also found an observable increase in heart rate during exercise in the luteal phase (Rael et al. 2021; Barba-Moreno et al. 2022), but this finding is not universal (Freemas et al. 2021; Goldsmith and Glaister, 2020). Heart rate variability has also been shown to decrease significantly in the luteal phase of the MC when compared to the follicular phase, and this is potentially more specifically in the late luteal phase, this is thought to primarily be attributed to changes in autonomic control and more specifically a reduced parasympathetic withdrawal (Tenan et al. 2014; Kokts-Porietis et al. 2020; Alzueta et al. 2022).

Again, linked to the changes in ovarian hormones, respiratory rate at rest has been shown to increase in the luteal phase of the MC (Slatkovska et al. 2006; MacNutt et al. 2012), some have also shown this to increase during exercise in the mid-luteal phase when compared to the follicular phase (Goldsmith and Glaister, 2020), but again, this finding is not universal (MacNutt et al. 2012).

As with all areas, the potential for individual variation here is likely to have a significant effect, and it is important to be mindful that many other factors can influence these variables (e.g., exercise, nutrition, alcohol, and sleep). That being said, when regularly monitoring readiness using cardiovascular and respiratory measures, it appears to be appropriate to monitor MC day/phase in parallel to help contextualize data.

Body Temperature

Due to the thermogenic nature of progesterone, there is an increase of 0.3 °C–0.7 °C in resting body temperature, which has been observed 24 h after a detectable increase in plasma progesterone (Charjoudian and Stachenfeld, 2016; Baker et al. 2020). Body temperature then reaches a peak and plateaus within around 48 h, remaining elevated until progesterone starts to decline pre-menstrually (Forman et al. 1987). This increase in basal body temperature can be detectable using oral, tympanic, vaginal, or rectal temperature at rest and can be used as an indicator that ovulation has occurred (Marsh and Jenkins, 2002). This increase in body temperature may be in part responsible for changes in physiological response throughout the MC and can affect sleep, although it is difficult to discern whether any effects are due to the change in body temperature alone or whether these are linked to the altered hormonal milieu. Further, if undertaking daily monitoring of body temperature, it is important to account for natural physiological rises and of course the impact of ambient temperature on skin temperature.

Muscle Soreness

A systematic review and meta-analysis have comprehensively evaluated changes in markers of muscle damage and strength loss in response to a damaging protocol across different MC phases, concluding that the lowest hormonal window (i.e., early-follicular phase) to be where recovery is most impaired and the more strength is lost

24–72 h post-exercise (Romero-Parra et al. 2021). The authors highlight a number of important limitations to this conclusion including only a few studies that met the inclusion criteria; the methods used for phase verification; most studies only compared two-time points; differing training levels of subjects; and the small sample sizes within studies. Despite this, the increased perception of delayed-onset muscle soreness (DOMS) in the early-follicular phase was compelling, and this could be attributed to several factors. Firstly, ovarian hormones may have a protective effect against muscle damage, thus when hormones are at their lowest, DOMS is increased. Second, other MC symptoms that could be experienced during the early-follicular phase may reduce the pain tolerance threshold, and some studies report pain threshold to be reduced in the early-follicular phase. Finally, while studies specifically looking at creatine kinase did not observe any changes across the MC, other markers of inflammation, e.g., C-reactive protein have been shown to fluctuate which can increase the likelihood of muscle damage.

Physiological Responses to Exercise

The data are not conclusive as to whether objective measures of performance are influenced by changes in ovarian hormones. One controlled laboratory study where trained runners completed a submaximal and maximal exercise test across the early-follicular, late-follicular, and mid-luteal phase specifically found a reduction in running economy, with an increase in respiratory rate and core body temperature in the luteal phase when compared to the follicular phase (Goldsmith and Glaister, 2020). Time to exhaustion, maximal oxygen uptake, blood lactate, and rating of perceived exhaustion did not differ. These findings are supported (Williams and Krahenbuhl, 1997), but also refuted (Dokumacı and Hazir, 2019). As with most research, the potential for inter-individual variation in response is significant, and importantly, further studies investigating more time points across the MC are needed.

Some studies have also demonstrated changes in markers of strength at different time points. Cook et al. (2018) showed an increase in peak power around ovulation when compared to the follicular and luteal phases, while others have found a decrease in peak power in the late luteal phase when compared to the late-follicular phase (Graja et al. 2020).

While an exhaustive review into the physiological responses throughout the MC is not the primary aim of this chapter, given the changes that some have seen as already noted, and discussed further elsewhere (Carmichael et al. 2021), it appears to be appropriate to track MCs alongside physiological metrics during exercise.

Cognitive Measures and Mood State

Estrogen and progesterone receptors have been located in regions of the brain that are involved in cognition, e.g., the amygdala, prefrontal cortex, and hippocampus, and it is well established that the ovarian hormones can cross the blood–brain barrier; thus

theoretically, changes in hormone concentrations through the MC may alter cognitive performance. However, research here is inconclusive, with most studies to date having small participant sizes and typically only measuring two-time points in the cycle. Some have found performance in mental rotation tasks and spatial awareness tasks to be better in the follicular phase (Courvoisier et al. 2013; Hampson et al. 2014; Le et al. 2020), and others have found verbal fluency to be better in the luteal phase (Solís-Ortiz and Corsi-Cabrera, 2008; Le et al. 2020). Others have observed no change (Gordon and Lee, 1993, Le et al. 2020). Regardless, it would be prudent to monitor the MC alongside markers of cognition to help contextualize data.

Mood-related changes are one of the most frequently experienced MC symptoms (Findlay et al. 2020; Bruinvels et al. 2021). When using the profile of mood states questionnaire with athletes to compare pre-menstrual and mid-cycle measures, a worsened profile was noted during the pre-menstrual window (Cockerill et al. 1992). Further, those who specifically experience pre-menstrual syndrome had higher levels of inflammation and anxiety than those who did not (Foster et al. 2017).

Other Considerations

The use of hormonal contraception affects the function of the HPO axis, resulting in the downregulation of endogenous female reproductive hormones. The extent to which endogenous hormones are downregulated depends on the type of hormonal contraception (e.g., combined or progestin-only), and the dose of exogenous hormones, therefore where possible, measuring endogenous hormones alongside other monitoring would be optimal. Experiencing symptoms appears to be as common in combined oral contraceptive users as non-users (Clarke et al. 2021; Oxfeldt et al. 2020); therefore, tracking these alongside markers of wellness and readiness would be sensible.

Conclusions

Overall, MC tracking can provide valuable insights for females which can potentially lead to positive health and performance gains. The following points summarize the chapter:

- There is a multitude of variables that could be tracked across MC phases. At the simplest level, recording the dates of menstruation together with symptoms may help females to understand and predict the impact of the MC, both positive and negative.
- MC characteristics (e.g., length and symptoms) can be affected by many internal and external variables.

- Since ovarian hormones and receptors are systemic in nature, almost all physiological systems may be affected to some degree by the MC, and some of which may have a meaningful effect on performance or perceived wellness.
- Monitoring can inform the selection and efficacy of interventions (e.g., a sleep or nutrition strategy to reduce symptoms associated with inflammation).
- Wide inter-individual variability exists for most variables.
- Layers of complexity, technology options, and cost can be added and may include blood, urine, or saliva biomarkers, accelerometry, heart rate, and heart rate variability, skin temperature, sleep tracking, physiological responses to exercise, and cognitive tests.

References

Agarwal A, Gupta S. The role of free radicals and antioxidants in female infertility and assisted reproduction. US Genito-Urinary Disease. 2006;24:2–7.

Agarwal A, Gupta S, Sharma R. Oxidative stress and its implications in female infertility—a clinician's perspective. Reprod BioMed Online. 2005;11:641–50.

Alzueta E, de Zambotti M, Javitz H, Dulai T, Albinni B, Simon KC, et al. Tracking sleep, temperature, heart rate, and daily symptoms across the menstrual cycle with the oura ring in healthy women. Int J Womens Health. 2022;8(14):491–503.

Angeli A, Lainé F, Lavenu A, Ropert M, Lacut K, Gissot V, et al. Joint model of iron and hepcidin during the menstrual cycle in healthy women. AAPS J. 2016;18(2):490–504. https://doi.org/10.1208/s12248-016-9875-4. Epub 2016 Feb 2.

Armour M, Parry KA, Steel K, Smith CA. Australian female athlete perceptions of the challenges associated with training and competing when menstrual symptoms are present. Int J Sports Sci Coach. 2020;15:316–23. https://doi.org/10.1177/1747954120916073

Ayre JE, Bauld WA. Thiamine deficiency and high estrogen findings in uterine cancer and in menorrhagia. Science. 1946;103(2676):441–5.

Bae J, Park S, Kwon JW. Factors associated with menstrual cycle irregularity and menopause. BMC Womens Health. 2018;18(1):36.

Baker FC, Driver HS. Self-reported sleep across the menstrual cycle in young, healthy women. J Psychosom Res. 2004;56(2):239–43.

Baker FC, Kahan TL, Trinder J, Colrain IM. Sleep quality and the sleep electroencephalogram in women with severe premenstrual syndrome. Sleep. 2007;30(10):1283–91.

Baker FC, Sassoon SA, Kahan T, Palaniappan L, Nicholas CL, Trinder J, Colrain IM. Perceived poor sleep quality in the absence of polysomnographic sleep disturbance in women with severe premenstrual syndrome. J Sleep Res. 2012;21(5):535–45. https://doi.org/10.1111/j.1365-2869.2012.01007.x. Epub 2012 Mar 14.

Baker FC, Sattari N, de Zambotti M, Goldstone A, Alaynick WA, Mednick SC. Impact of sex steroids and reproductive stage on sleep-dependent memory consolidation in women. Neurobiol Learn Mem. 2019;160:118–31.

Baker FC, Siboza F, Fuller A. Temperature regulation in women: effects of the menstrual cycle. Temperature (austin). 2020;7(3):226–62.

Baker FC, Driver HS, Paiker J, Rogers GG, Mitchell D. Acetaminophen does not affect 24-h body temperature or sleep in the luteal phase of the menstrual cycle. J Appl Physiol (1985). 2002;92(4):1684–1691

Barba-Moreno L, Cupeiro R, Romero-Parra N, Janse de Jonge XAK, Peinado AB. Cardiorespiratory responses to endurance exercise over the menstrual cycle and with oral contraceptive use. J Strength Cond Res. 2022 Feb 1;36(2):392–99.

Bell HK, Bloomer RJ. Impact of serum estradiol on postprandial lipemia, oxidative stress, and inflammation across a single menstrual cycle. Gend Med. 2010;7:166–78.

Bertone-Johnson ER, Ronnenberg AG, Houghton SC, Nobles C, Zagarins SE, Takashima-Uebelhoer BB, et al. Association of inflammation markers with menstrual symptom severity and premenstrual syndrome in young women. Hum Reprod. 2014;29(9):1987–94. https://doi.org/10.1093/humrep/deu170. Epub 2014 Jul 17.

Bomba M, Corbetta F, Bonini L, Gambera A, Tremolizzo L, Neri F, et al. Psychopathological traits of adolescents with functional hypothalamic amenorrhea: a comparison with anorexia nervosa. Eat Weight Disord. 2014;19(1):41–8. https://doi.org/10.1007/s40519-013-0056-5. Epub 2013 Aug 4.

Bruinvels G, Goldsmith E, Blagrove R, Simpkin A, Lewis N, Morton K, Suppiah A, Rogers JP, Ackerman KE, Newell J, Pedlar C. Prevalence and frequency of menstrual cycle symptoms are associated with availability to train and compete: a study of 6812 exercising women recruited using the Strava exercise app. Br J Sports Med. 2021;55(8):438–443. https://doi.org/10.1136/bjsports-2020-102792. Epub 2020 Nov 16. PMID: 33199360

Campbell LR, Scalise AL, DiBenedictis BT, Mahalingaiah S. Menstrual cycle length and modern living: a review. Curr Opin Endocrinol Diabetes Obes. 2021;28(6):566–573. https://doi.org/10.1097/MED.0000000000000681. PMID: 34545843; PMCID: PMC8631146

Carmichael MA, Thomson RL, Moran LJ, Wycherley TP. The impact of menstrual cycle phase on athletes' performance: a narrative review. Int J Environ Res Public Health. 2021;18(4):1667. https://doi.org/10.3390/ijerph18041667.

Caronia LM, Martin C, Welt CK, Sykiotis GP, Quinton R, Thambundit A, et al. A genetic basis for functional hypothalamic amenorrhea. N Engl J Med. 2011;364(3):215–25. https://doi.org/10.1056/NEJMoa0911064.

Chaireti R, Lindahl TL, Byström B, Bremme K, Larsson A. Inflammatory and endothelial markers during the menstrual cycle. Scand J Clin Lab Invest. 2016;76(3):190–4.

Charkoudian N, Stachenfeld N. Sex hormone effects on autonomic mechanisms of thermoregulation in humans. Auton Neurosci. 2016;196:75–80.

Cheng J, Santiago KA, Abutalib Z, et al. Menstrual irregularity, hormonal contraceptive use, and bone stress injuries in collegiate female athletes in the United States. PM R. 2021;13(11):1207–15.

Chuong CJ, Kim SR, Taskin O, Karacan I. Sleep pattern changes in menstrual cycles of women with premenstrual syndrome: a preliminary study. Am J Obstet Gynecol. 1997;177(3):554–8.

Clarke AC, Bruinvels G, Julian R, Inge P, Pedlar CR, Govus AD. Hormonal contraceptive use in football codes in Australia. Front Sports Act Living. 2021;25(3): 634866.

Cobin RH. Cardiovascular and metabolic risks associated with PCOS. Intern Emerg Med. 2013;8(Suppl 1):S61–4. https://doi.org/10.1007/s11739-013-0924-z.

Cockerill IM, Nevill AM, Byrne NC. Mood, mileage and the menstrual cycle. Br J Sports Med. 1992;26(3):145–50. https://doi.org/10.1136/bjsm.26.3.145.

Cook CJ, Kilduff LP, Crewther BT. Basal and stress-induced salivary testosterone variation across the menstrual cycle and linkage to motivation and muscle power. Scand J Med Sci Sports. 2018;28(4):1345–53.

Courvoisier DS, Renaud O, Geiser C, Paschke K, Gaudy K, Jordan K. Sex hormones and mental rotation: an intensive longitudinal investigation. Horm Behav. 2013;63(2):345–51.

Curran-Rauhut MA, Petersen SL. The distribution of progestin receptor mRNA in rat brainstem. Brain Res Gene Expr Patterns. 2002;1(3–4):151–7.

Czajkowska M, Drosdzol-Cop A, Naworska B, Galazka I, Gogola C, Rutkowska M, et al. The impact of competitive sports on menstrual cycle and menstrual disorders, including premenstrual syndrome, premenstrual dysphoric disorder and hormonal imbalances. Ginekol Pol. 2020;91:503–12.

Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38: 101019.

De Souza MJ, Toombs RJ, Scheid JL, O'Donnell E, West SL, Williams NI. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. Hum Reprod. 2010;25(2):491–503. https://doi.org/10.1093/humrep/dep411.

Dokumacı B, Hazır T. Effects of the menstrual cycle on running economy: oxygen cost versus caloric cost. Res Q Exerc Sport. 2019;90(3):318–26.

Driver HS, Dijk DJ, Werth E, Biedermann K, Borbely AA. Sleep and the sleep electroencephalogram across the menstrual cycle in young healthy women. J Clin Endocrinol Metab. 1996;81(2):728–35.

Fahrenholtz IL, Sjödin A, Benardot D, Tornberg ÅB, Skouby S, Faber J, et al. Within-day energy deficiency and reproductive function in female endurance athletes. Scand J Med Sci Sports. 2018;28(3):1139–46.

Findlay RJ, Macrae EHR, Whyte IY, Easton C, Forrest Née Whyte LJ. How the menstrual cycle and menstruation affect sporting performance: experiences and perceptions of elite female rugby players. Br J Sports Med. 2020 Sep;54(18):1108–13.

Forman RG, Chapman MC, Steptoe PC. The effect of endogenous progesterone on basal body temperature in stimulated ovarian cycles. Hum Reprod. 1987;2:631–4.

Foster R, Vaisberg M, Araújo MP, Martins MA, Capel T, Bachi ALL, et al. Relationship between anxiety and interleukin 10 in female soccer players with and without premenstrual syndrome (PMS). Rev Bras Ginecol Obstet. 2017 Nov;39(11):602–607. https://doi.org/10.1055/s-0037-1606244. Epub 2017 Aug 28.

Freemas JA, Baranauskas MN, Constantini K, Constantini N, Greenshields JT, Mickleborough TD, Raglin JS, Schlader ZJ. Exercise performance is impaired during the midluteal phase of the menstrual cycle. Med Sci Sports Exerc. 2021;53(2):442–52.

Frisch RE, Gotz-Welbergen AV, McArthur JW, Albright T, Witschi J, Bullen B, et al. Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. JAMA. 1981;246(14):1559–63.

Genzel L, Kiefer T, Renner L, et al. Sex and modulatory menstrual cycle effects on sleep related memory consolidation. Psychoneuroendocrinology. 2012;37(7):987–98. https://doi.org/10.1016/j.psyneuen.2011.11.006.

Giorgis-Allemand L, Thalabard JC, Rosetta L, Siroux V, Bouyer J, Slama R. Can atmospheric pollutants influence menstrual cycle function? Environ Pollut. 2020;257: 113605.

Goldsmith E, Glaister M. The effect of the menstrual cycle on running economy. J Sports Med Phys Fitness. 2020;60(4):610–7. https://doi.org/10.23736/S0022-4707.20.10229-9. Epub 2020 Feb 4.

Gollenberg AL, Hediger ML, Mumford SL, Whitcomb BW, Hovey KM, Wactawski-Wende J, et al. Perceived stress and severity of perimenstrual symptoms: the BioCycle Study. J Womens Health (larchmt). 2010;19(5):959–67.

Goodale BM, Shilaih M, Falco L, Dammeier F, Hamvas G, Leeners B. Wearable sensors reveal menses-driven changes in physiology and enable prediction of the fertile window: observational study. J Med Internet Res. 2019;21(4): e13404.

Gordon HW, Lee PA. No difference in cognitive performance between phases of the menstrual cycle. Psychoneuroendocrinology. 1993;18(7):521–31.

Graja A, Kacem M, Hammouda O, Borji R, Bouzid MA, Souissi N, et al. Physical, biochemical, and neuromuscular responses to repeated sprint exercise in eumenorrheic female handball players: effect of menstrual cycle phases. J Strength Cond Res. 2020 Mar 10.

Gupta R, Lahan V, Bansal S. Subjective sleep problems in young women suffering from premenstrual dysphoric disorder. N Am J Med Sci. 2012;4(11):593–5. https://doi.org/10.4103/1947-2714.103326. PMID: 23181235; PMCID: PMC3503382

Hacker NF, Gambone JC, Hobel CJ. Hacker & Moore's essentials of obstetrics and gynecology. In: Hacker NF, Gambone JC, Hobel CJ, editors. 6th ed. Elsevier; 2016

Hackney AC, Kallman AL, Ağgön E. Female sex hormones and the recovery from exercise: menstrual cycle phase affects responses. Biomed Hum Kinet. 2019;11(1):87–9. https://doi.org/10.2478/bhk-2019-0011.

Hammer KC, Veiga A, Mahalingaiah S. Environmental toxicant exposure and menstrual cycle length. Curr Opin Endocrinol Diabetes Obes. 2020;27(6):373–9.

Hampson E, Levy-Cooperman N, Korman JM. Estradiol and mental rotation: relation to dimensionality, difficulty, or angular disparity? Horm Behav. 2014;65(3):238–48.

Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiol Rev. 1995;17(2):265–86.

Jabbour HN, Kelly RW, Fraser HM, Critchley HO. Endocrine regulation of menstruation. Endocr Rev. 2006;27(1):17–46. https://doi.org/10.1210/er.2004-0021. Epub 2005 Sep 13. PMID: 16160098

Ju H, Jones M, Mishra GD. A u-shaped relationship between body mass index and dysmenorrhea: a longitudinal study. PLoS One. 2015;10(7):e0134187. https://doi.org/10.1371/journal.pone.0134187. PMID: 26218569; PMCID: PMC4517870

Koikawa N, Takami Y, Kawasaki Y, Kawana F, Shiroshita N, Ogasawara E, Kasai T. Changes in the objective measures of sleep between the initial nights of menses and the nights during the midfollicular phase of the menstrual cycle in collegiate female athletes. J Clin Sleep Med. 2020;16(10):1745–51.

Kokts-Porietis RL, Minichiello NR, Doyle-Baker PK. The effect of the menstrual cycle on daily measures of heart rate variability in athletic women. J Psychophysiol. 2020;34(1):60–8.

Le J, Thomas N, Gurvich C. Cognition, the menstrual cycle, and premenstrual disorders: a review. Brain Sci. 2020;10(4):198.

Lee KA, Shaver JF, Giblin EC, Woods NF. Sleep patterns related to menstrual cycle phase and premenstrual affective symptoms. Sleep. 1990;13(5):403–9.

Lee EC, Fragala MS, Kavouras SA, Queen RM, Pryor JL, Casa DJ. Biomarkers in sports and exercise: tracking health, performance, and recovery in athletes. J Strength Cond Res. 2017;31(10):2920–37.

Lim AJ, Huang Z, Chua SE, Kramer MS, Yong EL. Sleep duration, exercise, shift work and polycystic ovarian syndrome-related outcomes in a healthy population: a cross-sectional study. PLoS ONE. 2016;11(11): e0167048.

Livdans-Forret AB, Harvey PJ, Larkin-Thier SM. Menorrhagia: a synopsis of management focusing on herbal and nutritional supplements, and chiropractic. J Can Chiropr Assoc. 2007;51(4):235–46.

Loucks AB, Verdun M, Heath EM. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J Appl Physiol (1985). 1998 Jan;84(1):37–46.

MacNutt MJ, De Souza MJ, Tomczak SE, Homer JL, Sheel AW. Resting and exercise ventilatory chemosensitivity across the menstrual cycle. J Appl Physiol (1985). 2012 Mar;112(5):737–47.

Mahalingaiah S, Missmer SE, Cheng JJ, Chavarro J, Laden F, Hart JE. Perimenarchal air pollution exposure and menstrual disorders. Hum Reprod. 2018;33(3):512–9.

Maijala A, Kinnunen H, Koskimäki H, Jämsä T, Kangas M. Nocturnal finger skin temperature in menstrual cycle tracking: ambulatory pilot study using a wearable Oura ring. BMC Womens Health. 2019;19(1):150.

Marcus MD, Loucks TL, Berga SL. Psychological correlates of functional hypothalamic amenorrhea. Fertil Steril. 2001;76:310–6.

Marsh SA, Jenkins DG. Physiological responses to the menstrual cycle. Sports Med. 2002;32:601–14.

McKinley PS, King AR, Shapiro PA, Slavov I, Fang Y, Chen IS, Jamner LD, Sloan RP. The impact of menstrual cycle phase on cardiac autonomic regulation. Psychophysiology. 2009 Jul;46(4):904–11. https://doi.org/10.1111/j.1469-8986.2009.00811.x. Epub 2009 Apr 6. PMID: 19386049; PMCID: PMC4451597.

McNamara A, Harris R, Minahan C. 'That time of the month' … for the biggest event of your career! Perception of menstrual cycle on performance of Australian athletes training for the 2020 Olympic and Paralympic Games. BMJ Open Sport Exerc Med 2022;8:e001300.

Merklinger-Gruchala A, Jasienska G, Kapiszewska M. Effect of air pollution on menstrual cycle length-a prognostic factor of women's reproductive health. Int J Environ Res Public Health. 2017;14:816.

Mong JA, Baker FC, Mahoney MM, Paul KN, Schwartz MD, Semba K, Silver R. Sleep, rhythms, and the endocrine brain: influence of sex and gonadal hormones. J Neurosci. 2011;31(45):16107–16.

Mullen J, Bækken L, Bergström H, Björkhem Bergman L, Ericsson M, Ekström L. Fluctuations in hematological athlete biological passport biomarkers in relation to the menstrual cycle. Drug Test Anal. 2020;12(9):1229–40. https://doi.org/10.1002/dta.2873.

Nagma S, Kapoor G, Bharti R, et al. To evaluate the effect of perceived stress on menstrual function. J Clin Diagn Res. 2015;9(3):QC01–QC3.

Najmabadi S, Schliep KC, Simonsen SE, Porucznik CA, Egger MJ, Stanford JB. Menstrual bleeding, cycle length, and follicular and luteal phase lengths in women without known subfertility: a pooled analysis of three cohorts. Paediatr Perinat Epidemiol. 2020;34(3):318–27.

Nasiadek M, Stragierowicz J, Klimczak M, Kilanowicz A. The role of zinc in selected female reproductive system disorders. Nutrients. 2020;12(8):2464.

O'Donnell E, Goodman JM, Harvey PJ. Clinical review: cardiovascular consequences of ovarian disruption: a focus on functional hypothalamic amenorrhea in physically active women. J Clin Endocrinol Metab. 2011;96(12):3638–48.

Olean-Oliveira T, Figueiredo C, de Poli RAB, Lopes VHF, Jimenez-Maldonado A, Lira FS, et al. Menstrual cycle impacts adipokine and lipoprotein responses to acute high-intensity intermittent exercise bout. Eur J Appl Physiol. 2022;122(1):103–12.

Onieva-Zafra MD, Fernández-Martínez E, Abreu-Sánchez A, Iglesias-López MT, García-Padilla FM, Pedregal-González M, et al. Relationship between diet, menstrual pain and other menstrual characteristics among Spanish students. Nutrients. 2020;12(6):1759.

Oxfeldt M, Dalgaard LB, Jørgensen AA, Hansen M. Hormonal contraceptive use, menstrual dysfunctions, and self-reported side effects in elite athletes in Denmark. Int J Sports Physiol Perform. 2020;15(10):1377–84.

Palm-Fischbacher S, Ehlert U. Dispositional resilience as a moderator of the relationship between chronic stress and irregular menstrual cycle. J Psychosom Obstet Gynaecol. 2014;35(2):42–50.

Pauli SA, Berga SL. Athletic amenorrhea: energy deficit or psychogenic challenge? Ann N Y Acad Sci. 2010;1205:33–8.

Petkus DL, Murray-Kolb LE, Scott SP, Southmayd EA, De Souza MJ. Iron status at opposite ends of the menstrual function spectrum. J Trace Elem Med Biol. 2019;51:169–75.

Rael B, Alfaro-Magallanes VM, Romero-Parra N, Castro EA, Cupeiro R, Janse de Jonge XAK, et al. Menstrual cycle phases influence on cardiorespiratory response to exercise in endurance-trained females. Int J Environ Res Public Health. 2021 Jan 20;18(3):860.

Rafique N, Salem AM, Latif R, ALSheikh MH. Serum leptin level across different phases of menstrual cycle in normal weight and overweight/obese females. Gynecol Endocrinol. 2018;34:601–04.

Roberts RE, Farahani L, Webber L, Jayasena C. Current understanding of hypothalamic amenorrhoea. Ther Adv Endocrinol Metab. 2020;30(11):2042018820945854.

Romero-Parra N, Cupeiro R, Alfaro-Magallanes VM, Rael B, Rubio-Arias JÁ, Peinado AB, et al. IronFEMME study group. exercise-induced muscle damage during the menstrual cycle: a systematic review and meta-analysis. J Strength Cond Res. 2021 Feb 1;35(2):549–61.

Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016;37:467–520.

Ryterska K, Kordek A, Załęska P. Has menstruation disappeared? functional hypothalamic amenorrhea-what is this story about? Nutrients. 2021;13(8):2827.

Saei Ghare Naz M, Kiani Z, Rashidi Fakari F, Ghasemi V, Abed M, Ozgoli G. The effect of micronutrients on pain management of primary dysmenorrhea: a systematic review and meta-analysis. J Caring Sci. 2020 Mar 1;9(1):47–56.

Saxena AR, Seely EW, Goldfine AB. Cardiovascular risk factors and menstrual cycle phase in pre-menopausal women. J Endocrinol Invest. 2012;35(8):715–9.

Sharp GC, Fraser A, Sawyer G, Kountourides G, Easey KE, Ford G, et al. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. Int J Epidemiol. 2021 Dec 2:dyab239.
Shaw S, Ghosh D, Kumar U, Panjwani U, Kumar B. Impact of high altitude on key determinants of female reproductive health: a review. Int J Biometeorol. 2018;62(11):2045–55.
Shimizu K, Suzuki N, Nakamura M, Aizawa K, Imai T, Suzuki S, et al. Mucosal immune function comparison between amenorrheic and eumenorrheic distance runners. J Strength Cond Res. 2012;26(5):1402–6.
Shufelt CL, Torbati T, Dutra E. Hypothalamic amenorrhea and the long-term health consequences. Semin Reprod Med. 2017;35(3):256–62.
Shughrue PJ, Lane MV, Merchenthaler I. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. J Comp Neurol. 1997;388(4):507–25.
Slatkovska L, Jensen D, Davies GA, Wolfe LA. Phasic menstrual cycle effects on the control of breathing in healthy women. Respir Physiol Neurobiol. 2006;154(3):379–88.
Solís-Ortiz S, Corsi-Cabrera M. Sustained attention is favored by progesterone during early luteal phase and visuo-spatial memory by estrogens during ovulatory phase in young women. Psychoneuroendocrinology. 2008;33(7):989–98.
Solomon CG, Hu FB, Dunaif A, et al. Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. JAMA2001;286:2421–6.
Su SB, Lu CW, Kao YY, Guo HR. Effects of 12-hour rotating shifts on menstrual cycles of photoelectronic workers in Taiwan. Chronobiol Int. 2008;25(2):237–48.
Tenan MS, Brothers RM, Tweedell AJ, Hackney AC, Griffin L. Changes in resting heart rate variability across the menstrual cycle. Psychophysiology. 2014;51(10):996–1004. https://doi.org/10.1111/psyp.12250. Epub 2014 Jun 18. PMID: 24942292
Thein-Nissenbaum JM, Rauh MJ, Carr KE, Loud KJ, McGuine TA. Associations between disordered eating, menstrual dysfunction, and musculoskeletal injury among high school athletes. J Orthop Sports Phys Ther. 2011;41(2):60–9.
Thorpe RT, Atkinson G, Drust B, Gregson W. Monitoring fatigue status in elite team-sport athletes: implications for practice. Int J Sports Physiol Perform. 2017;12(Suppl 2):S227–34.
Timmons BW, Hamadeh MJ, Devries MC, Tarnopolsky MA. Influence of gender, menstrual phase, and oral contraceptive use on immunological changes in response to prolonged cycling. J Appl Physiol. 2005;99:979–85.
Vanheest JL, Rodgers CD, Mahoney CE, De Souza MJ. Ovarian suppression impairs sport performance in junior elite female swimmers. Med Sci Sports Exerc. 2014;46(1):156–66.
Vashishta S, Gahlot S, Goyal R. Effect of menstrual cycle phases on plasma lipid and lipoprotein levels in regularly menstruating women. J Clin Diagn Res. 2017 May;11(5):CC05–CC07.
Wei S, Schmidt MD, Dwyer T, Norman RJ, Venn AJ. Obesity and menstrual irregularity: associations with SHBG, testosterone, and insulin. Obesity. 2009;17:1070–6.
Wei M, Cheng Y, Bu H, et al. Length of menstrual cycle and risk of endometriosis: a meta-analysis of 11 case-control studies. Medicine (baltimore). 2016;95: e2922.
Wesselink AK, Wise LA, Hatch EE, et al. Menstrual cycle characteristics and fecundability in a North American preconception cohort. Ann Epidemiol. 2016;26:482-487.e1.
Whitcomb BW, Mumford SL, Perkins NJ, et al. Urinary cytokine and chemokine profiles across the menstrual cycle in healthy reproductive-aged women. Fertil Steril. 2014;101(5):1383–91.
Williams TJ, Krahenbuhl GS. Menstrual cycle phase and running economy. Med Sci Sports Exerc. 1997;29(12):1609–18.
Wronka I, Kliś K. Effect of air pollution on age at menarche in polish females, born 1993–1998. Sci Rep. 2022;12:4820.
Wyskida K, Franik G, Wikarek T, Owczarek A, Delroba A, Chudek J, et al. The levels of adipokines in relation to hormonal changes during the menstrual cycle in young, normal-weight women. Endocr Connect. 2017;6(8):892–900.
Xing X, Xue P, Li SX, Zhou J, Tang X. Sleep disturbance is associated with an increased risk of menstrual problems in female Chinese university students. Sleep Breath. 2020;24(4):1719–27.

Zheng H, Harlow SD, Kravitz HM, Bromberger J, Buysse DJ, Matthews KA, et al. Actigraphy-defined measures of sleep and movement across the menstrual cycle in midlife menstruating women: study of women's health across the nation sleep study. Menopause. 2015;22(1):66–74.

Zhou W, Zhang L, Tong C, Fang F, Zhao S, Tian Y, et al. Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women. Environ Health Perspect. 2017;125(6): 067012.

Zhu TY, Rothenbühler M, Hamvas G, et al. The accuracy of wrist skin temperature in detecting ovulation compared to basal body temperature: prospective comparative diagnostic accuracy study. J Med Internet Res. 2021;23(6):e20710. Published 2021 Jun 8. https://doi.org/10.2196/20710

Chapter 14
Pregnancy, Sex Hormones, and Exercise

Kirsty J. Elliott-Sale

Introduction

The sequence of events from fertilization to the formation of an adult organism is known as developmental anatomy. This timeline begins with ***pregnancy***, which specifically relates to: (i) the fertilization of a secondary oocyte (i.e., an immature egg, female sex cell) by a spermatozoon (i.e., mature motile male sex cell), which usually occurs 12–24 h following ovulation and results in the formation of a single nucleus (i.e., a segmentation nucleus) with genetic material contributed by the spermatozoon (i.e., the male pronucleus) and ovum (i.e., the mature egg, the female pronucleus); (ii) implantation of the blastocyst (i.e., the cleaved fertilized ovum) into the endometrium (i.e., the lining of the womb), which typically occurs six days after fertilization; (iii) embryonic (i.e., the first two months of development) and fetal (i.e., the remaining seven months of development) growth; and (iv) parturition (i.e., labor and delivery, childbirth). Even though pregnancy is initiated by fertilization, its tenure starts on the first day of the menstrual cycle in which fertilization occurs (i.e., on the first day of the woman's last period). Pregnancy typically lasts 40 weeks and is divided into three trimesters each lasting 12–14 weeks. ***Gestation***, on the other hand, refers to the time a zygote (i.e., the fertilized ovum), embryo, or fetus is carried in the female reproductive tract and is usually 266 days, which is counted from the estimated date of fertilization. Throughout pregnancy, a multitude of synchronous anatomical and physiological changes occur (Fig. 14.1); the physiological changes include alterations mediated by (i) estrogen and progesterone (i.e., sex hormones) and (ii) sex hormones plus other mechanisms (e.g., weight gain, growing fetus). This chapter

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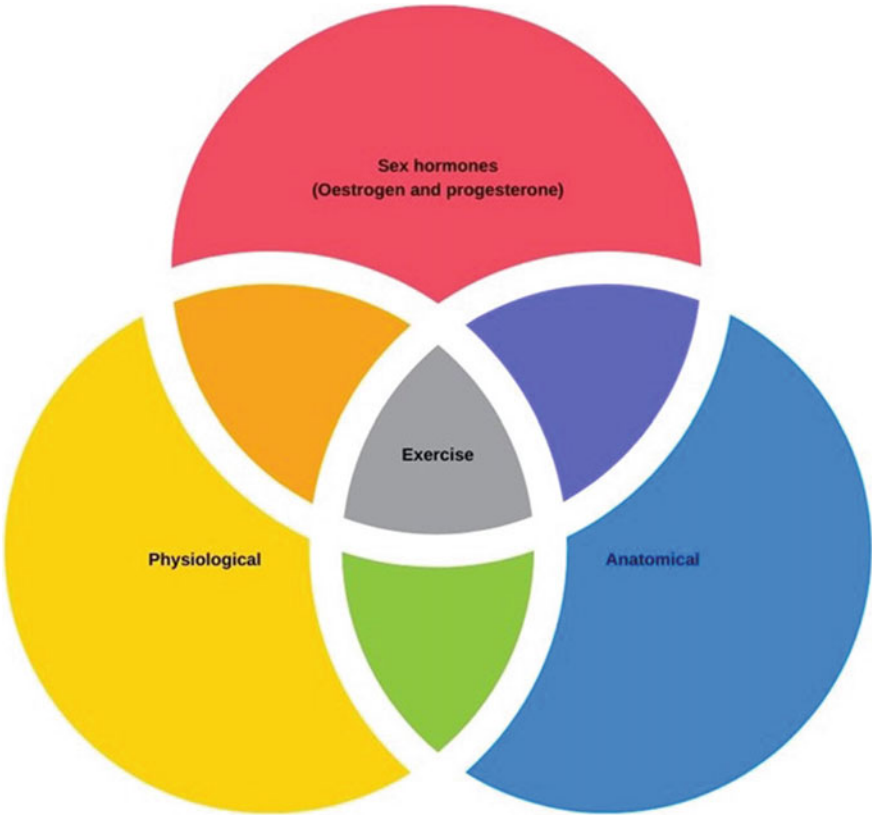

Fig. 14.1 Venn diagram showing the interaction among the hormonal (specifically sex hormones), physiological, and anatomical changes that occur during pregnancy and their potential to either individually and/or collectively influence exercise performance and capacity

aims to contextualize these changes and specifically focus on the impact of supra-physiological concentrations of estrogens and progesterone caused by pregnancy on exercise performance and capacity.

Changes and Outcomes Associated with Pregnancy

In the following sections, the pregnancy-related changes in sex hormone concentrations are discussed in detail (i.e., in keeping with the focus of this chapter), while the anatomical and wider physiological changes (i.e., all physiological changes excluding the changes in sex hormone concentrations) are just summarized with signposting provided to further specialized texts (Table 14.1).

Table 14.1 Abridged anatomical and wider physiological changes (i.e., all physiological changes excluding the changes in sex hormone concentrations) and outcomes, which occur during pregnancy, and their functional and practical implications on exercise performance and capacity

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
Panel a							
Changes	Weight gain and internal organ displacement	Deviations in pigmentation, nevi, vasculature, mucosa, connective tissue, glands, nails, and breasts	Increased cardiac load at rest and during exercise and altered mean arterial pressure	Disturbances in ventilatory function	Decreased digestive motility	Altered glucose metabolism	Altered response to evaporative and dry heat loss
Caused by	Growing fetus	Estrogen and progesterone and non-specific and specific pregnancy-related dermatoses	Mechanisms responsible for mediating the changes in systemic hemodynamics have yet to be completely elucidated—likely mediated by nitric oxide, relaxin, and estrogen	Hormonal (estrogen and progesterone) and mechanical effects (enlarged uterus)	Hormonal (estrogen and progesterone), mechanical (growing fetus), and hemodilution effects	Exact causes are unknown—likely affected by hormones (estrogen and progesterone), weight gain, a growing fetus, race, pre-gravid weight, pre-diabetes	Cardiovascular shifts that occur during pregnancy and changes in progesterone
Panel b							
Outcomes	Bladder irritation	Hyperpigmentation	Increased resting heart rate	Increased sensitivity to carbon dioxide	Constipation	Gestational diabetes mellitus	Enhanced thermoregulatory capacity

(continued)

Table 14.1 (continued)

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
	Reduced bladder volume	Edema	Increased stroke volume	Increased tidal volume	Gallstones—bloating, indigestion, heartburn, and gas	Increased maternal insulin resistance	Decreased body temperature thresholds for sweating
	Increased pelvic floor distensibility	Varicose veins	Hypotension	Decreased arterial carbon dioxide tension		Elevated maternal blood glucose levels	
	Incontinence, nocturia, and micturition	Spider angiomas, pyogenic granuloma, acne, and skin tags	Hypertension—leading to pre-eclampsia in severe cases	Increased arterial oxygen tension			
	Pelvic organ prolapse	Vulvar varicosity	Heart rate does not significantly correlate with ratings of perceived exertion	Respiratory discomfort (dyspnea)			
	Bladder and bowel dysfunction	Striae gravidarum					
	Gastrointestinal issues (e.g., gastroesophageal reflux, gallstones, diarrhea, and constipation)	Breast enlargement, tenderness, increased prominence of veins, striae, areolar enlargement, erectile nipples, and/or nipple sensitivity					

(continued)

Table 14.1 (continued)

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
	Decreased respiratory reserve volume	Hirsutism/hypertrichosis					
	Decreased functional residual capacity						
	Shift in center of gravity						
	Increased postural sway						
Panel c							
Functional implications (i.e., impact on exercise performance and/or capacity)	Altered gait and movement patterns (e.g., agility) Increased risk of falls	Edema—inability to stand for long periods of time	Hypotension can cause nausea, dizziness, unsteadiness fatigue, weakness, blurred vision, and cognitive impairment which can directly affect exercise performance and capacity	Dyspnea—can be compounded by some forms of exercise	Gastrointestinal distress—reduced exercise capacity	Women with gestational diabetes mellitus might experience hypoglycemia during and following exercise	Greatest blood flow (i.e., greater dry heat loss) and sweat losses (i.e., evaporation) at rest and during exercise occur in late pregnancy

(continued)

Table 14.1 (continued)

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
	Weight gain may significantly increase the forces across joints during weight-bearing exercise	Breasts/nipples—pain and/or sensitivity during exercise	Those with hypotension need to be watchful of post-exercise hypotension	Decreased oxygen availability for the performance of aerobic exercise		Women with gestational diabetes mellitus tend to gain more weight during pregnancy (see anatomical changes column for implications of weight gain)	
	Need to urinate more often	Some high-impact exercises could make varicose veins worse	A higher relative cardiac load during exercise				
	Leaking (urine), defecating, or vomiting during exercise		Distorted ratings of perceived exertion relative to exercising heart rate can lead to an increased risk of injury or adverse reaction				
	Feelings of vaginal heaviness and dragging during exercise						

(continued)

Table 14.1 (continued)

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
	Shortness of breath during exercise						
Panel d							
Practical considerations	Choice of activity (e.g., avoiding high-impact exercises), clothing (e.g., leak-proof underwear), and setting (e.g., access to toilets)	Choice of clothing (e.g., bra's) and footwear (e.g., comfortable shoes and socks)	Method of heart rate monitoring (i.e., direct recording rather than estimated or inferred is recommended)	Duration, intensity, and modality of activity (i.e., aerobic exercise is recommended for dyspnea)	Readiness to exercise due to side effects and symptoms	Continual self-monitoring of blood glucose levels—it may be better to exercise an hour after a meal and to take insulin medication well before exercise	Ability to distinguish between thermal sensation thermal discomfort and heat stress during exercise
	Inclination to exercise due to the extra burden and worry	Willingness to be seen in minimal or revealing clothing	Modality of exercise (e.g., aerobic exercise may be preferential)		Influence on the choice of activity and setting (e.g., access to toilets)	Motivation to exercise as gestational diabetes mellitus can cause mood dysregulations	Avoidance of hyperthermia in early pregnancy

(continued)

Table 14.1 (continued)

	Anatomical	Physiological					
		Integumentary	Cardiovascular	Respiratory	Digestion	Metabolism	Thermoregulatory
		Avoidance of activities with motionless standing	Supine positions should be avoided as much as possible during rest and exercise				Maintenance of euhydration, and therefore blood volume, is critical to heat balance
Panel e							
Supporting papers	Meekins and Siddiqui (2020)	Snarskaya et al. (2019)	Brislane et al. 2021	Milne et al. (1978)	Ferdinande et al. (2018)	Catalano et al. (1991)	Dervis et al. (2021)
	Cattani et al. (2021)	Motosko et al. (2017)	Magro-Malosso et al. (2017)	Kolarzyk et al. (2005)	Body and Christie (2016)	Stern et al. (2021)	Lindqvist et al. (2003)
	Body and Christie (2016)			Weissgerber et al. (1980)		Ali et al. (2020)	Clapp (1991)
	Nassikas et al. (2021)					Padayachee and Coombes (2015)	
	Forczek et al. (2018)						
	For an overview of the general changes that occur during pregnancy see Jackson et al. (2022), Tan and Tan (2013), and Artal and O'Toole (2003)						

Please note The details provided here are indicative, but not exhaustive

Sex Hormones

During the first trimester, the corpus luteum (i.e., an endocrine gland in the ovary formed when the follicle has discharged its secondary oocyte) secretes estrogens and progesterone in similar quantities to those produced during the luteal phase of the menstrual cycle. From the second trimester, the placenta adopts this secretory role. The placental unit, specifically the chorion (i.e., the fetal portion of the placenta), also secretes human chorionic gonadotropin (hCG), a glycoprotein hormone that imitates luteinizing hormone (LH), which further stimulates the production of estrogens and progesterone. Figure 14.2 shows the changes in 17-β-estradiol and progesterone before (panel a) and after (panel b) fertilization, during (panel c), and following pregnancy—with (panel d) and without (panel e) breastfeeding. The greatest increase in progesterone production occurs between weeks 18 and 30, during which time the placental unit produces approximately 250–500 mg of progesterone daily. During the last eight to ten weeks of gestation, little or no increase, and in some cases a slight decrease, in progesterone production occurs. At term, progesterone levels are 318–954 nmol L^{-1} (Tulchinsky et al. 1973), in comparison to 3–6 nmol L^{-1} and 32–111 nmol L^{-1} during the follicular and mid-luteal phases of the menstrual cycle (Abraham et al. 1972); a ninefold increase from the peak of the menstrual cycle to the peak of pregnancy. There is a rapid increase in 17-β-estradiol concentrations between weeks 20 and 35. At term, 17-β-estradiol levels are 22–110 nmol L^{-1} (Lindberg et al. 1974), in comparison to 0.4 and 1.5 nmol L^{-1}during the follicular and mid-luteal phases of the menstrual cycle (Abraham et al. 1972); a 73-fold increase from the peak of the menstrual cycle to the peak of pregnancy. In non-pregnant women, concentrations of estriol and estrone are less than 0.03 and 1 nmol L^{-1}; during pregnancy, these concentrations rise to approximately 35–104 and 7–110 nmol L^{-1} (Tulchinsky et al. 1973). In comparison to the other sex hormones, the rise in testosterone levels is weaker and more gradual; O'Leary et al. (1991) showed, between weeks 5 and 40 of pregnancy, a 1.7-fold increase in testosterone in comparison to a 33- and 11.9-fold increase in 17-β-estradiol and progesterone. As such, the concentrations of estrogens and progesterone during pregnancy are considered supraphysiological. During puerperium (i.e., the six weeks after childbirth when maternal physiologic changes related to pregnancy return to the non-pregnant state) and in the absence of lactation (i.e., the secretion and ejection of milk by the mammary glands), sex hormone levels return to normal values. Otherwise, following delivery, the withdrawal of progesterone coupled with the sharp rise in circulating prolactin levels—as a result of suckling—initiates and maintains milk production (i.e., lactation). Lactation can prevent ovarian cycles from occurring in the first few months following parturition, if suckling occurs eight to ten times per day, and is known as lactational amenorrhea. This phenomenon is, however, inconsistent; i.e., there is large between and within-individual variation in its occurrence and duration. It is worth noting that ovulation normally precedes the first postpartum menstrual bleed (i.e., ovulation is reinstated before menstruation returns).

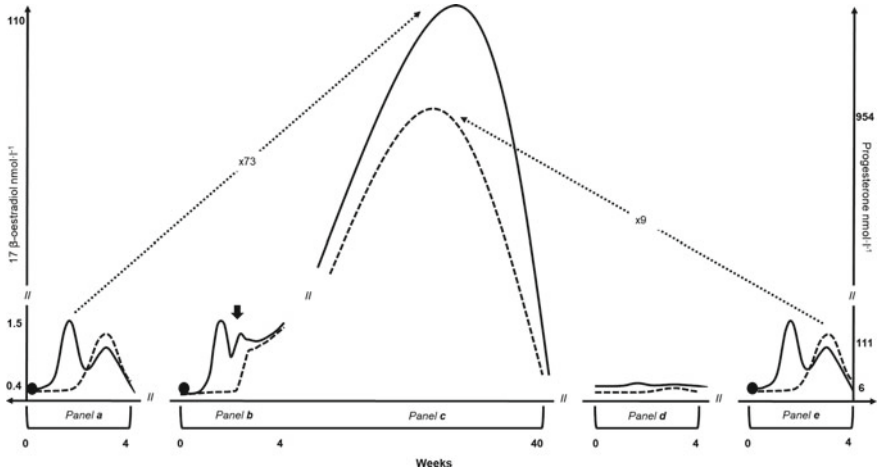

Fig. 14.2 Relative changes in 17-β-estradiol (solid line) and progesterone (dashed line) concentrations before, during, and after pregnancy. Panel **a** shows a eumenorrheic menstrual cycle without fertilization. Panel **b** shows a menstrual cycle with fertilization (as denoted by ↓). Panel **c** shows the hormonal changes during pregnancy. Panel **d** shows lactational amenorrhea (anovulatory cycles). Panel **e** shows the resumption of a eumenorrheic menstrual cycle following parturition. The circles denote menstruation. During pregnancy, the increase in 17-β-estradiol and progesterone can be as much as 73-fold and ninefold (Tal et al. 2001)

Anatomical and Physiological

During pregnancy, women gain approximately 11–16 kg, which consists of the following (approximate) changes: breasts 0.5 kg (equivalent to one to two bra cup sizes); uterus 1.6 kg (stretches 500–1000 times its pre-pregnancy size); placenta 0.7 kg; baby 3.5 kg; amniotic fluid 1–1.5 kg; and extra blood volume and fluid 4 kg. By the third trimester, the uterus occupies almost the entire pelvic cavity, resulting in the displacement of other organs (Fig. 14.3). These changes and subsequent outcomes are précised in Table 14.1 (panels a and b).

A myriad of physiological changes occurs during pregnancy. In short, pregnancy-related, physiological changes have been noted in the integumentary, cardiovascular, respiratory, digestive, metabolic, and thermoregulatory systems. These changes and downstream outcomes are summarized in Table 14.1 (panels a and b).

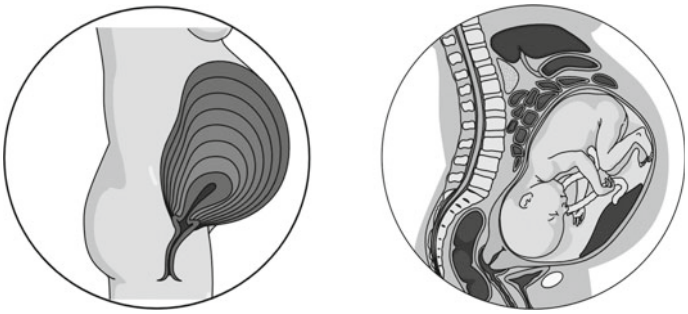

Fig. 14.3 Anatomical changes associated with pregnancy; note the enlargement of the uterus and the supplanting of the other internal organs

Functional Implications of Pregnancy on Exercise Performance and Capacity

In the absence of absolute and relative contraindications (Everson et al. 2014; Artal and O'Toole 2003), women are advised to maintain their current exercise and occupational habits (Mottola et al. 2018), as exercise has been shown to confer maternal and fetal benefits (Gregg and Ferguson 2017). Exercise performance and capacity could, however, be influenced by the changes that occur during pregnancy. In the following sections, the impact of supraphysiological concentrations of estrogen and progesterone on exercise performance and capacity is discussed in detail (i.e., in line with the focus of this chapter), while the impact of the anatomical and wider physiological changes (i.e., all physiological changes excluding the changes in sex hormone concentrations) is merely summarized in order to provide the backdrop information to the sex hormone-associated changes.

Sex Hormones

The following sections describe the relationship between sex hormones and athletic performance or components of athletic performance. These outcomes were explored as sex hormones have been implicated, either observed or theoretically, in the mediation, either solely or predominately, of these effects. This section complements the information provided in Table 14.1 related to the wider physiological data (i.e., all physiological changes excluding the changes in sex hormone concentrations).

Muscle

The potential influence of sex hormones on muscular function is often debated but seldom appropriately investigated (i.e., there is a lack of high-quality data on this topic). As such, the existence, direction, and magnitude of any effects remain to be scientifically (i.e., rather than anecdotally) established. Although muscle function has been assessed across menstrual and oral contraceptive pill cycles (McNulty et al. 2020; Elliott-Sale et al. 2020) and in response to menopause—with or without hormone replacement therapy—(Xu et al. 2020), it has rarely been assessed during pregnancy. Moreover, of the studies performed in this area, several have been cross-sectional study designs and few have included sex hormone analysis. For example, using a cross-sectional approach without the quantification of sex hormone status, Mbada et al. (2015) showed that pregnant women had significantly lower handgrip strength than non-pregnant women, while Abdullahi et al. (2021) did not observe any significant changes in handgrip strength between trimesters. Of those employing longitudinal study designs, Atay and Basalan (2015), Żelaźniewicz and Pawłowski (2018), and Bey et al. (2019), none measured sex hormone concentrations. Atay and Basalan (2015) measured handgrip strength at 20 and 32 weeks of pregnancy and observed a significant loss in strength as the pregnancy progressed. Similarly, Żelaźniewicz and Pawłowski (2018) showed that handgrip strength decreased from the first to the third trimester of pregnancy. Conversely, Bey et al. (2019) did not show any change in the lower limb (i.e., knee extensor) muscle strength between early and late pregnancy (16 ± 4 and 29 ± 4 weeks of pregnancy). Using a cross-sectional design—comparing pregnant (week 12, 20, and 36 of pregnancy) and postpartum women (six weeks following childbirth)—Elliott et al. (2005) showed that concentrations of total and bioavailable 17-β-estradiol, progesterone, and total testosterone were highest at week 36 of pregnancy (i.e., during the third trimester) and lowest at six weeks postpartum (Fig. 14.4). Bioavailable testosterone was also highest at 36 weeks of pregnancy but was still significantly elevated at six weeks postpartum. Concentrations of total estradiol were significantly different between all stages (all $p < 0.001$); concentrations of progesterone were significantly different between all stages (all $p < 0.001$) except between the first and second trimesters; concentrations of total testosterone concentration were significantly different between weeks 12 and 36, and 36 and 6 (all $p < 0.001$); concentrations of bioavailable estradiol were significantly different between all stages (all $p < 0.05$) except between weeks 20 and 36; and the concentration of bioavailable testosterone was significantly greater six weeks following childbirth than during week 20 ($p < 0.05$). Maximum voluntary isometric force per unit cross-sectional area of the first dorsal interosseus muscle was significantly higher at weeks 12 and 20 of pregnancy compared to six weeks postpartum; i.e., women in this study were stronger during the first and second trimesters than following parturition. The changes in strength did not, however, significantly and positively correlate to changes in sex hormone concentrations. As such, the authors proposed that the changes they observed in strength, during the first two trimesters of pregnancy, were not caused by supraphysiological concentrations of 17-β-estradiol and progesterone, although they suggested that further investigation

of this occurrence is warranted. Clearly, the impact of sex hormones on muscle function during pregnancy needs to be further investigated, ideally using longitudinal research designs (e.g., pre-pregnancy, throughout pregnancy, and postpartum—with and without lactation) with hormonal analysis. In addition, the quality of studies in this area could be further advanced by reporting gestational stage, parity, gravidity, and whether it is a singleton or twin/triplet/etc. pregnancy (Elliott-Sale et al. 2021), which will increase the accuracy and validity of the population sampled and reduce the variability in hormone status between participants.

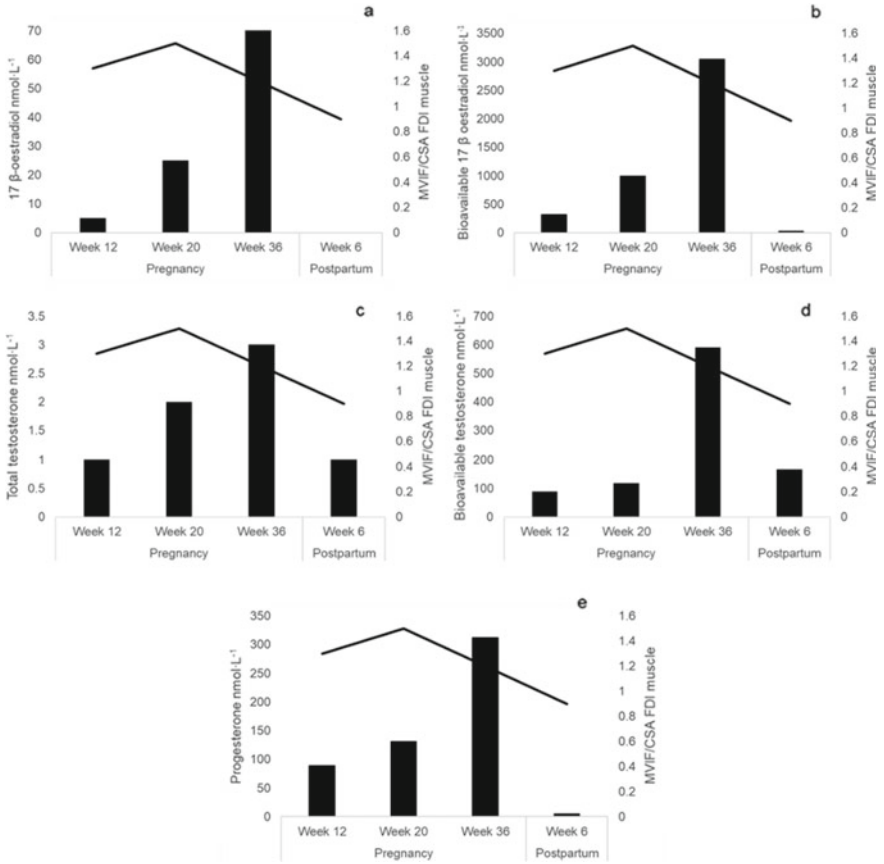

Fig. 14.4 Concentrations (bars) of total (panel **a**) and bioavailable (panel **b**) 17-β-estradiol, total (panel **c**) and bioavailable (panel **d**) testosterone and progesterone (panel **e**), and maximum voluntary isometric force per unit cross-sectional area (MVIF/CSA) of the first dorsal interosseus (FDI) muscle (lines) during (week 12, 24, and 36) and following (6 weeks) pregnancy

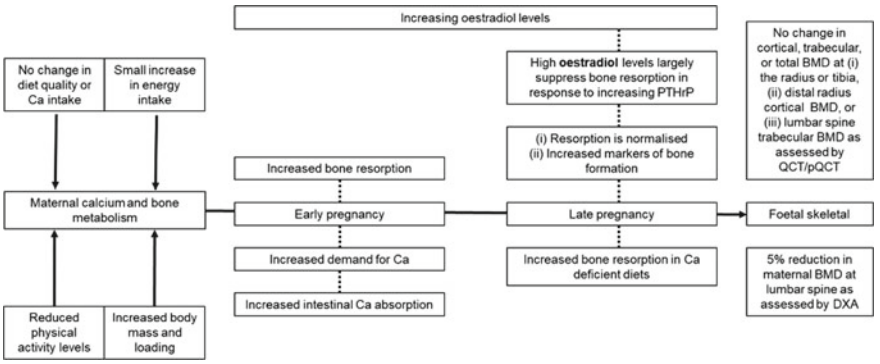

Fig. 14.5 Sequence of events involved in the regulation of maternal and fetal bone metabolism. Adapted from Winter et al. (2020). Abbreviations: *PTHrP* parathyroid hormone-related protein, *Ca* calcium, *BMD* bone mineral density, *DXA* dual X-ray absorptiometry, *QCT* quantitative computed tomography, *pQCT* peripheral quantitative computed tomography

Bone

During pregnancy, a complex cascade of events, involving many variables including 17-β-estradiol, is responsible for the changes in maternal bone health; these actions are summarized in Fig. 14.5. The effect of pregnancy on bone has been well documented (Kalkwarf and Specker 2002; Liu et al. 2019; Salari and Abdollahi 2014). The prevalence of pregnancy and lactation-induced osteoporosis is unknown but is believed to be rare. Its cause is currently unknown, although it is likely to be triggered by a combination of hormonal (oxytocin) influences and contributions from the sympathetic nervous system, genetics, and bone marrow fat (Winter et al. 2020). On the other hand, Song et al. (2017) showed, using a meta-analytical approach, that parity has a positive effect on bone in healthy, community-dwelling women, especially at the total hip site. In addition, fractures sustained during pregnancy appear to heal more quickly than during the non-pregnant state, and this effect is likely underpinned, at least in part, by estrogen (Beil et al. 2010), which is at supraphysiological levels during pregnancy.

Athletic Performance and Capacity

In the absence of complications, pregnancy-related confinement is no longer a viable (e.g., loss of earnings/sponsorship) or attractive (e.g., loss of training time and competition opportunity) option for competitive sportswomen. This sociocultural shift has prompted discussion on the effects of pregnancy on training and competition practices; however, the majority of previous research has examined the effects of exercise on pregnancy (i.e., maternal and fetal implications; see Wowdzia et al. 2021 for a review of this literature) as opposed to the effects of pregnancy on exercise (i.e.,

from a sports training or competition perspective). To date, no study has taken corresponding blood samples, to assess the hormonal milieu, alongside their outcome measures, meaning that the direct relationship between sex hormones and athletic performance and capacity during pregnancy is currently unknown. In the absence of this research, the general effects of pregnancy on exercise-related practices in elite and top-level sportswomen are summarized below. Of note, Hale and Milne (1996) commented that exercise in the elite athlete is only an accentuation of that found in the recreational athlete.

Using retrospective self-reported surveys, Beilock et al. (2001) showed that the number of athletes (89%) who trained during the first trimester fell by 24–65% in the third trimester, without a significant impact on their postpartum training programs. Similarly, Tenforde et al. (2015) reported that 70% of runners ran at some point during their pregnancy, but only 31% ran during their third trimester. They also showed that, on average, pregnant women reduced their training intensity to almost half of their non-pregnant running effort. Franklin et al. (2017) reported that 85% of pregnant recreational and elite rowers exercised during past pregnancies; 51.3, 42.4, and 15.7% of pregnant rowers met or exceeded the national guidelines during the first, second, and third trimesters. Sundgot-Borgen et al. (2019) also observed a downward trajectory in training volume from the first to the third trimester in 34 Norwegian elite athletes.

Conversely, when training was either monitored/tracked or prescribed, participation in moderate to high-level activity was (i) maintained and (ii) beneficial during pregnancy. Using a longitudinal observational approach, Clapp and Capeless (1991) showed a small but significant increase in maximum oxygen uptake in recreational athletes who maintained a moderate to high level of exercise training during and after pregnancy. Comparably, Kardel (2005) showed that top-level sportswomen maintained their high fitness levels during pregnancy when prescribed, appropriately strenuous, training.

Several case studies have investigated the lived experiences of elite athletes. Davies et al. (1999) conducted a case study on an elite marathon runner who preconceptionally ran 155 km week^{-1} at an intensity equivalent to 140–180 b min^{-1}. During pregnancy, the athlete completed 107 ± 19 km week^{-1} at an intensity equivalent to 130–140 b min^{-1}. Running velocity at a steady-state heart rate of 140, 150, and 160 b min^{-1} decreased by 20, 15, and 13% during pregnancy from week 1–32 antepartum. These data suggest it is possible for an elite endurance athlete to maintain a high exercise capacity during pregnancy. Soli and Sandbakk (2018) conducted a case study investigating the training characteristics and physiological capacity, of the world's most successful cross-country skier during pregnancy. Training volume was maintained at approximately 80–85% of pre-gravid load during the first and second trimesters but was reduced to approximately 50% in the third trimester. Training intensity was modified during pregnancy: (i) High-intensity training ceased at week 5 of pregnancy, and low and moderate-intensity training was used instead; and (ii) strength training was progressively modified. Oxygen uptake at the lactate threshold changed from 60.8 ml kg^{-1} min^{-1} before pregnancy to 57.0 ml kg^{-1} min^{-1} in the first trimester and 54.2 ml kg^{-1} min^{-1} in the second trimester. These findings suggest

that exercise (training) capacity can be maintained at a high level during the first two trimesters of pregnancy; however, substantial modifications are needed in the third trimester.

Psychosomatic

Although outside of the scope of this chapter, the psychological implications of pregnancy on exercise performance and capacity also need to be taken into account. Sex hormones have been shown to affect mood (i.e., resulting in mood disorders such as depression), especially during pregnancy and the postpartum period (Zsido et al. 2017) and, as such, the psychosomatic interactions between sex hormones, pregnancy, and exercise also need to be considered.

Anatomical and Physiological

The anatomical and physiological changes, which occur during pregnancy, largely result in discomfort (physical and emotional) for the exercising woman (Table 14.1; panel c). Moreover, these changes are associated with an increased risk of injury and illness. The prevalence and severity of these effects are subject to large within and between individual variability, but have been shown to impact the quality of life and exercise performance and capacity of physically active pregnant women (Barone Gibbs et al. 2021; Di Fabio et al. 2015; Everson and Wen 2011; Lagadec et al. 2018; Owe et al. 2009). Indeed, data from Whitaker et al. (2022) suggest that quality of life and participation in moderate to vigorous-intensity physical activity is affected by the stage of pregnancy, with better quality of life and participation in exercise seen in the second trimester, which is associated with fewer and less severe pregnancy-related symptoms.

Practical Implications of Pregnancy on Exercise Performance and Capacity

Sex Hormones

Given the paucity of information related to the effects of sex hormones on exercise performance and capacity, it is pre-mature to propose many practical considerations directly stemming from the changes in sex hormones experienced during pregnancy. Further high-quality research is needed and must include the determination of estrogens and progesterone from blood samples. Often, there is a reluctance to study the effects of pregnancy on exercise performance due to ethical concerns about the safety

of the mother and baby; however, the majority of recent evidence suggests that it is safe for both pre-gravid sedentary and well-trained women to exercise during pregnancy (Bø et al. 2016). At present, the only recommendations, based on the current state of the art, are related to the changes in bone health: (i) The choice (e.g., avoiding high-impact exercises, bending and twisting) and setting (e.g., slippery surfaces) of the activity need to be considered; and (ii) the disposition to exercise due to anxiety (i.e., fear of sustaining a fracture) needs to be taken into account.

Anatomical and Physiological

There are numerous practical considerations associated with the profound structural and functional changes that occur during pregnancy, as shown in Table 14.1 (panel d). Pregnant women, practitioners, and researchers need to be mindful of these factors in order to undertake/prescribe safe (i.e., to mother and fetus) and appropriate physical activity during pregnancy. In general, the mode, duration, intensity, frequency, and progression of the activity need to be assessed and potentially modified during pregnancy, perhaps even on a trimester-by-trimester basis. In addition, consideration needs to be given to the setting (e.g., location, environment), staffing (e.g., supervised versus unsupervised), equipment requirements (e.g., clothing, footwear), and motivation (e.g., weight management, elite sport, underlying medical conditions) associated with the proposed exercise program.

General Principles of Exercise Prescription During Pregnancy

In addition to the practical considerations listed above (i.e., as a result of the pregnancy-related changes in sex hormones, anatomy, and physiologic function), there are a number of general exercise principles that should be adhered to:

1. Medical screening (continual monitoring throughout pregnancy)—to establish relative and absolute contraindications to exercise (Artal and O'Toole 2003).
2. Consideration of pregnant women with comorbidities (e.g., obesity, chronic hypertension)—to further tailor the mode, duration, intensity, frequency, and progression of activity (Artal and O'Toole 2003).
3. Consideration of pre-gravid fitness—(i) 30 min or more of moderate-intensity physical activity on most, and preferably all, days of the week is suitable for all women with uncomplicated pregnancies regardless of pre-pregnancy activity level (Pate et al. 1995); (ii) competitive athletes experience the same pregnancy-related changes, implications, and limitations as recreational athletes, as such they require closer and more frequent obstetric supervision than routine care in order to maintain their more strenuous training programs (ACOG 2020).

4. Adequate fueling—to maximize maternal and fetal outcomes and limit excessive gestational weight gain (Elliott-Sale et al. 2019).
5. Consideration of post-exercise recovery—recovery time and hydration and nutrition strategies need to be considered (Soultanakis et al. 1996; Mottola et al. 2013).
6. Sports with a high likelihood of contact (e.g., ice hockey), falling (e.g., horse-riding, skating), and decompression sickness (e.g., scuba diving) should be avoided (ACOG 2002).
7. Consideration of altitude—(i) pregnant lowlanders can exercise (i.e., moderate intensity) safely between 1800 and 2500 m if acclimatized; (ii) pregnant highlanders can most likely exercise (i.e., moderate intensity) safely above 1800 m; and (iii) elite athletes need medical clearance to undertake strenuous (i.e., vigorous intensity) training at altitude (Artal et al. 1995; McManis 2021).

The Fourth Trimester

The first three months following childbirth are colloquially referred to as the ***fourth trimester***. For the majority of women with uncomplicated pregnancies and deliveries, most pregnancy-related anatomic and physiologic changes resolve spontaneously during the fourth trimester. As a result of gestational weight gain and the detraining that undoubtedly occurs during pregnancy, women should return gradually to exercise (Artal and O'Toole 2003). For some, pregnancy has been proposed as an ergogenic aid to athletic performance, due to the anecdotal accounts of improved exercise performance following childbirth; however, Pivarnik et al. (2017) concluded that there is insufficient data to confirm this tenet at present. Conversely, for other women, the legacy of pregnancy can be damaging, with sustained, long-term negative consequences, which need to be addressed (Jackson et al. 2022).

Conclusions

Pregnancy causes a multitude of morphological and physiological changes, which include supraphysiological concentrations of estrogens and progesterone. These changes result in numerous adaptations and implications for exercise capacity and performance. Given the diversity (Table 14.1) and interrelatedness (Fig. 14.1) of the changes associated with pregnancy, a multidisciplinary approach to exercise testing and prescription is recommended, with a specific focus needed on the direct and indirect effects of sex hormones on exercise performance and capacity, although the constellation of changes that occur during pregnancy makes it almost impossible to elucidate the discrete effects of sex hormones on exercise capacity and performance during pregnancy (Fig. 14.6).

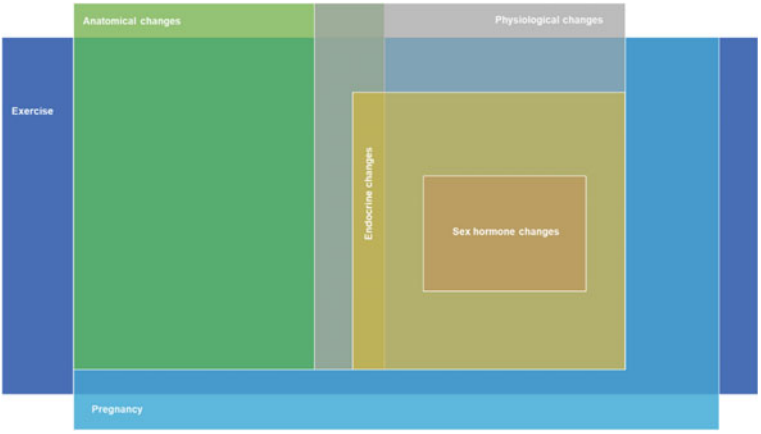

Fig. 14.6 Euler diagram showing the overlapping complexity of how the changes during pregnancy affect exercise performance and capacity

References

Abdullahi A, Bala AS, Danazumi SM, Abubakar SM, Adamu RI, Truijen S, et al. Determination of hand grip strength and its correlates during pregnancy: a cross-sectional study. BMC Pregnancy Childbirth. 2021;21:540. https://doi.org/10.1186/s12884-021-04003-0.

Abraham GE, Odell WD, Swerdloff RS, Hopper K. Simultaneous radioimmunoassay of plasma FSH, LH, progesterone, 17-hydroxyprogesterone, and estradiol-17 beta during the menstrual cycle. J Clin Endocrinol Metab. 1972;34:312–8. https://doi.org/10.1210/jcem-34-2-312.

ACOG Committee Obstetric Practice. ACOG Committee Opinion. Number 267, January 2002: exercise during pregnancy and the postpartum period. Obstet Gynecol. 2002;99:171–3. https://doi.org/10.1016/s0029-7844(01)01749-5

Ali AM, Kunugi H. Intermittent fasting, dietary modifications, and exercise for the control of gestational diabetes and maternal mood dysregulation: a review and a case report. Int J Environ Res Public Health. 2020;17:9379. https://doi.org/10.3390/ijerph17249379.

Artal R, Fortunato V, Welton A, Constantino N, Khodiguian N, Villalobos L, et al. A comparison of cardiopulmonary adaptations to exercise in pregnancy at sea level and altitude. Am J Obstet Gynecol. 1995;172:1170–8. https://doi.org/10.1016/0002-9378(95)91475-7.

Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. Br J Sports Med. 2003;37:6–12; discussion 12. https://doi.org/10.1136/bjsm.37.1.6

Atay E, Başalan IF. Investigation of the effect of changes in muscle strength in gestational age upon fear of falling and quality of life. Turk J Med Sci. 2015;45:977–83. https://doi.org/10.3906/sag-1404-9.

Barone Gibbs B, Jones MA, Jakicic JM, Jeyabalan A, Whitaker KM, Catov JM. Objectively measured sedentary behavior and physical activity across 3 trimesters of pregnancy: the monitoring movement and health study. J Phys Act Health. 2021;18:254–61. https://doi.org/10.1123/jpah.2020-0398.

Beil FT, Barvencik F, Gebauer M, Seitz S, Rueger JM, Ignatius A, et al. Effects of estrogen on fracture healing in mice. J Trauma. 2010;69:1259–65. https://doi.org/10.1097/TA.0b013e3181c4544d.

Beilock SL, Feltz DL, Pivarnik JM. Training patterns of athletes during pregnancy and postpartum. Res Q Exerc Sport. 2001;72:39–46. https://doi.org/10.1080/02701367.2001.10608930.

Bey ME, Marzilger R, Hinkson L, Arampatzis A, Legerlotz K. Vastus Lateralis architecture changes during pregnancy—a longitudinal study. Front Physiol. 2019;10:1163. https://doi.org/10.3389/fphys.2019.01163.

Bø K, Artal R, Barakat R, Brown W, Davies GA, Dooley M, et al. Exercise and pregnancy in recreational and elite athletes: 2016 evidence summary from the IOC expert group meeting, Lausanne. Part 1-exercise in women planning pregnancy and those who are pregnant. Br J Sports Med. 2016;50:571–89. https://doi.org/10.1136/bjsports-2016-096218

Body C, Christie JA. Gastrointestinal diseases in pregnancy: nausea, vomiting, hyperemesis Gravidarum, gastroesophageal reflux disease, constipation, and diarrhea. Gastroenterol Clin North Am. 2016;45:267–83. https://doi.org/10.1016/j.gtc.2016.02.005.

Brislane Á, Steinback CD, Davenport MH. The 9-month stress test: pregnancy and exercise-similarities and interactions. Can J Cardiol. 2021;37:2014–25. https://doi.org/10.1016/j.cjca.2021.09.003.

Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EAH. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol. 1991;165:1667–72. https://doi.org/10.1016/0002-9378(91)90012-g.

Cattani L, Decoene J, Page AS, Weeg N, Deprest J, Dietz HP. Pregnancy, labour and delivery as risk factors for pelvic organ prolapse: a systematic review. Int Urogynecol J. 2021;32:1623–31. https://doi.org/10.1007/s00192-021-04724-y.

Clapp JF 3rd, Capeless E. The VO_2max of recreational athletes before and after pregnancy. Med Sci Sports Exerc. 1991;23:1128–33.

Clapp JF. The changing thermal response to endurance exercise during pregnancy. Am J Obstet Gynecol. 1991;165:1684–9. https://doi.org/10.1016/0002-9378(91)90015-j.

Davies B, Bailey DM, Budgett R, Sanderson DC, Griffin D. Intensive training during a twin pregnancy. A case report. Int J Sports Med. 1999;20:415–8. https://doi.org/10.1055/s-2007-971155

Dervis S, Dobson KL, Nagpal TS, Geurts C, Haman F, Adamo KB. Heat loss responses at rest and during exercise in pregnancy: a scoping review. J Therm Biol. 2021;99:103011. https://doi.org/10.1016/j.jtherbio.2021.103011.

Di Fabio DR, Blomme CK, Smith KM, Welk GJ, Campbell CG. Adherence to physical activity guidelines in mid-pregnancy does not reduce sedentary time: an observational study. Int J Behav Nutr Phys Act. 2015;12:27. https://doi.org/10.1186/s12966-015-0191-7.

Elliott KJ, Cable NT, Reilly T, Sefton V, Kingsland C, Diver M. Effects of supra-physiological changes in human ovarian hormone levels on maximum force production of the first dorsal interosseus muscle. Exp Physiol. 2005;90:215–23. https://doi.org/10.1113/expphysiol.2004.028258.

Elliott-Sale KJ, Graham A, Hanley SJ, Blumenthal S, Sale C. Modern dietary guidelines for healthy pregnancy; maximising maternal and foetal outcomes and limiting excessive gestational weight gain. Eur J Sport Sci. 2019;19:62–70. https://doi.org/10.1080/17461391.2018.1476591.

Elliott-Sale KJ, McNulty KL, Ansdell P, Goodall S, Hicks KM, Thomas K, et al. The effects of oral contraceptives on exercise performance in women: a systematic review and meta-analysis. Sports Med. 2020;50:1785–812. https://doi.org/10.1007/s40279-020-01317-5.

Elliott-Sale KJ, Minahan CL, de Jonge XAKJ, Ackerman KE, Sipilä S, Constantini NW, Lebrun CM, Hackney AC. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51:843–61. https://doi.org/10.1007/s40279-021-01435-8.

Evenson KR, Barakat R, Brown WJ, Dargent-Molina P, Haruna M, Mikkelsen EM, et al. Guidelines for physical activity during pregnancy: comparisons from around the world. Am J Lifestyle Med. 2014;8:102–21. https://doi.org/10.1177/1559827613498204.

Evenson KR, Wen F. Prevalence and correlates of objectively measured physical activity and sedentary behavior among US pregnant women. Prev Med. 2011;53:39–43. https://doi.org/10.1016/j.ypmed.2011.04.014.

Ferdinande K, Dorreman Y, Roelens K, Ceelen W, De Looze D. Anorectal symptoms during pregnancy and postpartum: a prospective cohort study. Color Dis. 2018;20:1109–16. https://doi.org/10.1111/codi.14324.

Forczek W, Ivanenko YP, Bielatowicz J, Wacławik K. Gait assessment of the expectant mothers—systematic review. Gait Posture. 2018;62:7–19. https://doi.org/10.1016/j.gaitpost.2018.02.024.

Franklin A, Mishtal J, Johnson T, Simms-Cendan J. Rowers' self-reported behaviors, attitudes, and safety concerns related to exercise, training, and competition during pregnancy. Cureus. 2017;9(8):e1534. https://doi.org/10.7759/cureus.1534.

Gregg VH, Ferguson JE 2nd. Exercise in pregnancy. Clin Sports Med. 2017;36:741–52. https://doi.org/10.1016/j.csm.2017.05.005.

Jackson T, Bostock EL, Hassan A, Greeves JP, Sale C, Elliott-Sale KJ. The legacy of pregnancy: elite athletes and women in arduous occupations. Exerc Sport Sci Rev. 2022;50:14–24. https://doi.org/10.1249/JES.0000000000000274.

Kalkwarf HJ, Specker BL. Bone mineral changes during pregnancy and lactation. Endocrine. 2002;17:49–53. https://doi.org/10.1385/ENDO:17:1:49.

Kardel KR. Effects of intense training during and after pregnancy in top-level athletes. Scand J Med Sci Sports. 2005;15:79–86. https://doi.org/10.1111/j.1600-0838.2004.00426.x.

Kolarzyk E, Szot WM, Lyszczarz J. Lung function and breathing regulation parameters during pregnancy. Arch Gynecol Obstet. 2005;272:53–8. https://doi.org/10.1007/s00404-004-0691-1.

Lagadec N, Steinecker M, Kapassi A, Magnier AM, Chastang J, Robert S, Gaouaou N, Ibanez G. Factors influencing the quality of life of pregnant women: a systematic review. BMC Pregnancy Childbirth. 2018;18:455. https://doi.org/10.1186/s12884-018-2087-4.

Lindberg BS, Johansson ED, Nilsson BA. Plasma levels of nonconjugated oestrone, oestradiol-17beta and oestriol during uncomplicated pregnancy. Acta Obstet Gynecol Scand. 1974;32:21–36. https://doi.org/10.3109/00016347409156390.

Lindqvist PG, Marsal K, Merlo J, Pirhonen JP. Thermal response to submaximal exercise before, during and after pregnancy: a longitudinal study. J Matern Neonatal Med. 2003;13:152–6. https://doi.org/10.1080/jmf.13.3.152.156.

Liu XS, Wang L, de Bakker CMJ, Lai X. Mechanical regulation of the maternal skeleton during reproduction and lactation. Curr Osteoporos Rep. 2019;17:375–86. https://doi.org/10.1007/s11914-019-00555-5.

Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017;96:921–31. https://doi.org/10.1111/aogs.13151.

Mbada CE, Adeyemi AB, Omosebi O, Olowokere AE, Faremi FA. Hand grip strength in pregnant and non-pregnant females. Middle East J Rehabil Health Stud. 2015;2:e27641. https://doi.org/10.17795/mejrh-27641.

McManis BG. Integrative review of exercise at altitude during pregnancy. Int J Environ Res Public Health. 2021;18:9272. https://doi.org/10.3390/ijerph18179272.

McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, et al. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. Sports Med. 2020;50:1813–27. https://doi.org/10.1007/s40279-020-01319-3.

Meekins AR, Siddiqui NY. Diagnosis and management of postpartum pelvic floor disorders. Obstet Gynecol Clin North Am. 2020;47:477–86. https://doi.org/10.1016/j.ogc.2020.05.002.

Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. BJOG an Int J Obstet Gynaecol. 1978;85:260–3. https://doi.org/10.1111/j.1471-0528.1978.tb10497.x.

Motosko CC, Bieber AK, Pomeranz MK, Stein JA, Martires KJ. Physiologic changes of pregnancy: a review of the literature. Int J Womens Dermatol. 2017;3:219–24. https://doi.org/10.1016/j.ijwd.2017.09.003.

Mottola MF, Inglis S, Brun CR, Hammond JA. Physiological and metabolic responses of late pregnant women to 40 min of steady-state exercise followed by an oral glucose tolerance perturbation. J Appl Physiol. 2013;115:597–604. https://doi.org/10.1152/japplphysiol.00487.2013.

Mottola MF, Davenport MH, Ruchat SM, Davies GA, Poitras VJ, Gray CE, et al. 2019 Canadian guideline for physical activity throughout pregnancy. Br J Sports Med. 2018;52:1339–46. https://doi.org/10.1136/bjsports-2018-100056.

Nassikas N, Malhamé I, Miller M, Bourjeily G. Pulmonary considerations for pregnant women. Clin Chest Med. 2021;42:483–96. https://doi.org/10.1016/j.ccm.2021.04.008.

O'Leary P, Boyne P, Flett P, Beilby J, James I. Longitudinal assessment of changes in reproductive hormones during normal pregnancy. Clin Chem. 1991;37(5):667–72.

Owe KM, Nystad W, Bo K. Correlates of regular exercise during pregnancy: the Norwegian Mother and Child Cohort Study. Scand J Med Sci Sports. 2009;19:637–45. https://doi.org/10.1111/j.1600-0838.2008.00840.x.

Padayachee C, Coombes JS. Exercise guidelines for gestational diabetes mellitus. World J Diabetes. 2015;6:1033–44. https://doi.org/10.4239/wjd.v6.i8.1033.

Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995;273:402–7. https://doi.org/10.1001/jama.273.5.402

Physical Activity and Exercise During Pregnancy and the Postpartum Period: ACOG Committee Opinion, Number 804. Obstet Gynecol. 2020;135:e178-e188. https://doi.org/10.1097/AOG.0000000000003772.

Pivarnik JM, Connolly CP, Marshall MR, Schlaff RA. Can pregnancy be an ergogenic aid to athletic performance?: a review. Women Sport Phys Act J. 2017;25:111–7.

Salari P, Abdollahi M. The influence of pregnancy and lactation on maternal bone health: a systematic review. J Family Reprod Health. 2014;8:135–48.

Snarskaya ES, Olisova OY, Makatsariya AD, Kochergin NG, Radetskaya L, Bitsadze V, Khizroeva J. Skin pathologies in pregnancy. J Perinat Med. 2019;47:371–80. https://doi.org/10.1515/jpm-2018-0338.

Solli GS, Sandbakk Ø. Training characteristics during pregnancy and postpartum in the world's most successful cross country skier. Front Physiol. 2018;9:595. https://doi.org/10.3389/fphys.2018.00595.

Song SY, Kim Y, Park H, Kim YJ, Kang W, Kim EY. Effect of parity on bone mineral density: a systematic review and meta-analysis. Bone. 2017;101:70–6. https://doi.org/10.1016/j.bone.2017.04.013.

Soultanakis HN, Artal R, Wiswell RA. Prolonged exercise in pregnancy: glucose homeostasis, ventilatory and cardiovascular responses. Semin Perinatol. 1996;20:315–27. https://doi.org/10.1016/s0146-0005(96)80024-3.

Stern C, Schwarz S, Moser G, Cvitic S, Jantscher-Krenn E, Gauster M, Hiden U. Placental endocrine activity: adaptation and disruption of maternal glucose metabolism in pregnancy and the influence of fetal sex. Int J Mol Sci. 2021;22:12722. https://doi.org/10.3390/ijms222312722.

Sundgot-Borgen J, Sundgot-Borgen C, Myklebust G, Sølvberg N, Torstveit MK. Elite athletes get pregnant, have healthy babies and return to sport early postpartum. BMJ Open Sport Exerc Med. 2019;5:e000652. https://doi.org/10.1136/bmjsem-2019-000652.

Tal R, Taylor HS. Endocrinology of pregnancy. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al (eds). Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2001.

Tan EK, Tan EL. Alterations in physiology and anatomy during pregnancy. Best Pract Res Clin Obstet Gynaecol. 2013;27:791–802. https://doi.org/10.1016/j.bpobgyn.2013.08.001.

Tenforde AS, Toth KES, Langen E, Fredericson M, Sainani KL. Running habits of competitive runners during pregnancy and breastfeeding. Sports Health. 2015;7:172–6. https://doi.org/10.1177/1941738114549542.

Tulchinsky D, Hobel CJ. Plasma human chorionic gonadotropin, estrone, estradiol, estriol, progesterone, and 17 alpha-hydroxyprogesterone in human pregnancy. II. Clinical applications in Rh-isoimmunization disease. Am J Obstet Gynec. 1973;117:884–93. https://doi.org/10.1016/0002-9378(72)90556-x

Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and The Lung. Am Rev Respir Dis. 1980;121:559–81. https://doi.org/10.1164/arrd.1980.121.3.559.

Whitaker KM, Jones MA, Wallace MK, Catov J, Barone GB. Associations of objectively measured physical activity and sedentary time with pregnancy-specific health-related quality of life. Midwifery. 2022;104:103202. https://doi.org/10.1016/j.midw.2021.103202.

Winter EM, Ireland A, Butterfield NC, Haffner-Luntzer M, Horcajada MN, Veldhuis-Vlug AG, et al. Pregnancy and lactation, a challenge for the skeleton. Endocr Connect. 2020;9:R143–57. https://doi.org/10.1530/EC-20-0055.

Wowdzia JB, McHugh TL, Thornton J, Sivak A, Mottola MF, Davenport MH. Elite athletes and pregnancy outcomes: a systematic review and meta-analysis. Med Sci Sports Exerc. 2021;53:534–42. https://doi.org/10.1249/MSS.0000000000002510.

Xu Y, Deng KL, Xing TF, Mei YQ, Xiao SM. Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2020;27:827–35. https://doi.org/10.1097/GME.0000000000001538.

Żelaźniewicz A, Pawłowski B. Maternal hand grip strength in pregnancy, newborn sex and birth weight. Early Hum Dev. 2018;119:51–5. https://doi.org/10.1016/j.earlhumdev.2018.03.004.

Zsido RG, Villringer A, Sacher J. Using positron emission tomography to investigate hormone-mediated neurochemical changes across the female lifespan: implications for depression. Int Rev Psychiatry. 2017;29:580–96. https://doi.org/10.1080/09540261.2017.1397607.

Chapter 15
Physiology of Menopause

Abbie E. Smith-Ryan, Katie R. Hirsch, and Hannah E. Cabre

Stages of Normal Reproductive Aging in Women

Menopause is the natural transition in the female lifespan when the menstrual cycle ceases and reproductive capabilities are eliminated. Natural menopause is defined by 12 months of amenorrhea, due to reduced ovarian secretion of estrogen and progesterone and is not associated with a pathological cause (Nelson 2008). Cessation of the menstrual cycle and onset of menopause can also be induced by external perturbations, such as surgery, chemotherapy, or radiation.

Understanding the stages of normal reproductive aging in women is important to characterize the physiological and cardiometabolic changes that occur with the transition to menopause (Fig. 15.1). Hormones begin to change in women during puberty with the onset of menarche, at an average age of 12 years. A regular menstrual cycle coincides with predictable fluctuations of ovarian hormones including, estrogen, progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) (Oosthuyse and Bosch 2010). A regular menstrual cycle lasts an average of 28 days (ranging from 23 to 38 days) and consists of two main phases: the follicular phase (FP) and the luteal phase (LP), which are separated by ovulation. During the FP (days ~ 0–13), estrogen levels begin low (menstruation) and then peak at the peri-ovulatory phase. During the LP (days ~ 16–28), estrogen level rises again, and progesterone peaks until the premenstrual phases when estrogen and progesterone levels fall if pregnancy does not occur (Draper et al. 2018; El Khoudary et al. 2019).

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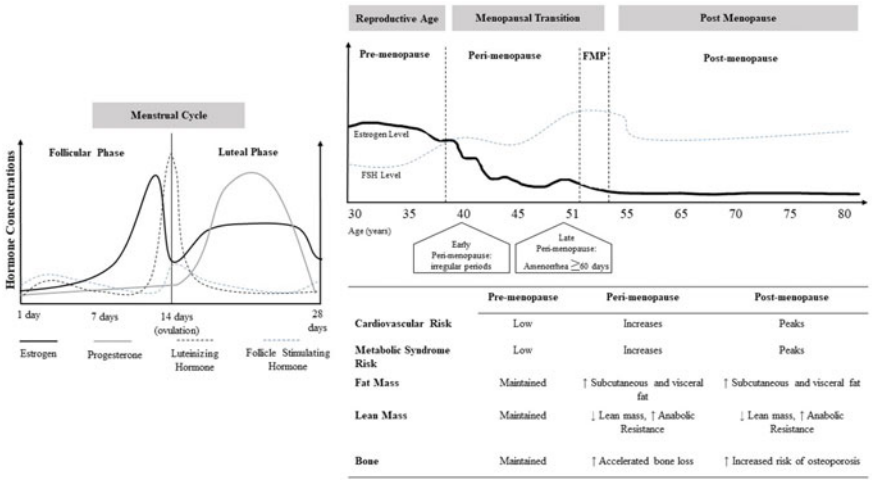

Fig. 15.1 Overview of a eumenorrheic menstrual cycle and model for the changes in hormones, cardiometabolic, and body composition from pre-, peri-, and postmenopause

The menopause transition begins when menstrual cycles become irregular, termed ***perimenopause***, which occurs at an average age of 40 years (Nelson 2008). Perimenopause can last an average of 2–8 years and involves a multitude of slow changes in hormone levels, which ultimately cause the well-known symptoms of menopause including hot flashes, mood disturbances, thermoregulatory issues, and other vasomotor symptoms (Santoro et al. 2015). These changes are driven by a decline in ovarian follicle number and a decrease in estrogen, which results in an increase in FSH. As menstrual irregularity continues, ovulation ceases, and the menstrual cycle lengthens and eventually stops. This demarks the transition to amenorrhea and ***menopause***, which occurs at an average age of 51 years. As ovarian follicles are lost, estrogen production ceases, with a steady-state of high FSH/low estrogen, which occurs for about two years following the final menstrual period (FMP) (Nelson 2008). When analyzing how sex hormones change in the years leading up to, during, and after menopause, an extensive longitudinal epidemiological evaluation (Study of Women's Health Across the Nation [SWAN]) demonstrated that mean serum estradiol did not significantly change until about two years before the FMP (Randolph et al. 2011). Estradiol appears to continually decline through two years after the FMP and then stabilize. While menopause primarily demarks the end of reproductive function, the associated hormonal changes extend into all areas of physiological health. There is robust evidence that ovarian hormones like estrogen and progesterone play a vital role in the metabolic, cardiovascular, and musculoskeletal health of women. Because life expectancy has continually risen through the previous decades, women can spend up to 40% of their lives in the postmenopausal stage. As such, changes in physiological health associated with the menopause transition can significantly impact the quality of life during the postmenopausal stage.

Physiological Changes Through Menopause

An estimated 2 million women reach menopause daily, with over 85% experiencing symptoms (Woods and Mitchell 2005). A natural consequence of aging, the menopause transition, demarks significant physiological alterations that result in dramatic changes in cardiometabolic health, the skeletal system, and functionality (El Khoudary et al. 2019).

Metabolic and Cardiovascular Changes

Estrogen is an important regulator of bioenergetics. Corresponding with changes in reproductive hormones, changes in systemic- and tissue-level metabolism lead to distinct changes in body composition and result in a drastic increase in cardiovascular disease (CVD) risk factors around the time of menopause (El Khoudary et al. 2019, 2020; Van Pelt et al. 2015). Starting in early perimenopause, changes in energy expenditure, substrate utilization, appetite, and energy intake contribute to increases in body fat and loss of lean mass. Together, these changes in body composition and metabolism contribute to the development of chronic inflammation, insulin resistance, dyslipidemia, and cardiovascular dysfunction (Lovejoy et al. 2008).

Metabolic Alterations

Energy Expenditure

There are two primary contributors to energy expenditure: resting energy expenditure (REE), also known as resting metabolic rate (RMR), and non-resting energy expenditure (NREE). Collectively, total energy expenditure (TEE) is relatively stable in both men and women throughout the adult years (20–60 years) and then begins to decline at around 63 years of age (95% confidence interval: 60.1, 65.9 years) (Pontzer et al. 2021). However, evidence from studies in women across the menopause transition suggests TEEs may subtly decline as women transition to menopause. When middle-aged women (46–48 years old) were tracked across four years, significant decreases in 24-h TEE (~200 kcal/d) and sleep energy expenditure (~100 kcal/d) were observed in women who became postmenopausal (Lovejoy et al. 2008). If energy intake is not adjusted for, these changes in TEE may be enough to influence weight gain (Wolfe 2006).

Components of NREE have also been shown to decline across the menopause transition. In the two years before menopause, free-living physical activity decreased by 50% and remained low into postmenopause (Lovejoy et al. 2008). Spontaneous physical activity has also been shown to decrease with age by as much as 30%.

Other studies have reported no changes in total physical activity across the transition, but significant decreases in exercise intensity (Gould et al. 2022). Declines in NREE may be attributed to increased menopausal symptoms, cultural/social activities for women, and a reduction in muscle quality. Together, declines in REE and NREE emphasize the importance of encouraging physical activities early in the perimenopausal period to prevent declines in energy expenditure during the menopause transition.

Substrate Utilization

Females are known to have a greater reliance on fat oxidation and lower reliance on carbohydrate and protein oxidation, both at rest and during exercise, compared to men (Devries 2016). These differences are attributed primarily to the influence of estrogen, which stimulates lipolysis and mitochondrial oxidative capacity (Rosa-Caldwell and Greene 2019). Progesterone may also play a role in substrate regulation (Devries 2016; Hackney et al. 2022), having anti-estrogenic effects on substrate oxidation. In premenopausal women, substrate oxidation varies across the menstrual cycle, in coordination with fluctuations in estrogen and progesterone (Oosthuyse and Bosch 2010). Relative fat and protein oxidation increase during the LP, when estrogen and progesterone are elevated, compared to the FP when estrogen and progesterone are lower. Differences in substrate oxidation between phases may be dependent on the estrogen and progesterone ratio, with fat oxidation shown to increase in a fairly linear fashion with increasing the estrogen to progesterone ratio (Hackney et al. 2022). As women traverse the menopause transition, reliance on fat oxidation declines and has been shown to be reduced by 32% as women become postmenopausal (Lovejoy et al. 2008). In contrast, carbohydrate oxidation remains constant (Lovejoy et al. 2008). Decreased fat oxidation across the menopause transition is primarily attributed to decreases in estrogen. Decreases in fat oxidation may also be attributed, in part, to a reduction in protein turnover (Wolfe 2006). Protein oxidation has also been shown to increase across the menopause transition (Lovejoy et al. 2008); increased protein oxidation may be a metabolic compensation to meet energy needs in response to declining fat oxidation. Increased protein oxidation may indicate reduced anabolic sensitivity in women, reflecting a decline in protein synthetic efficiency (Ferrando and Wolfe 2007).

Metabolic flexibility is the ability to adjust fuel oxidation to fuel availability in response to changes in metabolic or energy demands. Metabolic inflexibility is characterized by reduced fat oxidation at rest or when fasted, with little to no change in the ratio of fat to glucose oxidation during exercise or in response to insulin stimulation (Kelley and Mandarino 2000). Metabolic inflexibility is a sign of skeletal muscle metabolic dysfunction that is associated with intramuscular fat accumulation, mitochondrial dysfunction, and the development of insulin resistance (Goodpaster and Sparks 2017; Kelley and Mandarino 2000). During exercise, postmenopausal women have a lower overall capacity for lipid oxidation compared to premenopausal women (Johnson et al. 2010). Twelve weeks of endurance training (30–60 min,

3–5 d/wk, 65% VO_2max) improved fatty acid mobilization and oxidation during exercise in postmenopausal women, albeit not to the same extent as observed in premenopausal women; however, overall oxidative capacity was still lower in postmenopausal women (Johnson et al. 2010). Impairments in oxidative capacity may be most noticeable during moderate-intensity exercise (50–70% VO_2max) when fat oxidation has been reportedly lower in both peri- (− 17%) and postmenopausal (− 23 to 31%) women (Abildgaard et al. 2013; Gould et al. 2022).

Appetite and Energy Intake

On the other end of the energy balance equation, appetite and energy intake are known to vary across the menstrual cycle, but a paucity of data exists on changes across the menopause transition. Anecdotally, changes in appetite and hunger do seem to occur, with both increases and decreases in appetite being reported. Qualitative assessments suggest appetite and hunger increase and fullness decreases across the menopause transition (Duval et al. 2014). Hormonal profiling suggests an overall decline in regulatory controls of appetite across the menopause transition, supported by changes in hormones such as leptin, ghrelin, adiponectin, resistin, and orexin A and B (Karim et al. 2015; Lurati 2018). When interpreted collectively, it has been hypothesized that these changes in appetite could drive an increase in energy intake, creating a positive energy balance and contributing to increases in weight and body fat. However, studies of energy intake in women have reported no changes (Gould et al. 2022) or even a decrease in energy intake (Duval et al. 2014; Lovejoy et al. 2008) in the years leading up to menopause. It is unknown if changes in eating behaviors, such as dietary restriction, contribute to these findings. Analysis of macronutrient intake suggests decreases in dietary protein and fiber (Gould et al. 2022; Lovejoy et al. 2008), both of which are associated with appetite management and hunger/fullness regulation (Fuglsang-Nielsen et al. 2021).

Other factors that may influence appetite and energy intake include changes in sleep and gut health. About 30–60% of peri- and postmenopausal women report more frequent sleep disruptions and declines in sleep quality, related to vasomotor symptoms, changes in thermoregulation, and altered circadian rhythm (Gould et al. 2022; Kravitz et al. 2018). Inadequate sleep can lead to changes in appetite hormones that increase hunger and appetite (Kravitz et al. 2018). Changes in gut microbiota and motility with menopause may also have a significant impact on appetite and food choice. Greater incidence of constipation, bloating, gas, nausea, and gastric-related disorders are commonly reported during the menopause transition (Im et al. 2022). These changes may cause women to choose different foods or diet patterns in an effort to manage gastrointestinal symptoms. Changes in the gut may also alter the absorption of macro- and micronutrients which may have downstream impacts on health. As such, changes in sleep and/or the gut may have significant impacts on appetite and energy intake across the menopause transition.

Chronic Inflammation

Chronic, low-grade inflammation is a systemic condition characterized by small but detectable increases in plasma levels of pro-inflammatory cytokines (Chen et al. 2016). While cytokines are dynamic signaling molecules key to protein balance, metabolic regulation, and immune function, chronically elevated inflammatory signaling can lead to metabolic dysregulation and multiple disease comorbidities (Tsalamandris et al. 2019). Beyond what is detectable in circulation, individual tissues may also bear a significant inflammatory burden. Chronic and non-resolute skeletal muscle inflammation is a major contributor to age-related declines in muscle health (mass, strength, quality, function) (Merritt et al. 2013). There is evidence to suggest that the skeletal muscle environment is differentially impacted by aging in women compared to men (Lavin et al. 2019, 2020). Despite systemic inflammation levels that were considered clinically normal, women of menopausal age were found to have higher levels of both systemic and muscle inflammations compared to men (Bamman et al. 2015; Khera et al. 2005; Lavin et al. 2020). Lifelong aerobic exercise was also found to be ineffective at protecting older women against an age-related increase in circulating or muscle inflammation, as it did in older men (Lavin et al. 2020). Estrogen is considered to be an anti-inflammatory hormone (Dama et al. 2021; Kramer et al. 2004; Nedergaard et al. 2013), and decreases in estrogen are associated with decrements in cardiac (El Khoudary and Thurston 2018), vascular (Santos-Parker et al. 2017), and skeletal muscle health (Maltais et al. 2009) in postmenopausal women. Changes in gut permeability with the menopause transition are also associated with greater inflammation (Shieh et al. 2020).

Cardiometabolic and Cardiovascular Changes

Before the menopause transition, metabolic and vascular health is generally well preserved in women, with a lower prevalence of risk factors or cardiac episodes in women compared to men (El Khoudary et al. 2020; Marlatt et al. 2020). During the menopause transition, the prevalence of insulin resistance, dyslipidemia, and metabolic syndrome increase, leading to vascular and cardiac dysfunction, and ultimately a sharp increase in cardiovascular disease in the postmenopausal period (El Khoudary et al. 2020). As a result, menopause is considered a female-specific CVD risk factor by the American Heart Association.

Metabolic Syndrome

Metabolic syndrome (MetS) is defined as the presence of three or more risk factors associated with CVD and diabetes, including hypertension ($\geq$ 130/85 mmHg), elevated fasting glucose ($\geq$ 100 mg/dL), elevated triglycerides ($\geq$ 150 mg/dL), reduced HDL cholesterol ($<$ 50 mg/dL in women), and abdominal obesity (waist

circumference > 35 in for women). Odds of developing MetS progressively increase during the years leading up to and following menopause, with over 30% of women having MetS by the time they reach menopause (Janssen 2008). Hormonal changes during menopause, specifically the predominance of testosterone, have been implicated as the primary factor associated with the prevalence of MetS among women (Janssen 2008). The predominance of testosterone and declines in estrogen promote changes in fat distribution from subcutaneous to visceral. Visceral fat, insulin resistance, and dyslipidemia are closely linked, and cardiometabolic risk may track more closely with increases in visceral fat across the menopause transition than with a change in menopausal status itself (Marlatt et al. 2020, 2022).

Cardiovascular Dysfunction

With the loss of anti-inflammatory and anti-oxidative effects of estrogen, the vascular function begins to deteriorate in women (Marlatt et al. 2022). Endothelial function and arterial compliance have both been shown to decline in peri- and postmenopausal women, as indicated by decreases in flow-mediated dilation and pulse wave velocity, respectively (Marlatt et al. 2022). Changes in vascular function contribute to the development of hypertension, the prevalence of which increases during the menopause transition (Marlatt et al. 2022). Changes in peripheral vascular function can then contribute to central changes in the heart. Increases in systolic pressure, pulse pressure, and aortic impedance all drive an increase in afterload and work performed by the left ventricle. This can lead to left ventricle hypertrophy, altered diastolic filling, and decreased systolic reserve (Marlatt et al. 2022).

Skeletal System Changes

Menopause is linked to increased disease risk due, in part, to harmful changes in body composition (Van Pelt et al. 2015). In addition to the shift in body fat accumulation in the abdominal/visceral region, there is an overall increase in total body fat mass, decreased lean mass, and decreased bone mineral density, which cumulatively are incited mostly by the reduction of estrogen (Greendale et al. 2019).

Body Composition Changes

Fat Mass

The changes in fat mass throughout the menopause transition and during menopause have consistently demonstrated a significant linear increase in fat gain. In a 15-year, longitudinal study of body composition changes across the menopause transition,

women had a 1% annual increase in fat mass during premenopause and a 2.3-fold increase in the annual increase in fat mass during the menopause transition, followed by a more stable fat maintenance into postmenopause (Greendale et al. 2019). A recent meta-analysis that incorporated data from a large sample of premenopausal (~475,000) and postmenopausal (~570,000) women reported that fat mass, BMI, weight, %fat, waist circumference, hip circumference, waist-to-hip ratio, visceral fat, and trunk fat percentage were significantly greater in postmenopausal women (Ambikairajah et al. 2019). Similarly, longitudinal data from this sample reported that changes in BMI and percent body fat were similar to changes represented by age, indicating that menopause may not have a direct impact on BMI or %fat, but rather likely influences fat distribution (Ambikairajah et al. 2019; Siervogel et al. 1998).

Measures of fat distribution indicate that perimenopausal women experienced comparatively greater fat deposition in the abdominal region, with the android-to-gynoid ratio being on average 16% higher than premenopausal and 5% higher than postmenopausal (Gould et al. 2022). Similar differences were observed for visceral fat (Gould et al. 2022). When accounting for age and total body fat, previous data have demonstrated a significantly twofold greater increase in intraabdominal fat in postmenopausal women, compared to premenopausal women (Toth et al. 2006). Similarly, a longitudinal study found that while weight increased steadily over time, only postmenopausal women experienced a significant increase in visceral fat (mean increase of 9.5 cm^2) that was accompanied by a significant decrease in serum estradiol (mean decrease 62.9 pg/ml) (Lovejoy et al. 2008). Similarly, when adjusting for %fat, age, race, depression, and physical activity, postmenopausal women had on average 8.6 cm^2 more visceral fat than premenopausal women; these authors also found that bioavailable testosterone was a stronger predictor of visceral fat than estradiol, suggesting that testosterone may induce male-pattern fat distribution in postmenopausal women, especially when estradiol is simultaneously reduced (Janssen 2008).

Lean Mass

The effects of menopause on changes in lean mass are inconclusive, with some studies reporting accelerated losses (Carr 2003; Svendsen et al. 1995) and others reporting no significant impact attributable to menopause (Aloia et al. 1996; Greendale et al. 2019; Hodson et al. 2014; Lovejoy et al. 2008; Piers et al. 1998; Toth et al. 2006). One cross-sectional study reported no differences in lean mass or appendicular skeletal muscle mass in pre- and postmenopausal women (Toth et al. 2006). Similarly, a longitudinal study that assessed middle-aged women annually for 4 years did not find a significant difference in lean mass in women who became postmenopausal (Lovejoy et al. 2008). In contrast, a cross-sectional study that included women aged 18–79 years found that lean mass significantly decreased by an average of 2.7 kg each decade from 40 to 60 years, with the loss attributed to menopause (Svendsen et al. 1995). A recent cross-sectional study across pre-, peri-, and postmenopausal women

reported a 6.1 kg average lower lean mass in perimenopausal women compared to pre- (Gould et al. 2022), supporting perimenopause may be a key time point for lifestyle modification, particularly to support lean mass maintenance. Together, it appears that there is likely a decrease in lean mass throughout the menopause transition, with an average 0.5% decrease, which is beyond what can be attributed to age.

As a mechanism to understand the potential change in lean mass with menopause, estrogen is known for its role in maintaining muscle mass and mitochondrial efficiency in females (Rosa-Caldwell and Greene 2019), via stimulation of muscle protein turnover. Changes in estrogen during perimenopause and into postmenopause may lead to reduced responsiveness to anabolic stimuli, resulting in a reduction in protein turnover. The consequences of downregulated protein turnover are multifaceted but are directly related to a loss of muscle size. Furthermore, protein turnover at the muscle and whole-body level is a primary contributor to resting energy expenditure (Wolfe 2006). As such, the reduction in REE, as a result of decreased protein turnover, corresponds with/could explain the significant loss of lean mass and concomitant increases in fat mass that are characteristic of the menopause transition. Exercise and nutrition interventions that target upregulation of protein turnover, particularly during perimenopause, could be preventative in offsetting the negative physiological cascade into menopause.

Bone Tissue

Menopause is a critical turning point for bone health, with the prevalence of osteoporosis affecting one out of every three postmenopausal women (Brown et al. 2009). *Osteoporosis* is a skeletal condition characterized by the decreased bone mineral density that ultimately results in reduced bone strength and a greater risk of bone fractures. There are two subtypes of osteoporosis: Type 1 osteoporosis affects mostly postmenopausal women and is caused by estrogen deficiency, whereas Type 2 osteoporosis occurs in both men and women and is caused primarily by aging alone (Glaser and Kaplan 1997). SWAN studies have identified that the menopause transition is a key period during which accelerated bone loss occurs (lumbar spine bone mineral density 2.2% mean annual decline; femoral neck bone mineral density 1.8% mean annual decline) and that if precautionary nutritional and exercise strategies are not implemented, women will have an exacerbated risk of osteoporosis in the future decades, particularly during menopause (Karlamangla et al. 2018). The loss of bone mass appears to be further accelerated in the three years following cessation of the menstrual cycle and is driven by changes in estradiol and FSH.

Data from the SWAN studies have demonstrated the menopause transition as the key time to intervene to prevent rapid bone loss and delay osteoporosis (Zaidi et al. 2009). Lifestyle habits, particularly related to exercise, diet, spending time outside, smoking cessation, and reducing alcohol consumption, have all been reported to have an important role in preventing bone loss. When these lifestyle changes are implemented during perimenopause, there appears to be a greater impact on the risk and severity of osteoporosis.

Functional and Quality of Life Changes

Beginning at around the time of menopause, women report greater physical limitations and disabilities than men (Janssen 2008; Sowers et al. 2001). Data from the SWAN dataset indicate that 20% of postmenopausal women report some form of limitation in physical function (Pope et al. 2001). Women reporting substantial limitations (i.e., difficulty walking one block or climbing a single flight of stairs) were more likely to be postmenopausal and obese (Sowers et al. 2001). In postmenopausal women, skeletal muscle atrophy and frailty are major predictors of dependence, morbidity, and mortality (Gemmati et al. 2019; Kaunitz et al. 2020). Atrophy of individual muscle fibers is further exaggerated with advancing age (Juppi et al. 2020; Lavin et al. 2019), as the molecular environment favors a shift from protein synthesis to breakdown (Hansen 2018; Park et al. 2019). Physiologically, both grip strength and vertical jump height are significantly lower in early postmenopausal compared to premenopausal women (Bondarev et al. 2018). Together with the compounding effects of advancing age (Siglinsky et al. 2015), this pattern likely continues throughout late adulthood. Locomotor function or walking speed is not as consistently affected with menopause, likely due to large interindividual variability, but has clinical relevance in terms of social and psychological wellness. In postmenopausal women, walking speed is highly associated with positive affect and life satisfaction (Bondarev et al. 2018), as well as the ability to participate in social communities (Kennedy et al. 2017), thereby linking gait speed to the overall quality of life. In a cohort of Finnish women, locomotor function measured via a 6-min walk was positively impacted by physical activity, suggesting a direct effect of skeletal muscle loading on the preservation of function into and following menopause (Bondarev et al. 2018).

Racial/Ethnic Considerations

Menopause is a universal experience for women, but the experience itself is unique for each individual woman and is influenced by socioeconomic status, education level, health status, stress, and marital status, in addition to race, ethnic, and cultural differences (Richard-Davis and Wellons 2013). Menopausal onset, hormone levels and patterns, obesity and body composition changes, and symptom experience have all been shown to vary by race and ethnicity (Richard-Davis and Wellons 2013). Consideration of similarities and differences in the experience of the menopause transition improves the delivery of care and lifestyle interventions that may decrease symptoms and increase the quality of life (Richard-Davis and Wellons 2013).

The timing of menopause onset has significant implications for chronic health risks later in life. In White women, the median age of menopause is between 50 and 52 years of age (Gold 2011; Luoto et al. 1994; McKinlay et al. 1992; Stanford et al. 1987). Reports in other racial-ethnic groups are inconsistent but appear

to be relatively similar across different races and ethnicities, with an average age of ~50 years. However, Black and Hispanic women may experience menopause at a slightly earlier age (~48 years) (Richard-Davis and Wellons 2013), while Japanese women may experience menopause at a slightly later age (~52 years). Within the USA, menopausal onset may be more highly influenced by geographical region than race or ethnicity (McKnight et al. 2011). Southern women were found to experience menopause 10.8 months earlier than Northeastern women, 8.4 months earlier than Midwestern women, and 6.0 months earlier than Western women, suggesting a cultural and geographical influence on menopause onset (McKnight et al. 2011). Finally, a greater percentage of Black women undergo surgical menopause compared to White women; this percentage increases in Black women who reside in the South, who also have lower education and lower annual income (McKnight et al. 2011). Hispanic and Asian women are also more likely to undergo peripartum hysterectomy than White women (Lawson et al. 2020).

Racial and ethnic differences in obesity prevalence and body fat distribution (android vs. gynoid) may influence hormonal changes and disease risk in women across the menopause transition. Black women have the highest rates of obesity (~58%) and severe obesity (~19%) (Cunningham et al. 2012), followed by Mexican American women (Obesity: ~50%; severe obesity: ~15%) (Ogden et al. 2020). Obesity status may influence hormonal changes of perimenopause, exacerbate the inflammatory-related impacts of the menopause transition, and reduce functionality/increase functional disability, placing Black and Mexican/Hispanic women at the greatest risk for cardiometabolic dysfunction and CVD risk with the menopause transition. White and Black women appear to experience similar, above-average rates of fat mass gain per year during the menopause transition (2.1%), but Black women may experience a more gradual increase in fat mass around the time of menopause, which may be attributed to the greater amounts of fat mass before menopause (Greendale et al. 2019). Results of another multiyear study support these findings, demonstrating that Black women started with more abdominal fat prior to menopause, but reported more stable body composition and abdominal fat across the transition (Marlatt et al. 2020). Japanese and Chinese women have been shown to experience minimal fat mass gain during the menopause transition (Greendale et al. 2019).

There is a known interaction between obesity status and sex hormones. Black women often maintain estradiol concentrations and have smaller increases in FSH across the menopause transition (Marlatt et al. 2020). Despite less dynamic changes, Black women have reported greater increases in fasting glucose during the transition to menopause suggesting greater metabolic vulnerability (Marlatt et al. 2020). Race may also be a moderating factor in the presentation of menopausal symptoms. Vasomotor and psychological/psychosomatic symptoms are the two primary categories of menopausal symptoms (Avis et al. 2001). White women tend to report more psychosomatic symptoms, such as mood disturbances and decreased libido, compared to Black women who tend to report the highest prevalence and more severe vasomotor symptoms, such as night sweats and hot flashes (Avis et al. 2001; El Khoudary et al. 2019; Richard-Davis and Wellons 2013). Hispanic women reported the largest number of total symptoms (Im et al. 2010, 2022), while Asian women

tended to report the lowest number of total symptoms (Avis et al. 2001; Im et al. 2010). Partially related to menopausal symptoms, alterations in sleep characteristics have been shown to vary substantially by race and ethnicity. White women may be more likely to experience increased waking frequency around the time of menopause compared to other racial/ethnic groups (El Khoudary et al. 2019). Black women may also experience increased waking frequency, in addition to shorter sleep duration, longer sleep latency, and lower sleep efficiency (El Khoudary et al. 2019; Hall et al. 2009). Similar to Black women, Hispanic women tended to experience shorter sleep and lower sleep efficiency (El Khoudary et al. 2019; Hall et al. 2009). Finally, ethnic and cultural differences in energy expenditure/physical activity, calorie and macronutrient intake, and food preparation, all influence the physiological changes and overall experience of the menopause transition (Lovejoy et al. 2008). The relationship among race, obesity, and disease progression particularly across the menopause transition is clearly dynamic and complex and warrants deeper investigation. There is a need for more data across races/ethnicities, but it is important to note that there are key physiological differences for women of varied races.

Summary

Stages of the menopause transition include premenopause, perimenopause, and postmenopause, defined by changes in menstrual regularity and ovarian hormone levels. The corresponding changes in ovarian hormones, particularly estrogen and progesterone, have pleiotropic effects on metabolic, cardiovascular, and musculoskeletal health in aging women. Metabolic changes with the menopause transition include declines in energy expenditure, fat oxidation, and metabolic flexibility, along with changes in appetite and the development of chronic inflammation. Body fat has consistently been shown to increase across the menopause transition. Changes in body fat distribution, specifically increases within the abdominal/visceral region, significantly increase around the time of the FMP and are highly associated with increased cardiometabolic and cardiovascular disease. Effects of menopause on changes in lean mass are inconclusive, but the loss of lean mass during the perimenopausal period may exacerbate metabolic changes, related to a decrease in protein turnover, as well as influence the loss of bone mineral density seen through the transition. Menopausal onset, hormone levels and patterns, obesity and body composition changes, and symptom experience vary by race and ethnicity, changing the course of disease progression. More data across different races and ethnicities are needed to improve the delivery of care and lifestyle interventions for all women across the lifespan. Collectively, the physiological changes reported across the transition to menopause are associated with an increased risk and prevalence of cardiovascular disease and dysfunction.

References

Abildgaard J, Pedersen AT, Green CJ, Harder-Lauridsen NM, Solomon TP, Thomsen C, Juul A, Pedersen M, Pedersen JT, Mortensen OH, Pilegaard H, Pedersen BK, Lindegaard B. Menopause is associated with decreased whole body fat oxidation during exercise. Am J Physiol-Endocrinol Metab. 2013;304(11):E1227–36. https://doi.org/10.1152/ajpendo.00492.2012.

Aloia JF, Vaswani A, Ma R, Flaster E. Aging in women—the four-compartment model of body composition. Metabolism. 1996;45(1):43–8. https://doi.org/10.1016/S0026-0495(96)90198-5.

Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. Am J Obstet Gynecol. 2019;221(5):393-409.e50. https://doi.org/10.1016/j.ajog.2019.04.023.

Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, Kagawa-Singer M. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med. 2001;52(3):345–56. https://doi.org/10.1016/S0277-9536(00)00147-7.

Bamman MM, Ferrando AA, Evans RP, Stec MJ, Kelly NA, Gruenwald JM, Corrick KL, Trump JR, Singh JA. Muscle inflammation susceptibility: a prognostic index of recovery potential after hip arthroplasty? Am J Physiol Endocrinol Metab. 2015;308(8):E670-679. https://doi.org/10.1152/ajpendo.00576.2014.

Bondarev D, Laakkonen EK, Finni T, Kokko K, Kujala UM, Aukee P, Kovanen V, Sipilä S. Physical performance in relation to menopause status and physical activity. Menopause. 2018;25(12):1432–41. https://doi.org/10.1097/GME.0000000000001137.

Brown JP, Albert C, Nassar BA, Adachi JD, Cole D, Davison KS, Dooley KC, Don-Wauchope A, Douville P, Hanley DA, Jamal SA, Josse R, Kaiser S, Krahn J, Krause R, Kremer R, Lepage R, Letendre E, Morin S, Ste-Marie L-G. Bone turnover markers in the management of post-menopausal osteoporosis. Clin Biochem. 2009;42(10–11):929–42. https://doi.org/10.1016/j.clinbiochem.2009.04.001.

Carr MC. The Emergence of the Metabolic Syndrome with Menopause. J Clin Endocrinol Metab. 2003;88(6):2404–11. https://doi.org/10.1210/jc.2003-030242.

Chen S, Jiang H, Wu X, Fang J. Therapeutic effects of quercetin on inflammation, obesity, and type 2 diabetes. Mediators Inflamm. 2016;2016:1–5. https://doi.org/10.1155/2016/9340637.

Cunningham TJ, Seeman TE, Kawachi I, Gortmaker SL, Jacobs DR, Kiefe CI, Berkman LF. Racial/ethnic and gender differences in the association between self-reported experiences of racial/ethnic discrimination and inflammation in the CARDIA cohort of 4 US communities. Soc Sci Med. 2012;75(5):922–31. https://doi.org/10.1016/j.socscimed.2012.04.027.

Dama A, Baggio C, Boscaro C, Albiero M, Cignarella A. Estrogen receptor functions and pathways at the vascular immune interface. Int J Mol Sci. 2021;22(8):4254. https://doi.org/10.3390/ijms22084254.

Devries MC. Sex-based differences in endurance exercise muscle metabolism: impact on exercise and nutritional strategies to optimize health and performance in women: sex-based differences in muscle metabolism. Exp Physiol. 2016;101(2):243–9. https://doi.org/10.1113/EP085369.

Draper CF, Duisters K, Weger B, Chakrabarti A, Harms AC, Brennan L, Hankemeier T, Goulet L, Konz T, Martin FP, Moco S, van der Greef J. Menstrual cycle rhythmicity: metabolic patterns in healthy women. Sci Rep. 2018;8(1):14568. https://doi.org/10.1038/s41598-018-32647-0.

Duval K, Prud'homme D, Rabasa-Lhoret R, Strychar I, Brochu M, Lavoie J-M, Doucet É. Effects of the menopausal transition on dietary intake and appetite: a MONET Group Study. Eur J Clin Nutr. 2014;68(2):271–76. https://doi.org/10.1038/ejcn.2013.171.

El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA. On behalf of the American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation 2020;142(25). https://doi.org/10.1161/CIR.0000000000000912.

El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Waetjen LE, Matthews K. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause, Publish Ahead of Print; 2019. https://doi.org/10.1097/GME.0000000000001424.

El Khoudary SR, Thurston RC. Cardiovascular implications of the menopause transition. Obstet Gynecol Clin North Am. 2018;45(4):641–61. https://doi.org/10.1016/j.ogc.2018.07.006.

Ferrando AA, Wolfe RR. Restoration of hormonal action and muscle protein. Crit Care Med. 2007;35(Suppl):S630–4. https://doi.org/10.1097/01.CCM.0000278529.44899.57.

Fuglsang-Nielsen R, Rakvaag E, Langdahl B, Knudsen KEB, Hartmann B, Holst JJ, Hermansen K, Gregersen S. Effects of whey protein and dietary fiber intake on insulin sensitivity, body composition, energy expenditure, blood pressure, and appetite in subjects with abdominal obesity. Eur J Clin Nutr. 2021;75(4):611–9. https://doi.org/10.1038/s41430-020-00759-4.

Gemmati D, Varani K, Bramanti B, Piva R, Bonaccorsi G, Trentini A, Manfrinato MC, Tisato V, Carè A, Bellini T. "Bridging the gap" everything that could have been avoided if we had applied gender medicine, pharmacogenetics and personalized medicine in the gender-omics and sex-omics era. Int J Mol Sci. 2019;21(1):E296. https://doi.org/10.3390/ijms21010296.

Glaser DL, Kaplan FS. Osteoporosis: definition and clinical presentation. Spine. 1997;22(Supplement):12S–16S. https://doi.org/10.1097/00007632-199712151-00003.

Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am. 2011;38(3):425–40. https://doi.org/10.1016/j.ogc.2011.05.002.

Goodpaster BH, Sparks LM. Metabolic flexibility in health and disease. Cell Metab. 2017;25(5):1027–36. https://doi.org/10.1016/j.cmet.2017.04.015.

Gould LM, Gordon AN, Cabre HE, Hoyle AT, Ryan ED, Hackney AC, Smith-Ryan AE. Metabolic effects of menopause: a cross-sectional characterization of body composition and exercise metabolism. Menopause, Publish Ahead of Print; 2022. https://doi.org/10.1097/GME.0000000000001932.

Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, Cauley JA, Finkelstein JS, Jiang S-F, Karlamangla AS. Changes in body composition and weight during the menopause transition. JCI Insight. 2019;4(5): 124865. https://doi.org/10.1172/jci.insight.124865.

Hackney AC, Koltun KJ, Williett HN. Menstrual cycle hormonal changes: estradiol-β-17 and progesterone interactions on exercise fat oxidation. Endocrine. 2022. https://doi.org/10.1007/s12020-022-02998-w.

Hall MH, Matthews KA, Kravitz HM, Gold EB, Buysse DJ, Bromberger JT, Owens JF, Sowers M. Race and financial strain are independent correlates of sleep in midlife women: the SWAN sleep study. Sleep. 2009;32(1):73–82.

Hansen M. Female hormones: do they influence muscle and tendon protein metabolism? Proc Nutr Soc. 2018;77(1):32–41. https://doi.org/10.1017/S0029665117001951.

Hodson L, Harnden K, Banerjee R, Real B, Marinou K, Karpe F, Fielding BA. Lower resting and total energy expenditure in postmenopausal compared with premenopausal women matched for abdominal obesity. J Nutr Sci. 2014;3: e3. https://doi.org/10.1017/jns.2013.38.

Im E-O, Kim G, Choi M, Chee W. Gastrointestinal symptoms in four major racial/ethnic groups of midlife women: race/ethnicity and menopausal status. Menopause. 2022;29(2):156–63. https://doi.org/10.1097/GME.0000000000001898.

Im E-O, Lee B, Chee W, Brown A, Dormire S. Menopausal symptoms among four major ethnic groups in the United States. West J Nurs Res. 2010;32(4):540–65. https://doi.org/10.1177/0193945909354343.

Janssen I. Menopause and the metabolic syndrome: the study of women's health across the nation. Arch Intern Med. 2008;168(14):1568. https://doi.org/10.1001/archinte.168.14.1568.

Johnson ML, Zarins Z, Fattor JA, Horning MA, Messonnier L, Lehman SL, Brooks GA. Twelve weeks of endurance training increases FFA mobilization and reesterification in postmenopausal women. J Appl Physiol. 2010;109(6):1573–81. https://doi.org/10.1152/japplphysiol.00116.2010.

Juppi H-K, Sipilä S, Cronin NJ, Karvinen S, Karppinen JE, Tammelin TH, Aukee P, Kovanen V, Kujala UM, Laakkonen EK. Role of menopausal transition and physical activity in loss of lean

and muscle mass: a follow-up study in middle-aged Finnish women. J Clin Med. 2020;9(5):1588. https://doi.org/10.3390/jcm9051588.
Karim R, Stanczyk FZ, Brinton RD, Rettberg J, Hodis HN, Mack WJ. Association of endogenous sex hormones with adipokines and ghrelin in postmenopausal women. J Clin Endocrinol Metab. 2015;100(2):508–15. https://doi.org/10.1210/jc.2014-2834.
Karlamangla AS, Burnett-Bowie S-AM, Crandall CJ. Bone health during the menopause transition and beyond. Obstet Gynecol Clin North Am. 2018;45(4):695–708. https://doi.org/10.1016/j.ogc.2018.07.012.
Kaunitz AM, Pinkerton JV, Manson JE. Hormone therapy and sarcopenia: implications for the prevention of frailty as women age. Menopause. 2020;27(5):496–7. https://doi.org/10.1097/GME.0000000000001541.
Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes. 2000;49(5):677–83. https://doi.org/10.2337/diabetes.49.5.677.
Kennedy RE, Sawyer P, Williams CP, Lo AX, Ritchie CS, Roth DL, Allman RM, Brown CJ. Life-space mobility change predicts 6-month mortality. J Am Geriatr Soc. 2017;65(4):833–8. https://doi.org/10.1111/jgs.14738.
Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, Wians FH, Grundy SM, de Lemos JA. Race and gender differences in c-reactive protein levels. J Am Coll Cardiol. 2005;46(3):464–9. https://doi.org/10.1016/j.jacc.2005.04.051.
Kramer PR, Kramer SF, Guan G. 17β-estradiol regulates cytokine release through modulation of CD16 expression in monocytes and monocyte-derived macrophages. Arthritis Rheum. 2004;50(6):1967–75. https://doi.org/10.1002/art.20309.
Kravitz HM, Kazlauskaite R, Joffe H. Sleep, health, and metabolism in midlife women and menopause. Obstet Gynecol Clin North Am. 2018;45(4):679–94. https://doi.org/10.1016/j.ogc.2018.07.008.
Lavin KM, Perkins RK, Jemiolo B, Raue U, Trappe SW, Trappe TA. Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. J Appl Physiol. 2020;128(1):87–99. https://doi.org/10.1152/japplphysiol.00495.2019.
Lavin KM, Roberts BM, Fry CS, Moro T, Rasmussen BB, Bamman MM. The importance of resistance exercise training to combat neuromuscular aging. Physiology. 2019;34(2):112–22. https://doi.org/10.1152/physiol.00044.2018.
Lawson SM, Chou B, Martin KL, Ryan I, Eke AC, Martin KD. The association between race/ethnicity and peripartum hysterectomy and the risk of perioperative complications. Int J Gynecol Obstet. 2020;151(1):57–66. https://doi.org/10.1002/ijgo.13304.
Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes. 2008;32(6):949–58. https://doi.org/10.1038/ijo.2008.25.
Luoto R, Kaprio J, Uutela A. Age at natural menopause and sociodemographic status in Finland. Am J Epidemiol. 1994;139(1):64–76. https://doi.org/10.1093/oxfordjournals.aje.a116936.
Lurati AR. Effects of menopause on appetite and the gastrointestinal system. Nurs Women's Health. 2018;22(6):499–505. https://doi.org/10.1016/j.nwh.2018.09.004.
Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. J Musculoskelet Neuronal Interact. 2009;9(4):186–97.
Marlatt KL, Pitynski-Miller DR, Gavin KM, Moreau KL, Melanson EL, Santoro N, Kohrt WM. Body composition and cardiometabolic health across the menopause transition. Obesity. 2022;30(1):14–27. https://doi.org/10.1002/oby.23289.
Marlatt KL, Redman LM, Beyl RA, Smith SR, Champagne CM, Yi F, Lovejoy JC. Racial differences in body composition and cardiometabolic risk during the menopause transition: a prospective, observational cohort study. Am J Obstet Gynecol. 2020;222(4):365.e1–365.e18. https://doi.org/10.1016/j.ajog.2019.09.051.
McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas. 1992;14(2):103–15. https://doi.org/10.1016/0378-5122(92)90003-M.

McKnight KK, Wellons MF, Sites CK, Roth DL, Szychowski JM, Halanych JH, Cushman M, Safford MM. Racial and regional differences in age at menopause in the United States: findings from the reasons for geographic and racial differences in stroke (REGARDS) study. Am J Obstet Gynecol. 2011;205(4):353.e1–353.e8. https://doi.org/10.1016/j.ajog.2011.05.014.

Merritt EK, Stec MJ, Thalacker-Mercer A, Windham ST, Cross JM, Shelley DP, Craig Tuggle S, Kosek DJ, Kim J, Bamman MM. Heightened muscle inflammation susceptibility may impair regenerative capacity in aging humans. J Appl Physiol. 2013;115(6):937–48. https://doi.org/10.1152/japplphysiol.00019.2013.

Nedergaard A, Henriksen K, Karsdal MA, Christiansen C. Menopause, estrogens and frailty. Gynecol Endocrinol. 2013;29(5):418–23. https://doi.org/10.3109/09513590.2012.754879.

Nelson HD. Menopause. Lancet. 2008;371(9614):760–70. https://doi.org/10.1016/S0140-6736(08)60346-3.

Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q, Hales CM. Trends in obesity prevalence by race and hispanic origin-1999–2000 to 2017–2018. JAMA. 2020;324(12):1208–10. https://doi.org/10.1001/jama.2020.14590.

Oosthuyse T, Bosch AN. The effect of the menstrual cycle on exercise metabolism: implications for exercise performance in eumenorrhoeic women. Sports Med. 2010;40(3):207–27. https://doi.org/10.2165/11317090-000000000-00000.

Park Y-M, Keller AC, Runchey SS, Miller BF, Kohrt WM, Van Pelt RE, Kang C, Jankowski CM, Moreau KL. Acute estradiol treatment reduces skeletal muscle protein breakdown markers in early- but not late-postmenopausal women. Steroids. 2019;146:43–9. https://doi.org/10.1016/j.steroids.2019.03.008.

Piers LS, Soares MJ, McCormack LM, O'Dea K. Is there evidence for an age-related reduction in metabolic rate? J Appl Physiol. 1998;85(6):2196–204. https://doi.org/10.1152/jappl.1998.85.6.2196.

Pontzer H, Yamada Y, Sagayama H, Ainslie PN, Andersen LF, Anderson LJ, Arab L, Baddou I, Bedu-Addo K, Blaak EE, Blanc S, Bonomi AG, Bouten CVC, Bovet P, Buchowski MS, Butte NF, Camps SG, Close GL, Cooper JA, IAEA DLW Database Consortium§. Daily energy expenditure through the human life course. Science 2021;373(6556):808–812. https://doi.org/10.1126/science.abe5017.

Pope SK, Sowers M, Welch GW, Albrecht G. Functional limitations in women at midlife: the role of health conditions, behavioral and environmental factors. Women's Health Issues. 2001;11(6):494–502. https://doi.org/10.1016/S1049-3867(01)00089-5.

Randolph JF, Zheng H, Sowers MR, Crandall C, Crawford S, Gold EB, Vuga M. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. J Clin Endocrinol Metab. 2011;96(3):746–54. https://doi.org/10.1210/jc.2010-1746.

Richard-Davis G, Wellons M. Racial and ethnic differences in the physiology and clinical symptoms of menopause. Semin Reprod Med. 2013;31(05):380–6. https://doi.org/10.1055/s-0033-1348897.

Rosa-Caldwell ME, Greene NP. Muscle metabolism and atrophy: let's talk about sex. Biol Sex Differ. 2019;10(1):43. https://doi.org/10.1186/s13293-019-0257-3.

Santoro N, Epperson CN, Mathews SB. Menopausal symptoms and their management. Endocrinol Metab Clin North Am. 2015;44(3):497–515. https://doi.org/10.1016/j.ecl.2015.05.001.

Santos-Parker JR, Strahler TR, Vorwald VM, Pierce GL, Seals DR. Habitual aerobic exercise does not protect against micro- or macrovascular endothelial dysfunction in healthy estrogen-deficient postmenopausal women. J Appl Physiol. 2017;122(1):11–9. https://doi.org/10.1152/japplphysiol.00732.2016.

Shieh A, Epeldegui M, Karlamangla AS, Greendale GA. Gut permeability, inflammation, and bone density across the menopause transition. JCI Insight. 2020;5(2):e134092. https://doi.org/10.1172/jci.insight.134092.

Siervogel RM, Wisemandle W, Maynard LM, Guo SS, Roche AF, Chumlea WC, Towne B. Serial changes in body composition throughout adulthood and their relationships to changes in lipid and

lipoprotein levels: the Fels longitudinal study. Arterioscler Thromb Vasc Biol. 1998;18(11):1759–1764. https://doi.org/10.1161/01.atv.18.11.1759.

Siglinsky E, Krueger D, Ward RE, Caserotti P, Strotmeyer ES, Harris TB, Binkley N, Buehring B. Effect of age and sex on jumping mechanography and other measures of muscle mass and function. J Musculoskelet Neuronal Interact. 2015;15(4):301–8.

Sowers M, Pope S, Welch G, Sternfeld B, Albrecht G. The association of menopause and physical functioning in women at midlife. J Am Geriatr Soc. 2001;49(11):1485–92. https://doi.org/10.1046/j.1532-5415.2001.4911241.x.

Stanford JL, Hartge P, Brinton LA, Hoover RN, Brookmeyer R. Factors influencing the age at natural menopause. J Chronic Dis. 1987;40(11):995–1002. https://doi.org/10.1016/0021-9681(87)90113-5.

Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metab Clin Exp. 1995; 44(3):369–373. https://doi.org/10.1016/0026-0495(95)90168-x.

Toth MJ, Sites CK, Matthews DE, Casson PR. Ovarian suppression with gonadotropin-releasing hormone agonist reduces whole body protein turnover in women. Am J Physiol-Endocrinol Metabol. 2006;291(3):E483–E490. https://doi.org/10.1152/ajpendo.00600.2005.

Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis G-A, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol. 2019; 14(1):50–59. https://doi.org/10.15420/ecr.2018.33.1.

Van Pelt RE, Gavin KM, Kohrt WM. Regulation of body composition and bioenergetics by estrogens. Endocrinol Metab Clin North Am. 2015;44(3):663–76. https://doi.org/10.1016/j.ecl.2015.05.011.

Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84(3):475–82. https://doi.org/10.1093/ajcn/84.3.475.

Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005;118(12):14–24. https://doi.org/10.1016/j.amjmed.2005.09.031.

Zaidi M, Turner CH, Canalis E, Pacifici R, Sun L, Iqbal J, Guo XE, Silverman S, Epstein S, Rosen CJ. Bone loss or lost bone: rationale and recommendations for the diagnosis and treatment of early postmenopausal bone loss. Curr Osteoporos Rep. 2009;7(4):118–26. https://doi.org/10.1007/s11914-009-0021-4.

Chapter 16
Can Exercise Improve Symptoms in Menopausal Women?

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Introduction

Menopause (also known as climacteric), from the Greek words *men-* (month) and *pausis* (stop), is the end of a woman's menstrual cycle and is usually a point in time 12 months after the last cycle. There is a loss of ovarian follicular function which marks the end of fertility. Menopause is not sudden or abrupt and usually occurs over 5–10 years between the ages 45 and 55. During the transition period, a number of signs and symptoms may occur as a result of hormonal imbalances. Each woman experiences different symptoms and severity, although the most common are changes in their monthly cycles and hot flushes. Other symptoms include headaches, itchy skin, fatigue, night sweats, low libido, back pain, and muscle tension. In addition, women may experience psychological symptoms (mood swings, anxiety, depression, panic attacks, fatigue, irritability, tearfulness, insomnia), cognitive symptoms (lack of concentration, forgetfulness), and atrophic effects (atrophic vaginitis, bladder irritability, vaginal dryness) (Garzon et al. 2021; Lagana et al. 2018; Talaulikar 2022).

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Menopause symptoms, in some instances, can significantly disturb daily activities and overall quality of life. Many chronic diseases can develop within 10 years of menopause including osteoporosis, depression, dementia, cancer (Pudkasam et al. 2021a, b), cardiovascular disease, and type 2 diabetes. As such, making lifestyle changes such as increased exercise, healthier eating, and the use of hormone replacement therapy (HRT) is important to improving quality of life (Apostolopoulos et al. 2014; Mikkelsen et al. 2017; Shakoor et al. 2021; Stojanovska et al. 2014).

HRT uses synthetic hormones, estrogen, and progestin in women with an intact uterus, or estrogen alone for women who have undergone hysterectomy, and is the most effective treatment for the relief of menopause symptoms. However, there are risks associated with HRT use (Utian and Woods 2013). Data from the Women's Health Initiative of a randomized human clinical trial of 75,343 women with no history of cancer or cardiovascular disease had significantly higher levels of inflammation, interleukin (IL)-6, and C-reactive protein. Inflammation is associated with an increased risk of chronic diseases including heart disease (Pradhan et al. 2002). In a multicenter randomized, double-blinded, placebo-controlled trial, 10,739 women with prior hysterectomy (aged 50–79 years old) were randomly grouped to receive either estrogen alone or placebo. Although the study showed no association with increased risk of cardiovascular disease or breast cancer, the study was stopped prematurely as there were increased incidences of stroke (Anderson et al. 2004). In the analysis of the Taiwanese national health insurance databases, a clear association was noted between cardiovascular diseases and menopause symptoms (Huang et al. 2021). The Million Women Study from the Cancer Epidemiology Unit, UK, and the National Health Services assessed the effects of HRT use in more than 1 million women and confirmed that HRT was associated with an increased risk of breast cancer, especially when both estrogen and progestin were used (Banks et al. 2004; Beral et al. 2004; Gray 2003). In a UK data analysis of 98,611 women aged 50–79 with a breast cancer diagnosis, it was concluded that an increased risk of breast cancer was dependent on the type of HRT used, with increased risks for combined treatments and longer duration of use (Vinogradova et al. 2020). In addition, it was recently reported that the effects of HRT were associated with age, time since menopause, and duration of treatment (Hodis and Mack 2022). As a result of these studies, a large percentage of women have become hesitant to start or continue with HRT due to fear of adverse health risks, even though studies have shown a decrease in the incidence of breast cancer (Clarke et al. 2006). In November 2012, the International Menopause Society conducted a round table discussion involving members of the major regional menopause societies to reach a consensus regarding HRT recommendations. A global consensus statement on HRT was published, which was aimed at women and healthcare practitioners to aid in making appropriate decisions on the use of HRT (de Villiers et al. 2013). In addition, HRT has been linked to an increased risk of blood clots in particular HRT tables but not from the use of creams, transdermal patches, or gels (Vinogradova et al. 2020). In a 20-year prospective study an association between the length of HRT/estrogen exposure and risk of stroke in postmenopausal women (Mishra et al. 2021). As a consequence of the increased risks

associated with HRT, many women seek other alternative treatment modalities, such as complementary and alternative therapies.

Alternative therapies, although a viable approach that can provide relief for an array of menopausal symptoms, in most cases lack scientific support. In a recent study, however, it was noted that black cohosh 40 mg/day significantly improved mood and reduced hot flushes (Castelo-Branco et al. 2022). In addition, phytoestrogens, dong quai, wild yam ginseng, evening primrose oil, and *Lepidium meyenii* (maca) have been studied but with inconsistent data (Brooks et al. 2008; Maffei et al. 2022; Shakoor et al. 2021; Stojanovska et al. 2014). However, due to increased health risks associated with HRT and conflicting data from alternative treatments, physical activity and exercise have been proposed as another means to improve the quality of life (QoL) of females during the transition between menopause and postmenopause (Apostolopoulos et al. 2014; Daley 2011a, b; Daley et al. 2009, 2015; Honisett et al. 2016a, b; Mikkelsen et al. 2017; Stojanovska et al. 2014).

The Benefits of Exercise

The importance of physical activity for overall health and well-being has been recognized for thousands of years, with the first recorded physician, Hippocrates (460–370 BC), prescribing exercise daily (Tipton 2014). Hippocrates stated that "Eating alone will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health". Later, Galen (129–216 AD) recommended the use of exercise to manage the disease, and it prevailed until the 1500s (Tipton 2014).

Physical inactivity is ranked second only to cigarette smoking, and it is a detriment to good health, giving rise to huge economic costs worldwide. The US Department of Health and Human Services Surgeon General published a report on the effects of physical activity on health (USDHHS 1996) leading to an international awakening to this important aspect of public health. There are a number of short-term and long-term benefits of exercise in health and disease (Feehan et al. 2022). Participation in regular exercise, either as a lifestyle choice or as part of a disease intervention program, results in improved QoL and overall health benefits. In fact, exercise improves immunity (Apostolopoulos et al. 2014; Pudkasam and Apostolopoulos 2022), bone health (Honisett et al. 2016a, b), chronic pain (Buttigieg et al. 2022), neuropathic pain (Wright et al. 2022), chronic heart failure (Giuliano et al. 2022), osteoarthritis (Corcoran et al. 2022), cancer (Pudkasam et al. 2017, 2018, 2021a, b), neurological diseases (Dargahi et al. 2022; Irvine and Tangalakis 2022; Taylor et al. 2022), decreases depression (Mikkelsen et al. 2017; Musker 2022), etc.

A 12-week study in obese middle-aged women participating in 1 h of resistance and aerobic exercise 3 days per week showed that metabolic syndrome risk factors (blood pressure, fasting glucose, triglyceride, cholesterol, body fat) were significantly decreased with exercise (Seo et al. 2011). In addition, 3 classes per week of Bikram yoga improved glucose tolerance (Hunter et al. 2013), and resistance

exercise significantly decreased triglyceride levels in the blood (Agil et al. 2010). Furthermore, an analysis of 80 independent studies demonstrated a positive correlation between physical inactivity and clinical depression, regardless of gender, age, or health status (Cody et al. 2021; North et al. 1990; Sun et al. 2021). Patients that participated in regular exercise after the termination of anti-depressants had lower depression scores than those who did not (LaFontaine et al. 1992). In a recent study, 30 participants involved in moderate to vigorous walking exercise, decreased depression and severity, and improved QoL and cardiorespiratory fitness (Yu et al. 2022). Overall, regular physical activity enhances mental health and well-being, including improved mood and self-esteem, reduced anxiety, stress, and depression (Daley et al. 2009, 2011a, b; Hebron and Juniper 2022).

Menopause is commonly associated with a number of health complaints, most often hot flushes, joint and muscle pain, urinary disorders, and psychological distress (Berecki-Gisolf et al. 2009). In addition, chronic conditions such as osteoporosis and cardiovascular disease (Mishra et al. 2022) are more likely to occur postmenopause than premenopause, and menopausal women are generally of poorer overall health (El Khoudary et al. 2020; Ji and Yu 2015). Physical activity has a positive impact on both bone density and cardiovascular health in menopausal women. In the case of bone density, increased physical activity during both normal activity and recreationally is associated with higher peak femoral neck strength relative to load in over 1,900 menopausal women (Mori et al. 2014). Furthermore, physical activity has a positive effect on the tibial cartilage of the knee during menopause (Fontinele et al. 2013). A systematic review and meta-analysis of intervention studies in postmenopausal women undergoing exercise training showed an effect on bone mineral density at the lumbar spine; however, it was noted that there were large differences among exercise protocols and better-formulated studies are required (Shojaa et al. 2020). However, a study of HRT combination with walking showed that HRT but not walking reduced bone turnover in postmenopausal women (Honisett et al. 2016a, b).

There are a plethora of studies published and continuously being published on the benefits of exercise to health and disease. Hence, it is beneficial for women to be physically active throughout menopause and beyond (Hilary et al. 2022; Stojanovska et al. 2014).

Exercise During Menopause

According to the United States Centre for Disease Control and Prevention, regular exercise helps relieve stress, improves overall QoL, and reduces weight gain and muscle loss, which are commonly associated with menopause (Pudkasam et al. 2017; Warburton et al. 2006a, 2006b). A minimum of 150 min of aerobic activity and 75 min of vigorous activity per week are recommended for the maintenance of cardiovascular health. Strength training is also recommended to build bone and muscle strength, decrease body fat, and increase metabolism, which is also important factors during menopause (Mishra et al. 2011).

Significantly improved physical and mental health and overall QoL were noted in women undertaking an exercise program of 3 h per week for 12 months, compared to those who were sedentary (Villaverde-Gutierrez et al. 2006). The proportion of women in the group who completed the exercise program reported a drop from 50 to 37% in menopause symptoms, whereas the control group reported an increase from 58 to 68% in menopause symptoms during the 12-month period (Villaverde-Gutierrez et al. 2006). Hence, exercise alleviated menopause symptoms in a proportion of the participating women, and their ability to choose their preferred physical activity type increased the likelihood of adhering to exercise as a treatment method. Physical activity regimes that allow the person to choose the type of exercise have been shown to increase overall adherence to exercise in addition to motivational interviewing strategies (Pudkasam et al. 2021a, b; Pudkasam et al. 2020). In a study, 108 women randomized into 4 groups who participated in either aerobic exercise, nutritional education, combined nutritional education, and aerobic exercise or no intervention were assessed for QoL using the Greene and menopause-specific QoL (MENQOL) symptom scales (Asghari et al. 2017). Overall, the aerobic exercise intervention group had significantly lower symptom scores compared to the controls and nutritional education groups (Asghari et al. 2017). A 12-week program with or without exercise training in 80 menopausal women significantly showed higher QoL scores in the exercise group in particular in 2 domains of vitality and mental health (Dabrowska et al. 2016). Most importantly, women with greater levels of physical activity report improvements in mental and physical aspects of QoL (Ethosic et al. 2021). Such improvements can even be achieved with low-intensity aerobic activity, such as dancing (Teixeira et al. 2021) and walking. In fact, in Chinese postmenopausal women, walking was shown to improve menopausal symptoms (somatic, urogenital), self-esteem as well as mental health outcomes (Hu et al. 2017). In addition, the amount of time spent on light physical activity correlated to better outcomes in all domains of QoL compared to moderate and vigorous physical activity (Felipe et al. 2020). Exercise is therefore a cost-effective alternative therapy to manage menopause symptoms (Prakash et al. 2016).

However, not all studies show positive changes in menopause symptoms as a result of exercise (see Tables 16.1 and 16.2). A longitudinal study conducted in Norway of 2,002 women over 10 year period demonstrated that there was no correlation between the occurrence of symptoms, body mass index (BMI), parity or menarche age, and physical exercise (Gjelsvik et al. 2011). Likewise, in a Nigerian cohort, there was no association between physical activity and menopausal symptoms and overall health-related problems (Ogwumike et al. 2012). Hence, physical exercise has not consistently been shown to be beneficial in ameliorating symptoms associated with menopause (Mishra et al. 2011).

Table 16.1 Observational studies on the effect of exercise on menopausal symptoms

	Population	No.# subjects	Key observations	Reference
Positive effect	Women aged 45–55 years	151	• Regular physical activity was also associated with significantly lower total Greene score and specifically lower psychological subscore and sexual subscore • Regular exercise was the lifestyle parameter most significantly correlated with a lower total Greene score independent of menopausal status • Regular exercise was significantly correlated with lower psychological and physical subscores • Moreover, the higher the frequency of exercise (both aerobic and non-aerobic), the lower the severity of the climacteric symptoms reported, yet the vasomotor and sexual subscores remained unchanged	Haimov-Kochman et al. (2013)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Women aged 54–63 years, currently experiencing vasomotor symptoms	52	• Greater levels of habitual physical activity, particularly non-leisure time physical activity, are associated with more favorable sleep characteristics • Even relatively modest levels of physical activity characteristic of household physical activity may be important for women with vasomotor symptoms, a subgroup at high risk for sleep problems	Lambiase and Thurston (2013)
	Pre- and early perimenopausal women	1919	• Physical activity in each domain examined (sport, home, active living, and work) was associated with higher peak femoral neck strength relative to load in pre- and early perimenopausal women	Mori et al. (2014)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Women aged 45–64 years	1165	• Women whose physical activity increased or remained stable had greater chances for improved quality of life than women whose physical activity decreased • Women whose weight remained stable during follow-up also improved their quality of life compared to women who gained weight	Moilanen et al. (2012a, b)
	Women aged 45–64 years	1427	• Physically active women reported fewer somatic symptoms than did women with a sedentary lifestyle	Moilanen et al. (2010)
	Women aged 45–55 years	336	• The high physical activity group felt better and had less severe climacteric symptoms; 52.08% of the women had no climacteric symptoms	Skrzypulec et al. (2010)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Women of mean age 52 years	280	• An increase in physical activity correlated with reporting fewer total menopause symptoms • When the total menopause symptoms score was examined by domain, increased physical activity was found to be related to reporting fewer general symptoms attributed to menopause, but had no effect on specific vasomotor and sexual symptoms	McAndrew et al. (2009)
	Middle-aged women	648	• There was a significant positive correlation between the severity of menopausal symptoms and depression • The severity of menopausal symptoms and depression in subjects who exercised more than three times a week were significantly lower than in the subjects who did not exercise	Lee and Kim (2008)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Menopausal women aged 46–55 years	1206	• Women who were regularly active reported better health-related quality of life scores than women who were not regularly active • No difference in vasomotor symptoms was recorded for exercise status • Women who were obese reported significantly higher vasomotor and somatic symptom scores than women of normal weight	Daley et al. (2011a, b)
	Women of mean age 51 years	133	• Women who were more physically active reported significantly less severe vaso-somatic and general somatic symptoms	Elavsky and McAuley (2007)
	Women aged 45–55 years	350	• Low exercise levels were significantly associated with reporting bothersome hot flushes • In women reporting hot flushes, the hot flush index score decreased as their age and exercise level increased	Guthrie et al. (2015)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
No effect	Women aged 40–60 years	547	• No association between physical activity and menopausal symptoms and overall health-related problems	Ogwumike et al. (2012)
	Women aged 40–44 years	2002	• No correlation between reporting of symptoms, body mass index (BMI), parity or menarche age and physical exercise	Gjelsvik et al. (2011)
	Middle-aged women from the Australian Longitudinal Study on Women's Health	3330	• Physical activity was not associated with total menopausal symptoms, vasomotor, or psychological symptoms • A weak association between physical activity and somatic symptoms was found • Weight gain was associated with increased total, vasomotor, and somatic symptoms • Weight loss was associated with a reduction in total and vasomotor symptoms	Van Poppel and Brown (2008)
	Midlife women		• No significant relationship was seen among vasomotor symptoms, sexual function, and exercise	Mirzaiinjmabadi et al. (2006)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Women aged 48–52 years	171	• Perimenopausal exercise was not associated with reduced risk of frequent vasomotor symptoms. This lack of relationship was observed in all domains of activity • Physical activity was also unassociated with reduced risk of psychologic distress, depressive feelings, or somatic symptoms • Vasomotor symptoms were strongly associated with increased risk of experiencing psychologic distress, depressive feelings, or somatic symptoms	Sternfeld et al. (2014)
	Women aged 45–55 years	1181	• There was no significant association between levels of physical activity, psychological well-being, and women's experience of symptoms during the natural menopause transition	Guthrie et al. (2015)
Negative effect	Women aged 40–60 years	273	• A negative significant correlation wasfound between somatic complaints including sexual problems and vaginal dryness as well as joint-muscular discomfort, and the level of physical activity	Javadivala et al. (2013)

(continued)

Table 16.1 (continued)

	Population	No.# subjects	Key observations	Reference
	Perimenopausal and postmenopausal women	512	• Highly active women between the ages of 35 and 40 were significantly more likely to report moderate to severe hot flushes and daily hot flushes than minimally active women	Whitcomb et al. (2007)

Table 16.2 Intervention studies on the effect of exercise on menopausal symptoms

	Population	No.# subjects	Intervention	Key observations	References
Total symptoms	Early menopausal women	108	Nutritional education, aerobic exercise, or combined nutritional education and aerobic exercise	• The aerobic exercise intervention group achieved significantly lower symptom scores than control and nutritional education groups	Asghari et al. (2017)
	Menopausal women aged 45–60 years	36	Aerobic or resistance exercise 3 days/week for 8 weeks	• In the resistance exercise group, there were significant improvements in all subscales of Menopausal Rating Scale (MRS), excluding urogenital complaints. There were also significant improvements in all subscales of The Symptom Checklist, excluding the phobic anxiety • Depression levels significantly decreased in both groups • Improvements were observed in all subscales of menopause-specific quality of life (MENQOL) questionnaire in both groups except for sexual symptoms	Agil et al. (2010)
	Menopausal women aged 55–72 years	48	Two sessions/week of cardiorespiratory, stretching, muscle-strengthening, and relaxation exercises totaling 3 h weekly for 12 months	• At the beginning of the study, 50% of women in the exercise group reported menopausal symptoms, which dropped to 37% at the study's conclusion • In the control group, the proportion of women reporting menopause symptoms rose from 58% at the beginning of the study to 68% at the end of the study	Villaverde-Gutierrez et al. (2006)

(continued)

Table 16.2 (continued)

	Population	No.# subjects	Intervention	Key observations	References
Vasomotor symptoms and sleep quality	Perimenopausal and postmenopausal women experiencing hot flushes/night sweats	261	30-min moderate-intensity exercise at least 3 days/week increasing to at least 30 min 3–5 days/week by week 24	• This study indicates that exercise is not an effective treatment for hot flushes/night sweats, with neither of the exercise interventions resulting in women reporting significantly fewer hot flushes/night sweats per week compared with controls at the 6- and 12-month follow-ups	Daley et al. (2015)
	Women aged 40–62 years in menopausal transition or postmenopause	237	Yoga	• No improvements to vasomotor symptom frequency were noted	Newton et al. (2014)
	Midlife women aged 40–60 years	121	30-min moderate-intensity aerobic exercise	• Both total objective and total subjective hot flushes decreased after acute exercise • Daily physical activity was not associated with self-reported hot flushes • Performing more moderate physical activity than usual was associated with more self-reported hot flushes in women with lower fitness levels	Elavsky et al. (2012)
	Symptomatic, sedentary women aged 43–63 years	176	Aerobic training for 50 min 4 times/week during 6 months	• The exercise group had a larger decrease in the frequency of night-time hot flushes and less depressed mood than control women • Changes in depressed mood and menopausal symptoms in the exercise group were significantly dependent on frequency of training sessions	Luoto et al. (2012)

(continued)

Table 16.2 (continued)

	Population	No.# subjects	Intervention	Key observations	References
	Sedentary women aged 43–63 years with menopausal symptoms	176	Aerobic training for 50 min 4 times/week for 6 months	• Sleep quality improved significantly more in the intervention group than in the control group • The odds for sleep improvement were 2% per week in the intervention group and a decrease of 0.5% per week in the control group • The amount of hot flushes related to sleep diminished by the end of the intervention	Mansikkamaki et al. (2012)
	Women aged 45–65 years	173	Walking 4 times/week for 20–30 min for 24 weeks	• After 24 weeks, there were no differences between the walking and control group on change in symptoms • However, frequency of walking along with change in physical symptoms and menopausal status were significant predictors of change in sleep symptoms	Wilbur et al. (2005)
	Postmenopausal, overweight or obese, sedentary aged 50 to 75 years	173	Year-long moderate-intensity exercise and a low-intensity stretching program	• Among morning exercisers, those who exercised at least 225 min per week had less trouble falling asleep compared with those who exercised less than 180 min per week • However, among evening exercisers, those who exercised at least 225 min per week had more trouble falling asleep compared to those who exercised less than 180 min per week • Stretchers were less likely to use sleep medication and have trouble falling asleep during the intervention period compared with baseline	Tworoger et al. (2003)

(continued)

Table 16.2 (continued)

	Population	No.# subjects	Intervention	Key observations	References
Psychological symptoms	Women aged 57–75 years	121	Moderate-intensity walking for 40 min 3 times/week over 6 months	• Participants in the walking intervention showed a significant decrease in depression as compared with controls	Bernard et al. (2015)
	Late peri- and postmenopausal sedentary women with frequent vasomotor symptoms	106	Moderate-intensity aerobic exercise 3 times/week for 12 weeks	• Exercise did not alleviate vasomotor symptoms, but did result in improved sleep quality, insomnia, and depression	Sternfeld et al. (2014)
	Sedentary, sexually active women who had undergone menopause no more than 5 years earlier	32	3-month physical exercise protocol including pelvic floor muscle training	• In the exercise group, there was a significant decrease in the number of women suffering from anxiety, but there was no effect on sexual function	Lara et al. (2012)
	Postmenopausal women aged 60–70 years	60	Mixed physical exercises	• In the exercise group, statistically significant improvements were observed in subjects with moderate and severe depression (18 and 22%, respectively) and in those with symptoms of anxiety. No such changes were observed in the control group	Villaverde-Gutierrez et al. (2012)
	Previously low-active middle-aged women of mean age 50 years	164	Walking or yoga	• Walking and yoga were effective in enhancing positive affect and menopause-related quality of life and reducing negative affect • Women who experienced decreases in menopausal symptoms across the trial also experienced improvements in all positive mental health outcomes and reductions in negative mental health outcomes	Elavsky and McAuley (2007)

Vasomotor Symptoms

Vasomotor symptoms are the most commonly reported symptoms during perimenopause ("around menopause") which is the time the body transition to menopause. The symptoms occur due to decreased levels of estrogen and progesterone which is the start of perimenopause. Common symptoms include hot flushes, night sweats, sleep disturbances, and insomnia. Symptoms are sometimes so severe that a woman's overall QoL is disturbed. HRT has been shown to alleviate such symptoms; however, prolonged use can have serious side effects. Some non-hormonal interventions include vitamin E, omega-3 (Maghalian et al. 2022), black cohosh (Castelo-Branco et al. 2022), soy isoflavones (Ahsan and Mallick, 2017), and acupuncture (Soares et al. 2020); however, these effects are controversial with huge placebo effects and show overall minimal benefits. As a result, many women resort to lifestyle changes such as improvements in diet, cessation of smoking, and regular structured exercise and physical activity; these have the potential to reduce vasomotor symptoms associated with menopause (Daley et al. 2009, 2011a, b). However, the evidence remains controversial. Intervention studies are largely inconsistent, with about half of the observational studies reporting no effect while others suggest a protective effect (Guthrie et al. 2015; Rowe and Baber, 2021; Soares et al. 2020). Some studies even report increased vasomotor symptoms with increased physical activity (Romani et al. 2009; Whitcomb et al. 2007) (Fig. 16.1).

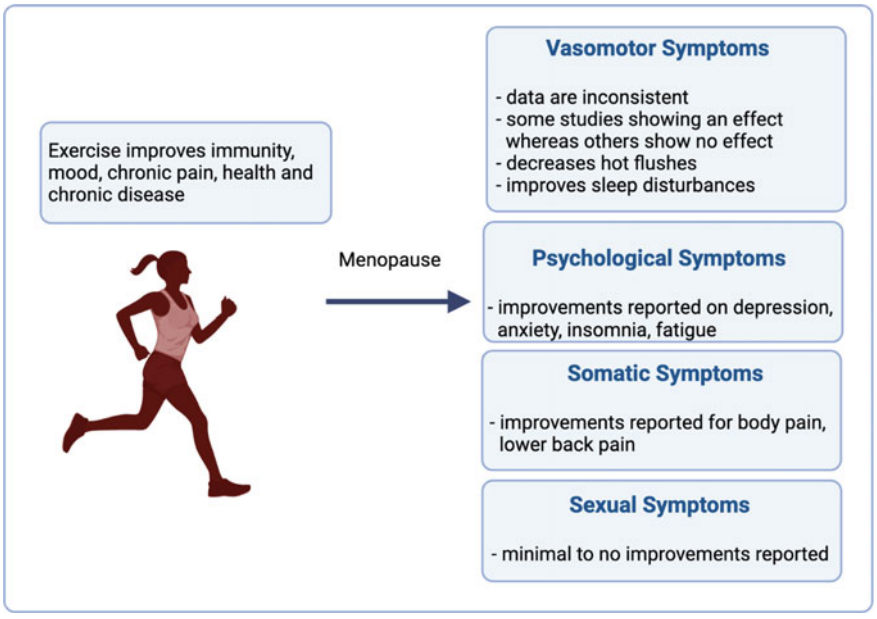

Fig. 16.1 Summary of effects of exercise in menopausal women

No Effects of Exercise on Vasomotor Symptoms

In response to these conflicting reports, the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MeFLASH) Research Network conducted a 12-week randomized controlled trial of aerobic exercise training in previously sedentary menopausal women (Newton et al. 2014). The study demonstrated that moderate-intensity aerobic exercise for 12 weeks did not alleviate vasomotor symptoms, but did result in improved sleep quality, insomnia, and depression (Sternfeld et al. 2014). In a study comparing exercise to HRT, it was not clear whether exercise was effective in treating vasomotor menopausal symptoms, nor was it clear whether exercise was more beneficial compared to HRT (Daley et al. 2011a, b). The same research group updated this with an analysis of 5 additional studies and again noted no evidence for exercise as an effective treatment for menopause-associated vasomotor symptoms (Daley et al. 2015). Likewise, the Australian Longitudinal Study on Women's Health reported no improvement in vasomotor or psychological symptoms and only marginal improvements in somatic symptoms upon commencement of physical activity (van Poppel and Brown, 2008). In a study of 280 women, increasing their level of physical activity had no effect on vasomotor or sexual symptoms of menopause (McAndrew et al. 2009). In several studies including 16,000 American women from a range of backgrounds (Gold et al. 2007), 173 African-American and Caucasian women (Wilbur et al. 2005), and 338 overweight women (Huang et al. 2010), no associations were noted among vasomotor symptom severity and physical activity. Similarly, in 164 women participating in moderate physical activity, such as walking and yoga, no improvement was shown in sleep quality (Elavsky and McAuley 2007). Furthermore, in a randomized controlled study of 237 women participating in yoga classes, no improvements in vasomotor symptom frequency were noted (Newton et al. 2014). Pooled analysis of 6 pharmacologic and non-pharmacologic interventions showed no effect on vasomotor symptom frequency or severity with either aerobic exercise or yoga (Guthrie et al. 2015). A study comparing at-home DVD-based exercise and social exercise to control menopausal women showed no significant decrease in the frequency of hot flushes or night sweats in either exercise group (Daley et al. 2015). Another randomized controlled trial at 3 different sites, where 106 women participated in moderate exercise for 12 weeks and were compared to 142 women with no addition of exercise to their daily routine, showed no improvement to vasomotor symptoms, although slight improvements in sleep quality, insomnia, mood, and depressive symptoms were noted in the exercise group (Sternfeld et al. 2014). Likewise, in a recent cross-sectional study, 627 Lebanese women hot flushes were correlated to smoking, BMI, education level, age, spicy food consumption, but no improvements were noted with physical activity status and other dietary factors (Ahmadieh and Jradi 2021).

Exercise Decreases Hot Flushes

The longitudinal Melbourne Women's Midlife Health Project, where 438 women were monitored over 8 and 13 years, demonstrated that those who exercised daily were 49% less likely to report hot flushes, and more exercise was associated with shorter vasomotor symptoms duration (Col et al. 2009). Moderate physical activity was associated with decreased objective and subjective hot flushes 24 h post-exercise, although increased symptoms were noted in women with lower fitness levels (Elavsky et al. 2012). In slightly overweight women, aerobic exercise (50 min, 4 times per week over 6 months) decreased the frequency of hot flushes and improved overall QoL (Luoto et al. 2012). A randomized controlled trial of 65 postmenopausal women participating in moderate to severe resistance training, rather than aerobic exercise 3 times per week compared to control, was recently reported to improve vasomotor symptoms (sleep, menstrual symptoms) (Berin et al. 2022). Reports from the FLAMENCO project which assessed 112 middle-aged women who were involved in a 60-min 3 days per week exercise intervention over 4 months showed significant improvements in vasomotor symptoms (Baena-Garcia et al. 2022).

Exercise Improves Sleep Disturbances

Studies specifically assessing the effects of high-intensity exercise on chronic insomnia, while varied in their design, type of exercise prescribed, and outcome measures, show overwhelming support for the benefit of exercise (Attarian et al. 2015). A cross-sectional observational study of 339 perimenopausal women demonstrated that high levels of physical activity such as recreational sports were associated with significantly improved sleep quality with fewer disturbances (Kline et al. 2013). Another year-long randomized trial of low-intensity stretching versus high-intensity exercise also demonstrated improvement in sleep in both groups (Tworoger et al. 2003). In a small trial of 52 perimenopausal women with chronic insomnia and vasomotor symptoms, those that were more physically active reported better subjective sleep and improvement in vasomotor symptoms (Lambiase and Thurston 2013). Another randomized trial of 176 perimenopausal women with chronic insomnia and vasomotor symptoms prescribed subjects either 50 min of aerobic exercise a day, 4 times per week, or sedentary activity for 6 months. The exercise group reported significant improvement in sleep and decreased the number of hot flushes (Mansikkamaki et al. 2012). An observational cross-sectional study of 336 menopausal women demonstrated a significant correlation between the absence of vasomotor symptoms and high levels of physical activity, compared to those who had low or moderate levels of physical activity (Skrzypulec et al. 2010). This was not independent of weight as perimenopausal women that were more highly physically active had lower BMI, and obesity was associated with increased frequency of chronic insomnia and vasomotor symptoms (Skrzypulec et al. 2010).

Effects of Physical Activity on Vasomotor Symptoms and Metabolic Measures

It is generally accepted that physical activity has positive effects in reducing cholesterol, triglyceride levels, apolipoprotein, and blood glucose levels (Muscella et al. 2020; Wang and Xu 2017). In 3201 42–52-year-old women, monitored annually for 8 years, hot flushes were associated with higher cholesterol, triglyceride, and apolipoprotein A levels (Thurston et al. 2012a, b). In addition, in 3,075 women, a strong correlation between hot flushes and insulin resistance was noted (Thurston et al. 2012a, b). As a consequence, it is conceivable to associate exercise with reducing hot flush symptoms and metabolic measures. In addition, sleep disturbances are less prevalent in menopausal women who are physically active (Newton et al. 2014), with fewer awakenings during the night (Lambiase and Thurston 2013) and improved quality of sleep (Mansikkamaki et al. 2012).

Moreover, excess body weight is associated with increased menopause symptoms. Indeed, the Australian Longitudinal Study on Women's Health showed in 3330 mid-aged women that although there was no association between physical activity and total menopausal symptoms, there was an association between reduced weight and vasomotor symptoms (van Poppel and Brown 2008). In addition, in 1165 Finnish females aged 45–64, followed for 8 years, overall QoL was improved in those who were physically active and whose weight remained stable during follow-up, compared to those who had gained weight (Moilanen et al. 2012a, b). Hot flushes and night sweats are more prevalent in women with higher BMI (Gold et al. 2007), and in an intensive weight loss intervention study that included physical activity, exercise led to an improvement in hot flushes occurrence in obese women (Huang et al. 2010). Conversely, 430 women in a 6-month controlled study demonstrated no correlation between weight change with mental and physical QoL. In a 5-year cohort study in 631 women, no significant associations were noted in BMI and weight change to hot flushes outcomes (Gallicchio et al. 2014). Further studies are required and should involve weight loss by means of physical activity and its effect on menopausal symptoms.

Despite the growing body of data evaluating the effects of exercise on vasomotor symptoms, there are inconsistencies, mainly due to the different exercise duration, exercise intensity, type of exercise, age, and timing since vasomotor symptoms onset. For this reason, the 2015 position statements of both the North American Menopause Society and the European Menopause and Andropause Society (EMAS) do not recommend exercise as an alternative therapy for menopause-associated vasomotor symptoms (Mintziori et al. 2015; NAMS 2015).

Psychological Symptoms

Exercise Improves Psychological Symptoms in Menopausal Women

Although psychological symptoms such as depression, anxiety, mood changes, panic attacks, forgetfulness, irritability, tearfulness, and feelings of sadness are not directly caused by menopause, about 75% of women report such symptoms. Changes in estrogen hormone levels during pre-, peri-, and postmenopause impact mental health (Borkoles et al. 2015). Often, such symptoms could be managed through lifestyle changes, including healthy eating, exercise, and meditation. In fact, in a study of middle-aged Australian women, it was noted that exercise was beneficial for somatic and psychological symptoms including depression and anxiety, but not for vasomotor symptoms or sexual function (Mirzaiinjmabadi et al. 2006). Similarly, a randomized controlled trial of 121 inactive postmenopausal women showed that the group prescribed a walking intervention of 40 min per session, 3 times a week for 6 months experienced a significant decrease in depression compared to controls (Bernard et al. 2015). More recently, physical activity showed positive effects in pre- ($n = 304$), peri- ($n = 198$), and postmenopausal ($n = 387$) women in QoL and depressive symptoms (Bondarev et al. 2020). In a cohort of 60 Saudi Arabian women (early to mid-50 s), physical activity improved depression symptoms as well as other parameters including insomnia and fatigue compared to inactive counterparts (Almurdi and Buragadda 2021).

Depression has also been associated with other symptoms of menopause, particularly vasomotor symptoms (Borkoles et al. 2015). In a cross-sectional Korean study of 648 women aged 40–60 years, a positive correlation was shown between the severity of menopausal symptoms and depression; those who exercised on a regular basis were less depressed and less symptomatic than those who were sedentary (Lee and Kim 2008). These findings suggest that women who are depressed have more severe menopausal symptoms and exercise may aid in alleviating some of these symptoms (McAndrew et al. 2009). In addition, habitual physical activities (those that are part of a person's lifestyle) such as household chores, gardening, walking, cycling, and work-related physical activities of up to 1 h per day have positive effects on menopause symptoms and QoL (Netz et al. 2008). Habitual practice improves social outcomes and psychological symptoms and decreases body weight (de Azevedo Guimaraes and Baptista 2011). Likewise, in a cross-sectional study involving 151 physically active women, psychological symptoms are improved (Haimov-Kochman et al. 2013), and 60 postmenopausal women who have exercised reported improvements in anxiety and depressive symptoms (Villaverde Gutierrez et al. 2012). Exercise is believed to impart psychological benefits to its participants by providing mental distraction and social interaction (Agil et al. 2010; Mirzaiinjmabadi et al. 2006). A common barrier for menopausal women considering an exercise regime is the demands at their stage of life, their lack of time, safety concerns when exercising outdoors, weather, and lack of company (Harkin et al. 2022; Im et al. 2008, 2010, 2012a, b, 2013). Breaking up exercise regimes into multiple shorter bursts and encouraging social interaction as

part of the exercise are important in maintaining compliance among midlife women (Fig. 16.1).

Somatic Symptoms

Exercise Improves Somatic Symptoms in Menopausal Women

Somatic from the Greek word *soma-* (body), symptoms are those related to the body. Somatic symptoms include dizziness, headaches, feeling faint, pressure-like sensation in the head or body, muscle and joint pain, numbness, or tingling in the extremities. The Health 2000 population-based study of 1427 Finnish women aged 45–64 years noted that those who were physically active reported significantly fewer somatic symptoms and pain than women with a sedentary lifestyle (Moilanen et al. 2010). Interestingly, smoking showed no correlation with symptoms. Eight years later, those that remained physically active exhibited improved QoL compared to those who were not physically active (Moilanen et al. 2012a, b). In addition, in a longitudinal study of 3,300 Australian women, increased physical activity was associated with fewer somatic symptoms (van Poppel and Brown, 2008). In the study of Women's Health Across the Nation (SWAN), a multiethnic observational cohort study of the menopause transition in 3,302 women across 7 sites in the US, it was noted that physically active women experienced less bodily pain during menopause (Avis et al. 2009). Likewise, a 3-year longitudinal study of over 2,400 women from SWAN demonstrated that women who were more physically active at midlife experienced less bodily pain over time regardless of menopausal status (Dugan et al. 2009). A 16-year follow-up study of the Erlangen fitness and osteoporosis prevention study (EFOPS) showed that postmenopausal women in the high-intensity exercise group had fewer bone fractures and improved lower back pain (Kemmler et al. 2017). Likewise, more recently, pilates and elastic resistance activity improved lower back pain associated with postmenopausal women (Castro et al. 2022). Based on these studies, there is a correlation between physical activity and improvement in somatic symptoms in menopausal women which increases their overall QoL (Fig. 16.1).

Sexual Symptoms

Due to the decline of estrogen levels during menopause and the drop in blood supply to the vagina, many symptoms are reported including loss of lubrication, vaginal dryness or thinning of the wall, and sexual dysfunction. In a study of 42 postmenopausal women, divided into 2 groups of aerobic or resistance exercise programs for 3 days per week over 8 weeks, no effects were noted for urogenital complaints and sexual symptoms (van Poppel and Brown 2008). In another study of 24 women participating in a

3-month exercise regime, no improvements in sexual function were noted, although reduced anxiety and improvement in pelvic floor muscular strength were reported (Lara et al. 2012). Likewise, a cross-sectional study of 1071 postmenopausal Turkish women showed no association between regular exercise and improvement in urogenital symptoms (Aydin et al. 2014). However, in another cross-sectional study of 151 women, those who exercised regularly (at least 3 times a week) reported improved menopausal symptoms including a decrease in sexual symptoms (Haimov-Kochman et al. 2013). In addition, in a Brazilian cohort of middle-aged women, those who led sedentary lifestyles had a higher prevalence of sexual dysfunction compared to active women (Cabral et al. 2014). Further, in 273 Iranian women, a significant negative correlation was noted between sexual problems and vaginal dryness and the level of physical activity (Javadivala et al. 2013). In a systematic review of sexual function in menopausal women and the effects of aerobic exercise showed inconsistent results and resistance training did not convey any benefits (Carcelen-Fraile et al. 2020). It is clear that exercise and sexual functioning are ambiguous, and further studies are required (Fig. 16.1).

Expert Opinion

Habitual physical activity has numerous health benefits, including decreased risk of obesity, cardiovascular disease, type 2 diabetes, stroke, metabolic syndromes, cancer, osteoporosis, psychological symptoms, and improved muscle and bone health. The risk of having one of these health issues is greatest postmenopause, independent of traditional risk factors (Hilary et al. 2022; Kline et al. 2013; Sternfeld and Dugan 2011; Sternfeld et al. 2014).

Inflammatory Markers and Menopause Symptoms

Many of the menopause conditions are associated with chronic inflammation. The link between exercise and inflammation in menopausal women has recently been given much attention. Emerging evidence suggests that perimenopause itself is pro-inflammatory, and estrogen receptor beta regulates innate immune responses (inflammasome) resulting in systemic and central nervous system inflammation (McCarthy and Raval 2020). In a randomized controlled trial studying the effects of exercise on inflammatory cytokine levels, 28 sedentary postmenopausal women were grouped as controls or prescribed 25–30 min of low–moderate-intensity treadmill training 3–4 times a week for 16 weeks (Tartibian et al. 2015). The exercise group showed a significant decrease in pro-inflammatory markers, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) and, hence, decreased inflammation (Tartibian et al. 2015). Similarly, a study on the effect of resistance training in postmenopausal women showed that high volume resistance training, but not low volume resistance training,

prevented increased inflammation as measured by circulating levels of TNF-α and IL-6 (Nunes et al. 2016). More recently, in a systematic review and meta-analysis, IL-6, TNF-α, and C-reactive protein were decreased and adiponectin was increased following exercise training compared to no intervention control group (Khalafi et al. 2021).

Exercise Improves Cardiometabolic Disease in Postmenopausal Women

The incidence of cardiovascular disease is increased in postmenopausal women, but the risk is lower in physically active women. Indeed, blood pressure is lower in physically active postmenopausal women compared to healthy sedentary women (Silva et al. 2021), and resistance training with an intensity of 60% once a week for 12 weeks has beneficial effects on blood pressure, heart rate, and cholesterol levels (Gelecek et al. 2012). Similarly, a modified relaxation technique used as an intervention in Thai postmenopausal women lowered blood pressure as early as 4 weeks after treatment commenced (Saensak et al. 2013). Interestingly, whole-body vibration exercise training improves systemic and local leg arterial stiffness, leg muscle strength, and blood pressure in postmenopausal women with pre-hypertension or hypertension (Figueroa et al. 2014a, b). Furthermore, aerobic exercise and calorie restriction improve insulin sensitivity and reduce the risk of diabetes in postmenopausal women (Elsayed et al. 2022; Ryan et al. 2012).

Concluding Remarks

Physical activity plays an important role in maintaining good health and reducing the risk of diseases beyond menopause, including cancer, cardiovascular disease, and diabetes. Exercise intervention programs reduce menopause symptoms, particularly psychological and somatic symptoms, and to a lesser extent vasomotor and sexual symptoms. Overall, exercise increases bone and muscle mass, improves mood and cognition, and prevents weight gain. Though exercise has not been shown to treat menopausal symptoms, physically active women are less stressed and have better overall QoL during and postmenopause. It is therefore important for exercise to play a major role in the lives of pre-, peri-, and postmenopausal women, with the aim of decreasing risks of disease and improving overall QoL. Importantly, exercise is safe with no adverse side effects. However, due to some inconsistencies between studies on the effects of exercise on menopause symptoms, in particular those relating to vasomotor and sexual symptoms, there is a need for well-designed and sufficiently powered randomized trials in order to further elucidate the benefits of exercise on

menopause symptoms. Possible explanations for the ambiguous findings on vasomotor and sexual symptoms in particular and exercise may be: (i) varying sample sizes, (ii) non-randomized designs, (iii) inadequate specified exercise dose (vigorous vs. moderate intensity; frequency, duration), (iv) mode (aerobic vs. resistance exercise), and (v) inadequate follow-up. Studies have often assessed physical activity and exercise behaviors by means of self-reporting and questionnaires rather than objectively. In addition, some studies included participants who were already physically active, whereas other studies included women who started exercise to alleviate symptoms. Furthermore, different mechanisms might underlie symptom etiology in those that are active prior to and during menopause compared to those who take up exercise during menopause. Nonetheless, it is clear that exercise has numerous benefits for menopausal symptoms. Regular exercise is also known to boost the immune system and decrease chronic inflammation in menopausal women. Moreover, studies relating to physical activity, immunological outcomes, and menopausal symptoms during menopause and beyond are critically needed, as they may hold the key to understanding the underlying mechanisms of menopause symptoms.

References

Agil A, Abike F, Daskapan A, Alaca R, Tuzun H. Short-term exercise approaches on menopausal symptoms, psychological health, and quality of life in postmenopausal women. Obstet Gynecol Int. 2010.

Ahmadieh H, Jradi N. Prevalence of menopausal hot flashes in Lebanon: a cross-sectional study. Int J Reprod Biomed. 2021;19(9):789–800.

Ahsan M, Mallick AK. The effect of soy Isoflavones on the menopause rating scale scoring in Perimenopausal and postmenopausal women: a pilot study. J Clin Diagn Res. 2017; 11(9): FC13-FC16.

Almurdi M, Buragadda S. Association between physical activity and post menopausal symptoms in Saudi women: a cross-sectional study. Iran Rehabil J. 2021;19(2):157–64.

Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A. Women's Health Initiative Steering, C. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004; 291(14):1701−1712.

Apostolopoulos V, Borkoles E, Polman R, Stojanovska L. Physical and immunological aspects of exercise in chronic diseases. Immunotherapy. 2014;6(10):1145–57.

Asghari M, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, Malakouti J, Nedjat S. Effect of aerobic exercise and nutrition educationon quality of life and early menopause symptoms: a randomized controlled trial. Women Health. 2017;57(2):173–88.

Attarian H, Hachul H, Guttuso T, Phillips B. Treatment of chronic insomnia disorder in menopause: evaluation of literature. Menopause. 2015;22(6):674–84.

Avis NE, Brockwell S, Randolph JF, Shen S, Cain VS, Ory M, Greendale GA. Longitudinal changes in sexual functioning as women transition through menopause: results from the study of women's health; 2009.

Aydin Y, Hassa H, Oge T, Yalcin OT, Mutlu FS. Frequency and determinants of urogenital symptoms in postmenopausal Islamic women. Menopause. 2014;21(2):182–7.

Baena-Garcia L, Flor-Alemany M, Marin-Jimenez N, Aranda P, Aparicio VA. A 16-week multicomponent exercise training program improves menopause-related symptoms in middle-aged women. The FLAMENCO project randomized control trial. Menopause. 2022; 29(5):537–544.

Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis MG, Wilson M, Patnick J. Impact of use of hormone replacement therapy on false positive recall in the NHS breast screening programme: results from the Million Women Study. BMJ. 2004;328(7451):1291–2.

Beral V, Banks E, Reeves G, Million Women Study C. Effects of estrogen-only treatment in postmenopausal women. JAMA. 2004: 292(6):684; author reply 685–686.

Berecki-Gisolf J, Begum N, Dobson AJ. Symptoms reported by women in midlife: menopausal transition or aging? Menopause. 2009;16(5):1021–9.

Berin E, Hammar M, Lindblom H, Lindh-Astrand L, Spetz Holm AC. Effects of resistance training on quality of life in postmenopausal women with vasomotor symptoms. Climacteric. 2022;25(3):264–70.

Bernard P, Ninot G, Bernard PL, Picot MC, Jaussent A, Tallon G, Blain H. Effects of a six-month walking intervention on depression in inactive post-menopausal women: a randomized controlled trial. Aging Ment Health. 2015;19(6):485–92.

Bondarev D, Sipila S, Finni T, Kujala UM, Aukee P, Laakkonen EK, Kovanen V, Kokko K. The role of physical activity in the link between menopausal status and mental well-being. Menopause. 2020;27(4):398–409.

Borkoles E, Reynolds N, Thompson DR, Ski CF, Stojanovska L, Polman RC. The role of depressive symptomatology in peri- and post-menopause. Maturitas. 2015;81(2):306–10.

Brooks NA, Wilcox G, Walker KZ, Ashton JF, Cox MB, Stojanovska L. Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. Menopause. 2008;15(6):1157–62.

Buttigieg B, Efthimiou N, Sim A. Exercise for chronic pain. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 193–220.

Cabral PU, Canario AC, Spyrides MH, Uchoa SA, Eleuterio J, Giraldo PC, Goncalves AK. Physical activity and sexual function in middle-aged women. Rev Assoc Med Bras. 2014 (1992);60(1):47–52.

Carcelen-Fraile MDC, Aibar-Almazan A, Martinez-Amat A, Cruz-Diaz D, Diaz-Mohedo E, Redecillas-Peiro MT, Hita-Contreras F. Effects of physical exercise on sexual function and quality of sexual life related to menopausal symptoms in Peri- and postmenopausal women: a systematic review. Int J Environ Res Public Health. 2020: 17(8).

Castelo-Branco C, Navarro C, Beltran E, Losa F, Camacho M, on the behalf of the Natural Products Study Group of the Spanish Menopause S. Black cohosh efficacy and safety for menopausal symptoms. The Spanish Menopause Society statement. Gynecol Endocrinol. 2022; 38(5):379–384.

Castro JB, Lima VP, Mello DB, Lopes GC, Peixoto JC, Santos AOD, Nunes RA, Souza Vale RG. Effects of Pilates with and without elastic resistance on health variables in postmenopausal women with low back pain. Pain Manag. 2022;12(4):509–20.

Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol. 2006;24(33):e49-50.

Cody R, Kreppke JN, Beck J, Donath L, Eckert A, Imboden C, Hatzinger M, Holsboer-Trachsler E, Lang UE, Ludyga S, Mans S, Mikoteit T, Oswald A, Rogausch A, Schweinfurth N, Zahner L, Faude O, Gerber M. Psychosocial health and physical activity in people with major depression in the context of COVID-19. Front Sports Act Living. 2021;3: 685117.

Col NF, Guthrie JR, Politi M, Dennerstein L. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause. 2009;16(3):453–7.

Corcoran D, Hiney J, Ellis L, Feehan J, Tripodi N. Exercise for the management of osteoarthritis. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 289–300.

Dabrowska J, Dabrowska-Galas M, Rutkowska M, Michalski BA. Twelve-week exercise training and the quality of life in menopausal women—clinical trial. Prz Menopauzalny. 2016;15(1):20–5.

Daley AJ, Stokes-Lampard H, MacArthur C. Exercise for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2011a; 5: CD006108.

Daley AJ, Stokes-Lampard H, Wilson S, Rees M, Roalfe A, Macarthur C. What women want? Exercise Preferences of Menopausal Women Maturitas. 2011b;68(2):174–8.

Daley AJ, Stokes-Lampard HJ, Macarthur C. Exercise to reduce vasomotor and other menopausal symptoms: a review. Maturitas. 2009;63(3):176–80.

Daley AJ, Thomas A, Roalfe AK, Stokes-Lampard H, Coleman S, Rees M, Hunter MS, MacArthur C. The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. BJOG. 2015;122(4):565–75.

Dargahi N, Haritopoulou-Sinanidou M, Apostolopoulos V. Exercise in the management of multiple sclerosis. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 163–73.

de Azevedo Guimaraes AC, Baptista F. Influence of habitual physical activity on the symptoms of climacterium/menopause and the quality of life of middle-aged women. Int J Womens Health. 2011;3:319–28.

de Villiers TJ, Gass ML, Haines CJ, Hall JE, Lobo RA, Pierroz DD, Rees M. Global consensus statement on menopausal hormone therapy. Maturitas. 2013;74(4):391–2.

Dugan SA, Everson-Rose SA, Karavolos K, Sternfeld B, Wesley D, Powell LH. The impact of physical activity level on SF-36 role-physical and bodily pain indices in midlife women. J Phys Act Health. 2009;6(1):33–42.

El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA, American Heart Association Prevention Science Committee of the Council on, E., Prevention, Council on, C, Stroke N. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American heart association. Circulation. 2020; 142(25): e506−e532.

Elavsky S, Gonzales JU, Proctor DN, Williams N, Henderson VW. Effects of physical activity on vasomotor symptoms: examination using objective and subjective measures. Menopause. 2012;19(10):1095–103.

Elavsky S, McAuley E. Lack of perceived sleep improvement after 4-month structured exercise programs. Menopause. 2007;14(3 Pt 1):535–40.

Elsayed MM, El Refaye GE, Rabiee A, Abouzeid S, Elsisi HF. Aerobic exercise with diet induces hormonal, metabolic, and psychological changes in postmenopausal obese women. Heliyon. 2022;8(3): e09165.

Ethosic A, Zivkovic D, Milanovic Z, Zivkovic M, Bjelakovic L, Bratic M, Pantelic S. The association between level of physical activity and body mass index, and quality of life among elderly women. Front Psychol. 2021;12: 804449.

Feehan J, Tripodi N, Apostolopoulos V. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan, Elsevier Inc; 2022.

Felipe J, Viezel J, Reis AD, da Costa Barros EA, de Paulo TRS, Neves LM, Junior IFF. Relationship of different intensities of physical activity and quality of life in postmenopausal women. Health Qual Life Outcomes. 2020;18(1):123.

Figueroa A, Kalfon R, Madzima TA, Wong A. Effects of whole-body vibration exercise training on aortic wave reflection and muscle strength in postmenopausal women with prehypertension and hypertension. J Hum Hypertens. 2014a;28(2):118–22.

Figueroa A, Kalfon R, Madzima TA, Wong A. Whole-body vibration exercise training reduces arterial stiffness in postmenopausal women with prehypertension and hypertension. Menopause. 2014b;21(2):131–6.

Fontinele RG, Mariotti VB, Vazzolere AM, Ferrao JS, Kfoury JR, De Souza RR. Menopause, exercise, and knee. What happens? Microsc Res Tech. 2013; 76(4): 381–387.
Gallicchio L, Miller SR, Kiefer J, Greene T, Zacur HA, Flaws JA. Change in body mass index, weight, and hot flashes: a longitudinal analysis from the midlife women's health study. J Womens Health (larchmt). 2014;23(3):231–7.
Garzon S, Apostolopoulos V, Stojanovska L, Ferrari F, Mathyk BA, Lagana AS. Non-oestrogenic modalities to reverse urogenital aging. Prz Menopauzalny. 2021;20(3):140–7.
Gelecek N, Ilcin N, Subasi SS, Acar S, Demir N, Ormen M. The effects of resistance training on cardiovascular disease risk factors in postmenopausal women: a randomized-controlled trial. Health Care Women Int. 2012;33(12):1072–85.
Giuliano C, Levinger I, Woessner M. Exercise for chronic heart failure. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 261–71.
Gjelsvik B, Rosvold EO, Straand J, Dalen I, Hunskaar S. Symptom prevalence during menopause and factors associated with symptoms and menopausal age. Results from the Norwegian Hordaland Women's Cohort study. Maturitas. 2011; 70(4): 383–390.
Gold EB, Lasley B, Crawford SL, McConnell D, Joffe H, Greendale GA. Relation of daily urinary hormone patterns to vasomotor symptoms in a racially/ethnically diverse sample of midlife women: study of women's health across the nation. Reprod Sci. 2007;14(8):786–97.
Gray S. Breast cancer and hormone-replacement therapy: the Million Women Study. Lancet. 2003; 362(9392): 1332; author reply 1332.
Guthrie KA, LaCroix AZ, Ensrud KE, Joffe H, Newton KM, Reed SD, Caan B, Carpenter JS, Cohen LS, Freeman EW, Larson JC, Manson JE, Rexrode K, Skaar TC, Sternfeld B, Anderson GL. Pooled analysis of six pharmacologic and nonpharmacologic interventions for vasomotor symptoms. Obstet Gynecol. 2015;126(2):413–22.
Haimov-Kochman R, Constantini N, Brzezinski A, Hochner-Celnikier D. Regular exercise is the most significant lifestyle parameter associated with the severity of climacteric symptoms: a cross sectional study. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):229–34.
Harkin, K., Pascal, B. M., Irvine, S., Tangalakis, K., & Apostolopoulos, V. (2022). Physical activity adherence: Worldwide trends, barriers and facilitators and tools to improve it. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan, Elsevier Inc; pp 49–62.
Hebron C, Juniper J. The lived experience of exercise in persons with depression: a journey to finding a sense of contentment. Physiother Theory Pract. 2022; 1–11.
Hilary S, Ali HI, Ismail LC, Al Dhaheri AS, Stojanovska L. Exercise and menopause. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 175–92.
Hodis HN, Mack WJ. Menopausal hormone replacement therapy and reduction of all-cause mortality and cardiovascular disease: it is about time and timing. Cancer J. 2022;28(3):208–23.
Honisett SY, Pagliaro D, Tangalakis K, Kingwell B, Ebeling P, Craven R, Antonopillai J, Apostolopoulos V, Stojanovska L. Hormone therapy reduces bone resorption but not bone formation in postmenopausal athletes. Pril (makedon Akad Nauk Umet Odd Med Nauki). 2016a;37(2–3):15–21.
Honisett SY, Tangalakis K, Wark J, Apostolopoulos V, Stojanovska L. The effects of hormonal therapy and exercise on bone turnover in postmenopausal women: a randomised double-blind pilot study. Pril (makedon Akad Nauk Umet Odd Med Nauki). 2016b;37(2–3):23–32.
Hu L, Zhu L, Lyu J, Zhu W, Xu Y, Yang L. Benefits of walking on menopausal symptoms and mental health outcomes among chinese postmenopausal women. Int J Gerontol. 2017;11(3):166–70.
Huang AJ, Subak LL, Wing R, West DS, Hernandez AL, Macer J, Grady D. Program to reduce incontinence by D, Exercise I. An intensive behavioral weight loss intervention and hot flushes in women. Arch Intern Med. 2010; 170(13): 1161−1167.

Huang CH, Kor CT, Lian IB, Chang CC. Menopausal symptoms and risk of heart failure: a retrospective analysis from Taiwan national health insurance database. ESC Heart Fail. 2021;8(4):3295–307.

Hunter SD, Dhindsa M, Cunningham E, Tarumi T, Alkatan M, Tanaka H. Improvements in glucose tolerance with Bikram Yoga in older obese adults: a pilot study. J Bodywork Mov Ther. 2013;17(4):404–7.

Im EO, Chang SJ, Ko Y, Chee W, Stuifbergen A, Walker L. A national internet survey on midlife women's attitudes toward physical activity. Nurs Res. 2012a;61(5):342–52.

Im EO, Chee W, Lim HJ, Liu Y, Kim HK. Midlife women's attitudes toward physical activity. J Obstet Gynecol Neonatal Nurs. 2008;37(2):203–13.

Im EO, Ko Y, Hwang H, Chee W, Stuifbergen A, Lee H, Chee E. Asian American midlife women's attitudes toward physical activity. J Obstet Gynecol Neonatal Nurs. 2012b;41(5):650–8.

Im EO, Ko Y, Hwang H, Chee W, Stuifbergen A, Walker L, Brown A. Racial/ethnic differences in midlife women's attitudes toward physical activity. J Midwifery Womens Health. 2013;58(4):440–50.

Im EO, Stuifbergen AK, Walker L. A situation-specific theory of midlife women's attitudes toward physical activity (MAPA). Nurs Outlook. 2010;58(1):52–8.

Irvine S, Tangalakis K. Exercise and Alzheimer's disease. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 413–21.

Javadivala Z, Kousha A, Allahverdipour H, Asghari Jafarabadi M, Tallebian H. Modeling the relationship between physical activity and quality of life in menopausal-aged women: a cross-sectional study. J Res Health Sci. 2013;13(2):168–75.

Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med. 2015;1(1):9–13.

Kemmler W, Kohl M, von Stengel S. Long-term effects of exercise in postmenopausal women: 16-year results of the Erlangen fitness and osteoporosis prevention study (EFOPS). Menopause. 2017;24(1):45–51.

Khalafi M, Malandish A, Rosenkranz SK. The impact of exercise training on inflammatory markers in postmenopausal women: a systemic review and meta-analysis. Exp Gerontol. 2021;150: 111398.

Kline CE, Irish LA, Krafty RT, Sternfeld B, Kravitz HM, Buysse DJ, Bromberger JT, Dugan SA, Hall MH. Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: the SWAN sleep study. Sleep. 2013; 36(9): 1279–1288.

LaFontaine TP, DiLorenzo TM, Frensch PA, Stucky-Ropp RC, Bargman EP, McDonald DG. Aerobic exercise and mood. A brief review, 1985–1990. Sports Med. 1992; 13(3): 160–170.

Lagana AS, Vitale SG, Stojanovska L, Lambrinoudaki I, Apostolopoulos V, Chiofalo B, Rizzo L, Basile F. Preliminary results of a single-arm pilot study to assess the safety and efficacy of visnadine, prenylflavonoids and bovine colostrum in postmenopausal sexually active women affected by vulvovaginal atrophy. Maturitas. 2018;109:78–80.

Lambiase MJ, Thurston RC. Physical activity and sleep among midlife women with vasomotor symptoms. Menopause. 2013;20(9):946–52.

Lara LA, Montenegro ML, Franco MM, Abreu DC, Rosa e Silva AC, Ferreira CH. Is the sexual satisfaction of postmenopausal women enhanced by physical exercise and pelvic floor muscle training? J Sex Med. 2012; 9(1): 218−223.

Lee Y, Kim H. Relationships between menopausal symptoms, depression, and exercise in middle-aged women: a cross-sectional survey. Int J Nurs Stud. 2008;45(12):1816–22.

Luoto R, Moilanen J, Heinonen R, Mikkola T, Raitanen J, Tomas E, Ojala K, Mansikkamaki K, Nygard CH. Effect of aerobic training on hot flushes and quality of life–a randomized controlled trial. Ann Med. 2012;44(6):616–26.

Maffei S, Franchini M, Fortunato L, Guiducci L. Long-term effects of a combination of isoflavones, agnus castus and magnolia extracts on climacteric symptoms and cardiometabolic risk profile in postmenopausal women. Gynecol Endocrinol. 2022;38(4):339–44.

Maghalian M, Hasanzadeh R, Mirghafourvand M. The effect of oral vitamin E and omega-3 alone and in combination on menopausal hot flushes: a systematic review and meta-analysis. Post Reprod Health. 2022;20533691221083196.

Mansikkamaki K, Raitanen J, Nygard CH, Heinonen R, Mikkola T, EijaTomas, Luoto R. Sleep quality and aerobic training among menopausal women--a randomized controlled trial. Maturitas. 2012; 72(4): 339−345.

McAndrew LM, Napolitano MA, Albrecht A, Farrell NC, Marcus BH, Whiteley JA. When, why and for whom there is a relationship between physical activity and menopause symptoms. Maturitas. 2009;64(2):119–25.

McCarthy M, Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. J Neuroinflammation. 2020;17(1):317.

Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. Maturitas. 2017;106:48–56.

Mintziori G, Lambrinoudaki I, Goulis DG, Ceausu I, Depypere H, Erel CT, Perez-Lopez FR, Schenck-Gustafsson K, Simoncini T, Tremollieres F, Rees M. EMAS position statement: non-hormonal management of menopausal vasomotor symptoms. Maturitas. 2015;81(3):410–3.

Mirzaiinjmabadi K, Anderson D, Barnes M. The relationship between exercise, body mass index and menopausal symptoms in midlife Australian women. Int J Nurs Pract. 2006;12(1):28–34.

Mishra N, Mishra VN, Devanshi. Exercise beyond menopause: dos and don'ts. J Midlife Health. 2011; 2(2):51−56.

Mishra SR, Waller M, Chung HF, Mishra GD. Association of the length of oestrogen exposure with risk of incident stroke in postmenopausal women: insights from a 20-year prospective study. Int J Cardiol. 2021;328:206–14.

Mishra SR, Waller M, Chung HF, Mishra GD. Association between reproductive lifespan and risk of incident type 2 diabetes and hypertension in postmenopausal women: Findings from a 20-year prospective study. Maturitas. 2022;159:52–61.

Moilanen J, Aalto AM, Hemminki E, Aro AR, Raitanen J, Luoto R. Prevalence of menopause symptoms and their association with lifestyle among Finnish middle-aged women. Maturitas. 2010;67(4):368–74.

Moilanen JM, Aalto AM, Raitanen J, Hemminki E, Aro AR, Luoto R. Physical activity and change in quality of life during menopause–an 8-year follow-up study. Health Qual Life Outcomes. 2012a;10:8.

Moilanen JM, Mikkola TS, Raitanen JA, Heinonen RH, Tomas EI, Nygard CH, Luoto RM. Effect of aerobic training on menopausal symptoms–a randomized controlled trial. Menopause. 2012b;19(6):691–6.

Mori T, Ishii S, Greendale GA, Cauley JA, Sternfeld B, Crandall CJ, Han W, Karlamangla AS. Physical activity as determinant of femoral neck strength relative to load in adult women: findings from the hip strength across the menopause transition study. Osteoporos Int. 2014;25(1):265–72.

Muscella A, Stefano E, Marsigliante S. The effects of exercise training on lipid metabolism and coronary heart disease. Am J Physiol Heart Circ Physiol. 2020;319(1):H76–88.

Musker M. Exercise and depression. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 243–50.

NAMS. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of the North American menopause society. Menopause. 2015; 22(11), 1155–1172; quiz 1173–1154.

Netz Y, Zach S, Taffe JR, Guthrie J, Dennerstein L. Habitual physical activity is a meaningful predictor of well-being in mid-life women: a longitudinal analysis. Climacteric. 2008;11(4):337–44.

Newton KM, Reed SD, Guthrie KA, Sherman KJ, Booth-LaForce C, Caan B, Sternfeld B, Carpenter JS, Learman LA, Freeman EW, Cohen LS, Joffe H, Anderson GL, Larson JC, Hunt JR, Ensrud KE, LaCroix AZ. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. Menopause. 2014;21(4):339–46.

North TC, McCullagh P, Tran ZV. Effect of exercise on depression. Exerc Sport. 1990.

Nunes PR, Barcelos LC, Oliveira AA, Furlanetto Junior R, Martins FM, Orsatti CL, Resende EA, Orsatti FL. Effect of resistance training on muscular strength and indicators of abdominal adiposity, metabolic risk, and inflammation in postmenopausal women: controlled and randomized clinical trial of efficacy of training volume. Age (dordr). 2016;38(2):40.

Ogwumike OO, Kaka B, Adegbemigun O, Abiona T. Health-related and socio-demographic correlates of physical activity level amongst urban menopausal women in Nigeria. Maturitas. 2012;73(4):349–53.

Pradhan AD, Manson JE, Rossouw JE, Siscovick DS, Mouton CP, Rifai N, Wallace RB, Jackson RD, Pettinger MB, Ridker PM. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA. 2002;288(8):980–7.

Prakash MD, Stojanovska L, Nurgali K, Apostolopoulos V. Exercise in menopausal women. In: Hackney AC, editor. Sex hormones, exercise and women: scientific and clinical aspects. Springer; 2016. p. 285–307.

Pudkasam S, Apostolopoulos V. Exercise and immunity. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 7–21.

Pudkasam S, Feehan J, Talevski J, Vingrys K, Polman R, Chinlumprasert N, Stojanovska L, Apostolopoulos V. Motivational strategies to improve adherence to physical activity in breast cancer survivors: a systematic review and meta-analysis. Maturitas. 2021a;152:32–47.

Pudkasam S, Harkin K, Tangalakis K, Feehan J, Apostolopoulos V. Work it out: exercise as an anti-cancer intervention. In: Esteves D, Lewis K, editors. Exercise: physical, physiological and psychological benefits. Nova Medicine and Health; 2021b. p. 295–340.

Pudkasam S, Pitcher M, Fisher M, O'Connor A, Chinlumprasert N, Stojanovska L, Polman R, Apostolopoulos V. The PAPHIO study protocol: a randomised controlled trial with a 2 × 2 crossover design of physical activity adherence, psychological health and immunological outcomes in breast cancer survivors. BMC Public Health. 2020;20(1):696.

Pudkasam S, Polman R, Pitcher M, Fisher M, Chinlumprasert N, Stojanovska L, Apostolopoulos V. Physical activity and breast cancer survivors: importance of adherence, motivational interviewing and psychological health. Maturitas. 2018;116:66–72.

Pudkasam S, Tangalakis K, Chinlumprasert N, Apostolopoulos V, Stojanovska L. Breast cancer and exercise: the role of adiposity and immune markers. Maturitas. 2017;105:16–22.

Romani WA, Gallicchio L, Flaws JA. The association between physical activity and hot flash severity, frequency, and duration in mid-life women. Am J Hum Biol. 2009;21(1):127–9.

Rowe IJ, Baber RJ. The effects of phytoestrogens on postmenopausal health. Climacteric. 2021;24(1):57–63.

Ryan AS, Ortmeyer HK, Sorkin JD. Exercise with calorie restriction improves insulin sensitivity and glycogen synthase activity in obese postmenopausal women with impaired glucose tolerance. Am J Physiol Endocrinol Metab. 2012;302(1):E145-152.

Saensak S, Vutyavanich T, Somboonporn W, Srisurapanont M. Modified relaxation technique for treating hypertension in Thai postmenopausal women. J Multidiscip Healthc. 2013;6:373–8.

Seo DI, So WY, Ha S, Yoo EJ, Kim D, Singh H, Fahs CA, Rossow L, Bemben DA, Bemben MG, Kim E. Effects of 12 weeks of combined exercise training on visfatin and metabolic syndrome factors in obese middle-aged women. J Sports Sci Med. 2011;10(1):222–6.

Shakoor H, Apostolopoulos V, Feehan J, Ali HI, Ismail LC, Al Dhaheri A, Stojanovska L. Effect of calorie restriction and exercise on type 2 diabetes. Pril (makedon Akad Nauk Umet Odd Med Nauki). 2021;42(1):109–26.

Shojaa M, Von Stengel S, Schoene D, Kohl M, Barone G, Bragonzoni L, Dallolio L, Marini S, Murphy MH, Stephenson A, Manty M, Julin M, Risto T, Kemmler W. Effect of exercise training on bone mineral density in post-menopausal women: a systematic review and meta-analysis of intervention studies. Front Physiol. 2020;11:652.

Silva AM, Vieira LR, Rodrigues RD, de Oliveira THC, Machado MGR, Goncalves GKN. Impact of physical exercise in cardiovascular and metabolic parameters in post-menopausal women. Brazilian J Developm. 2021; 7(3): 24590–24605.

Skrzypulec V, Dabrowska J, Drosdzol A. The influence of physical activity level on climacteric symptoms in menopausal women. Climacteric. 2010;13(4):355–61.

Soares JM Jr, Branco-de-Luca AC, da Fonseca AM, Carvalho-Lopes CM, Arruda-Veiga EC, Roa CL, Bagnoli VR, Baracat EC. Acupuncture ameliorated vasomotor symptoms during menopausal transition: single-blind, placebo-controlled, randomized trial to test treatment efficacy. Menopause. 2020;28(1):80–5.

Sternfeld B, Dugan S. Physical activity and health during the menopausal transition. Obstet Gynecol Clin North Am. 2011;38(3):537–66.

Sternfeld B, Guthrie KA, Ensrud KE, LaCroix AZ, Larson JC, Dunn AL, Anderson GL, Seguin RA, Carpenter JS, Newton KM, Reed SD, Freeman EW, Cohen LS, Joffe H, Roberts M, Caan BJ. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. Menopause. 2014;21(4):330–8.

Stojanovska L, Apostolopoulos V, Polman R, Borkoles E. To exercise, or, not to exercise, during menopause and beyond. Maturitas. 2014;77(4):318–23.

Sun Q, Qi M, Moyle W, Jones C, Weeks B, Xie Z, Li P. Physical activity participation and psychological wellbeing in university office workers in China and Australia: an online survey. Healthcare (Basel). 2021; 9(12).

Talaulikar V. Menopause transition: physiology and symptoms. Best Pract Res Clin Obstet Gynaecol. 2022;81:3–7.

Tartibian B, FitzGerald LZ, Azadpour N, Maleki BH. A randomized controlled study examining the effect of exercise on inflammatory cytokine levels in post-menopausal women. Post Reprod Health. 2015;21(1):9–15.

Taylor RM, Curtin D, Hendrikse JJ, Cadwallader CJ, Stout JC, Chong TTJ, Coxon JP. Exercise in Parkinson's disease. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan 2022; 30:403–412.

Teixeira GR, Veras ASC, Rocha APR, Chedid SS, Freitas Junior IF, Neto RAF, Gobbo LA, Buonani C. Dance practice modifies functional fitness, lipid profile, and self-image in postmenopausal women. Menopause; 2021.

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

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

Tipton CM. The history of "Exercise Is Medicine" in ancient civilizations. Adv Physiol Educ. 2014;38(2):109–17.

Tworoger SS, Yasui Y, Vitiello MV, Schwartz RS, Ulrich CM, Aiello EJ, Irwin ML, Bowen D, Potter JD, McTiernan A. Effects of a yearlong moderate-intensity exercise and a stretching intervention on sleep quality in postmenopausal women. Sleep. 2003;26(7):830–6.

Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. Menopause. 2013;20(10):1098–105.

van Poppel MN, Brown WJ. "It's my hormones, doctor"–does physical activity help with menopausal symptoms? Menopause. 2008;15(1):78–85.

Villaverde Gutierrez C, Torres Luque G, Abalos Medina GM, Argente del Castillo MJ, Guisado IM, Guisado Barrilao R, Ramirez Rodrigo J. Influence of exercise on mood in postmenopausal women. J Clin Nurs. 2012;21(7–8):923–8.

Villaverde-Gutierrez C, Araujo E, Cruz F, Roa JM, Barbosa W, Ruiz-Villaverde G. Quality of life of rural menopausal women in response to a customized exercise programme. J Adv Nurs. 2006;54(1):11–9.

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ. 2020;371: m3873.

Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipids Health Dis. 2017;16(1):132.

Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006a;174(6):801–9.

Warburton DE, Nicol CW, Bredin SS. Prescribing exercise as preventive therapy. CMAJ. 2006b;174(7):961–74.

Whitcomb BW, Whiteman MK, Langenberg P, Flaws JA, Romani WA. Physical activity and risk of hot flashes among women in midlife. J Womens Health (larchmt). 2007;16(1):124–33.

Wilbur J, Miller AM, McDevitt J, Wang E, Miller J. Menopausal status, moderate-intensity walking, and symptoms in midlife women. Res Theory Nurs Pract. 2005;19(2):163–80.

Wright B, Lawton A, Wong D. Exercise in the management of neuropathic pain. In: Feehan J, Tripodi N, Apostolopoulos V, editors. Exercise to prevent and manage chronic disease across the lifespan. Elsevier Inc.; 2022. p. 221–32.

Yu DJ, Yu AP, Leung CK, Chin EC, Fong DY, Cheng CP, Yau SY, Siu PM. Comparison of moderate and vigorous walking exercise on reducing depression in middle-aged and older adults: a pilot randomized controlled trial. Eur J Sport Sci. 2022; 1–23.

Chapter 17
The Transgender Woman and Sport Performance

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Introduction

The Tokyo 2020 Olympic games were the first time in which openly transgender women athletes competed. Specifically, the athletes, Laurel Hubbard, a New Zealand weightlifter, Quinn, a Canadian women's soccer player, and Chelsea Wolfe, an US bicycle motocross (BMX) alternate.

In 2003, the International Olympic Committee (IOC) published the "Stockholm Consensus", a policy statement for transgender participation in the Olympic games. This document allowed participation of transgender athletes only if:

1. Gender-affirming surgery has been completed, including external genitalia changes and gonadectomy.
2. Legal recognition of the assigned sex has been conferred by the appropriate official authorities.
3. Gender-affirming hormonal therapy (GAHT) appropriate for the assigned sex has been administered in a verifiable manner and for two years after gonadectomy.

In the twenty years since, the IOC has changed its policy twice (as discussed below), many international and national sports organizations have published their own rules on transgender athletes, and the debate on the issue continues. The elements

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of the debate are, on the one hand, the desire for inclusion and giving every person the opportunity to compete according to his gender identity, and on the other hand the "fair play" principle which gives equal chances without giving advantage to some participants.

Background—Transgender Individuals

Transgender individuals are people whose gender identity differs from the sex they were assigned at birth. Reports suggest that 0.3 to 0.6% of the adult population consider themselves transgender (Conron et al. 2012; Reisner et al. 2014). One study estimated that there are approximately 25 million transgender people worldwide (Winter et al. 2016) and approximately half of them are transgender women.

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) has coined the term Gender Dysphoria to describe the mental distress experienced by many transgender subjects from the incongruence between their expressed gender and their assigned at birth sex, de facto removing this condition from the list of mental disorders. (Campo-Arias and Herazo 2018; Hembree et al. 2017).

Most transgender individuals come out in adulthood or late adolescence. Some seek treatments such as GAHT, gender-affirming surgery, or psychotherapy. Not all transgender people desire these treatments, and some cannot undergo them for financial, medical, social, or political reasons.

The World Professional Association for Transgender Health (WPATH) criteria for starting GAHT include persistent, well-documented gender dysphoria/gender incongruence, the capacity to make a well-informed decision, and the knowledge that relevant medical or mental health issues are well controlled (The World Professional Association for Transgender Health 2012).

Criteria for initiating gender-affirming surgery are the same as mentioned for GAHT, in addition to at least a year of continuous GAHT while living in the desired gender role, unless it was determined the GAHT is not medically indicated. This criterion is not a prerequisite for surgeries such as chest reconstruction or other non-genital surgeries (The World Professional Association for Transgender Health 2012).

Gender-Affirming Hormonal Therapy of Transgender Women

Generally speaking, GAHT aims to induce physical changes to match gender identity. The treatment goal is to maintain hormone levels in the normal physiological range for the target gender (Hembree et al. 2017; "Standard of Care—WPATH World Professional Association for Transgender Health" n.d.).

Specifically, in the case of transgender women, the goal of treatment is to reduce male characteristics, while enabling the appearance of female secondary sex characteristics. To this end, exogenous estrogen helps to suppress endogenous testosterone secretion while creating the desired hormonal milieu. However, to achieve adequate testosterone suppression, higher doses of estrogen are usually required, which may expose the woman to a higher risk of venous thromboembolic events (VTEs). Thus, the more common medical approach employs the combination of a moderate dose of estrogen together with an anti-androgen pharmaceutical agent.

There is a wide range of estrogens available; however, 17-beta-estradiol is the most prescribed. Estradiol can be given orally, usually in 2–4 mg/day doses, or transdermally via patches that deliver 50–200 mcg/24 h, applied once or twice a week, or in the form of an estradiol gel applied daily. While ethinyl estradiol was commonly used in the early days of GAHT, VTE, the most important risk associated with estrogen therapy, has mostly been associated with the use of this compound, thus current guidelines recommend against its use (Hembree et al. 2017).

The transdermal use has been associated with a lower risk of VTEs and stroke in postmenopausal women on hormone replacement therapy (HRT). By analogy, the transdermal route is the preferred method of administration in older transgender women or in women at higher risk of VTE such as smokers. Parenteral estrogens (estradiol valerate or cypionate) are sometimes used if target serum estradiol (E2) levels cannot be achieved with oral or transdermal preparations.

Conjugated estrogen levels are not detected by commercial E2 assays, and therefore, estradiol preparations may be preferred for better monitoring.

To achieve suppression of testosterone secretion and block its action, several pharmaceutical agents are available:

1. Spironolactone, a mineralocorticoid receptor antagonist, is also a competitive inhibitor of the androgen receptor as well as an inhibitor of testicular steroidogenesis. The recommended dose of spironolactone is 100–300 mg/day.
2. Cyproterone acetate (CPA)—A potent androgen receptor antagonist is not approved for use in the USA. However, it is the most widely used agent outside the USA. The doses range from 25 to 100 mg/day; however, we have recently shown that a lower dose of 10 mg daily is as effective, and possibly safer (Even Zohar et al. 2021) *N.B.*, both spironolactone in the USA, and CPA in Europe, are popular as first-line therapies given their effectiveness and low cost.
3. Long-acting Gonadotropin-releasing hormone (GnRH) agonists, used parenterally, inhibit gonadotropin secretion and, as a result, suppress testicular testosterone production with few adverse events. However, their cost along with the more difficult administration makes them a second-tier therapy in most centers.

The monitoring schedule recommended by the Endocrine Society is every three months in the first year to tailor the doses to the subject's (patient's) individual need, and then once to twice yearly thereafter (The World Professional Association for Transgender Health 2012; Winter et al. 2016).

The recommended serum E2 concentration should not exceed 200 pg/mL (734 pmol/L), and the serum testosterone levels should be lowered to the normal

physiologic female range. Serum potassium should be monitored under spironolactone, while prolactin and triglycerides levels should be monitored in all subjects, as they may rise significantly under treatment.

The main clinical changes achieved by GAHT include decreased rates of growth of facial and body hair, reduced oiliness of the skin, redistribution of fat mass (subcutaneous fat tissue expands, while there is a decrease in lean body mass), and body weight usually increases (Lapauw et al. 2008). As a result of estrogen exposure, the development of breast tissue takes place, while the decreasing concentrations of testosterone usually result in lower sexual desire and erectile function.

In transgender women treated after completion of puberty, prior effects of testosterone on the skeleton, such as the size and shape of hands, feet, jaws, and pelvis, as well as on the anatomy of the larynx (including voice pitch and laryngeal prominence) cannot be reversed (The World Professional Association for Transgender Health 2012).

Transgender Women Affirming Surgery

Currently, the surgical procedures for gender affirmation in transgender women include the following:

1. Facial feminization surgeries to create more feminine features.
2. Breast augmentation.
3. Genital reconstruction surgery includes a bilateral orchiectomy performed to remove the main source of endogenous testosterone (gonadectomy).

In addition to gonadectomy, other procedures can include penectomy and vaginoplasty (typically with surgical construction of a vagina, clitoris, and labia, usually using the penile skin for vaginal lining and scrotal skin for the labia (Hembree et al. 2017).

Athletic Performance in the Transgender Athlete

Data on athletic performance in transgender athletes are very limited. While there are no limitations on transgender men's competition, the controversy about transgender women's participation in the female sport is still ongoing and hotly debated. The performance gap between males and females amounts to 10–50% depending extensively on the sport (Hilton and Lundberg 2021), and is more pronounced in sports that rely on muscle mass and explosive strength, particularly in the upper body (Hilton and Lundberg 2021).

Those who object to transgender women competing in women's (female) sports categories argue that some advantages of androgen exposure since birth cannot be erased through GAHT. This includes skeletal physical characteristics such as height,

limb length, hand span, and the cardiovascular (heart size) and respiratory systems (lung size) that remain unchanged during, and after GAHT, and give a performance advantage over cisgender women (Knox et al. 2019).

Limited research suggests that other important features, such as muscle size and strength, are affected by GAHT; however, the initial advantage is greater than the observed average reduction even after years of GAHT (Harper et al. 2021; Hilton and Lundbe 2021). Hemoglobin and hematocrit do decrease to the female range in approximately four months of GAHT in parallel to the decrease seen in testosterone (Harper et al. 2021).

Gaps of Knowledge on Sports Performance in Transgender Women

After reviewing the limited available literature, we wish to highlight several points that were encountered, and which merit much further consideration when trying to effectively answer questions on transgender women's participation in female sports:

1. Different sports require different sets of skills, i.e., aerobic capacity, strength, speed, and recovery. Thus, in some sports, the advantages of testosterone are more prominent, while in others, such as equestrian disciplines, they are negligible so that competitions are not gender-segregated. On the same note, advantages are more pronounced in individual competitions compared to team sports (Knox et al. 2019).
2. Legal gender reassignment is still banned in parts of the world, and even when allowed, not all athletes are willing to be exposed. For example, in the study by Harper et al., some data were collected anonymously through questionnaires and not through direct measurements, creating a dilemma between the need to verify data and the need to protect privacy (Harper 2015).
3. Most data available rely on surrogate parameters for athletic performance. For example, no studies were found that directly measure maximal oxygen uptake (VO_{2max}) change for endurance athletes. Only two studies report running times, either measured (Roberts et al. 2020) or self-reported (Harper 2015). Similarly, there are no direct measurements of maximal power, and studies report substitute parameters such as body composition, muscle area, and handgrip (Harper et al. 2021; (Hilton and Lundberg 2021). While handgrip serves as a good proxy for general strength, different sports require assessments of different muscle groups.
4. There are a limited number of studies comparing the same individual before and after GAHT. In these studies, it is difficult to correct for age as a possible confounder for declining performance. Harper used an age-graded formula to correct for age (Harper 2015).
5. Most data from longitudinal studies demonstrate differences after a year of treatment. Some data exist up to three years of GAHT. Furthermore, very limited

data are available for longer treatment periods (Harper et al. 2021; Hilton and Lundberg 2021).

6. Some studies that compared transgender women to cisgender men indicate inherent differences between the two populations even before GAHT, indicating that transgender women tend to exercise less, to begin with (perhaps to maintain a more feminine physique) (Van Caenegem et al. 2015; Lapauw et al. 2008).
7. Hilton et al. point out that athletic differences are evident even in prepubertal children and could be mediated by genetic factors and/or the hypothalamic–pituitary–gonadal axis during the neonatal period termed "*mini-puberty*" (Hilton and Lundberg 2021). Data from several studies demonstrate that boys typically can run faster, throw harder, and throw farther compared to girls (similar age) (Catley and Tomkinson 2013; Tambalis et al. 2016). It should also be pointed out that the reason for these differences could stem from the cultural or sociological differences between boys and girls in societies. However, it is possible that transgender women that started GAHT before or during puberty will have certain physiological aspects (such as muscle mass) that are different from transgender women who transition after the end of puberty. Currently, most data available are for the latter group, and more research is needed.
8. There is considerable variability in drug regimens used (type of estrogen and antiandrogen agents) for GAHT and testosterone levels achieved during treatment. Not all studies report testosterone levels (Harper et al. 2021).
9. We could not find scientific information on other factors related to testosterone and performance such as aggressiveness, coordination, mood, and many other factors contributing to overall performance in a sports-physical activity.

Athletic Performance in Transgender Women

Athletic Performance in Untrained Transgender Women

As mentioned previously, the most current available data are from untrained transgender women populations. A systematic review published in 2021 by Harper et al. (Harper et al. 2021) and a second review published the same year by Hilton et al. (Hilton and Lundberg 2021) examined changes in body composition, muscle strength, and hemoglobin levels in non-athletic transgender women. Overall, they conclude that transgender women experience a decline in the parameters examined; however, for the most part, they still retain physical advantages over cisgender women.

Muscle Cross-Sectional Area (CSA)

The seminal work by Gooren et al. (Gooren and Bunck 2004) measured thigh muscle area by magnetic resonance imaging (MRI) in 19 transgender women. They demonstrated a 12% reduction in muscle area after 36 months of GAHT, and when compared to the muscle area in transgender men, muscle area was 13% larger in transgender women suggesting that testosterone suppression does not reverse muscle size to that of females. Since then, several studies assessed muscle areas using MRI or peripheral quantitative computed tomography (pQCT).

Wilk et al. assessed thigh muscle volume in 11 transgender women after 12 months of GAHT and demonstrated a modest decrease of approximately 5% (Wiik et al. 2020). In the Harper et al. systematic review, CSA was decreased after 12 months of GAHT (Harper et al. 2021). Overall, in follow-up studies, the decrease in CSA ranged from 1.5 to 11.7% over a 24 to 36-month period. None exceeded the 12% decrease demonstrated by the study of Gooren and associates (Gooren and Bunck 2004). In two studies comparing transgender women to cisgender men, Van Caenegen and associates (Van Caenegem et al. 2015) showed a 9% lower forearm and calf CSA using pQCT in 49 hormone-naïve transgender women and a further 4% decrease after 24 months of GAHT. Likewise, Lapauw and colleagues (Lapauw et al. 2008) further demonstrated a 24% decrease in CSA after 24 months of GAHT.

Lean Body Mass (LBM) and Fat Mass

In the systematic review by Harper et al., follow-up studies examining lean body mass (LBM) before and after GAHT found that LBM decreased an average of 3–5.4% after a year of GAHT (*N.B.,* in most studies LBM, was determined using dual-energy X-ray absorptiometry [DXA]) (Harper et al. 2021). In a cross-sectional study by Van Caenegem (Van Caenegem et al. 2015), that compared hormone-naïve transgender women (before GAHT) to cisgender men, it was found that LBM was 4% lower, to begin with, and a further 4% reduction in LBM was demonstrated after 12 months of GAHT (Van Caenegem et al. 2015). Fat mass increased in parallel by 25%. Lapauw, and associates reported (Lapauw et al. 2008) 20% lower LBM in transgender women following two years of GAHT compared to comparable cisgender men. All the studies in the Harper et al. review reported an increase in total body fat mass (Harper et al. 2021).

In addition, the review by Hilton and Lundberg similarly states that several longitudinal studies demonstrate a 5% decrease in LBM after 12 months of GAHT, with a slightly greater reduction in the arm compared to the leg region. They conclude that given the large initial advantage men have with a 40% larger muscle mass, a 5% reduction by 12 months and three years is not enough to bring transgender women to the level of cisgender women (Hilton and Lundberg 2021).

Strength Measurements

In the studies we examined, muscular strength was mostly evaluated through handgrip dynamometry measurements. In the review by Harper and associates (Harper et al. 2021), most studies looking at strength measurements before and after GAHT found a significant reduction of 4.3–7.1% after a year of GAHT. When comparing strength measurements in transgender women to cisgender men, two cross-sectional studies, Van Caenegem, and associates found 14% lower handgrip strength in hormone-naïve transgender women and a further 7% reduction after a year of GAHT (Van Caenegem et al. 2015). While Lapauw and associates found a 22–25% reduction in handgrip and quadriceps strength using knee extension after two years of GAHT (Lapauw et al. 2008).

Summary

Taken together, current evidence supports that muscle area, LBM, and strength in transgender women remain above those of cisgender women even after 36 months of GAHT. This suggests that transgender women retain a muscular performance advantage over cisgender women. However, whether longer duration GAHT would yield further decrements is unknown. Since no data exist on trained transgender women (*N.B.,* it is possible that the above-mentioned differences would be even smaller in exercise-trained individuals).

Of note, considerable variability exists in drug regimens and testosterone levels achieved. Although Harper et al. found (Harper et al. 2021) that in most studies, testosterone levels were within the reference range for cisgender women, in five studies levels were above 5 nmol/L and of them, and four were in adolescents.

Athletic Performance in Trained Transgender Women

We found only two studies that have examined athletic performance in trained transgender women and none on professional or elite athletes. In a study published by Harper, self-reported race times from eight transgender women track distance runners were collected over seven years (Harper 2015). The collection process consisted of seeking out female transgender distance runners, mostly online, and then asking them to voluntarily submit race times. None were elite runners. Running distances ranged from 5 K to a full marathon. Most runners were over the age of 30 years. For six of the eight runners, race times could be verified; however, two runners remained anonymous. Some athletes reported a stable training pattern, whereas others suffered injuries and changes in body weight which influenced their training volume. Seven reported a substantial reduction in running speed upon transition. The study also used an age grading formula to compare the performance of older track and field athletes.

Harper found that as the female performance was corrected for age, their running performance was almost identical to their male age-graded performance.

In an interesting study, Roberts and associates reported on the physical performance of 46 transgender women that started GAHT while in the US Air Force (Roberts et al. 2020). They reviewed fitness test results and medical records for the number of push-ups, the number of sit-ups done in a minute, and a 1.5-mile run time documented before and two years into GAHT. Their age prior to GAHT was 26 ± 5.5 years (mean $\pm$ SD). Age at initiation of GAHT had no significant effect on outcome, but all subjects started after puberty. After GAHT, average body weight and waist circumference were not significantly changed. Prior to GAHT (i.e., as males), transgender women did 31% more push-ups, 15% more sit-ups in a minute, and ran 1.5 miles 21% faster compared to cisgender women. After two years of GAHT, the push-up and sit-up differences disappeared, but transgender women were still 12% faster. The authors conclude that among transgender women, a competitive advantage from prior testosterone level exposure (i.e., before GAHT) continues to exert an influence beyond 12 months, a standard currently proposed by most international federations for inclusion in women's elite competition. However, the authors acknowledged there were several limitations to their study: (1) Repeated maximal efforts as opposed to a single maximal effort capture endurance and strength and are more relevant to sports with sustained effort; (2) transgender women weighed more than cisgender women and thus had higher power output which might underestimate the advantages of strength in transgender women compared to cisgender women; (3) hormone levels were not presented, only the time to the first therapeutic level; (4) findings cannot be applied to sports requiring explosive strength such as weightlifting; and, (5) training habits were unknown and could have influenced results.

The Current Stands of Sport Organizations

The IOC stated in 2015 that transgender men are allowed to compete in the male category without restrictions. Transgender women, however, must declare a gender identity as female (a declaration that cannot be changed, for sporting purposes, for a minimum of four years prior) and have total levels below 10 nmol/L for at least 12 months prior to competition. In contrast to this statement and the accumulating scientific evidence, the IOC published in November 2021 a new framework on fairness, inclusion, and non-discrimination based on gender identity and sex variation (Pigozzi et al. 2022). This framework was drafted mainly from a human rights perspective, i.e., inclusion, rather than looking at the biological, medical, and scientific issues which show that transgender women maintain significant advantages from undergoing male puberty even when they subsequently lower their testosterone level. According to this latest IOC framework, there is no need for transgender women to lower their testosterone to compete against cisgender women, a statement that applies also to athletes with disorders of sexual development (DSD), such as the South African 800 m runner Caster Semenya. Essentially, the agenda of the IOC was

to leave the responsibility of dealing with this delicate and controversial issue to the International Sports Federations (ISF) on an individual basis rather than establishing their own criteria/stance.

In response, the International Federation of Sports Medicine (FIMS) and the European Federation of Sports Medicine (EFSMA) published a joint position statement emphasizing the need for a discussion and revision of the IOC framework according to their point of view, while they strongly support the right of each athlete to make their own choice based on "their own needs and situation", they should seek to ensure that "*all athletes remain entitled to fair competition consistent with the World Anti-Doping Agency (WADA) code*" that protects an athlete's fundamental right to participate in a sport where fellow athletes have not been modified to their advantage by doping or other means". They believe that the IOC, as a multisport international organization, should take the responsibility to set standards and expectations based on competitive fairness and the best available science that all International Sports Federations (ISF) can follow, and fund research to support more evidence-based scientific solutions that are consistent with human rights and fairness.

Due to the change of the IOC policy from 2015 to 2021 and new scientific data, many ISF and national sports organizations created their eligibility criteria for transgender women to compete in the female category, and published position stands and recommendations. A sample of eligibility criteria for participation of transgender athletes in the women's category is given in Table 17.1.

At a working meeting organized by World Athletics in Lausanne in October 2019, with the participation of several ISF, experts, and representatives of transgender and cisgender athletes, it was agreed that if a federation decides to use testosterone as an indicator, transgender women athletes will only be eligible to compete in the women category if their blood total level is below 5 nmol/L. However, this level was not accepted by all ISF. For instance, the International Powerlifting Federation (IPF) uses total levels equal to or below 2.4 nmol/L and/or free testosterone equal to or below 0.433 nmol/L (alternatively, at or below the upper limit of normal of a particular laboratory reference) as a cutoff (see Table 17.1). There are many other differences between ISF regarding eligibility criteria, where some federations have a panel of experts that approve the eligibility criteria, others require that the therapy is given by certain professionals, or the need for a specific testosterone testing method, etc.

While many ISF allows transgender women to compete under several conditions, there are some ISF that totally ban the participation of transgender women in the women category such as World Rugby (Table 17.1) which as of October 2020 does not allow participation of transgender women in elite and international women's rugby.

Interestingly, the International Federation of Water Sports–Federation Internationale De Natation (FINA) has not published any position statement until recently, although, one of the most famous transgender woman athletes is Lia Thomas, who is the first transgender athlete to win NCAA Division I (USA) national swimming championship. The controversy over her case raised numerous opinions, reports, podcasts, and articles, and in February 2022 USA Swimming released its "*Athlete*

Table 17.1 Olympic International Federations policies on integrating transgender women into the female category

International Federation/Year/Link	Rule	Comments
World Athletics (previously called International Association of Athletics Federations [IAAF]) 2019	Serum total < 5 nmol/L continuously for at least 12 months prior to participation and as long as she competes in the female category	
International Tennis Federation 2018	Same as above (Re-test level) + provide a written and signed declaration that her gender identity is female	
Union Cycliste Internationale (UCI) 2020	Same as above (Re-test level) + serum total tests conducted using a benchmark method (mass spectrometry)	Approved and monitored by a commission of experts + UCI's medical manager All NF must include these directives in their regulations
World Rugby 2020	TW who transitioned post-puberty and has experienced the biological effects of testosterone during puberty and adolescence cannot currently play women's rugby	TW who transitioned prepuberty and not experienced the biological effects of testosterone during puberty and adolescence can play women's rugby (subject to confirmation of medical treatment and the timing thereof)
World Rowing 2020	Same as above (Re-test level) + The gender of the rower is female in the rower's passport or national identity card	Approved and monitored by Executive Committee of the World Rowing Gender Advisory Panel
International Powerlifting Federation (IPF) 2022	Serum total ≤ 2.4 nmol/L and/or free test. ≤ 0.433 nmol/L (or at or below the upper limit of normal of a particular laboratory reference) for at least 12 months to participation and as long as she competes in the female category + Declaration of gender identity as female and a valid passport bearing a female gender	Monitored by IPF Medical Commission (MC) Declarations cannot be changed, for competition purposes, for a minimum of four years

(continued)

Table 17.1 (continued)

International Federation/Year/Link	Rule	Comments
Federation Internationale De Natation (FINA)	TW athletes are not eligible to participate in elite women's competitions unless "they can establish to FINA's comfortable satisfaction that they have not experienced any part of male puberty beyond Tanner Stage 2 (of puberty) or before age 12, whichever is later"	FINA is going to create a working group to establish an "open" category for TW in some events as part of a new policy
The Association of Boxing Commissions (ABC) 2012	2 years of documented test. suppression therapy	Hormone suppression therapy must be administered by specific doctors

TW transgender women; *NF* national federation; *Test* testosterone

Inclusion, Competitive Equity and Eligibility Policy" (https://www.usaswimming.org/inclusion). The policy requires a panel of three independent medical experts to approve the participation of transgender women swimmers in women's events based on two eligibility criteria:

1. Evidence that the prior physical development of the athlete as a male, as mitigated by any medical intervention, does not give the athlete a competitive advantage over the athlete's ciswomen competitors.
2. Evidence that the blood concentration of total in the athlete has been less than 5 nmol/L (as measured by liquid chromatography/mass spectrometry [LCMS]) continuously for a period of at least 36 months before the date of application.

The FINA decision, as of June 19, 2022, was to restrict the participation of transwomen in elite women's competitions and create a working group to establish an "open" category for them in some events as part of a new policy. The new eligibility policy for FINA competitions states that transwomen athletes are eligible to compete only if "*they can establish to FINA's comfortable satisfaction that they have not experienced any part of male puberty beyond Tanner Stage 2 (of puberty) or before age 12, whichever is later*" (https://resources.fina.org/fina/document/2022/06/19/525de003-51f4-47d3-8d5a-716dac5f77c7/FINA-INCLUSION-POLICY-AND-APPENDICES-FINAL-.pdf).

It should be noted that Table 17.1 includes only Olympic sports. There are many other ISF of non-Olympic sports that have their policy regarding including transgender women in women's sports such as CrossFit that as of 2019 allows transgender women to compete in the annual CrossFit Games, reversing their policy from 2018 that allowed athletes to compete only in the category of their sex assigned at birth, a decision that was criticized.

Many national sports federations (NSF) adhere to ISF policies if they exist. However, there are many such sports organizations that do not have guidelines (the

reader is directed to see for commentary—https://www.transathlete.com/policies-by-organization).

Possible Solutions Proposed for Sports

Possible solutions that have previously been suggested (Bianchi 2019) argue for eliminating sex segregation and categorizing athletes based on sport-specific factors rather than gender since genetic advantages already exist in sports making a fair and equal starting point impossible to achieve. Extending this notion Knox and associates suggested an extended algorithm with an analogy to the divisions in the Paralympic sport with the creation of multiple divisions rather than simply male and female categories (Knox et al. 2019). Such an algorithm would be tailored to specific sports. The current state of affairs is such that many potential options may be proposed, but a universal "one-size fits all" answer to every sports activity may not exist.

Summary and Conclusions

In this unprecedented time, when openly transgender people are present and influential at all levels of society, the fair involvement of transgender women in gender-segregated competitive sports remains one of the thorniest and most unresolved issues. Clearly, no one envisions that transgender women athletes will ever overwhelm the female competitive stage; thus, the whole topic could be considered a mere theoretical exercise. However, a case like that of Lia Thomas helps to rekindle the quandary between the right of transgender people not to be victims of discrimination and fairness in competitive sports.

The zigzag and stammering of the various sports organizations over the matter in the last decade is eloquent proof that this issue is far from being resolved. There are obviously several sports in which superior explosive strength is not as crucial such as equestrian sports, shooting, and archery. However, in the authors' opinion, beyond testosterone thresholds, much scientific work is urgently needed to define criteria (such as muscle mass and composition parameters, and tissue oxygenation capacity) that will allow to select transgender women who may compete alongside cisgender women in sports where muscle mass and strength are of paramount importance, without enjoying an inadmissible advantage. Until better scientific evidence emerges, and until such criteria are clearly defined for each relevant sports category, in the interest of competitive fairness and safety, participation of transgender women in the women's category should be reconsidered, regardless of testosterone levels.

References

Bianchi A. Something's got to give: reconsidering the justification for a gender divide in sport. Philosophies. 2019;4(2):23. https://doi.org/10.3390/philosophies4020023.

Campo-Arias A, Herazo E. Innovations, reviews and proposals on the dsm-5: the case of sexual dysfunctions, gender dysphoria and paraphilic disorders. Revista Colombiana De Psiquiatria (english Ed). 2018;47(1):56–64. https://doi.org/10.1016/j.rcp.2016.08.008.

Catley MJ, Tomkinson GR. Normative health-related fitness values for children: analysis of 85347 test results on 9–17-year-old Australians since 1985. Br J Sports Med. 2013;47(2):98–108. https://doi.org/10.1136/bjsports-2011-090218.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. Am J Public Health. 2012;102(1):118–22. https://doi.org/10.2105/AJPH.2011.300315.

Even Zohar N, Sofer Y, Yaish I, Serebro M, Tordjman K, Greenman Y. Low-dose cyproterone acetate treatment for transgender women. J Sex Med. 2021;18(7):1292–8. https://doi.org/10.1016/j.jsxm.2021.04.008.

Gooren LJG, Bunck MCM. Transsexuals and competitive sports. Eur J Endocrinol. 2004;151(4):425–9. https://doi.org/10.1530/eje.0.1510425.

Harper J, O'Donnell E, Sorouri Khorashad B, McDermott H, Witcomb GL. How does hormone transition in transgender women change body composition, muscle strength and haemoglobin? Systematic review with a focus on the implications for sport participation. Br J Sports Med. 2021;55(15):865–72. https://doi.org/10.1136/bjsports-2020-103106.

Harper J. Race times for transgender athletes. J of Sporting Cultures Identities. 2015;6(1):1–9. https://doi.org/10.18848/2381-6678/CGP/v06i01/54079.

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, … T'Sjoen GG. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(11):3869–3903. https://doi.org/10.1210/jc.2017-01658

Hilton EN, Lundberg TR. Transgender women in the female category of sport: perspectives on testosterone suppression and performance advantage. Sports Med. 2021;51(2):199–214. Auckland, N.Z. https://doi.org/10.1007/s40279-020-01389-3

Knox T, Anderson LC, Heather A. Transwomen in elite sport: scientific and ethical considerations. J Med Ethics. 2019;45(6):395–403. https://doi.org/10.1136/medethics-2018-105208.

Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, … T'Sjoen GG. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone. 2008;43(6):1016–21. https://doi.org/10.1016/j.bone.2008.09.001

Pigozzi F, Bigard X, Steinacker J, Wolfarth B, Badtieva V, Schneider C, … Pitsiladis YP. Joint position statement of the International Federation of Sports Medicine (FIMS) and European Federation of Sports Medicine Associations (EFSMA) on the IOC framework on fairness, inclusion and non-discrimination based on gender identity and sex variations. BMJ Open Sport Exerc Med. 2022;8(1):e001273. https://doi.org/10.1136/bmjsem-2021-001273

Reisner SL, Conron KJ, Tardiff LA, Jarvi S, Gordon AR, Austin SB. Monitoring the health of transgender and other gender minority populations: validity of natal sex and gender identity survey items in a U.S. national cohort of young adults. BMC Public Health. 2014;14:1224. https://doi.org/10.1186/1471-2458-14-1224

Roberts TA, Smalley J, Ahrendt D. Effect of gender affirming hormones on athletic performance in transwomen and transmen: implications for sporting organisations and legislators. Br J Sports Med. 2020. https://doi.org/10.1136/bjsports-2020-102329.

Standards of Care—WPATH World Professional Association for Transgender Health. (n.d.). Retrieved 30 May 2022, from https://www.wpath.org/publications/soc

Tambalis KD, Panagiotakos DB, Psarra G, Daskalakis S, Kavouras SA, Geladas N, … Sidossis LS. Physical fitness normative values for 6-18-year-old Greek boys and girls, using the empirical

distribution and the lambda, mu, and sigma statistical method. Eur J Sport Sci. 2016;16(6):736–46. https://doi.org/10.1080/17461391.2015.1088577

The World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender-nonconforming people. 2012

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, … T'Sjoen G. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. Osteoporos Int. 2015;26(1):35–47. https://doi.org/10.1007/s00198-014-2805-3

Wiik A, Lundberg TR, Rullman E, Andersson DP, Holmberg M, Mandić M, … Gustafsson T. Muscle strength, size, and composition following 12 months of gender-affirming treatment in transgender individuals. J Clin Endocrinol Metab. 2020;105(3). https://doi.org/10.1210/clinem/dgz247

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. The Lancet. 2016;388(10042):390–400. https://doi.org/10.1016/S0140-6736(16)00683-8.

Chapter 18
Stress Reactivity and Exercise in Women

Tinna Traustadóttir

Introduction

Stress reactivity can be defined as any physiological response to a perturbation to homeostasis and generally includes both the response and recovery to a stressor. More broadly, in addition to the physiological response, it can include behavioral, subjective, and cognitive responses to stress (Schlotz 2013). It is important to note that a robust response can be more beneficial than a lower response, as long as recovery is optimized after the removal of the stressor and not prolonged. In the context of this chapter, the literature on stress reactivity will be limited to cardiovascular and neuroendocrine responses to acute mental or physical challenges. Cardiovascular responses include heart rate and blood pressure responses to a stimulus and are driven by activation of the sympathetic nervous system. The neuroendocrine response is most often represented by measures of cortisol (salivary or plasma) as an indicator of hypothalamic–pituitary–adrenal (HPA) axis activity.

Stress Reactivity and Health

Assessing stress reactivity can have implications for future disease risk. One example is heart rate recovery in the first minute after a maximal graded exercise test; individuals who recover less than 12 bpm in the first minute of recovery have a fourfold increase in mortality compared to individuals who recover faster, regardless of the maximal heart rate response during the test (Gupta 2005; Cole et al. 1999). Similarly, exaggerated blood pressure response and poorer recovery after a laboratory stressor are associated with a greater risk for future hypertension (Trivedi et al. 2008; Stewart

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et al. 2006; Carroll et al. 2012). A greater cortisol response to a psychosocial or mental laboratory challenge is associated with a risk for coronary heart disease, hypertension, and future risk of depression (Morris et al. 2012; Hamer et al. 2012; Steptoe et al. 2016); however, a blunted response is also associated with worse health outcomes (Carroll et al. 2017; de Rooij 2013). There are important differences between the effects of acute and chronic stress on the organism, and these effects are also mediated by the stress reactivity of an individual. Evolutionary speaking, the activation of the HPA axis in response to acute stress can be considered beneficial since it helps the individual survive a challenge by mobilizing fuel for energy, inhibiting reproductive behavior, and increasing arousal and vigilance. However, when the system is chronically challenged, either continuously or too frequently to allow for recovery and adaptation, the stress response becomes maladaptive and leads to an increased risk for diseases such as cardiovascular disease, diabetes, hypertension, osteoporosis, and cognitive dysfunction (McEwen 1998, 2007; Lazzarino et al. 2013; Nagaraja et al. 2016; Feeney et al. 2020; Nafisa et al. 2021).

Methods for Testing Stress Reactivity

There are several established protocols for evaluating stress reactivity under standard laboratory conditions. By far the most commonly used one is the *Trier Social Stress Test* (TSST), a psychosocial laboratory challenge established by investigators at the University of Trier (Kirschbaum et al. 1993). The test has a few variations but typically consists of an anticipatory period, a 5-min free speech, and a 5-min mental arithmetic task of serial subtraction, performed in front of a panel of evaluators (sometimes videotaping is added as well) (Birkett 2011). For additional information on the TSST, the reader is referred to some excellent previously published reviews (e.g., Dickerson and Kemeny 2004; Allen et al. 2014; Foley and Kirschbaum 2010). *The Iowa Singing Stress Test* (I-SST) is a test similar to the TSST but with the added task of public singing (Reschke-Hernandez et al. 2017).

The *Montreal Imaging Stress Task* (MIST) is a challenge that is specifically used in conjunction with imaging such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) and uses a series of computerized arithmetic challenges along with social evaluative threat components presented within the program or by an investigator (Dedovic et al. 2005). A recent study investigated the possibility of using the MIST in a longitudinal design (repeated testing) and found some habituation effects on heart rate and salivary cortisol response (De Calheiros Velozo et al. 2021).

The *Matt Stress Reactivity Protocol* (MSRP) is another laboratory challenge that consists of a series of stressors in a set order: Stroop color-word task, mental arithmetic, anagram task, a cold pressor test, and an interpersonal interview about a particularly stressful event in the person's life (Bosch et al. 2009; Traustadóttir et al. 2005). Other studies have used driving simulation challenges (Seeman et al. 1995)

or a combination of cognitive tests such as the Stroop color-word task and mirror tracing task (Seeman et al. 2001; Gotthardt et al. 1995).

These laboratory challenges are all designed to elicit a stress response as demonstrated by increases in cardiovascular and HPA-axis activity. The latter is usually assessed by changes in plasma and/or salivary cortisol. Recently, other measures including markers of sympathetic nervous system activity such as salivary alpha-amylase (sAA) and heart rate variability are also being included in studies on stress reactivity (Allen et al. 2014).

Are There Sex Differences in Stress Reactivity?

Since this chapter and book focus on studies on women, it is important to establish that there are in fact sex differences—otherwise, it would not be necessary to differentiate the discussion based on sex. Numerous studies have shown significant differences in the HPA-axis response to psychosocial or mental stressors between men and women. However, the results have not always been consistent in regard to which sex is more stress reactive, with some finding greater responses in men (Seeman et al. 2001; Traustadóttir et al. 2003; Uhart et al. 2006; Kirschbaum et al. 1992, 1999; Earle et al. 1999; Kudielka et al. 1999; Henze et al. 2021) and other in women (Seeman et al. 1995; Ahwal et al. 1997), and some showing an interaction with age (Seeman et al. 2001; Kudielka et al. 2004). One potential explanation for the unequivocal results may be due to the different stressors used. To this effect, it has been shown that women have a greater cortisol response to a stressor invoking social rejection, while men are more reactive to achievement-related stressors (Stroud et al. 2002). Other explanations may be due to not controlling for potential confounding variables such as menstrual cycle phase, fitness levels, or mental conditions that could influence the HPA-axis response such as depression, anxiety, or other psychiatric disorders (Allen et al. 2014). Nevertheless, these studies illustrate that sex definitely has an effect on psychosocial stress reactivity, and data from men and women should not be lumped together in analyses.

A fairly recent study by Stephens et al. (2016) may have put the question of "which sex is more stress reactive" finally to rest, at least in young individuals (18–30 years). They had a much larger sample size than any of the previous studies, with a total of 282 subjects who underwent the TSST. The women were tested in the early-follicular phase. Their results show equivocally that men had greater HPA-axis response to the psychosocial stressor as measured by plasma ACTH, serum cortisol, and salivary cortisol (see Fig. 18.1), analyzed by the change across time points, overall response (area-under-the-response-curve), as well as slopes of baseline-to-peak and peak-to-end.

It is worth noting that the results from psychosocial stressors do not extend to other stimuli of the HPA axis such as pharmacological challenges where women tend to have a more pronounced response (Heuser et al. 1994; Greenspan et al. 1993; Born et al. 1995) or exhibit blunted negative feedback sensitivity (Wilkinson

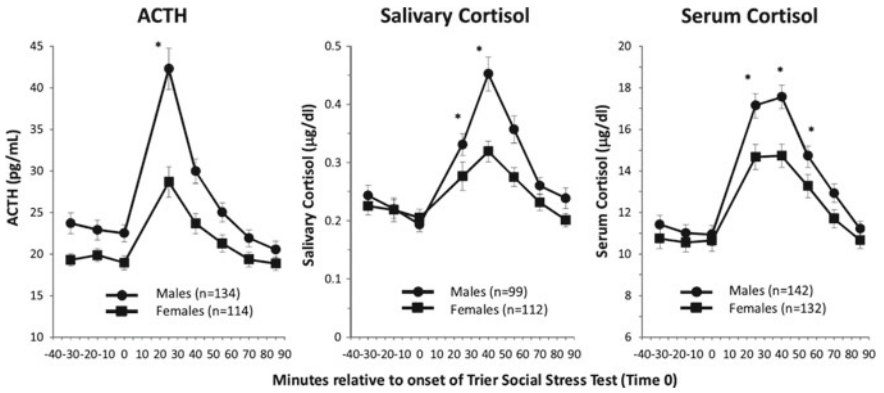

Fig. 18.1 Mean HPA-axis hormone levels (means ± SE) in response to the TSST for men (black circles) and women (black squares) in the follicular phase of the menstrual cycle. Times prior to the test are shown as negative values on the *x*-axis (time). *Significant interaction with gender ($p < 0.05$). Reprinted from Stephens et al. (2016) with permission from Elsevier

et al. 1997) or acute exercise where the responses in men and women are similar (Sandoval and Matt 2002; Szivak et al. 2013; Kraemer et al. 1993). However, sex differences in responses to psychosocial or mental stress may contribute to differences in morbidity and mortality of diseases that have distinct differences in prevalence between men and women such as cardiovascular disease (prior to menopause) and autoimmune diseases (Stoney et al. 1987; Bjorntorp 1997; Sternberg et al. 1990). One reason for the discrepancies in results of studies using pharmacological challenges versus psychosocial challenges may be related to where they stimulate the HPA axis. Many of the pharmacological challenges, such as infusion of corticotropin release hormone (CRH), stimulate the axis at the level of the pituitary. Psychosocial challenges, on the other hand, require the stressor to be processed in the brain and therefore acts as a supra-pituitary stimulus, activating the HPA-axis response by stimulating the paraventricular nucleus (PVN) through the limbic system (prefrontal cortex, hippocampus, amygdala), whereas physiological stressors have a more direct pathway to the PVN (Herman and Cullinan 1997).

A general consensus from the literature is that men exhibit greater cardiovascular and HPA-axis responses to psychological stress than women when compared between puberty and menopause, whereas sex differences are smaller when compared in individuals before puberty or after menopause (Kajantie and Phillips 2006).

Effects of Estrogen on Stress Reactivity

Sex hormones, particularly estrogen, have been shown to influence the HPA-axis response in both animal and human studies. Animal studies where estrogen levels are decreased by removing the ovaries and increased with estrogen replacement

show that the effect of estrogen is an enhanced HPA-axis response (Lesniewska et al. 1990a, b). The same finding was shown in young men treated with an estrogen patch or a placebo for 24–48 h before being exposed to the TSST (Kirschbaum et al. 1996). The estrogen-treated group had significantly higher ACTH and cortisol responses as compared to the placebo group.

Menstrual Cycle Phases

The question is whether these results from extreme differences in estrogen extend to normal estrogen fluctuations across the menstrual cycle. Based on the fact that estrogen levels are higher in the mid-luteal phase compared to the early-follicular phase, it would be predicted that stress reactivity would be greater in the luteal phase. This prediction is supported by many studies (Tersman et al. 1991; Sato and Miyake 2004; Lustyk et al. 2010, Kirschbaum et al. 1999), but there is also a number of studies that have not found significant differences in stress reactivity between follicular and luteal phases (Pico-Alfonso et al. 2007; Shenoy et al. 2014; Veldhuijzen van Zanten et al. 2009; Choi and Salmon 1995). Using exercise as a stimulus to induce a cortisol response, Boisseau et al. (2013) found no differences in salivary or urinary cortisol response in women tested in the follicular and luteal phases of the menstrual cycle. In contrast, one study found that the effect of the menstrual cycle on neuroendocrine activation to Stroop test and handgrip exercise depended on trait anxiety where women who had high trait anxiety had greater responses in the follicular phase versus luteal phase (Hlavacova et al. 2008). One caveat in many of these studies is that the comparison is not made in the same subjects across the different phases of the menstrual cycles but compares two different cohorts. The reason for this is because an important component of psychosocial stressors such as the TSST is the "element of surprise" and therefore these tests do not lend themselves to repeated measures. However, comparing within-subjects as opposed to between-subjects would be a much stronger research design to get at this question properly. One such study, that did not use a challenge, compared heart rate and blood pressure responses in the everyday working life of women who reported their perceived stress (Pollard et al. 2007). They found that heart rate response to perceived stress was greater in the luteal phase, but blood pressure was unaffected (Pollard et al. 2007). Another study tested cardiovascular and epinephrine reactivity to the TSST in women in the early-follicular, late-follicular, and luteal phases using a within-subject design (Gordon and Girdler 2014). Their results were in agreement with the previously discussed study and showed that the autonomic stress reactivity in response to the TSST was significantly greater in the luteal phase. In contrast to most other studies, the TSST did not elicit a significant increase in cortisol in this cohort. However, this is probably related to their methodology where the only sampling times for plasma cortisol were at baseline and at the end of the recovery period.

Cook et al. (2021) studied acute changes in salivary testosterone and cortisol in female athletes in response to a physical and psychological stressor at three-time

points in the menstrual cycle (day 7, 14, and 21). Their results demonstrated that baseline testosterone levels were predictive of the cortisol response to the stressor, which could relate to one possible mechanism regarding sex differences.

How does the potential effect of the menstrual cycle phase translate to female athletes and exercise performance? Athletes typically do not schedule their races or tournaments around their menstrual cycle. However, it would be interesting to evaluate the performance of female athletes who compete in sports where *control* of stress reactivity is of particular importance such as archery, biathlons, and shooting. A PubMed search revealed that no such studies have been conducted, and hence, this is an area in need of future research.

Oral Contraceptives

It is well known that basal cortisol levels are increased in women who take oral contraceptives (Burke 1969). This increase is seen in free and total cortisol, and there is increased production of cortisol-binding globulin (CBG). CBG levels are negatively correlated with salivary cortisol response to the TSST in women (Kumsta et al. 2007). Perhaps not surprising then is that women on oral contraceptives exhibit a blunted cortisol response to stress reactivity challenges, particularly when measured in saliva (free cortisol) (Kirschbaum et al. 1995, 1999; Rohleder et al. 2003). These results are corroborated in studies using exercise as the HPA-axis stimulus (Boisseau et al. 2013; Bonen et al. 1991). However, when cortisol response was measured in elite female athletes during heavy training sessions and competitions, there were no differences between oral contraceptive users and non-users suggesting that high-intensity and competition stress overrides the effects of oral contraceptives (Crewther et al. 2015).

Taken together, the data from the comparison between menstrual cycle phases and oral contraceptives suggest that estrogen may modulate the effects on cardiovascular and neuroendocrine stress response in premenopausal women, but it is dependent on the type of stressor and potentially an interaction with other factors such as trait anxiety.

Effects of Aging on Stress Reactivity in Women

General HPA-axis function is altered with aging, and these changes appear to be more extensive in women (Luisi et al. 1998; Wilkinson et al. 1997). These changes include increases in 24-h mean cortisol concentrations, decreased diurnal variability, and blunting of negative feedback sensitivity (Traustadóttir et al. 2004; Deuschle et al. 1997; Van Cauter et al. 1996; Nater et al. 2013). Maximal response of the axis appears to be maintained with aging, while the response to a submaximal challenge is often greater in older women.

The literature on the effects of aging on psychosocial stress reactivity in women is still surprisingly sparse. Traustadóttir et al. (2005) used the MSRP to induce a cardiovascular and HPA-axis response in young and older women. The older women exhibited a significantly greater plasma cortisol response to the challenge (see Fig. 18.2). Markers of cardiovascular reactivity were divided with the young exhibiting a significantly higher heart rate response and the older women having a significantly greater increase in systolic blood pressure in response to the challenge. Interestingly, the age-related increase in cortisol reactivity was attenuated in age-matched older women who were physically fit (the effects of fitness are discussed further in the sections of this chapter on the "Effect of Exercise on Stress Reactivity in Women—Regular Exercise"). Similar results were found using the TSST where older women had significantly greater plasma cortisol response; however, there were no age-related differences in the response of salivary cortisol (Kudielka et al. 2004). A recent study also reported greater cardiovascular reactivity in postmenopausal women compared to premenopausal women as indicated by systolic blood pressure and heart rate variability (Hirokawa et al. 2014).

The specific role of estrogen in the age-related changes in stress reactivity in women has not been well elucidated. Postmenopausal women on hormone replacement therapy had higher baseline levels of cortisol compared to age-matched women not on hormone replacement therapy, but there were no differences in the cortisol response to a psychological stressor between the groups (Burleson et al. 1998). Similarly, another study that compared postmenopausal women treated with estrogen or a placebo for two weeks prior to undergoing the TSST found no significant differences in ACTH, cortisol (plasma or salivary), or heart responses between these groups (Kudielka et al. 1999). This study also included a group of premenopausal women as a control, but there were no reported differences between the young and older

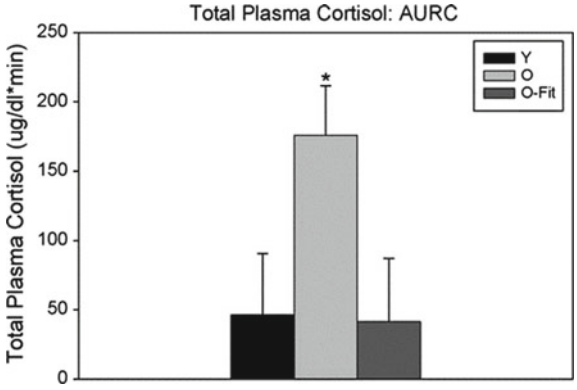

Fig. 18.2 Plasma cortisol response to a psychological challenge, calculated as area-under-the-response-curve (AURC) in young (black bar, $n = 10$), older (light-gray bar, $n = 12$), and older-fit (dark-gray bar, $n = 11$) women. The cortisol response was significantly greater in the older women compared to young and older-fit ($p < 0.05$). Reprinted from Traustadóttir et al. (2005), with permission from Elsevier

women in contrast to a subsequent study from the same laboratory (Kudielka et al. 2004). The discrepancy between these two studies may potentially be due to the way the data were analyzed in the earlier study which treated the baseline values as a covariate, essentially losing the initial response to the challenge.

Effects of Exercise on Stress Reactivity in Women

Acute exercise is a potent stimulus of the neuroendocrine system, including catecholamines and the HPA-axis response, with the magnitude of response related to the intensity and duration of the exercise bout (Hackney 2006; Hill et al. 2008). There appears to be a critical threshold of the relative intensity of 50–60% of maximal aerobic capacity ($VO_{2\,max}$) that must be exceeded before a rise in cortisol occurs (Farrell et al. 1983; Davies and Few 1973). The main effect of repeated bouts of exercise, as in regular training, in terms of the stress response is that the threshold of activation is higher (Buono et al. 1987). In other words, the work required to stimulate the same response after training as before is greater, and comparing an exercise response at the same absolute intensity pre- to post-training shows a lower response after an exercise intervention (Eliakim et al. 2013; Galbo 2001). These adaptations to training occur to a similar extent in older individuals (Korkushko et al. 1995).

Acute Exercise

A single bout of acute exercise leads to improved insulin sensitivity and greater resistance to oxidative stress, even 16 h after acute exercise (Weiss et al. 2008; Nordin et al. 2014). A related question of importance for understanding the beneficial effects of exercise on lowering the risk for chronic diseases is whether acute exercise leads to increased psychosocial stress resilience for a period after the exercise session. Rejeski et al. (1992) studied premenopausal women who were low to moderately fit. Subjects completed a psychosocial challenge comprised of Stroop color-word task and public speech on two occasions: with a 40-min exercise session at 70% of age-predicted maximal heart rate preceding the stress challenge and a non-exercising control condition. The outcome variables were limited to heart rate and blood pressure measurements. The psychosocial stressor elicited significantly lower blood pressure responses when preceded by acute exercise compared to the control trial, but there were no differences in heart rate reactivity (Rejeski et al. 1992). A meta-analysis specifically on blood pressure responses to psychosocial stressors also concluded that acute exercise provided protection in form of lower hemodynamic reactivity (Hamer et al. 2006). Another study designed around this same research question included measures of salivary cortisol and sAA although the study cohort was limited to highly trained and sedentary young men (Zschucke et al. 2015). Due to the paucity of information on the effect of acute exercise, the results of this study

are included here, and the reader can ponder whether these data would translate to women. The stress challenge used in this study was the MIST, and the response was tested approximately 90 min after an exercise bout that was performed at 60–70% of maximal aerobic capacity for 30 min and compared to a non-exercise control condition. The MIST following acute exercise elicited a significantly lower cortisol response as compared to the control trial in support of the hypothesis that acute exercise can act as a stress buffer. There were no differences in sAA responses between trials (Zschucke et al. 2015). Additionally, the effects of acute exercise on subsequent response to a psychosocial stressor may be dependent on the intensity of exercise and the time frame between the exercise bout and the administration of the stress challenge (Alderman et al. 2007).

In summary, there are limited data available to make a definitive conclusion on the effect of acute exercise on lowering subsequent stress reactivity and the mechanisms are unclear. Certainly, this appears to be an area that warrants further studying.

Regular Exercise

Regular exercise or training results in physiological adaptations where tolerance to an acute exercise stimulus is increased due to greater capacity. In the context of the HPA-axis response, these adaptations manifest in a lower pituitary-adrenal response at a given absolute workload (Galbo 2001; Buono et al. 1987; Eliakim et al. 2013). In addition, the maximal capacity of the adrenal gland is also increased with training, allowing for a greater response when appropriate such as very high-intensity exercise or prolonged duration (Luger et al. 1987; Kjaer 1992). Regular lifelong physical activity is associated with many health benefits, and recent data support that habitual exercise may protect older individuals from changes in diurnal endocrine rhythms and increased cortisol levels during periods of high stress (Heaney et al. 2014).

The early studies on whether physical fitness is associated with a lower response to psychosocial stress were almost all designed around measuring cardiovascular and hemodynamic reactivity. The data demonstrate that physical fitness (measured by $VO_{2\,max}$, physical activity questionnaires, or activity monitoring) is generally associated with a blunted heart rate and blood pressure response to laboratory stress challenges. These studies have been reviewed extensively elsewhere, and the reader is referred to the following narrative and meta-analytic reviews: Crews and Landers (1987), Huang et al. (2013), Forcier et al. (2006).

The studies that have been designed to test this hypothesis around measures of HPA-axis response have reported either a significant effect of fitness on attenuating the response or no difference between groups of different levels of physical fitness. Of these studies, only two have been conducted on women. Two other studies included both men and women but did not report separate analyses based on gender. These studies are reviewed in further detail below.

Studies on Women

Traustadóttir et al. (2005) were one of the first studies to show a significant effect of physical fitness on psychosocial stress resilience as demonstrated by significantly lower plasma cortisol response in older women who were physically fit (as measured by $VO_{2\ max}$) compared to age-matched unfit controls (see Fig. 18.2) in response to the MSRP. In contrast, Jayasinghe et al. (2016) found no differences in plasma cortisol or catecholamine responses to the TSST between fit and unfit women. Aside from the different challenges used in these studies, the cohorts differed in age. The former study compared postmenopausal women that were not on hormone replacement therapy (mean age 66 years), while the latter study compared premenopausal women (mean age 38–40 years) tested in the mid-follicular phase.

Studies on Men and Women Combined

Two studies that analyzed men and women grouped together found no effect of fitness on the HPA-axis response to psychosocial stress. One of those studies assessed physical activity levels through a questionnaire and defined exercisers as those who reported exercising $\geq 1x$/week (Childs and de Wit 2014). They found no differences in salivary cortisol responses between the two groups who were comprised of young individuals (mean age 22 years). It could be argued that their definition of physical fitness is not rigorous enough and that may have minimized the chance of seeing differences between the groups. Another study assessed fitness levels by measuring $VO_{2\ peak}$ and found no correlation with plasma ACTH or cortisol responses to the TSST (Arvidson and Jonsdottir 2015). Subjects in this study ranged in age from 20 to 50 years. Interestingly, children who were more physically active as measured with an activity monitor exhibited lower salivary cortisol response to the TSST compared to their peers who were less physically active (Martikainen et al. 2013).

Studies on Men

Rimmele and colleagues completed two similar studies, one compared elite athletes to untrained (Rimmele et al. 2007) while the other compared three groups of young men; elite athletes, amateur athletes, and untrained (Rimmele et al. 2009). The salivary cortisol response to the TSST was significantly lower in the elite athletes in both studies and in the latter, the other two groups did not differ. These data suggest that perhaps the effects of fitness on increasing stress resilience in young individuals is only seen in very high levels of fitness such as in elite athletes. In contrast, Zschucke et al. (2015) did not find differences between trained and sedentary in their salivary cortisol response to the MIST. They did however find a significant negative correlation between $VO_{2\ max}$ levels and cortisol reactivity, supporting the idea of greater fitness leading to lower stress reactivity. It is worth noting that the average $VO_{2\ max}$ levels reported for their sedentary group were 47.5 mL/kg/min which despite being

significantly lower than their fit group would not be considered sedentary according to any norms.

Summary of Studies on Regular Exercise

Taken together, there are a few things that surface as possibilities for explaining the discrepancies in results. One explanation could be related to the age of the subjects. It is likely that the effects of fitness would be greater in individuals that have compromised stress resilience, and therefore, the effects would be more readily seen when fitness is layered onto aging. This is analogous to the effect of exercise training on blood pressure. Exercise training lowers blood pressure, but only in individuals with hypertension and not in normotensive individuals. If we consider healthy young individuals to have appropriate or normal stress responses, then there is no reason to expect physical fitness to change the response. Alternatively, there may be a higher threshold of fitness needed in the young to actually see an effect, as seen by the differences in elite athletes versus fit young men (Rimmele et al. 2009). Finally, as men generally show greater stress reactivity to a psychosocial stressor such as the TSST compared to women, the effects of fitness may be more pronounced in men than women—although this has not been compared to date.

Conclusions and Future Directions

Stress reactivity is clinically relevant because of the association with risk for many chronic diseases such as cardiovascular disease, diabetes, osteoporosis, and Alzheimer's disease. Stress-related cortisol secretion is positively correlated with risk factors for these diseases such as visceral obesity, metabolic dysregulation, hypertension, and cognitive dysfunction (Bjorntorp 1997, 1999; Rosmond et al. 1998; Brindley and Rolland 1989; Stoney et al. 1987). While the understanding of factors that affect stress reactivity and stress resilience has increased and the studies have become more standardized in terms of challenges used and outcome variables measured, there is still much work to be done especially on whether lowering of stress reactivity translates to lower disease risk. There is a need for more studies on women, in particular older women. It also would be beneficial if more studies would employ specific analyses of recovery after a peak response as that may be more informative regarding stress resilience and therefore more relevant to health.

In order to really understand whether exercise increases psychosocial stress resilience, we need randomized controlled trials (RCT) with successful exercise interventions and comparison to non-exercising control groups. The obstacle has been that psychosocial laboratory stressors often are not conducive to repeated testing due to habituation or desensitization. To my knowledge, there has only been one exercise intervention study completed that measured cortisol responses to a laboratory stressor (Klaperski et al. 2014). This study used a version of the TSST adapted for groups

(von Dawans et al. 2011), and the challenge stimulated a significant increase in salivary cortisol and heart rate at both measurement times, before and after a 12-week intervention. Cortisol reactivity was attenuated in both the endurance training group and the relaxation group, while there was no change in the control group (Klaperski et al. 2014). These results are promising for future studies and need to be replicated in women.

References

Ahwal WN, Mills PJ, Kalshan DA, Nelesen RA. Effects of race and sex on blood pressure and hemodynamic stress response as a function of the menstrual cycle. Blood Press Monit. 1997;2:161–7.

Alderman BL, Arent SM, Landers DM, Rogers TJ. Aerobic exercise intensity and time of stressor administration influence cardiovascular responses to psychological stress. Psychophysiology. 2007;44:759–66.

Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: focus on the trier social stress test. Neurosci Biobehav Rev. 2014;38:94–124.

Arvidson E, Jonsdottir IH. The relationship between HPA-axis response, perceived stress and peak aerobic capacity. Psychoneuroendocrinology. 2015;61:71.

Birket, MA. The trier social stress test protocol for inducing psychological stress. J Vis Exp. 2011

Bjorntorp P. Stress and cardiovascular disease. Acta Physiol Scand Suppl. 1997;640:144–8.

Bjorntorp P. Neuroendocrine perturbations as a cause of insulin resistance. Diabetes Metab Res Rev. 1999;15:427–41.

Boisseau N, Enea C, Diaz V, Dugue B, Corcuff JB, Duclos M. Oral contraception but not menstrual cycle phase is associated with increased free cortisol levels and low hypothalamo-pituitary-adrenal axis reactivity. J Endocrinol Invest. 2013;36:955–64.

Bonen A, Haynes FW, Graham TE. Substrate and hormonal responses to exercise in women using oral contraceptives. J Appl Physiol. 1991;1985(70):1917–27.

Born J, Ditschuneit I, Schreiber M, Dodt C, Fehm HL. Effects of age and gender on pituitary-adrenocortical responsiveness in humans. Eur J Endocrinol. 1995;132:705–11.

Bosch PR, Traustadóttir T, Howard P, Matt KS. Functional and physiological effects of yoga in women with rheumatoid arthritis: a pilot study. Altern Ther Health Med. 2009;15:24–31.

Brindley DN, Rolland Y. Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in atherosclerosis. Clin Sci (lond). 1989;77:453–61.

Buono MJ, Yeager JE, Sucec AA. Effect of aerobic training on the plasma ACTH response to exercise. J Appl Physiol. 1987;1985(63):2499–501.

Burke CW. Biologically active cortisol in plasma of oestrogen-treated and normal subjects. Br Med J. 1969;2:798–800.

Burleson MH, Malarkey WB, Cacioppo JT, Poehlmann KM, Kiecolt-Glaser JK, Berntson GG, Glaser R. Postmenopausal hormone replacement: effects on autonomic, neuroendocrine, and immune reactivity to brief psychological stressors. Psychosom Med. 1998;60:17–25.

Carroll D, Ginty AT, Painter RC, Roseboom TJ, Phillips AC, de Rooij SR. Systolic blood pressure reactions to acute stress are associated with future hypertension status in the Dutch Famine Birth Cohort Study. Int J Psychophysiol. 2012;85:270–3.

Carroll D, Ginty AT, Whittaker AC, Lovallo WR, de Rooij SR. The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. Neurosci Biobehav Rev. 2017;77:74–86.

Childs E, de Wit H. Regular exercise is associated with emotional resilience to acute stress in healthy adults. Front Physiol. 2014;5:161.

Choi PY, Salmon P. Stress responsivity in exercisers and non-exercisers during different phases of the menstrual cycle. Soc Sci Med. 1995;41:769–77.
Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med. 1999;341:1351–7.
Cook CJ, Fourie P, Crewther BT. Menstrual variation in the acute testosterone and cortisol response to laboratory stressors correlate with baseline testosterone fluctuations at a within- and between-person level. Stress. 2021;24:458–67.
Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc. 1987;19:S114–20.
Crewther BT, Hamilton D, Casto K, Kilduff LP, Cook CJ. Effects of oral contraceptive use on the salivary testosterone and cortisol responses to training sessions and competitions in elite women athletes. Physiol Behav. 2015;147:84–90.
Davies CT, Few JD. Effects of exercise on adrenocortical function. J Appl Physiol. 1973;35:887–91.
de Calheiros Velozo J, Vaessen T, Pruessner J, van Diest I, Claes S, Myin-Germeys I. The repeated Montreal Imaging Stress Test (rMIST): testing habituation, sensitization, and anticipation effects to repeated stress induction. Psychoneuroendocrinology. 2021;128:105217.
de Rooij SR. Blunted cardiovascular and cortisol reactivity to acute psychological stress: a summary of results from the Dutch Famine Birth Cohort Study. Int J Psychophysiol. 2013;90:21-7.
Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The montreal imaging stress task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. J Psychiatry Neurosci. 2005;30:319–25.
Deuschle M, Gotthardt U, Schweiger U, Weber B, Korner A, Schmider J, Standhardt H, Lammers CH, Heuser I. With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. Life Sci. 1997;61:2239–46.
Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull. 2004;130:355–91.
Earle TL, Linden W, Weinberg J. Differential effects of harassment on cardiovascular and salivary cortisol stress reactivity and recovery in women and men. J Psychosom Res. 1999;46:125–41.
Eliakim A, Portal S, Zadik Z, Meckel Y, Nemet D. Training reduces catabolic and inflammatory response to a single practice in female volleyball players. J Strength Cond Res. 2013;27:3110–5.
Farrell PA, Garthwaite TL, Gustafson AB. Plasma adrenocorticotropin and cortisol responses to submaximal and exhaustive exercise. J Appl Physiol Respir Environ Exerc Physiol. 1983;55:1441–4.
Feeney JC, O'Halloran AM, Kenny RA. The Association between hair cortisol, hair cortisone, and cognitive function in a population-based cohort of older adults: results from the irish longitudinal study on ageing. J Gerontol A Biol Sci Med Sci. 2020;75:257–65.
Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. Neurosci Biobehav Rev. 2010;35:91–6.
Forcier K, Stroud LR, Papandonatos GD, Hitsman B, Reiches M, Krishnamoorthy J, Niaura R. Links between physical fitness and cardiovascular reactivity and recovery to psychological stressors: a meta-analysis. Health Psychol. 2006;25:723–39.
Galbo H. Influence of aging and exercise on endocrine function. Int J Sport Nutr Exerc Metab. 2001;11(Suppl):S49-57.
Gordon JL, Girdler SS. Mechanisms underlying hemodynamic and neuroendocrine stress reactivity at different phases of the menstrual cycle. Psychophysiology. 2014;51:309–18.
Gotthardt U, Schweiger U, Fahrenberg J, Lauer CJ, Holsboer F, Heuser I. Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am J Physiol. 1995;268:R865–73.
Greenspan SL, Rowe JW, Maitland LA, McAloon-Dyke M, Elahi D. The pituitary-adrenal glucocorticoid response is altered by gender and disease. J Gerontol. 1993;48:M72–7.
Gupta SB. Exercise ECG testing–is it obsolete? J Assoc Physicians India. 2005;53:615–8.
Hackney AC. Exercise as a stressor to the human neuroendocrine system. Medicina (kaunas). 2006;42:788–97.

Hamer M, Endrighi R, Venuraju SM, Lahiri A, Steptoe A. Cortisol responses to mental stress and the progression of coronary artery calcification in healthy men and women. PLoS ONE. 2012;7: e31356.

Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Biol Psychol. 2006;71:183–90.

Heaney JL, Carroll D, Phillips AC. Physical activity, life events stress, cortisol, and DHEA: preliminary findings that physical activity may buffer against the negative effects of stress. J Aging Phys Act. 2014;22:465–73.

Henze GI, Konzok J, Kreuzpointner L, Bartl C, Giglberger M, Peter H, Streit F, Kudielka BM, Kirsch P, Wust S. Sex-specific interaction between cortisol and striato-limbic responses to psychosocial stress. Soc Cogn Affect Neurosci. 2021;16:972–84.

Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 1997;20:78–84.

Heuser IJ, Gotthardt U, Schweiger U, Schmider J, Lammers CH, Dettling M, Holsboer F. Age-associated changes of pituitary-adrenocortical hormone regulation in humans: importance of gender. Neurobiol Aging. 1994;15:227–31.

Hill EE, Zack E, Battaglini C, Viru M, Viru A, Hackney AC. Exercise and circulating cortisol levels: the intensity threshold effect. J Endocrinol Invest. 2008;31:587–91.

Hirokawa K, Nagayoshi M, Ohira T, Kajiura M, Kitamura A, Kiyama M, Okada T, Iso H. Menopausal status in relation to cardiovascular stress reactivity in healthy Japanese participants. Psychosom Med. 2014;76:701–8.

Hlavacova N, Wawruch M, Tisonova J, Jezova D. Neuroendocrine activation during combined mental and physical stress in women depends on trait anxiety and the phase of the menstrual cycle. Ann NY Acad Sci. 2008;1148:520–5.

Huang CJ, Webb HE, Zourdos MC, Acevedo EO. Cardiovascular reactivity, stress, and physical activity. Front Physiol. 2013;4:314.

Jayasinghe SU, Lambert GW, Torres SJ, Fraser SF, Eikelis N, Turner AI. Hypothalamo-pituitary adrenal axis and sympatho-adrenal medullary system responses to psychological stress were not attenuated in women with elevated physical fitness levels. Endocrine. 2016;51:369–79.

Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology. 2006;31:151–78.

Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med. 1999;61:154–62.

Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28:76–81.

Kirschbaum C, Pirke KM, Hellhammer DH. Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. Psychoneuroendocrinology. 1995;20:509–14.

Kirschbaum C, Schommer N, Federenko I, Gaab J, Neumann O, Oellers M, Rohleder N, Untiedt A, Hanker J, Pirke KM, Hellhammer DH. Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men. J Clin Endocrinol Metab. 1996;81:3639–43.

Kirschbaum C, Wust S, Hellhammer D. Consistent sex differences in cortisol responses to psychological stress. Psychosom Med. 1992;54:648–57.

Kjaer M. Regulation of hormonal and metabolic responses during exercise in humans. Exerc Sport Sci Rev. 1992;20:161–84.

Klaperski S, von Dawans B, Heinrichs M, Fuchs R. Effects of a 12-week endurance training program on the physiological response to psychosocial stress in men: a randomized controlled trial. J Behav Med. 2014;37:1118–33.

Korkushko OV, Frolkis MV, Shatilo VB. Reaction of pituitary-adrenal and autonomic nervous systems to stress in trained and untrained elderly people. J Auton Nerv Syst. 1995;54:27–32.

Kraemer WJ, Fleck SJ, Dziados JE, Harman EA, Marchitelli LJ, Gordon SE, Mello R, Frykman PN, Koziris LP, Triplett NT. Changes in hormonal concentrations after different heavy-resistance exercise protocols in women. J Appl Physiol (1985). 1993;1985(75):594–604.

Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. Psychoneuroendocrinology. 2004;29:83–98.

Kudielka BM, Schmidt-Reinwald AK, Hellhammer DH, Kirschbaum C. Psychological and endocrine responses to psychosocial stress and dexamethasone/corticotropin-releasing hormone in healthy postmenopausal women and young controls: the impact of age and a two-week estradiol treatment. Neuroendocrinology. 1999;70:422–30.

Kumsta R, Entringer S, Hellhammer DH, Wust S. Cortisol and ACTH responses to psychosocial stress are modulated by corticosteroid binding globulin levels. Psychoneuroendocrinology. 2007;32:1153–7.

Lazzarino AI, Hamer M, Gaze D, Collinson P, Steptoe A. The association between cortisol response to mental stress and high-sensitivity cardiac troponin T plasma concentration in healthy adults. J Am Coll Cardiol. 2013;62:1694–701.

Lesniewska B, Miskowiak B, Nowak M, Malendowicz LK. Sex differences in adrenocortical structure and function. XXVII. The effect of ether stress on ACTH and corticosterone in intact, gonadectomized, and testosterone- or estradiol-replaced rats. Res Exp Med (berl). 1990a;190:95–103.

Lesniewska B, Nowak M, Malendowicz LK. Sex differences in adrenocortical structure and function. XXVIII. ACTH and corticosterone in intact, gonadectomised and gonadal hormone replaced rats. Horm Metab Res. 1990b;22:378–81.

Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, Loriaux DL, Chrousos GP. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. N Engl J Med. 1987;316:1309–15.

Luisi S, Tonetti A, Bernardi F, Casarosa E, Florio P, Monteleone P, Gemignani R, Petraglia F, Luisi M, Genazzani AR. Effect of acute corticotropin releasing factor on pituitary-adrenocortical responsiveness in elderly women and men. J Endocrinol Invest. 1998;21:449–53.

Lustyk MK, Olson KC, Gerrish WG, Holder A, Widman L. Psychophysiological and neuroendocrine responses to laboratory stressors in women: implications of menstrual cycle phase and stressor type. Biol Psychol. 2010;83:84–92.

Martikainen S, Pesonen AK, Lahti J, Heinonen K, Feldt K, Pyhala R, Tammelin T, Kajantie E, Eriksson JG, Strandberg TE, Raikkonen K. Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. J Clin Endocrinol Metab. 2013;98:E619–27.

McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338:171–9.

McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873–904.

Morris MC, Rao U, Garber J. Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. J Affect Disord. 2012;143:223–30.

Nafisa A, Wattoo FH, Qayyum M, Gulfraz M. The association between chronic stress, hair cortisol, and angiographically documented coronary atherosclerosis, a case-control study. Stress. 2021;24:1008–15.

Nagaraja AS, Sadaoui NC, Dorniak PL, Lutgendorf SK, Sood AK. SnapShot: stress and disease. Cell Metab. 2016;23(388–388): e1.

Nater UM, Hoppmann CA, Scott SB. Diurnal profiles of salivary cortisol and alpha-amylase change across the adult lifespan: evidence from repeated daily life assessments. Psychoneuroendocrinology. 2013;38:3167–71.

Nordin TC, Done AJ, Traustadóttir T. Acute exercise increases resistance to oxidative stress in young but not older adults. Age (dordr). 2014;36:9727.

Pico-Alfonso MA, Mastorci F, Ceresini G, Ceda GP, Manghi M, Pino O, Troisi A, Sgoifo A. Acute psychosocial challenge and cardiac autonomic response in women: the role of estrogens, corticosteroids, and behavioral coping styles. Psychoneuroendocrinology. 2007;32:451–63.

Pollard TM, Pearce KL, Rousham EK, Schwartz JE. Do blood pressure and heart rate responses to perceived stress vary according to endogenous estrogen level in women? Am J Phys Anthropol. 2007;132:151–7.

Rejeski WJ, Thompson A, Brubaker PH, Miller HS. Acute exercise: buffering psychosocial stress responses in women. Health Psychol. 1992;11:355–62.

Reschke-Hernandez AE, Okerstrom KL, Bowles Edwards A, Tranel D. Sex and stress: men and women show different cortisol responses to psychological stress induced by the Trier social stress test and the Iowa singing social stress test. J Neurosci Res. 2017;95:106–14.

Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M. The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. Psychoneuroendocrinology. 2009;34:190–8.

Rimmele U, Zellweger BC, Marti B, Seiler R, Mohiyeddini C, Ehlert U, Heinrichs M. Trained men show lower cortisol, heart rate and psychological responses to psychosocial stress compared with untrained men. Psychoneuroendocrinology. 2007;32:627–35.

Rohleder N, Wolf JM, Piel M, Kirschbaum C. Impact of oral contraceptive use on glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress. Psychoneuroendocrinology. 2003;28:261–73.

Rosmond R, Dallman MF, Bjorntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab. 1998;83:1853–9.

Sandoval DA, Matt KS. Gender differences in the endocrine and metabolic responses to hypoxic exercise. J Appl Physiol. 2002;1985(92):504–12.

Sato N, Miyake S. Cardiovascular reactivity to mental stress: relationship with menstrual cycle and gender. J Physiol Anthropol Appl Human Sci. 2004;23:215–23.

Schlotz, W. Stress reactivity. In: Gellman MD, Turner JR, editors. Encyclopedia of behavioral medicine. New York, NY: Springer; 2013.

Seeman TE, Singer B, Charpentier P. Gender differences in patterns of HPA axis response to challenge: Macarthur studies of successful aging. Psychoneuroendocrinology. 1995;20:711–25.

Seeman TE, Singer B, Wilkinson CW, McEwen B. Gender differences in age-related changes in HPA axis reactivity. Psychoneuroendocrinology. 2001;26:225–40.

Shenoy JP, Sahana PA, Shivakumar J. Study of cardiovascular reactivity to mental stress in different phases of menstrual cycle. J Clin Diagn Res. 2014;8:BC01-4

Stephens MA, Mahon PB, McCaul ME, Wand GS. Hypothalamic-pituitary-adrenal axis response to acute psychosocial stress: effects of biological sex and circulating sex hormones. Psychoneuroendocrinology. 2016;66:47–55.

Steptoe A, Kivimaki M, Lowe G, Rumley A, Hamer M. Blood pressure and fibrinogen responses to mental stress as predictors of incident hypertension over an 8-year period. Ann Behav Med. 2016;50:898–906.

Sternberg EM, Wilder RL, Gold PW, Chrousos GP. A defect in the central component of the immune system–hypothalamic-pituitary-adrenal axis feedback loop is associated with susceptibility to experimental arthritis and other inflammatory diseases. Ann NY Acad Sci. 1990;594:289–92.

Stewart JC, Janicki DL, Kamarck TW. Cardiovascular reactivity to and recovery from psychological challenge as predictors of 3-year change in blood pressure. Health Psychol. 2006;25:111–8.

Stoney CM, Davis MC, Matthews KA. Sex differences in physiological responses to stress and in coronary heart disease: a causal link? Psychophysiology. 1987;24:127–31.

Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. Biol Psychiatry. 2002;52:318–27.

Szivak TK, Hooper DR, Dunn-Lewis C, Comstock BA, Kupchak BR, Apicella JM, Saenz C, Maresh CM, Denegar CR, Kraemer WJ. Adrenal cortical responses to high-intensity, short rest, resistance exercise in men and women. J Strength Cond Res. 2013;27:748–60.

Tersman Z, Collins A, Eneroth P. Cardiovascular responses to psychological and physiological stressors during the menstrual cycle. Psychosom Med. 1991;53:185–97.
Traustadóttir T, Bosch PR, Cantu T, Matt KS. Hypothalamic-pituitary-adrenal axis response and recovery from high-intensity exercise in women: effects of aging and fitness. J Clin Endocrinol Metab. 2004;89:3248–54.
Traustadóttir T, Bosch PR, Matt KS. Gender differences in cardiovascular and hypothalamic-pituitary-adrenal axis responses to psychological stress in healthy older adult men and women. Stress. 2003;6:133–40.
Traustadóttir T, Bosch PR, Matt KS. The HPA axis response to stress in women: effects of aging and fitness. Psychoneuroendocrinology. 2005;30:392–402.
Trivedi R, Sherwood A, Strauman TJ, Blumenthal JA. Laboratory-based blood pressure recovery is a predictor of ambulatory blood pressure. Biol Psychol. 2008;77:317–23.
Uhart M, Chong RY, Oswald L, Lin PI, Wand GS. Gender differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity. Psychoneuroendocrinology. 2006;31:642–52.
van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab. 1996;81:2468–73.
Veldhuijzen van Zanten JJ, Carroll D, Ring C. Mental stress-induced haemoconcentration in women: effects of menstrual cycle phase. Br J Health Psychol. 2009;14: 805–16.
von Dawans B, Kirschbaum C, Heinrichs M. The Trier Social Stress Test for Groups (TSST-G): a new research tool for controlled simultaneous social stress exposure in a group format. Psychoneuroendocrinology. 2011;36:514–22.
Weiss EP, Arif H, Villareal DT, Marzetti E, Holloszy JO. Endothelial function after high-sugar-food ingestion improves with endurance exercise performed on the previous day. Am J Clin Nutr. 2008;88:51–7.
Wilkinson CW, Peskind ER, Raskind MA. Decreased hypothalamic-pituitary-adrenal axis sensitivity to cortisol feedback inhibition in human aging. Neuroendocrinology. 1997;65:79–90.
Zschucke E, Renneberg B, Dimeo F, Wustenberg T, Strohle A. The stress-buffering effect of acute exercise: evidence for HPA axis negative feedback. Psychoneuroendocrinology. 2015;51:414–25.

Chapter 19
Exercise, Depression–Anxiety Disorders, and Sex Hormones

Shannon K. Crowley

Introduction

Research has consistently shown that sex differences exist across many mental health disorders. In general, women have a higher prevalence of most affective disorders, whereas men have higher rates of substance use disorders (Kendler and Gardner 2014; Kessler et al. 1993). Depression, now considered to be the leading cause of global disability (World Health Organization 2020), is twice as common in women compared to men Labaka et al. (2018). Additionally, the prevalence of anxiety disorders is approximately twice as high in women, compared to men (Young and Pfaff 2014; Green et al. 2018). The precise mechanisms underlying sex differences in depression and anxiety rates are currently unknown; however, observations that the risk for depressive and anxiety disorders appears to be higher during certain periods of a woman's life including, puberty, the reproductive years, and the menopause transition (Soares and Zitek 2008) suggest that fluctuations in female hormone status may play a role. Additionally, chronic stress, early-life adversity, and negative cognitive styles are more common in women than in men (Dunn et al. 2012; Matud 2004) and may also contribute to sex differences in depression and anxiety disorder prevalence. Considering that chronic stress has been consistently and strongly associated with the precipitation and exacerbation of depressive and anxiety disorders (Brilman and Ormel 2001; Mundy et al. 2015; Eiland and McEwen 2012), heightened sensitivity to stress during periods of reproductive hormone change (Slentz et al. 2004) may be one pathway by which susceptibility to depression and anxiety disorders is higher in women than in men.

Low levels of physical activity have been consistently observed in individuals with depression and/or anxiety disorders (Daumit et al. 2005; Goodwin 2003; Teychenne

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and York 2013; Dugan et al. 2015). This association appears to be even stronger in women with depressive and anxiety disorders (Goodwin 2003). It is possible that mental health symptomatology (e.g., low motivation, lethargy, depressed mood, anhedonia, etc.) may impede the initiation and motivation to engage in physical activity in affected individuals (Leventhal 2012). To date, however, there has been limited study of the influence of reproductive-related mood and anxiety disorders on participation in physical activity.

Literature reviews maintain that exercise compares favorably to antidepressant medications as a first-line and/or adjuvant treatment for mild to moderate depression in adults (Mead et al. 2009; Lawlor and Hopker 2001; Byrne and Byrne 1993), and studies suggest that participation in physical activity may be protective against the development of mood and anxiety disorders (Kritz-Silverstein et al. 2001; Jacka et al. 2011; Harvey et al. 2018; McDowell et al. 2019; Rothon et al. 2010; Guintivano et al. 2018). The protective and treatment effects of physical exercise for depression and anxiety might be mediated through the positive impact of exercise on fundamental psychological processes of affective dysregulation (e.g., emotion regulation, mood), stress-processing systems, and/or comorbid conditions (e.g., sleep problems). This chapter aims to provide an overview of women's reproductive-related mood disorders, the role of sex hormones in the development and maintenance of women's reproductive-related mood disorders, and the associations among physical activity and women's reproductive-related mood disorders.

Women's Reproductive-Related Mood Disorders

Reproductive-related mood disorders in women consist of psychiatric disorders whose etiology and pathophysiology are linked to reproductive-related processes. With regards to reproductive-related depressive disorders, it is important to note that anxiety-like features are often the predominant presenting symptoms (Yonkers 1997; Wisner et al.2010; Falah-Hassani et al. 2016). Consequently, studies indicate that women have a greater propensity to develop comorbid anxiety and depression, compared to men (Angst and Vollrath 1991; Breslau et al. 1995; Howell et al. 2001; Yonkers 1997). There is evidence that psychosocial stressors (e.g., early-life adversity, chronic stress, low social support) may play a large role in the development of women's reproductive-related mood disorders (Crowley et al. 2015a; Gordon et al. 2015; Kendler and Gardner 2014; Girdler et al. 2003; Girdler et al. 2003), perhaps by increasing sensitivity to stress during hormone-mediated events (Albert et al. 2019; Gordon et al. 2016; Hodes et al. 2019; Schmidt et al. 2004; Schmidt and Rubinow 2009; Schiller et al. 2015). Research also suggests that some women may be differentially sensitive to changes in gonadal steroid hormones, including estrogen and progesterone (PROG) (Schiller et al. 2015; Soares and Zitek 2008), increasing vulnerability to the development of mood disorders during periods of gonadal steroid hormone flux. The increased prevalence of depression in women during periods of reproductive hormone change suggests a potential role of gonadal steroid hormones,

perhaps via their interactions with behavior-modulating physiological systems, in the development and maintenance of depression and anxiety disorders.

Menstrually Related Mood Disorders (MRMDs)

Menstrually related mood disorders (MRMDs), including premenstrual syndrome (PMS) and pre-menstrual dysphoric disorder (PMDD), are characterized by the cyclic recurrence of emotional and physical symptoms during the luteal phase of the menstrual cycle that remit with the onset of menses. Epidemiological evidence suggests that, during their reproductive years, 20–25% of women exhibit clinically relevant PMS, and approximately 5–8% of women meet diagnostic criteria for PMDD (Ismaili et al. 2016). Affective (mood lability, irritability, anxiety/tension, depressed mood) and physical (breast tenderness/swelling, joint/muscle pain, bloating) symptoms associated with MRMDs may significantly interfere with occupational, academic, and social activities (Bloch et al. 1997; Borenstein et al. 2005; Ekholm and Backstrom 1994; Heinemann et al. 2012).

PMDD, the most severe form of an MRMD, results in luteal phase impairment equivalent to that of major depression, panic disorder, and post-traumatic stress disorder (PTSD) (Freeman and Sondheimer 2003; Halbreich et al. 2003). The DSM-V diagnosis of PMDD is based upon a pre-menstrual pattern of at least five physical, affective, and/or behavioral symptoms that are associated with significant distress or interference in role or social functioning, with the requirement that at least one of the key affective symptoms must be: (1) marked affective lability (mood swings, tearfulness, sensitivity to rejection); (2) marked irritability or anger; (3) marked depressed mood; or (4) marked anxiety or tension (American Psychiatric Association 2013). Less severe than PMDD, PMS encompasses the cyclic recurrence of pre-menstrual symptoms with minimal impairment or distress (the presence of a mood symptom is not required for the PMS diagnosis) (Freeman 2003; Kessel 2000).

Hormonal regulation of the ovarian cycle in premenopausal women is characterized by a complex interaction of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and PROG (see Chap. 1). Menstruation marks the first day of the follicular phase, characterized by low and steady levels of PROG and estradiol (Farage et al. 2009). The ovulatory phase begins with a surge in LH and FSH, peak estrogen levels, and increasing PROG levels (Farage et al. 2009). Ending the cycle, the luteal phase is characterized by decreasing LH and FSH levels and peak PROG production from the corpus luteum (Gandara et al. 2007; Farage et al. 2009). It is important to note that inter- and intraindividual variations can exist across cycles, including occurrence of some non-ovulatory cycles (Metcalf 1983; Metcalf et al. 1983).

The etiology of MRMDs is currently unknown; however, it has been suggested that some women may be differentially sensitive to changes in gonadal steroid fluctuations occurring during the ovarian cycle, increasing risk for the development of pre-menstrual symptoms (Bixo et al. 2015; Schiller et al. 2014; 2014; Lentz

et al. 2007). Research suggests that luteal phase changes in reproductive hormones, perhaps particularly their neuroactive steroid derivatives (of which allopregnanolone is the most widely studied), may trigger affective dysregulation in susceptible women (Bixo et al. 2015; Hantsoo et al. 2020; Schiller et al. 2014). It is also possible that sex steroid fluctuations across the ovarian cycle may modulate other neurobiological processes implicated in affective regulation including serotonin availability (Eriksson et al. 2008; Hantsoo et al. 2015; Hindberg and Naesh 1992; Kikuchi et al. 2010), circadian rhythms (Parry et al. 2011; Shechter et al 2012), neuronal growth factors such as brain-derived neurotrophic factor (BDNF; Cubeddu et al. 2011; Pluchino et al. 2009), hypothalamic–pituitary–adrenal-axis (HPA-axis) regulation (Beddig et al. 2019; Crowley and Girdler 2014; Kirschbaum et al. 1999; Kulkarni et al. 2022), and immune system function (Faas et al. 2000; Oertelt-Prigione 2012). Increased sensitivity to changes in the reproductive hormone environment, in some women, may stem from a complex interplay of genetic (Huo et al. 2007; Kendler et al. 1992), physiological (Masho et al. 2015), and psychosocial (e.g., early life adversity, chronic stress) factors (Bertone-Johnson et al. 2014; Kulkarni et al. 2022; Crowley et al. 2015a).

Perinatal Depression

Perinatal depression, including antepartum depression (APD) and postpartum depression (PPD), describes a wide range of mood disorders that can affect women during pregnancy and after childbirth. Despite the classification of "perinatal depression," many women with the disorder experience symptoms of anxiety, mood lability, ruminative thoughts, panic attacks, and obsessive thoughts (particularly related to infant well-being; O'Hara and Wisner 2014; Putnam et al. 2017; Wisner et al. 2013; Reck et al. 2008). The prevalence of APD is estimated at 10–20 % of childbearing women (Breedlove and Fryzelka 2011), and PPD is estimated to affect between 10 and 20 % of childbearing women (Gavin et al. 2005; O'Hara and McCabe 2013; O'Hara and Wisner 2014; Shorey et al. 2018). According to the DSM-V, PPD is defined as the onset of depressive symptoms during pregnancy or within 4 weeks of delivery (American Psychiatric Association 2013). However, some research suggests that some women may experience late onset PPD up to a year post-delivery (de Moraes et al. 2017; Stuart-Parrigon et al. 2014; Tebeka et al. 2021).

The DSM-V diagnosis of major depressive disorder (MDD) with "peripartum" specifier (perinatal depression) requires the presentation of five of the following nine symptoms most of the day, nearly every day for at least a 2 week period: (1) depressed mood, (2) marked diminished interest or pleasure in all, or almost all, activities, (3) significant weight loss or weight gain, or a decrease or increase in appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or psychomotor retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or excessive or inappropriate guilt, (8) cognitive difficulties such as diminished ability to think/concentrate, or indecisiveness, and (9) recurrent thoughts of death or recurrent suicidal ideation. To

meet the diagnostic criteria for perinatal depression, the defining symptoms must represent a change from previous functioning and have had onset during pregnancy or within four weeks of delivery (American Psychiatric Association 2013).

The precise psychological, social, and biological factors which may help to identify and treat women with perinatal depression are still being understood. Several factors may be associated with increased risk for the development of depression and anxiety during pregnancy and the postpartum period, including: (1) a previous history of psychiatric disease; (2) a family history of psychiatric disease; (3) a history of chronic stress, anxious, and depressive symptoms during pregnancy; and (4) low social support (Guintivano et al. 2018; O'Hara and Wisner 2014; Verreault et al. 2014; Falah-Hassani et al. 2016). In addition, disturbed sleep has been associated with both depressed mood (Emamian et al. 2019; Okun et al. 2013; Okun 2015; Osnes t al. 2021; Skouteris et al. 2008) and stress during pregnancy (Okun et al. 2013) and has also been shown to be a potential predictor of depressive mood postpartum (Okun et al. 2013; Goyal et al. 2009; Bei et al. 2010; McEvoy et al. 2019). Underlying biological processes which may be associated with these behavioral risk factors for perinatal depression include HPA-axis dysregulation, inflammatory processes, and genetic vulnerabilities (Crowley et al. 2016; Glynn et al. 2013; Garfield et al. 2015; Guintivano et al. 2015; Posillico and Schwarz 2016; Barth et al. 2015). Treatment of perinatal depression is essential, considering the potential negative impacts of perinatal depression on both maternal and child health outcomes (Schiller et al. 2015).

Reproductive steroid hormones (such as estrogen and PROG) have been implicated in the etiology and pathophysiology of perinatal depression, and this is thought to be due to heightened sensitivity, in some women, to the substantial and rapid changes in gonadal steroid hormone concentrations that occur during the perinatal period (particularly after delivery) (Mehta et al. 2019; Schiller et al. 2015). Indeed, both human and animal studies have suggested that gonadal steroid hormones, and/or their neuroactive steroid derivatives, may be linked to key physiological processes underlying affective regulation, including modulation of the HPA axis, facilitation of neuroplasticity, and regulation of immune processes (McEwen 2002; Crowley et al. 2016 ; Pluchino et al. 2013; Morrow et al. 1995; Kipp et al. 2012; Maki et al. 2019).

Depression During the Menopause Transition (Perimenopausal Depression)

Cross-sectional studies of midlife women indicate that women in the 40- to 55-year age group are more likely to report depressive symptoms than premenopausal and postmenopausal women (Soares and Almeida 2001; Avis et al. 2001; Dennerstein et al. 2004); however, prevalence rates for mood and anxiety disorders during the menopause transition are difficult to ascertain, in part due to the variability

in how women biologically and psychosocially experience the menopause transition. Additionally, there is substantially less research in this area compared to other reproductive-related disorders (such as PMDD and perinatal depression). Some research has suggested that women may be at increased risk for the development of mood and anxiety disorders during the menopause transition (Gordon et al. 2012; Maki et al. 2019), particularly if there is a history of psychiatric disease (Freeman 2010; Willi et al. 2021). Yet even in women without a previous history of depression, the transition to menopause appears to confer some heightened risk for the development of new onset depression (217), and mood disturbances during this period are commonly reported (Caruso et al. 2019; Natari et al. 2018).

Research suggests that a previous and/or family history of psychiatric disease, poor sleep, stressful or negative life events, lack of employment, higher body mass index (BMI), smoking, younger age, race (prevalence rates of depression during the menopause transition are substantially higher in African American women) and a history of reproductive-related mood disorders (e.g., PMDD, PPD) may be associated with increased risk for the development of mood disturbances during the menopause transition (Colvin et al. 2021; Epperson et al. 2017; Gibbs et al. 2014; Gibbs and Kulkarni 2014; Willi et al. 2020). Evidence that women with a history of reproductive-related mood disorders (e.g., pre-menstrual syndrome, postpartum depression) are at elevated risk for the development of depression during the menopause transition suggests, at least in part, a hormonally mediated pathophysiology.

Typically occurring between the ages of 45 and 49, the menopause transition lasts an average of 5 years and is characterized by increased variability in menstrual cycles (with long cycles becoming more common as the menopause transition progresses), skipped cycles, and changes in hormone levels including estrogen, PROG, and FSH (Burger et al. 2001). It is important to note that there are substantial individual differences in hormone patterns during the menopause transition (Santoro et al. 2004). However, most women experience an increase in FSH levels; a decline in luteal phase (prior to menses) PROG (Gordon et al. 2015); erratic changes in estradiol (the most prevalent endogenous estrogen) concentrations, including elevated estradiol (compared to premenopausal levels), which coincide with the increasing frequency of anovulatory cycles (O'Connor et al. 2009); and eventual cessation of estradiol and PROG production (Schmidt and Rubinow 2009). Longitudinal studies have suggested that these perimenopausal changes in reproductive function may be associated with an increased risk of depression in susceptible women (Freeman et al. 2014; Gordon et al. 2015; Cohen et al. 2006; Schmidt et al. 2004).

Though the precise biological underpinnings of depression during the menopause transition are still under investigation, findings that depression prevalence appears to increase concurrent to changes in reproductive hormones (including elevated FSH and diminished estradiol and PROG) during the menopause transition (Schmidt et al. 2021), combined with the efficacy of estradiol therapy in the acute treatment of depression during this period (Gordon et al. 221; Schmidt et al. 2015; de Novaes Soares et al. 2001), suggest that risk for depression during the menopause transition is likely influenced by changes in reproductive-related steroid hormones. It has been

suggested that susceptible women may experience heightened sensitivity to environmental stressors during periods of hormonal fluctuation (including the menopause transition), thus increasing risk for the development of mood disorders during this time (Gordon et al. 2015, 2016). Additionally, endocrine events during the menopause transition have been associated with increased prevalence of somatic complaints including vasomotor symptoms (e.g., hot flushes, night sweats) and sleep disturbances (Brown et al. 2002; Dennerstein et al. 2000; Kravitz et al. 2008), which may precipitate or exacerbateperimenopausal depressive disorders (Chung et al. 2018; Joffe et al. 2002; Gallicchio et al. 2007; Chung et al. 2018; Bromberger et al. 2016).

Physical Activity and Women's Reproductive-Related Mood Disorders

Regular participation in physical activity may offer women a non-pharmacological means to help relieve depressive and anxious symptoms. For example, regular physical activity has been shown to have salutary effects on core symptoms of depression and anxiety disorders including sleep problems (Herring et al. 2015; Kline 2014; Rubio-Arias et al. 2017; Wang et al. 2018), fatigue (McDowell et al. 2019; Tomlinson et al. 2014), depressed mood (Da Costa et al. 2009; Lawlor and Hopker 2001; Mata et al. 2013; 229; Paolucci 2018), anxious symptoms (Petruzzello et al. 1991; Bennie et al. 2019), and cognitive difficulties (Hopkins et al. 2012; Bherer et al. 2014; Dauwan et al. 2021). Several mechanisms have been proposed to explain the antidepressant and anxiolytic effects of regular physical activity and exercise, including: (1) increased availability of neurotransmitters including serotonin and dopamine; (2) positive effects on HPA-axis reactivity to stressors; (3) enhanced neuroplasticity; and (4) reduced systemic inflammation (Kandola et al. 2019; Tsatsoulis and Fountoulakis 2006; Tomlinson et al. 2014). Considering that reproductive hormone fluctuation may confer risk for the development of mood and anxiety disorders via increased sensitivity to environmental stressors, the potential for exercise to prevent or treat affective disorders during reproductive states might involve adaptations resulting from regular physical exercise training which also positively impact physiological adaptations to psychological stressors. Despite the potential positive impact of exercise training on affective regulation, symptoms associated with depression and anxiety disorders may impede the initiation and motivation to engage in physical activity in affected individuals (Leventhal 2012; McDevitt et al. 2006). This may be particularly salient to reproductive-related mood disorders, which are also associated with heightened somatic and pain-related symptoms (Bunevicius et al. 2013; Wang et al. 2003; Straneva et al. 2002; Joffe et al. 2002; Kaiser et al. 2018).

Relationships BetweenPhysical Activity and Menstrually Related Mood Disorders

It has long been suggested that participation in regular physical activity may help to ameliorate pre-menstrual symptoms associated with MRMDs. Indeed, regular physical activity and exercise are often recommended by healthcare providers for pre-menstrual symptom management (Appleton et al. 2018; Kraemer and Kraemer 1998). However, epidemiological studies of the association between regular physical activity and pre-menstrual symptoms have produced mixed results. Several studies have reported a reduction in pre-menstrual symptoms in physically active women, while other studies have reported either negative effects or no association (Aganoff and Boyle 1994; Choi and Salmon 1995; Kroll-Desrosiers et al. 2017; Freeman et al. 2003; Johnson et al. 1995; Rasheed and Al-Sowielem 2003; Samadi et al. 2013). Studies which have employed a physical activity-based intervention for the treatment of MRMDs have reported reductions in PMS-related symptomatology, though these studies have important methodical limitations, including small sample sizes, and failure to control for important covariates (including BMI; Samadi et al. 2021; Steege and Blumenthal 1993; Stoddard et al. 2007). A recent meta-analytic review of randomized controlled trials of exercise for PMS found that exercise significantly reduced symptoms of PMS, though the study authors also noted that significant heterogeneity existed among the fifteen RCTs included in the analysis (2020).

The biopsychosocial mechanisms by which PA may be protective against the development of depression and anxiety not related to reproductive events may also confer protection against the development of MRMDs in susceptible women. For example, the notable central and peripheral physiological stress responses to exercise have led to the theory of "cross-stressor adaptation," which posits that physiological adaptations resulting from physical training may also result in physiological adaptations to psychological stressors (Sothmann et al. 1996). In line with this concept, some studies have shown that exercise training and/or cardiovascular fitness (CRF) may decrease sympathetic nervous system (SNS) (Spalding et al. 2004; Anshel 1996; Rimmele et al. 2009) and HPA-axis activity (Rimmele et al. 2007, 2009) in response to psychological stressors. It is important to note that clinical populations (e.g., individuals with diagnosed depression or anxiety) were not included in these studies, and differences (compared to healthy matched subjects) in baseline and stress-induced cortisol levels in individuals with depression and anxiety disorders have been reported (Burke et al. 2005; Sousa-Lima et al. 2019). Related, a recent randomized controlled trial which investigated the effect of a six-week moderate intensity aerobic exercise program on cortisol stress reactivity in individuals with diagnosed MDD found no significant difference in cortisol reactivity to a laboratory-based psychosocial stressor between patients who completed the aerobic exercise intervention and those in the control condition (Gerber et al. (2020). It is important to note that this small study included both men and women, and menstrual cycle phase was not controlled for, nor included as a covariate in this study. Whether stress reactivity in women with depressive or anxiety disorders might be differentially affected (compared to healthy

controls) by exercise training will require more investigation. Nevertheless, considering the strong correlation between chronic stress and the development of MRMDs and the potential for exercise training to positively modulate physiological stress reactivity to psychosocial stressors, it is possible that exercise training may help to prevent or treat MRMDs by attenuating the negative physiologic effects of stress.

There are other plausible biological mechanisms by which exercise could reduce MRMD symptoms. For example, some studies suggest that exercise training may influence levels of gonadal steroid hormones including estrogen and PROG (Ennour-Idrissi et al. 2015; Crowley et al. 2015b; Stoddard et al. 2008). The concept that exercise training may impact circulating steroid hormone levels in reproductive aged women and, in so doing, reduce the adverse cyclic symptoms associated with MRMDs is an intriguing, yet understudied phenomena. The plausibility of exercise training, through its modulatory effects on gonadal steroid hormones, to reduce depressive symptoms in women with MRMDs is supported by evidence which suggests that menstruating athletes with anovulatory menstrual cycles and low steroid hormone levels exhibit reduced menstrual cycle symptomatology (Shangold et al. 1990). In addition, shorter luteal phases during the menstrual cycle have been shown to correlate with low serum LH, FSH, estrogen, and PROG levels in female athletes (Shangold 1982; Prior et al. 1982; Shangold et al. 1979), and experimental evidence suggests that, in women with a history of PMDD, pharmacologically induced ovarian suppression eliminates PMDD symptoms while hormone (estradiol and PROG) addback precipitates symptom return (Schmidt et al. 1988). Whether moderate exercise training may alleviate cyclic depressive symptoms in women via modulatory effects on reproductive steroid hormone levels has not yet been investigated.

Obesity (which is highly correlated with physical inactivity) has also been associated with increased risk for the development of MRMDs (Bertone-Johnson et al. 2010; Masho et al. 2005). For example, a large cross-sectional study by Masho et al. (2005) found that women with a BMI ≥ 30 had nearly a threefold increased risk for a MRMD, compared to non-obese women [odds ratio (OR) = 2.8 (95 % CI = 1.1–7.2)], and a study by Bertone-Johnson et al. (2010) found that, during a ten-year follow-up of 1057 women, every 1 kg/m^2 increase in BMI was associated with a 3% increase in PMS risk. Considering that regular physical activity and exercise are key tools for weight management, it is possible that participation in regular physical activity may be protective against the development of MRMDs via its positive effects on body fat.

Though aerobic exercise may be effective at relieving symptoms of MRMDs, participation in exercise requires motivation to engage in physical activity during a period of time when MRMD symptoms may limit the desire to engage in physically active behaviors. As such, the initiation and maintenance of a physical activity program may be especially difficult for women with MRMDs. Epidemiological studies have found reduced physical activity levels in women with MRMDs (including PMS and PMDD), compared to women without MRMDs (Morino et al. 2016; Seedhom et al. 2013), and a recent study of 232 female collegiate athletes found that pre-menstrual symptoms such as difficulty concentrating and fatigue/lack of energy negatively impacted athletic performance (Takeda et al. 2015). More research

is needed to determine whether the impairing symptoms of MRMDs adversely impact the ability to participate in exercise training.

Relationships Between Physical Activity and Perinatal Depression

Regular participation in physical activity (PA) has been shown to improve maternal cardiovascular fitness (Melzer et al. 2010; Nascimento et al.2010; Price et al. 2012), reduce adverse maternal obstetric complications and improve fetal/infant health outcomes (Joy et al. 2013; Currie et al. 2013; da Silva et al. 2017; The International Weight Management in Pregnancy (i-WIP) Collaborative Group 2017), reduce postpartum weight retention (da Silva et al. 2017; Joy et al. 2013), and improve maternal mood in euthymic perinatal women (Demissie et al. 2011; Sanchez-Polan et al. 2021; Takahasi et al. 2013). Non-pharmacological treatments (including exercise) for perinatal depression may be particularly favored by women who have concerns about possible adverse effects of antidepressant medications on the developing fetus or newborn. To date, however, little is known regarding the modality, intensity, or appropriate duration of PA interventions for the treatment of perinatal depression. Evidence suggests an inverse association between regular participation in PA (either pre-pregnancy or during pregnancy or postpartum) and the presence of postpartum depressive symptoms (Teychenne and York 2013). However, the majority of studies which have investigated physical activity interventions for the treatment of perinatal depression have been conducted on non-clinical samples (women without depression at study baseline), with risk for PPD as an outcome. For example, results from a recent meta-analysis of 17 available studies (representing 93,676 women) indicated a small effect size [SMD=−0.22 (95% CI−0.42 to−0.01), p=0.04)] for PA during pregnancy to significantly reduce risk of PPD (Nakamura et al. 2019). However, interpretations of these data warrant caution due to methodological limitations including the use of non-clinical samples, significant heterogeneity between studies, and large variability in PPD outcome measures. Indeed, many studies in this area fail to report key components of PA interventions including intensity, modality, and/or duration of sessions (Teychenne and York 2013), and participant attrition was reported to be high in multiple studies, which may limit the generalizability of some of these studies for perinatal populations.

Fewer studies have investigated the effect of exercise on perinatal depression or perinatal depressive symptoms in women exhibiting perinatal depression or perinatal depressive symptomology at study baseline. In an RCT by Daley et al. (2015b), 94 participants who met the Edinburgh Postnatal Depression Scale (EPDS) score of 13+ (indicative of PPD) were randomized to 6 months of moderate intensity facilitated home-based aerobic exercise 3–5 days/week vs. 6 months of standard care (Daley et al. 2015b). In this study, the exercise intervention resulted in significantly reduced EPDS scores (mean difference: − 2.26, p = 0.03; after controlling for baseline EPDS

score and demographic covariates), compared to the control (standard care) group. In addition, Daley and colleagues found that significantly more women in the exercise training group exhibited EPDS scores indicative of recovery (EPDS scores < 13) than women in the standard care condition, suggesting that exercise training may have salutary effects on postpartum depressive symptoms in women with PPD. In support of this concept, results from a recent meta-analysis of six RCTs (where study participants met PPD criteria, as assessed via the EPDS, at baseline) suggested a moderate effect for exercise interventions to reduce postpartum depressive symptoms (Poyatos-Leon et al. 2017). Additionally, a recent meta-analysis of the effect of walking interventions on PPD (including five RCTs and 242 total participants who met PPD criteria as assessed via the EPDS) found that, compared to matched control participants, walking interventions yielded significant decreases in mean EPDS scores from baseline (SMD = − 4.01; 95% CI: − 7.18 to − 0.84) (Pentland et al. 2021). Taken together, evidence suggests that physical activity interventions may be beneficial for reducing depressive symptoms in women with PPD, but more research is needed in this area.

Current American College of Obstetricians and Gynecologists recommendations suggest that, in the absence of medical or obstetric complications, perinatal women can follow the current Centers for Disease Control and Prevention and American College of Sports Medicine recommendations for participation in moderate to vigorous physical activity (MVPA) for 30 min or more on most, if not all, days of the week (2002). However, epidemiological evidence suggests that ~70 % of pregnant women are inactive (Evenson et al. 2004) and that participation in PA declines across gestation (Hausenblas and Downs 2005; Schmidt et al. 2006) and the postpartum period (Pereira et al. 2007). Interestingly, this occurs even though, physiologically, most healthy women have the capacity to perform exercise at moderate to vigorous levels exist throughout gestation (Watson et al. 1991).

The precise biological mechanisms by which exercise may help to reduce or prevent perinatal depression have not yet been elucidated, but may involve similar physiological and psychological adaptations which have been shown to be beneficial for non-perinatal depression (e.g., positive modulation of stress-responsive systems). Considering that exercise is also a physiologic and psychological stressor (Hackney 2006) and depression has been associated with disruption in stress-processing systems, examination of the safety and efficacy of PA interventions for women with perinatal depression may be particularly important. For example, research suggests that women exhibit different physiologic and psychological responses to stress across gestation (Christian 2006), and that these responses may be modified by the presence of a depressive or anxiety disorder (Evans et al. 2008). Therefore, in addition to exercise intensity, the timing of exercise initiation (e.g., prior to pregnancy or during certain gestational stages) may be an important consideration for women with perinatal depression.

Relationships Between Physical Activity and Affective Disorders During the Menopause Transition

There are limited data regarding exercise as a treatment for depression during the menopausal transition. Several RCTs have investigated the efficacy of aerobic exercise training in improving mental health and quality of life in euthymic perimenopausal and postmenopausal women (Luoto et al. 2012; Reed et al. 2014; Mansikkamaki et al. 2012). Though these studies found that aerobic exercise training produced the modest improvements in negative symptoms during midlife (including mood swings, irritability, vasomotor symptoms, sleep difficulties, and depressed mood), the use of non-clinical samples and varied midlife periods limits the ability to generalize these studies to women with mood and anxiety disorders during the menopause transition. One prospective population-based study of 2891 midlife women participating in the Study of Women's Health Across the Nation (SWAN) investigated the longitudinal relationship between regular participation in physical activity [assessed via the Kaiser Physical Activity Survey, a self-administered questionnaire which asks about PA in the past year, and assesses PA in four domains: (1) sports/exercise, (2) active living, (3) occupational, and (4) household/caregiving] and the development of depressive symptoms [assessed via the 20-item Center for Epidemiological Studies Depression Scale (CES-D)] (Dugan et al. 2015). Dugan and colleagues found that participation in physical activity at the public health guidelines recommended dose of 150 min of moderate-intensity PA weekly (Haskell et al. 2007) was associated with lower levels of depressive symptoms over a ten-year period in midlife women during the menopause transition. Several recent cross-sectional studies of the association between physical activity and perimenopausal depression also suggest that regular physical activity and exercise may be associated with reduced depressive symptoms during the menopause transition. For example, a recent study by Bondarev et al. (2020) found that in early perimenopausal women, depression scores on the CES-D were significantly lower in women with high levels of self-reported leisure time PA, compared to women with medium and low levels of leisure time PA (Bondarev et al. 2020). Another recent cross-sectional study by Aparicio et al. (2019) found a similar inverse relationship between self-reported physical fitness and depressive and anxious symptoms in perimenopausal women (Aparicio et al. 2019). This study suggests a possible protective role for PA on the development of depression during the menopause transition.

The extent to which exercise may have a positive impact on core impairing menopausal symptoms, and subsequent mental health, in women during the menopause transition is not known, although there are reasons for assuming that exercise may be beneficial. There are a limited number of RCTs that have investigated the effect of exercise on core symptoms of the menopausal transition that have been linked to increased risk for depression (including vasomotor symptoms and sleep disturbances)(Brown et al. 2009; Natari et al. 2018). Those that have investigated effects of exercise on menopausal symptoms, for example, have found weak associations, or failed to find significant differences in core menopausal symptoms

between perimenopausal women who participated in moderate- to vigorous-intensity aerobic exercise interventions and matched controls (Aparicio et al. 2017; Sternfeld et al. 2014; Daley et al. 2015a). To date, there is insufficient evidence that PA alleviates vasomotor symptoms in midlife women. However, there is some limited evidence that exercise training may be beneficial for sleep disturbances (which are commonly associated with depression) in middle-aged and menopausal women (Mansikkamaki et al. 2012; Kline et al. 2017; Rubio-Arias et al. 2017). Whether exercise training may help to alleviate depressive symptoms during the menopause transition via improvements in vasomotor symptoms and sleep disturbances remains to be fully explored.

Summary

The complex relationships among reproductive steroid hormones and the development and maintenance of affective disorders across the female lifespan are still being elucidated, and there remain many unanswered questions regarding the role of exercise in these associations. Physical activity may serve as a unique opportunity to help women cope with the multiple somatic, sleep-related, and mental health symptoms associated with fluctuating levels of reproductive steroid hormones. However, more research is needed in order to better understand the role of physical activity (and mechanisms underlying this role) in the prevention and treatment of women's reproductive-related mood and anxiety disorders. There has been limited study of the impact of reproductive-related affective disorders on the initiation and maintenance of regular participation in physical activity. Reproductive hormones play a major role in emotion regulation, arousal, cognition, and motivation. Therefore, it is also possible that changes in reproductive steroid hormones, and more specifically sensitivity to these changing hormone levels, may influence participation in physical activity via impacts on psychosocial and physical risk factors for inactivity.

References

Aganoff JA, Boyle GJ. Aerobic exercise, mood states and menstrual cycle symptoms. J Psychosom Res. 1994;38(3):183–92.

Albert KM, Newhouse PA, Estrogen stress and depression: cognitive and biological interactions. Ann Rev Clin Psychol. 2019;15(1):399–423. https://doi.org/10.1146/annurev-clinpsy-050718-095557.

American College of Obstetricians and Gynecologists (ACOG). Physical activity and exercise during pregnancy and the postpartum period: ACOG committee opinion, number 804. Obstet Gynecol. 2020;135(4):e178–88.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.

Angst J, Vollrath M. The natural history of anxiety disorders. Acta Psychiatr Scand. 1991;84(5):446–52.

Aparicio VA, Borges-Cosic M., Ruiz-Cabello P, Coll-Risco I, Acosta-Manzano P, Špacírová Z, Soriano-Maldonado A. Association of objectively measured physical activity and physical fitness with menopause symptoms. The Flamenco Project. Climacteric. 2017;20(5) 456–461. https://doi.org/10.1080/13697137.2017.1329289.

Aparicio VA, Marín-Jiménez N, Coll-Risco I, de la Flor-Alemany M, Baena-García L, Acosta-Manzano P, Aranda P. Doctor ask your perimenopausal patient about her physical fitness; association of self-reported physical fitness with cardiometabolic and mental health in perimenopausal women. Menopause. 2019. https://doi.org/10.1097/GME.0000000000001384.

Appleton SM. Premenstrual syndrome: evidence-based evaluation and treatment. Clin Obstet Gynecol 2018;61(1):52–61. https://doi.org/10.1097/GRF.0000000000000339.

Anshel MH. Effect of chronic aerobic exercise and progressive relaxation on motor performance and affect following acute stress. Behav Med (Washington, DC). 1996;21(4):186–96. https://doi.org/10.1080/08964289.1996.9933757.

Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, Kagawa-Singer M. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med. 2001;52(3):345–56.

Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci. 2015;9.

Beddig T, Reinhard I, Kuehner C. Stress mood and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD). Psychoneuroendocrinology 2019;109:104,372. https://doi.org/10.1016/j.psyneuen.2019.104372.

Bei B, Milgrom J, Ericksen J, Trinder J. Subjective perception of sleep, but not its objective quality, is associated with immediate postpartum mood disturbances in healthy women. Sleep. 2010;33(4):531–8.

Bennie JA., Teychenne MJ, De Cocker K, Biddle SJH. Associations between aerobic and muscle-strengthening exercise with depressive symptom severity among 17839 U.S. adults. Prev Med 121121–127. https://doi.org/10.1016/j.ypmed.2019.02.022.

Bertone-Johnson ER, Whitcomb BW, Missmer SA, Manson JE, Hankinson SE, Rich-Edwards JW. Early life emotional, physical, and sexual abuse and the development of premenstrual syndrome: a longitudinal study. J Womens Health. 2014;23(9):729–39.

Bertone-Johnson ER, Hankinson SE, Willett WC, Johnson SR, Manson JE. Adiposity and the development of premenstrual syndrome. J Women's Health 2010;19(11):1955–62. https://doi.org/10.1089/jwh.2010.212810.1089/jwh.2010.2128.

Bherer L, Erickson KI, Liu-Ambrose T. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. J Aging Res. 2013;2013.

Borenstein J, Chiou C-F, Dean B, Wong J, Wade S. Estimating direct and indirect costs of premenstrual syndrome. J Occup Environ Med. 2005;47(1):26–33. https://doi.org/10.1097/01.jom.0000150209.44312.d1.

Breedlove G, Fryzelka D. Depression screening during pregnancy. J Midwifery Womens Health. 2011;56(1):18–25. https://doi.org/10.1111/j.1542-2011.2010.00002.x.

Breslau N, Schultz L, Peterson E. Sex differences in depression: a role for preexisting anxiety. Psychiatry Res. 1995;58(1):1–12.

Bromberger JT, Kravitz HM, Youk A, Schott LL, Joffe H. Patterns of depressive disorders across 13 years and their determinants among midlife women: SWAN mental health study. J Affecti Disord 2016;20631–40. https://doi.org/10.1016/j.jad.2016.07.005.

Bixo M, Johansson M, Timby E, Michalski L, Bäckström T. Effects of GABA active steroids in the female brain with a focus on the premenstrual dysphoric disorder. J Neuroendocrinol. 2015;30(2):e12553. https://doi.org/10.1111/jne.12553.

Bloch M, Schmidt PJ, Rubinow DR. Premenstrual syndrome: evidence for symptom stability across cycles. Am J Psychiatry. 1997;154(12):1741–6. https://doi.org/10.1176/ajp.154.12.1741.

Bondarev D, Sipilä S, Finni T, Kujala UM, Aukee P, Laakkonen EK, Kovanen V, Kokko K. The role of physical activity in the link between menopausal status and mental well-being. Menopause. 27(4):398–409. https://doi.org/10.1097/GME.0000000000001490.

Brilman EI, Ormel J. Life events, difficulties and onset of depressive episodes in later life. Psychol Med. 2001;31(5):859–69.
Brown WJ, Mishra GD, Dobson A. Changes in physical symptoms during the menopause transition. Int J Behav Med. 2002;9(1):53–67.
Brown JP, Gallicchio L, Flaws JA., Tracy JK. Relations among menopausal symptoms sleep disturbance and depressive symptoms in midlife. Maturitas 2009;62(2):184–9. https://doi.org/10.1016/j.maturitas.2008.11.019.
Bunevicius A, Rubinow DR, Calhoun A, Leserman J, Richardson E, Rozanski K, Girdler SS. The association of migraine with menstrually related mood disorders and childhood sexual abuse. J Womens Health. 2013;22(10):871–6.
Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. Recent Prog Horm Res. 2001;57:257–75.
Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 2005;30(9):846–56. https://doi.org/10.1016/j.psyneuen.2005.02.010.
Byrne A, Byrne D. The effect of exercise on depression, anxiety and other mood states: a review. J Psychosom Res. 1993;37(6):565–74.
Caruso D, Masci I, Cipollone G, Palagini L. Insomnia and depressive symptoms during the menopausal transition: theoretical and therapeutic implications of a self-reinforcing feedback loop. Maturitas. 2019;12:378–81. https://doi.org/10.1016/j.maturitas.2019.02.007.
Choi PY, Salmon P. Symptom changes across the menstrual cycle in competitive sportswomen, exercisers and sedentary women. Br J Clin Psychol. 1995;34(3):447–60.
Christian LM. Physiological reactivity to psychological stress in human pregnancy: current knowledge and future directions. Prog Neurobiol. 2012;99(2):106–16. https://doi.org/10.1016/j.pneurobio.2012.07.003.
Chung HF, Pandeya N, Dobson AJ, Kuh D, Brunner EJ, Crawford SL, Avis NE, Gold EB, Mitchell ES, Woods NF, Bromberger JT, Thurston RC, Joffe H, Yoshizawa T, Anderson D, Mishra GD. The role of sleep difficulties in the vasomotor menopausal symptoms and depressed mood relationships: an international pooled analysis of eight studies in the InterLACE consortium. Psychological Med. 2018;48(15):2550–61. https://doi.org/10.1017/S0033291718000168.
Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry. 2006;63(4):385–90.
Colvin A, Richardson GA, Cyranowski JM, Youk A, Bromberger JT. The role of family history of depression and the menopausal transition in the development of major depression in midlife women: study of women's health across the nation mental health study (SWAN MHS). Depression Anxiety. 2021;34(9):826–35. https://doi.org/10.1002/da.22651.
Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150(6):782–6.
Crowley SK, Girdler SS. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans? Psychopharmacology (Berl). 2014;231(17):3619–34. https://doi.org/10.1007/s00213-014-3572-8.
Crowley SK, Pedersen CA, Leserman J, Girdler SS. The influence of early life sexual abuse on oxytocin concentrations and premenstrual symptomatology in women with a menstrually related mood disorder. Biol Psychol. 2015a;109:1–9. https://doi.org/10.1016/j.biopsycho.2015.04.003.
Crowley SK, Wilkinson LL, Wigfall LT, Reynolds AM, Muraca ST, Glover SH, Wooten NR, Sui X, Beets MW, Durstine JL, Newman-Norlund RD, Youngstedt SD. Physical fitness and depressive symptoms during army basic combat training. Med Sci Sports Exerc. 2015b;47(1):151–8. https://doi.org/10.1249/mss.0000000000000396.
Crowley SK, O'Buckley TK, Schiller CE, Stuebe A, Morrow AL, Girdler SS. Blunted neuroactive steroid and HPA axis responses to stress are associated with reduced sleep quality and negative affect in pregnancy: a pilot study. Psychopharmacology (Berl). 2016. https://doi.org/10.1007/s00213-016-4217-x.

Crowley SK, Rebellon J, Huber C, Leonard AJ, Henderson D, Magal M. Cardiorespiratory fitness sleep and physiological responses to stress in women. Eur J Sport Sci. 2020;20(10):1368–77. https://doi.org/10.1080/17461391.2020.1716855.

Cubeddu A, Bucci F, Giannini A, Russo M, Daino D, Russo N, Merlini S, Pluchino N, Valentino V, Casarosa E. Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. Psychoneuroendocrinology. 2011;36(4):523–30.

Currie LM, Blackman K, Clancy L, Levy DT. The effect of tobacco control policies on smoking prevalence and smoking-attributable deaths in Ireland using the IrelandSS simulation model. Tob Control. 2013;22(e1):e25–32. https://doi.org/10.1136/tobaccocontrol-2011-050248.

Da Costa D, Lowensteyn I, Abrahamowicz M, Ionescu-Ittu R, Dritsa M, Rippen N, Cervantes P, Khalifé S. A randomized clinical trial of exercise to alleviate postpartum depressed mood. J Psychosomat Obstetr Gynecol. 2009;30(3):191–200.

Daley A, Thomas A, Roalfe A, Stokes-Lampard H, Coleman S, Rees M, Hunter M, MacArthur C. The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. BJOG. 2015a;122(4):565–75.

Daley AJ, Blamey RV, Jolly K, Roalfe AK, Turner KM, Coleman S, McGuinness M, Jones I, Sharp DJ, MacArthur C. A pragmatic randomized controlled trial to evaluate the effectiveness of a facilitated exercise intervention as a treatment for postnatal depression: the PAM-PeRS trial. Psychol Med. 2015b;45(11):2413–25. https://doi.org/10.1017/s0033291715000409.

Daley AJ, Foster L, Long G, Palmer C, Robinson O, Walmsley H, Ward R. The effectiveness of exercise for the prevention and treatment of antenatal depression: systematic review with meta-analysis. BJOG. 2015c;122(1):57–62. https://doi.org/10.1111/1471-0528.12909.

Dauwan M, Begemann MJH, Slot MIE, Lee EHM, Scheltens P, Sommer IEC. Physical exercise improves quality of life depressive symptoms and cognition across chronic brain disorders: a transdiagnostic systematic review and meta-analysis of randomized controlled trials. J Neurol. 2021;268(4):1222–46. https://doi.org/10.1007/s00415-019-09493-9.

Daumit GL, Goldberg RW, Anthony C, Dickerson F, Brown CH, Kreyenbuhl J, Wohlheiter J, Dixon J. Physical activity patterns in adults with severe mental illness. J Nerv Ment Dis. 2005;193(10):641–6.

deMoraes GPA, Lorenzo L, Pontes GAR, Montenegro MC, Cantilino A. Screening and diagnosing postpartum depression: when and how? Trends Psychiatry Psychother 2017;39(1):54–61. https://doi.org/10.1590/2237-6089-2016-0034.

de Novaes Soares C, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry. 2001;58(6):529–34.

da Silva SG, Ricardo LI, Evenson KR, Hallal PC, Leisure-time physical activity in pregnancy and maternal-child health: a systematic review and meta-analysis of randomized controlled trials and cohort studies. Sports Med. 2017;47(2):295–317. https://doi.org/10.1007/s40279-016-0565-2.

Demissie Z, Siega-Riz AM, Evenson KR, Herring AH, Dole N, Gaynes BN. Physical activity and depressive symptoms among pregnant women: the PIN3 study. Arch Womens Ment Health. 2011;14(2):145–57. https://doi.org/10.1007/s00737-010-0193-z.

Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstetr Gynecol. 2000;96(3):351–8.

Dennerstein L, Guthrie JR, Clark M, Lehert P, Henderson VW. A population-based study of depressed mood in middle-aged, Australian-born women. Menopause (New York, NY). 2004;11(5):563–8.

Dugan SA, Bromberger JT, Segawa E, Avery E, Sternfeld B. Association between physical activity and depressive symptoms: midlife women in SWAN. Med Sci Sports Exerc. 2015;47(2):335–42.

Dunn EC, Gilman SE, Willett JB, Slopen NB, Molnar BE. The impact of exposure to interpersonal violence on gender differences in adolescent-onset major depression: results from the National Comorbidity Survey Replication (NCS-R). Depress Anxiety. 2012;29(5):392–9. https://doi.org/10.1002/da.21916.

Eiland L, McEwen BS. Early life stress followed by subsequent adult chronic stress potentiates anxiety and blunts hippocampal structural remodeling. Hippocampus. 2012;22(1):82–91.
Ekholm UB, Backstrom T. Influence of premenstrual syndrome on family, social life, and work performance. Int J Health Serv. 1994;24(4):629–47.
Eriksson E, Ekman A, Sinclair S, Sorvik K, Ysander C, Mattson UB, Nissbrandt H. Escitalopram administered in the luteal phase exerts a marked and dose-dependent effect in premenstrual dysphoric disorder. J Clin Psychopharmacol. 2008;28(2):195–202. https://doi.org/10.1097/JCP.0b013e3181678a28.
Emamian F, Khazaie H, Okun ML, Tahmasian M, Sepehry AA. Link between insomnia and perinatal depressive symptoms: a meta-analysis. J Sleep Res. 2019;28(6). https://doi.org/10.1111/jsr.12858.
Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res. 2015;17(1). https://doi.org/10.1186/s13058-015-0647-3.
Epperson CN, Sammel MD, Bale TL, Kim DR, Conlin S, Scalice S, Freeman K, Freeman EW. Adverse childhood experiences and risk for first-episode major depression during the menopause transition. J Clin Psychiatry 2017;78(3):e298–e307. https://doi.org/10.4088/JCP.16m10662.
Evans LM, Myers MM, Monk C. Pregnant women's cortisol is elevated with anxiety and depression—but only when comorbid. Arch Womens Ment Health. 2008;11(3):239–48. https://doi.org//10.1007/s00737-008-0019-4.
Evenson KR, Savitz DA, Huston SL. Leisure-time physical activity among pregnant women in the US. Paediatr Perinat Epidemiol. 2004;18(6):400–7. https://doi.org/10.1111/j.1365-3016.2004.00595.x.
Faas M, Bouman A, Moesa H, Heineman MJ, de Leij L, Schuiling G. The immune response during the luteal phase of the ovarian cycle: a Th2-type response? Fertil Steril. 2000;74(5):1008–13.
Falah-Hassani K, Shiri R, Dennis C-L. Prevalence and risk factors for comorbid postpartum depressive symptomatology and anxiety. J Affect Disord. 2016;198:142–7.
Farage MA, Neill S, MacLean AB. Physiological changes associated with the menstrual cycle: a review. Obstet Gynecol Surv. 2009;64(1):58–72. https://doi.org/10.1097/OGX.0b013e3181932a37.
Freeman EW. Premenstrual syndrome and premenstrual dysphoric disorder: definitions and diagnosis. Psychoneuroendocrinology. 2003;28:25–37.
Freeman EW. Depression in the menopause transition: risks in the changing hormone milieu as observed in the general population. Women Midlife Health. 2015;1(1):1.
Freeman EW, Sondheimer SJ. Premenstrual dysphoric disorder: recognition and treatment. Prim Care Companion J Clin Psychiatry. 2003;5(1):30–9.
Freeman EW, Sondheimer SJ, Rickels K. Effects of medical history factors on symptom severity in women meeting criteria for premenstrual syndrome. Obstet Gynecol. 1988;72(2):236–9.
Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry. 2006;63(4)375. https://doi.org/10.1001/archpsyc.63.4.375.
Freeman EW. Associations of depression with the transition to menopause. Menopause. 2010;17(4):823–7. https://doi.org/10.1097/gme.0b013e3181db9f8b.
Freeman EW, Sammel MD, Boorman DW, Zhang R. Longitudinal pattern of depressive symptoms around natural menopause. JAMA Psychiatry. 2014;71(1):36–43.
Gallicchio L, Schilling C, Miller SR, Zacur H, Flaws JA. Correlates of depressive symptoms among women undergoing the menopausal transition. J Psychosom Res. 2007;63(3):263–8.
Gandara BK, Leresche L, Mancl L. Patterns of salivary estradiol and progesterone across the menstrual cycle. Ann N Y Acad Sci. 2007;1098:446–50. https://doi.org/10.1196/annals.1384.022.
Garfield L, Mathews HL, Janusek LW. Inflammatory and epigenetic pathways for perinatal depression. Biol Res Nurs. 2015. https://doi.org/10.1177/1099800415614892.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106(5 Pt 1):1071–83. https://doi.org/10.1097/01.AOG.0000183597.31630.db.

Gerber M, Imboden C, Beck J, Brand S, Colledge F, Eckert A, Holsboer-Trachsler E, Pühse U, Hatzinger M. Effects of aerobic exercise on cortisol stress reactivity in response to the trier social stress test in inpatients with major depressive disorders: a randomized controlled trial. J Clin Med 2020;9(5):1419. https://doi.org/10.3390/jcm9051419.

Gibbs Z, Kulkarni J. Risk factors for depression during perimenopause. In: Barnes D, editor. Women's reproductive mental health across the lifespan. New, York, NY: Springer; 2014. p. 215–33.

Gibbs Z, Lee S, Kulkarni J. What factors determine whether a woman becomes depressed during the perimenopause? Arch Womens Ment Health. 2012;15(5):323–32. https://doi.org/10.1007/s00737-012-0304-0.

Girdler SS, Sherwood A, Hinderliter AL, Leserman J, Costello NL, Straneva PA, Pedersen CA, Light KC. Biological correlates of abuse in women with premenstrual dysphoric disorder and healthy controls. Psychosom Med. 2003;65(5):849–56.

Glynn LM, Davis EP, Sandman CA. New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. Neuropeptides. 2013;47(6):363–70. https://doi.org/10.1016/j.npep.2013.10.007.

Goodwin RD. Association between physical activity and mental disorders among adults in the United States. Prev Med. 2003;36(6):698–703.

Gordon JL, Girdler SS, Meltzer-Brody SE, Stika CS, Thurston RC, Clark CT, Prairie BA, Moses-Kolko E, Joffe H, Wisner KL. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. Am J Psychiatry. 2015;172(3):227–36. https://doi.org/10.1176/appi.ajp.2014.14070918.

Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Leserman J, Girdler SS. Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition. Menopause (New York, NY). 2016;23(3):257–66. https://doi.org/10.1097/gme.0000000000000528.

Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition. JAMA Psychiatry 2018;75(2):149. https://doi.org/10.1001/jamapsychiatry.2017.3998.

Gordon JL, Sander B, Eisenlohr-Moul TA., Tottenham LS. Mood sensitivity to estradiol predicts depressive symptoms in the menopause transition. Psychol Med. 2021;51(10):1733–41. https://doi.org/10.1017/S0033291720000483.

Goyal D, Gay C, Lee K. Fragmented maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. Arch Womens Ment Health. 2009;12(4):229–37. https://doi.org/10.1007/s00737-009-0070-9.

Green T, Flash S, Reiss AL. Sex differences in psychiatric disorders: what we can learn from sex chromosome aneuploidies. Neuropsychopharmacology 2018;44(1) 9–21. https://doi.org/10.1038/s41386-018-0153-2.

Guintivano J, Manuck T, Meltzer-Brody S. Predictors of postpartum depression: a comprehensive review of the last decade of evidence. Clin Obstet Gynecol. 2018;61(3):591–603. https://doi.org/10.1097/GRF.0000000000000368.

Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. BMJ j3119. https://doi.org/10.1136/bmj.j3119.

Hackney AC. Exercise as a stressor to the human neuroendocrine system. Medicina (Kaunas). 2006;42(10):788–97.

Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). Psychoneuroendocrinology. 2003;28 Suppl 3:1–23.

Hallgren M, Kandola A, Stubbs B, Nguyen T-T-D, Wallin P, Andersson G, Ekblom-Bak E. Associations of exercise frequency and cardiorespiratory fitness with symptoms of depression and anxiety—a cross-sectional study of 36595 adults. Mental Health Phys Act 2021;19100351. https://doi.org/10.1016/j.mhpa.2020.100351.

Handa RJ, Burgess LH, Kerr JE, O'Keefe JA. Gonadal steroid hormone receptors and sex differences in the hypothalamo-pituitary-adrenal axis. Horm Behav. 1994;28(4):464–76.

Hantsoo L, Epperson CN. Premenstrual dysphoric disorder: epidemiology and treatment. Curr Psychiatry Rep. 2015;17(11). https://doi.org/10.1007/s11920-015-0628-3.

Hantsoo L, Epperson CN. Allopregnanolone in premenstrual dysphoric disorder (PMDD): evidence for dysregulated sensitivity to GABA-A receptor modulating neuroactive steroids across the menstrual cycle. Neurobiol Stress. 2020;12:100,213. https://doi.org/10.1016/j.ynstr.2020.100213.

Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(8):1423–34. https://doi.org/10.1249/mss.0b013e3180616b27.

Hausenblas HA, Downs DS. Prospective examination of leisure-time exercise behavior during pregnancy. J Appl Sport Psychol. 2005;17(3):240–6.

Harvey SB, Øverland S, Hatch SL, Wessely S, Mykletun A, Hotopf M. Exercise and the prevention of depression: results of the HUNT cohort study. Am J Psychiatry 2018;175(1):28–36. https://doi.org/10.1176/appi.ajp.2017.16111223.

Hodes GE, Epperson CN. Sex differences in vulnerability and resilience to stress across the life span. Biolog Psychiatry. 2019;86(6) 421-432. https://doi.org/10.1016/j.biopsych.2019.04.028.

Heinemann LAJ, Minh TD, Heinemann K, Lindemann M, Filonenko A. Intercountry assessment of the impact of severe premenstrual disorders on work and daily activities. Health Care Women Int. 2012;33(2):109–24. https://doi.org/10.1080/07399332.2011.610530.

Herring MP, Kline CE, O'Connor PJ. Effects of exercise on sleep among young women with generalized anxiety disorder. Ment Health Phys Act. 2015;9:59–66. https://doi.org/10.1016/j.mhpa.2015.09.002.

Hindberg I, Naesh O. Serotonin concentrations in plasma and variations during the menstrual cycle. Clin Chem. 1992;38(10):2087–9.

Hopkins ME, Davis FC, VanTieghem MR, Whalen PJ, Bucci DJ. Differential effects of acute and regular physical exercise on cognition and affect. Neuroscience. 2012;215:59–68.

Hou L, Huang Y, Zhou R. Premenstrual syndrome is associated with altered cortisol awakening response. Stress. 2019;22(6):640–6. https://doi.org/10.1080/10253890.2019.1608943.

Howell HB, Brawman-Mintzer O, Monnier J, Yonkers KA. Generalized anxiety disorder in women. Psychiatr Clin North Am. 2001;24(1):165–78.

Huo L, Straub RE, Roca C, Schmidt PJ, Shi K, Vakkalanka R, Weinberger DR, Rubinow DR. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. Biol Psychiatry. 2007;62(8):925–33.

Ismaili E, Walsh S, O'Brien PMS, Bäckström T, Brown C, Dennerstein L, Eriksson E, Freeman EW, Ismail KMK, Panay N, Pearlstein T, Rapkin A, Steiner M, Studd J, Sundström-Paromma I, Endicott J, Epperson CN, Halbreich U, Reid R, Rubinow D, Schmidt P, Yonkers K, Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): auditable standards for diagnosis and management of premenstrual disorder. Arch Women's Mental Health 2016;19(6):953–958. https://doi.org/10.1007/s00737-016-0631-7.

Jacka F, Pasco J, Williams L, Leslie E, Dodd S, Nicholson G, Kotowicz M, Berk M. Lower levels of physical activity in childhood associated with adult depression. J Sci Med Sport. 2011;14(3):222–6.

Joffe H, Hall JE, Soares CN, Hennen J, Reilly CJ, Carlson K, Cohen LS. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. Menopause (New York, NY). 2002;9(6):392–8.

Johnson WG, Carr-Nangle RE, Bergeron KC. Macronutrient intake, eating habits, and exercise as moderators of menstrual distress in healthy women. Psychosom Med. 1995;57(4):324–30.
Joy EA, Mottola MF, Chambliss H. Integrating exercise is medicine(R) into the care of pregnant women. Curr Sports Med Rep. 2013;12(4):245–7. https://doi.org/10.1249/JSR.0b013e31829a6f7e.
Kaiser G, Janda C, Kleinstäuber M, Weise C. Clusters of premenstrual symptoms in women with PMDD: appearance stability and association with impairment. J Psychosom Res. 2018;11538–43. https://doi.org/10.1016/j.jpsychores.2018.10.004.
Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical activity and depression: towards understanding the antidepressant mechanisms of physical activity. Neurosci Biobehav Rev 2019;107525–539. https://doi.org/10.1016/j.neubiorev.2019.09.040.
Kendler K, Silberg J, Neale M, Kessler R, Heath A, Eaves L. Genetic and environmental factors in the aetiology of menstrual, premenstrual and neurotic symptoms: a population-based twin study. Psychol Med. 1992;22(01):85–100.
Kendler KS, Gardner CO. Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. Am J Psychiatry. 2014;171(4):426–35. https://doi.org/10.1176/appi.ajp.2013.13101375.
Kessel B. Premenstrual syndrome: advances in diagnosis and treatment. Obstet Gynecol Clin North Am. 2000;27(3):625–39.
Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: lifetime prevalence, chronicity and recurrence. J Affect Disord. 1993;29(2-3):85–96.
Kikuchi H, Nakatani Y, Seki Y, Yu X, Sekiyama T, Sato-Suzuki I, Arita H. Decreased blood serotonin in the premenstrual phase enhances negative mood in healthy women. J Psychosom Obstet Gynaecol. 2010;31(2):83–9. https://doi.org/10.3109/01674821003770606.
Kipp M, Berger K, Clarner T, Dang J, Beyer C. Sex steroids control neuroinflammatory processes in the brain: relevance for acute ischaemia and degenerative demyelination. J Neuroendocrinol. 2012;24(1):62–70. https://doi.org/10.1111/j.1365-2826.2011.02163.x.
Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med. 1999;61(2):154–62.
Kline CE. The bidirectional relationship between exercise and sleep: implications for exercise adherence and sleep improvement. Am J Lifestyle Med. 2014;8(6):375–9. https://doi.org/10.1177/1559827614544437.
Kline CE, Sui X, Hall MH, Youngstedt SD, Blair SN, Earnest CP, Church TS. Dose-response effects of exercise training on the subjective sleep quality of postmenopausal women: exploratory analyses of a randomised controlled trial. BMJ Open. 2012;2(4):e001044. https://doi.org/10.1136/bmjopen-2012-001044.
Kossman DA, Williams NI, Domchek SM, Kurzer MS, Stopfer JE, Schmitz KH. Exercise lowers estrogen and progesterone levels in premenopausal women at high risk of breast cancer. J Appl Physiol. 2011;111(6):1687–93.
Kraemer GR, Kraemer RR. Premenstrual syndrome: diagnosis and treatment experiences. J Womens Health. 1998;7(7):893–907.
Kravitz HM, Zhao X, Bromberger JT, Gold EB, Hall MH, Matthews KA, Sowers MR. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep. 2008; https://doi.org/10.5665/sleep/31.7.979.
Kritz-Silverstein D, Barrett-Connor E, Corbeau C. Cross-sectional and prospective study of exercise and depressed mood in the elderly the Rancho Bernardo Study. Am J Epidemiol. 2001;153(6):596–603.
Kroll-Desrosiers AR, Ronnenberg AG, Zagarins SE, Houghton SC, Takashima-Uebelhoer BB, Bertone-Johnson ER, Stepto NK. Recreational physical activity and premenstrual syndrome in young adult women: a cross-sectional study. PLOS ONE 2017;12(1):e0169728. https://doi.org/10.1371/journal.pone.0169728.

Kulkarni J, Leyden O, Gavrilidis E, Thew C, Thomas EHX. The prevalence of early life trauma in premenstrual dysphoric disorder (PMDD). Psychiatry Res. 2022;308:114,381. https://doi.org/10.1016/j.psychres.2021.114381.

Labaka A, Goni-Balentziaga O, Lebena A, Perez-Tejada J. Biological sex differences in depression: a systematic review. Biolog Res Nurs. 2018;20(4):383–92.

Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. BMJ. 2001;322(7289):763.

Lentz MJ, Woods N, Heitkemper M, Mitchell E, Henker R, Shaver J. Ovarian steroids and premenstrual symptoms: a comparison of group differences and intra-individual patterns. Res Nurs Health. 2007;30(3):238–49. https://doi.org/10.1002/nur.20188.

Leventhal AM. Relations between anhedonia and physical activity. Am J Health Behav. 2012;36(6):860–72. https://doi.org/10.5993/ajhb.36.6.12.

Liu Na, Wang Jie, Chen Dan-dan, Sun Wei-jia, Li Ping, Zhang Wei, Effects of exercise on pregnancy and postpartum fatigue: A systematic review and meta-analysis. European J Obstet Gynecol Reproductive Biol. 253285–295. https://doi.org/10.1016/j.ejogrb.2020.08.013.

Luoto R, Moilanen J, Heinonen R, Mikkola T, Raitanen J, Tomas E, Ojala K, Mansikkamaki K, Nygard CH. Effect of aerobic training on hot flushes and quality of life – a randomized controlled trial. Ann Med. 2012;44(6):616–26. https://doi.org/10.3109/07853890.2011.583674.

Maki PM, Kornstein SG, Joffe H, Bromberger JT, Freeman EW, Athappilly G, Bobo WV, Rubin LH, Koleva HK, Cohen LS, Soares CN. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. Menopause. 2019;25(10):1069–85. https://doi.org/10.1097/GME.0000000000001174.

Mansikkamaki K, Raitanen J, Nygard CH, Heinonen R, Mikkola T, EijaTomas Luoto R. Sleep quality and aerobic training among menopausal women – a randomized controlled trial. Maturitas. 2012;72(4):339–45. https://doi.org/10.1016/j.maturitas.2012.05.003.

Masho SW, Adera T, South-Paul J. Obesity as a risk factor for premenstrual syndrome. J Psychosomat Obstetr Gynecol. 2005;26(1):33–9.

Mata J, Hogan CL, Joormann J, Waugh CE, Gotlib IH. Acute exercise attenuates negative affect following repeated sad mood inductions in persons who have recovered from depression. J Abnorm Psychol. 2013;122(1):45.

Matud MP. Gender differences in stress and coping styles. Personal Individ Differ. 2004;37(7):1401–15.

McDevitt J, Snyder M, Miller A, Wilbur J. Perceptions of barriers and benefits to physical activity among outpatients in psychiatric rehabilitation. J Nurs Scholarsh. 2006;38(1):50–5.

McDowell CP, Dishman RK, Gordon BR, Herring MP. Physical activity and anxiety: a systematic review and meta-analysis of prospective cohort studies. Am J Prevent Med 2019;57(4):545–56. https://doi.org/10.1016/j.amepre.2019.05.012.

McEvoy KM, Rayapati D, Washington Cole KO, Erdly C, Payne JL, Osborne LM. Poor postpartum sleep quality predicts subsequent postpartum depressive symptoms in a high-risk sample. J Clin Sleep Med. 2019;15(9):1303–10. https://doi.org/10.5664/jcsm.7924.

McEwen B. Estrogen actions throughout the brain. Recent Prog Horm Res. 2002;57:357–84.

Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. Cochrane Database Syst Rev. 2009;3.

Mehta D, Rex-Haffner M, Søndergaard HB, Pinborg A, Binder EB, Frokjaer VG. Evidence for oestrogen sensitivity in perinatal depression: pharmacological sex hormone manipulation study. Br J Psychiatry. 2019;215(3):519–27. https://doi.org/10.1192/bjp.2018.234.

Melzer K, Schutz Y, Soehnchen N, Othenin-Girard V, Martinez de Tejada B, Irion O, Boulvain M, Kayser B. Effects of recommended levels of physical activity on pregnancy outcomes. Am J Obstet Gynecol. 2010;202(3):261–6. https://doi.org/10.1016/j.ajog.2009.10.876.

Metcalf MG. Incidence of ovulation from the menarche to the menopause: observations of 622 New Zealand women. N Z Med J. 1983;96(738):645–8.

Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. J Endocrinol. 1983;97(2):213–9.
Morino S, Egawa M, Hirata H, Nishimura F, Aoyama T, Konishi I. Association between Premenstrual Syndrome and Daily Physical Activity Levels. J Womens Health Issues Care 2016;5(5). https://doi.org/10.4172/2325-9795.1000241.
Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci. 1995;771:257–72.
Mundy EA, Weber M, Rauch SL, Killgore WD, Simon NM, Pollack MH, Rosso IM. Adult anxiety disorders in relation to trait anxiety and perceived stress in childhood. Psychol Rep. 2015;117(2):473–89. https://doi.org/10.2466/02.10.PR0.117c17z6.
Nascimento SL, Surita FG, Cecatti JG. Physical exercise during pregnancy: a systematic review. Curr Opin Obstet Gynecol. 2012;24(6):387–94. https://doi.org/10.1097/GCO.0b013e328359f131.
Natari RB, Clavarino AM, McGuire TM, Dingle KD, Hollingworth SA. The bidirectional relationship between vasomotor symptoms and depression across the menopausal transition: a systematic review of longitudinal studies. Menopause. 2018a;25(1) 109–20. https://doi.org/10.1097/GME.0000000000000949.
Nakamura A, van der Waerden J, Melchior M, Bolze C, El-Khoury F, Pryor L. Physical activity during pregnancy and postpartum depression: systematic review and meta-analysis. J Affect Disord. 2019;24629–41. https://doi.org/10.1016/j.jad.2018.12.009.
O'Connor KA, Ferrell R, Brindle E, Trumble B, Shofer J, Holman DJ, Weinstein m. Progesterone and ovulation across stages of the transition to menopause. Menopause (New York, NY). 2009;16(6):1178–87. https://doi.org/10.1097/gme.0b013e3181aa192d.
Oertelt-Prigione S. Immunology and the menstrual cycle. Autoimmun Rev. 2012;11(6):A486–92.
O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annu Rev Clin Psychol. 2013;9:379–407. https://doi.org/10.1146/annurev-clinpsy-050212-185612.
O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol. 2014;28(1):3–12. https://doi.org/10.1016/j.bpobgyn.2013.09.002.
Okun ML, Kline CE, Roberts JM, Wettlaufer B, Glover K, Hall M. Prevalence of sleep deficiency in early gestation and its associations with stress and depressive symptoms. J Womens Health (Larchmt). 2013;22(12):1028–37. https://doi.org/10.1089/jwh.2013.4331.
Okun ML. Sleep and postpartum depression. Curr Opin Psychiatry. 2015;28(6):490–6. https://doi.org/10.1097/yco.0000000000000206.
Osnes RS, Eberhard-Gran M, Follestad T, Kallestad H, Morken G, Roaldset JO. Mid-Pregnancy Insomnia and its association with perinatal depressive symptoms: a prospective cohort study. Behavioral Sleep Med. 2021;19(3):285–302. https://doi.org/10.1080/15402002.2020.1743705.
Parry BL, Meliska CJ, Sorenson DL, Martinez LF, Lopez AM, Elliott JA, Hauger RL. Reduced phase-advance of plasma melatonin after bright morning light in the luteal, but not follicular, menstrual cycle phase in premenstrual dysphoric disorder: an extended study. Chronobiol Int. 2011;28(5):415–24. https://doi.org/10.3109/07420528.2011.567365.
Paolucci EM, Loukov D, Bowdish DME, Heisz JJ. Exercise reduces depression and inflammation but intensity matters. Biolog Psychol. 2018;13379–84. https://doi.org/10.1016/j.biopsycho.2018.01.015.
Pereira MA, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Peterson KE, Gillman MW. Predictors of change in physical activity during and after pregnancy: project viva. Am J Prev Med. 2007;32(4):312–9. https://doi.org/10.1016/j.amepre.2006.12.017.
Pentland V, Spilsbury S, Biswas A, Mottola MF, Paplinskie S, Mitchell MS. Does walking reduce postpartum depressive symptoms? A systematic review and meta-analysis of randomized controlled trials. J Women's Health. https://doi.org/10.1089/jwh.2021.0296.
Petruzzello SJ, Landers DM, Hatfield BD, Kubitz KA, Salazar W. A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Sports Med. 1991;11(3):143–82.
Pearce E, Jolly K, Jones LL, Matthewman G, Zanganeh M, Daley A. Exercise for premenstrual syndrome: a systematic review and meta-analysis of randomised controlled trials. BJGP Open. 2020;4(3):bjgpopen20X101032. https://doi.org/10.3399/bjgpopen20X101032.

Pluchino N, Cubeddu A, Begliuomini S, Merlini S, Giannini A, Bucci F, Casarosa E, Luisi M, Cela V, Genazzani A. Daily variation of brain-derived neurotrophic factor and cortisol in women with normal menstrual cycles, undergoing oral contraception and in postmenopause. Hum Reprod. 2009;24(9):2303–9.

Pluchino N, Russo M, Santoro AN, Litta P, Cela V, Genazzani AR. Steroid hormones and BDNF. Neuroscience. 2013;239:271–9. https://doi.org/10.1016/j.neuroscience.2013.01.025.

Posillico CK, Schwarz JM. An investigation into the effects of antenatal stressors on the postpartum neuroimmune profile and depressive-like behaviors. Behav Brain Res. 2016;298(Pt B):218–28. https://doi.org/10.1016/j.bbr.2015.11.011.

Poyatos-León R, García-Hermoso A, Sanabria-Martínez G, Álvarez-Bueno C, Cavero-Redondo I, Martínez-Vizcaíno V. Effects of exercise-based interventions on postpartum depression: a meta-analysis of randomized controlled trials. Birth. 2017;44(3):200–8. https://doi.org/10.1111/birt.12294.

Price BB, Amini SB, Kappeler K, Exercise in pregnancy. Medicine Sci Sports Exerc 2012;44(12):2263–69. https://doi.org/10.1249/MSS.0b013e318267ad67.

Putnam KT, Wilcox M, Robertson-Blackmore E, Sharkey K, Bergink V, Munk-Olsen T, Deligiannidis KM, Payne J, Altemus M, Newport J, Apter G, Devouche E, Viktorin A, Magnusson P, Penninx B, Buist A, Bilszta J, O'Hara M, Stuart S, Brock R, Roza S, Tiemeier H, Guille C, Epperson CN, Kim D, Schmidt P, Martinez P, Di Florio A, Wisner KL, Stowe Z, Jones I, Sullivan PF, Rubinow D, Wildenhaus K, Meltzer-Brody S, Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry 2017;4(6):477–85. https://doi.org/10.1016/S2215-0366(17)30136-0.

Prior JC, Yuen BH, Clement P, Bowie L, Thomas J. Reversible luteal phase changes and infertility associated with marathon training. Lancet (Lond). 1982;2(8292):269–70.

Rasheed P, Al-Sowielem LS. Prevalence and predictors of premenstrual syndrome among college-aged women in Saudi Arabia. Ann Saudi Med. 2003;23(6):381–7.

Reck C, Struben K, Backenstrass M, Stefenelli U, Reinig K, Fuchs T, Sohn C, Mundt C. Prevalence, onset and comorbidity of postpartum anxiety and depressive disorders. Acta Psychiatr Scand. 2008;118(6):459–68. https://doi.org/10.1111/j.1600-0447.2008.01264.x.

Reed SD, Guthrie KA, Newton KM, Anderson GL, Booth-LaForce C, Caan B, Carpenter JS, Cohen LS, Dunn AL, Ensrud KE, Freeman EW, Hunt JR, Joffe H, Larson JC, Learman LA, Rothenberg R, Seguin RA, Sherman KJ, Sternfeld BS, LaCroix AZ. Menopausal quality of life: RCT of yoga, exercise, and omega-3 supplements. Am J Obstet Gynecol. 2014;210(3):241–4. https://doi.org/10.1016/j.ajog.2013.11.016.

Rimmele U, Zellweger BC, Marti B, Seiler R, Mohiyeddini C, Ehlert U, Heinrichs M. Trained men show lower cortisol, heart rate and psychological responses to psychosocial stress compared with untrained men. Psychoneuroendocrinology. 2007;32(6):627–35.

Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M. The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. Psychoneuroendocrinology. 2009;34(2):190–8. 10.1016/j.psyneuen.2008.08.023.

Rogers A, Obst S, Teague SJ, Rossen L, Spry EA., Macdonald JA., Sunderland M, Olsson CA, Youssef G, Hutchinson D.Association between maternal perinatal depression and anxiety and child and adolescent development. JAMA Pediatr 2020;174(11):1082. https://doi.org/10.1001/jamapediatrics.2020.2910.

Rothon C, Edwards P, Bhui K, Viner RM, Taylor S, Stansfeld SA. Physical activity and depressive symptoms in adolescents: a prospective study. BMC Med. 2010;8(1):1.

Rubio-Arias JÁ., Marín-Cascales E, Ramos-Campo DJ, Hernandez AV, Pérez-López FR. Effect of exercise on sleep quality and insomnia in middle-aged women: a systematic review and meta-analysis of randomized controlled trials. Maturitas 10049–56. https://doi.org/10.1016/j.maturitas.2017.04.003.

Rubio-Arias JÁ, Marín-Cascales E, Ramos-Campo DJ, Hernandez AV, Pérez-López FR. Effect of exercise on sleep quality and insomnia in middle-aged women: a systematic review and meta-analysis of randomized controlled trials. Maturitas 2017;10049–56. https://doi.org/10.1016/j.maturitas.2017.04.003.

Samadi Z, Taghian F, Valiani M. The effects of 8 weeks of regular aerobic exercise on the symptoms of premenstrual syndrome in non-athlete girls. Iran J Nurs Midwif Res. 2013;18(1).

Santoro N, Lasley B, McConnell D, Allsworth J, Crawford S, Gold EB, Finkelstein JS, Greendale GA, Kelsey J, Korenman S, Luborsky JL, Matthews K, Midgley R, Powell L, Sabatine J, Schocken M, Sowers MF, Weiss G. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: the study of women's health across the nation (SWAN) daily hormone study. J Clin Endocrinol Metab. 2004;89(6):2622–31. https://doi.org/10.1210/jc.2003-031578.

Sánchez-Polán M, Franco E, Silva-José C, Gil-Ares J, Pérez-Tejero J, Barakat R, Refoyo I. Exercise during pregnancy and prenatal depression: a systematic review and meta-analysis. Front Physiol. 2021;12. https://doi.org/10.3389/fphys.2021.640024.

Schiller CE, Schmidt PJ, Rubinow DR. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. Psychopharmacology (Berl). 2014;231(17):3557–67. https://doi.org/10.1007/s00213-014-3599-x.

Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. CNS Spectr. 2015;20(1):48–59. https://doi.org/10.1017/s1092852914000480.

Schiller CE, Johnson SL, Abate AC, Schmidt PJ, Rubinow DR. Reproductive steroid regulation of mood and behavior. Compr Physiol. 2016;6(3):1135.

Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med. 1998;338(4):209–16. https://doi.org/10.1056/nejm199801223380401.

Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Am J Psychiatry. 2004;161(12):2238–44.

Schmidt MD, Pekow P, Freedson PS, Markenson G, Chasan-Taber L. Physical activity patterns during pregnancy in a diverse population of women. J Womens Health (Larchmt). 2006;15(8):909–18. https://doi.org/10.1089/jwh.2006.15.909.

Schmidt PJ, Rubinow DR. Sex hormones and mood in the perimenopause. Ann N Y Acad Sci. 2009;1179:70–85. https://doi.org/10.1111/j.1749-6632.2009.04982.x.

Schmidt PJ, Ben Dor R, Martinez PE, Guerrieri GM, Harsh VL, Thompson K, Koziol DE, Nieman LK, Rubinow DR. Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. JAMA Psychiatry. 2015;72(7):714–26. https://doi.org/10.1001/jamapsychiatry.2015.0111.

Schmidt PJ, Martinez PE, Nieman LK, Koziol DE, Thompson KD, Schenkel L, Wakim PG, Rubinow DR. Premenstrual dysphoric disorder symptoms following ovarian suppression: triggered by change in ovarian steroid levels but not continuous stable levels. Am J Psychiatry 2017;174(10):980–89. https://doi.org/10.1176/appi.ajp.2017.16101113.

Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, Hallgren M, Ponce De Leon A, Dunn AL, Deslandes AC, Fleck MP, Carvalho AF, Stubbs B. Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am J Psychiatry. 2018;175(7):631–648. https://doi.org/10.1176/appi.ajp.2018.17111194.

Seedhom AE, Mohammed ES, Mahfouz EM. Life style factors associated with premenstrual syndrome among El-Minia University Students Egypt. ISRN Public Health. 2013;1–6. https://doi.org/10.1155/2013/617123.

Shangold M, Freeman R, Thysen B, Gatz M. The relationship between long-distance running, plasma progesterone, and luteal phase length. Fertil Steril. 1979;31(2):130–3.

Shangold MM. Menstrual irregularity in athletes: basic principles, evaluation, and treatment. Can J Appl Sport Sci. 1982;7(2):68–73.

Shangold M, Rebar RW, Wentz AC, Schiff I. Evaluation and management of menstrual dysfunction in athletes. JAMA. 1990;263(12):1665–9.

Shechter A, Lespérance P, Kin NNY, Boivin DB. Pilot investigation of the circadian plasma melatonin rhythm across the menstrual cycle in a small group of women with premenstrual dysphoric disorder. PLoS One. 2012;7(12), e51929.

Shorey S, Chee CYI, Ng ED, Chan YH, Tam WWS, Chong YS. Prevalence and incidence of postpartum depression among healthy mothers: a systematic review and meta-analysis. J Psychiatric Res 2018;104, 235–48. https://doi.org/10.1016/j.jpsychires.2018.08.001.

Skouteris H, Germano C, Wertheim EH, Paxton SJ, Milgrom J. Sleep quality and depression during pregnancy: a prospective study. J Sleep Res. 2008;17(2):217–20. https://doi.org/10.1111/j.1365-2869.2008.00655.x.

Slentz CA, Duscha BD, Johnson JL, Ketchum K, Aiken LB, Samsa GP, Houmard JA, Bales CW, Kraus WE. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study. Arch Intern Med. 2004;164(1):31–9.

Soares CN, Almeida OP. Depression during the perimenopause. Arch Gen Psychiatry. 2001;58(3):306.

Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? J Psychiatry Neurosci. 2008;33(4):331–43.

Sothmann MS, Buckworth J, Claytor RP, Cox RH, White-Welkley JE, Dishman RK. Exercise training and the cross-stressor adaptation hypothesis. Exerc Sport Sci Rev. 1996;24:267–87.

Spalding TW, Lyon LA, Steel DH, Hatfield BD. Aerobic exercise training and cardiovascular reactivity to psychological stress in sedentary young normotensive men and women. Psychophysiology. 2004;41(4):552–62. https://doi.org/10.1111/j.1469-8986.2004.00184.x.

Steege JF, Blumenthal JA. The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. J Psychosom Res. 1993;37(2):127–33.

Sternfeld B, Guthrie KA, Ensrud KE, LaCroix AZ, Larson JC, Dunn AL, Anderson GL, Seguin RA, Carpenter JS, Newton KM. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. Menopause (New York, NY). 2014;21(4):330.

Stoddard JL, Dent CW, Shames L, Bernstein L. Exercise training effects on premenstrual distress and ovarian steroid hormones. Eur J Appl Physiol. 2007;99(1):27–37. https://doi.org/10.1007/s00421-006-0313-7.

Straneva PA, Maixner W, Light KC, Pedersen CA, Costello NL, Girdler SS. Menstrual cycle, beta-endorphins, and pain sensitivity in premenstrual dysphoric disorder. Health Psychol. 2002;21(4):358.

Stuart-Parrigon K, Stuart S. Perinatal depression: an update and overview. Curr Psychiatry Rep. 2014;16(9):468. https://doi.org/10.1007/s11920-014-0468-6.

Sousa-Lima J, Moreira PS, Raposo-Lima C, Sousa N, Morgado P. Relationship between obsessive compulsive disorder and cortisol: systematic review and meta-analysis. Eur Neuropsychopharmacol. 2019;29(11):1185–98. https://doi.org/10.1016/j.euroneuro.2019.09.001.

Takahasi EH, Alves MT, Alves GS, Silva AA, Batista RF, Simoes VM, Del-Ben CM, Barbieri MA. Mental health and physical inactivity during pregnancy: a cross-sectional study nested in the BRISA cohort study. Cad Saude Publica. 2013;29(8):1583–94.

Takeda T, Imoto Y, Nagasawa H, Muroya M, Shiina M. Premenstrual syndrome and premenstrual dysphoric disorder in Japanese collegiate athletes. J Pediatr Adolesc Gynecol. 2015;28(4):215–8.

Tebeka S, Le Strat Y, De Higgons AP, Benachi A, Dommergues M, Kayem G, Lepercq J, Luton D, Mandelbrot L, Ville Y, Ramoz N, du Tezenas MS, Mullaert J, Dubertret C, Bertin E, Bourneuf C, Colombe J, Couppa L, Dommergue M, Dubertret C, Georges F, Hebbache C, Kayem G, Le Bars M, Le Strat Y, Lepercq J, Luton D, Madhavi JG, Mandelbrot L, Mullaert J, Parent C, de Premorel A, Ramoz N, Tebeka S, Ville Y. , Prevalence and incidence of postpartum depression and environmental factors: The IGEDEPP cohort. J Psychiatric Res. 2021;138366–74. https://doi.org/10.1016/j.jpsychires.2021.04.004.

Teychenne M, York R. Physical activity, sedentary behavior, and postnatal depressive symptoms: a review. Am J Prev Med. 2013;45(2):217–27. https://doi.org/10.1016/j.amepre.2013.04.004.

Tomlinson D, Diorio C, Beyene J, Sung L. Effect of exercise on cancer-related fatigue: a meta-analysis. Am J Phys Med Rehabil. 2014;93(8):675–86.

Tsatsoulis A, Fountoulakis S. The protective role of exercise on stress system dysregulation and comorbidities. Ann N Y Acad Sci. 2006;1083:196–213. https://doi.org/10.1196/annals.1367.020.

Verreault N, Da Costa D, Marchand A, Ireland K, Dritsa M, Khalife S. Rates and risk factors associated with depressive symptoms during pregnancy and with postpartum onset. J Psychosom Obstet Gynaecol. 2014;35(3):84–91. https://doi.org/10.3109/0167482x.2014.947953.

Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. Headache. 2003;43(5):470–8.

Wang W-L, Chen K-H, Pan Y-C, Yang S-N, Chan Y-Y. The effect of yoga on sleep quality and insomnia in women with sleep problems: a systematic review and meta-analysis. BMC Psychiatry 2020;20(1). https://doi.org/10.1186/s12888-020-02566-4.

Watson WJ, Katz VL, Hackney AC, Gall MM, McMurray RG. Fetal responses to maximal swimming and cycling exercise during pregnancy. Obstet Gynecol. 1991;77(3):382–6.

Willi J, Süss H, Grub J, Ehlert U. Prior depression affects the experience of the perimenopause—findings from the Swiss perimenopause study. J Affect Disord. 2020;277:603–611. https://doi.org/10.1016/j.jad.2020.08.062.

Willi J, Süss H, Grub J, Ehlert U. Biopsychosocial predictors of depressive symptoms in the perimenopause—findings from the Swiss Perimenopause Study. Menopause. 2021;28(3) 247–54. https://doi.org/10.1097/GME.0000000000001704.

Wisner KL, Moses-Kolko EL, Sit DK. Postpartum depression: a disorder in search of a definition. Arch Womens Ment Health. 2010;13(1):37–40. https://doi.org/10.1007/s00737-009-0119-9.

Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, Eng HF, Luther JF, Wisniewski SR, Costantino ML, Confer AL, Moses-Kolko EL, Famy CS, Hanusa BH. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry. 2013;70(5):490–8. https://doi.org/10.1001/jamapsychiatry.2013.87.

World Health Organization. Depression and other common mental disorders: global health estimates. World Health Organization; 2017.

Yonkers KA. Anxiety symptoms and anxiety disorders: how are they related to premenstrual disorders? J Clin Psychiatry. 1997;58 Suppl 3:62–7. discussion 68-69.

Young LJ, Pfaff DW. Sex differences in neurological and psychiatric disorders. Front Neuroendocrinol. 2014;35(3):253–4. https://doi.org/10.1016/j.yfrne.2014.05.005.

Chapter 20
Sex Hormones and Physical Activity in Women: An Evolutionary Framework

Ann E. Caldwell and Paul L. Hooper

Introduction

Over recent decades, researchers, athletes, and coaches have been interested in understanding the bidirectional relationships between sex hormones and exercise in women. This interest comes from evidence suggesting that sex hormones are related to exercise in both among highly active women and athletes as well as among sedentary women. In a laboratory-controlled study, for example, sedentary women who were not using hormonal contraceptives and were in the early follicular phase had steeper increases in perceived exertion and pain during moderate-intensity exercise compared to those in the late follicular or luteal phases (Caldwell Hooper et al. 2011). One potential explanation for this result is that estrogen has analgesic effects, and the absence of endogenous estrogen during the menstrual phase makes first-time moderate exercise relatively more aversive compared to cycle phases with higher levels of estrogen. This is important because subjective experience (perception) of exercise has been shown to influence intentions to exercise and behavior (Kwan and Bryan 2010). That is, a more negative subjective experience may influence women's motivation to exercise again and could affect the likelihood that sedentary women successfully take up exercise. This study shows that understanding the relationships between sex hormones and exercise can not only improve performance and health in highly trained athletes, but can also inform interventions aimed at increasing activity among sedentary women. Identifying female-specific barriers and approaches to overcome those barriers can to make exercise less aversive and more accessible, to make meaningful contributions to public health. To that end, the

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goal of this chapter is to present a framework from evolutionary biology, including life history theory, which can illuminate *why* sex hormones and exercise are related. This perspective can lead to theoretically driven predictions about the bidirectional relationships between sex hormones and exercise among women that may not be considered from more strictly physiological approaches.

Life History Theory: An Evolutionary Framework for Understanding Sex Hormones and Exercise in Women

In general, evolutionary theory aims to explain how traits, behaviors, and the underlying mechanisms leading to a trait or behavior have been shaped by natural selection. Natural selection operates through differential reproductive success—or fitness, in the evolutionary sense—as the genes of individuals who successfully survive and reproduce are passed on to subsequent generations at a relatively higher rate than the genes of those who reproduce less or not at all. The environmental forces that determine which traits or behaviors result in greater reproductive success are called selection pressures. Selection pressures differ considerably depending on an organism's natural environment, their ecological or social niche (their way of "making a living"), as well as age, sex, and physical condition.

Selection continues to act on traits, behaviors, and their underlying psychological and physiological mechanisms so long as they exhibit heritable variation that is associated with differential reproductive success. For traits or behaviors with one optimal solution within a species regardless of environment or individual condition, that trait or behavior will tend to become universal over time. However, when there is more than one optimal solution and/or the optimum depends on individual or environmental circumstances, variation will remain. A flexible system that responds to the individual and/or environmental circumstances with behaviors that increase the probability of survival and reproductive success can evolve. Thus, while the universality of a trait or behavior is often used as evidence that it has been shaped by evolutionary forces, this is not a necessary condition for evolved traits or behaviors. In the case of exercise or physical activity—the costs and benefits of which vary widely between individuals and environments—a flexible, condition-dependent system is more likely to have evolved.

Given the numerous mental and physical health benefits associated with exercise and the deleterious health outcomes related to physical inactivity in modern environments (Hillman et al. 2008; Kohl et al. 2012; Lee et al. 2012; Ramesh and Science 1997; Warburton et al. 2006), it is intuitively appealing to imagine that exercise might be a universally adaptive behavior. Moreover, there is evidence that humans have anatomical (Bramble and Lieberman 2004) and neurological (Raichlen et al. 2012) adaptations for endurance activity. There is another side to the story, however, suggesting that physical *in*activity and energy *conservation* are also adaptive in humans (Caldwell 2016b). Many of the currently adaptive benefits of exercise

and physical activity reflect a mismatch between the environments in which humans evolved and the ones we have built.

Human patterns of activity have changed drastically over a relatively short amount of evolutionary time. Over the past 10,000 years—and especially in the last two centuries—humans have created novel environments that require very little physical energy expenditure in order to fulfill basic biological needs. Cumulative technological innovations have increased the efficiency of resource extraction, storage, and transportation. Why did humans create this environment that enables inactivity, in spite of adaptations that make endurance physical activity rewarding and relatively efficient?

From an evolutionary perspective, humans, like all other organisms, have evolved to strategically allocate time and energy in ways that increase the likelihood of reproductive success. This is the central premise of life history theory, an evolutionary framework that aims to understand how natural selection has shaped the allocation of time and energy across species and organisms between the competing demands of growth, reproduction, and maintenance across the lifespan (Gomulkiewicz 1994; Hill and Kaplan 1999; Winemiller 1994). Selection pressures arise from the interaction of an individual's genome, condition, and environment to determine optimal duration and rates of growth, rate and timing of reproductive maturation, the pace of reproduction, rate and timing of reproductive decline, and senescence (Kaplan et al. 2010). Life history theory also fundamentally considers that there are inherent trade-offs between allocations to different (potentially) fitness-enhancing activities across the lifespan because energy and time put toward one activity cannot be invested elsewhere. Because exercise inherently requires energy expenditure, exercise necessarily trades off against growth, reproduction, and maintenance in important ways.

The drive for optimizing energy allocation affects exercise and physical activity because allocation strategies have been shaped throughout human evolution to flexibly respond to factors—such as sex, age, environment, and individual condition—that influence the evolutionary fitness costs and benefits of physical activity. In humans and other mammals, in particular, the energetic demands of reproduction are much higher for females than males, in terms of investment in sex cells (eggs vs. sperm), gestation, and breastfeeding. As a result, the energetic trade-offs and opportunity costs of investing energy in physical activity tend to be higher for women of reproductive age than men.

Within a life history framework, hormones are considered to be the physiological mechanism orchestrating where energy is allocated between the competing short- and long-term demands of growth, reproduction, and maintenance (Lancaster and Kaplan 2009; Worthman 2009; Zera and Harshman 2001). Energy expenditure in the form of physical activity or exercise necessarily trades off against these competing demands and is partially regulated through hormones (Caldwell 2016b; Ellison 2017). Therefore, when considering the role of sex hormones and exercise, it is important to keep in mind that the primary function of sex hormones is their role in reproduction and that traits and behaviors have been shaped over evolutionary time to increase the probability of survival *and* reproductive success. A thorough understanding of how

this system is predicted to operate can help illuminate *how and why* sex hormones and exercise are related.

One example of an exercise phenomenon illuminated by evolutionary principles is the decrease in physical activity across adolescence that is well documented in Western populations (Cumming et al. 2008; Sherar et al. 2007; Thompson et al. 2003). Although epidemiological researchers have tended to interpret this pattern of decrease as a by-product of the psychosocial stress of puberty, life history theory predicts that activity declines at this stage because pubertal adolescents increase the energy invested in growth and reproductive maturation, which trades off against exercise and non-obligatory forms of activity (e.g., active play, running games, riding bikes). Evidence supporting this interpretation comes from a study of activity levels of indigenous Tsimane' adolescents (Caldwell 2016b; Caldwell et al. n.d.). The Tsimane' are a small-scale society that lives in the Amazonian lowlands of Bolivia. They have a subsistence-based economy and primarily produce food through hunting, fishing, foraging, and small-scale horticulture; all requiring high levels of obligatory physical activity. Even in this setting, which shares many features with the conditions of our remote evolutionary past, age is inversely associated with device measured physical activity during adolescence. This relationship, moreover, is mediated by indicators of energetic investment in growth (height velocity) and reproductive maturation (Tanner stage of reproductive maturation and dehydroepandrosterone [DHEA]). Estrogen, progesterone, and testosterone may also mediate these decreases, with higher levels of sex hormones predicting lower levels of physical activity/exercise, but to our knowledge, this has not been examined empirically. Notably, however, decreases in estradiol following ovariectomy in rodents are associated with reductions in spontaneous physical activity (Witte et al. 2010). In humans, experimentally suppressing the hypothalamic–pituitary–ovarian axis leads to lower resting and total energy expenditure and therefore could be associated with lower physical activity (Day et al. 2005; Melanson et al. 2015).

More generally, life history theory is an ideal theoretical framework for understanding exercise and sex hormones in women because they both influence and are influenced by life history parameters such as reproductive maturation, reproduction, and physical condition. The framework suggests that human physiology and psychology have been shaped by natural selection to maintain physical fitness and *selectively* engage in physical activity and exercise when the adaptive benefits outweigh the metabolic and opportunity costs (Caldwell 2016a). When the benefits do not outweigh the costs, humans, like other animals, have evolved to conserve energy through behavioral and physiological shifts in energy allocation.

Another important consideration in employing evolutionary theory in this area is that over the vast majority of human history, optimal energy allocation strategies have been constrained by finite resource availability and resource scarcity (Shetty 1999; Vickers et al. 2003). Innate drives to conserve energy have only recently been coupled with massive abundances of calorically dense, easy-to-acquire foods. When environments change rapidly, or are vastly different from the environment in which selection was acting to shape a trait or behavior, a discordance or mismatch can occur (Eaton et al. 1988, 2002; Kaplan 1996; Lieberman 2014). In these mismatched environments,

previously adaptive behaviors or mechanisms may no longer increase reproductive success and can even be detrimental to reproduction or survival. Energy-conserving behaviors and metabolic adaptations that increased the likelihood of survival and reproduction in environments with fewer and less predictable resources now lead to health disorders like obesity and cardiovascular disease, which can hinder reproduction in women (Metwally et al. 2007). One must thus consider the mechanisms and behaviors that would have been adaptive in the environments during the majority of human history, when selection was acting to shape them, rather than just those that are expected to be currently adaptive. In current environments, exercise and physical fitness significantly decrease the risks of chronic disease mortality and physical activity has been shown to induce epigenetic changes that decrease cancer risk (Bryan et al. 2013). Current environments therefore create the potential for selection to begin to favor higher levels of activity and exercise, because those who are more active and physically fit are more likely to live longer and be healthy enough to provide better support for offspring and grand-offspring relative to less active and physically fit individuals. This is particularly true in environments in which parental and grandparental investment significantly improves survival and reproduction of younger generations.

Reproductive Ecology, Sex Hormones, and Exercise in Women

Given that selection operates through differential reproductive success, the effects of physical activity on reproductive function are central to an evolutionary framework. An evolutionary approach can also draw on work in human reproductive ecology, a subfield of evolutionary anthropology that aims to understand the ways the human reproductive system responds to environmental cues (Ellison 2001; Kaptein 2016). Importantly, this body of research establishes that women's reproductive systems have evolved to be remarkably sensitive to energetic cues in the environment in order to shift effort adaptively.

Human females incur much higher energetic costs to reproduce compared to males. This imbalance begins at the level of the gamete, but energetic costs increase through pubertal maturation, gestation, and breastfeeding. Childbirth also involves significant, potentially mortal, risks for females. The energetic trade-offs between reproduction and exercise or physical activity alone are substantial enough to help explain why exercise and sex hormones are related in women. Both activities can be hugely metabolically taxing. The metabolic costs of pregnancy during the third trimester are estimated to be around 465 kcal/day above pre-pregnancy levels, while breastfeeding can increase metabolic load by 625–700 kcal/day (Butte and King 2005). Research in reproductive ecology also shows that women's reproductive systems have physiological mechanisms that decrease the likelihood of conception in response to cues of short-term energetic stress, particularly through reductions in ovarian steroid hormone levels in response to low energy availability, negative energy

balance, and high and low levels of energy flux (Ellison 2003). This makes conception less probable during unfavorable conditions when women are less capable of meeting the energetic demands of pregnancy and lactation.

Women's biological capacity to reproduce, or fecundity, is greatly influenced by sex hormones. Ovarian function varies along a continuum of fecundity, which can be assessed by sex hormones. Low levels of estradiol during the follicular phase or progesterone during the luteal phase have been shown to reflect decreased fecundity (Lipson and Ellison 1996). Menstrual cycle irregularities measured by a short luteal phase (<10 days), or by oligomenorrhea (cycle length >35 days) also signal potential disturbances in reproductive function and fecundity.

There is evidence that transient shifts in energy availability influence female fecundity in both Western and non-Western human samples, as well as in chimpanzees (Thompson and Wrangham 2008). Low ovarian steroid levels have been observed among women in Western populations who have low energy availability (i.e., are losing weight, are restraining their intake below appetite, or have less stored fat, lower lipid profiles, or high energy expenditure through exercise or workload, reviewed in Ellison 2008; Vitzthum 2009). The combination of high energy expenditure and low energy intake has a particularly pronounced negative effect on fecundity (Ellison 2001). It is worth noting that even when food is not limited, increased physical workloads have been shown to decrease sex hormones (Jasienska 2006b; e.g., Jasienska and Ellison 2004; Williams et al. 2015).

Seminal research examining the reproductive function and energy availability (dietary intake minus expenditure) has demonstrated that very low energy availability (less than 30 kcal/kg lean body mass per day) disrupts LH pulsatility, which is critical for reproductive function (Loucks et al. 1994, 1998; Loucks and Thuma 2003). Building on this research, a recent study attempted to tease apart the effects of energy expenditure and negative energy balance on menstrual cycle irregularities in a randomized control trial of sedentary women in the USA (Williams et al. 2015). In one condition, participants increased exercise but had compensatory increases in energy intake to attain a neutral energy balance. In the other conditions, participants exercised *and* reduced caloric intake, resulting in deficits of 15%, 30%, or 60% across three conditions. Over three months, around 13% of the women in the exercise-only condition experienced menstrual cycle irregularities (short luteal phase, <10 days, or inadequate urinary progesterone during the luteal phase, <5.0 μg/ml). In contrast, nearly all of those in the most extreme energy deficient condition (88%) exhibited irregularities. In addition to demonstrating the dose–response nature of energetics on fecundity, this study demonstrated the wide variability in the response of the reproductive systems to energetic stress. While some women's reproductive systems were highly sensitive, showing menstrual irregularities even when energy expenditure was compensated by increased consumption, others were much more robust and did not show signs of menstrual irregularities despite increased exercise *and* substantial caloric deficits. This interindividual variability may help explain why so much work in this area has led to equivocal findings and may make it more difficult for future research to produce consistent findings. However, an evolutionary framework

can also lead shed light on what factors may underlie these individual differences in predictable ways.

It can be difficult to know where to begin testing moderators of the relationships between exercise and the reproductive axis. Does it have something to do with socioeconomic status, ethnicity, education, or other stressors? Within a life history framework, reproductive responsiveness to low energy availability may be influenced by energy availability in prenatal and developmental environments, as well as factors that determine energetic trade-offs: age, parity, overall health, immune function, and immune burden (i.e., parasite and infection load) and previous experiences with physical activity and physical fitness. This framework would further predict that women whose reproductive system is particularly sensitive to energetic stress face higher costs of performing exercise than those whose systems are more robust. Women facing higher costs may be less likely to engage in exercise that is not related to tangible evolutionary fitness benefits (i.e., mating, parental investment). Future research can also test if there are psychological mediators between these relationships, such as whether women who have particularly responsive reproductive systems have higher ratings of perceived exertion, are less likely to feel motivated to exercise, or enjoy exercise less when facing steep competing demands for reproductive function.

The flexibility of the relationships between physical workloads, dietary intake, and reproductive function is nicely illustrated by a study of the Tamang in Nepal. The Tamang practice small-scale agriculture and pastoralism, and they have seasonal variation in physical workloads—from moderately heavy in winter to very heavy during the monsoon season. Overall, Tamang women exhibit weight loss and decreased ovulation in the heavy-work monsoon season (38% ovulating during the monsoon versus 71% in the winter). Notably, however, this effect differed by age, with younger women (those aged 17–23) exhibiting negligible seasonal changes in ovarian function and no weight loss during the heavy-work season compared to older menstruating women (Panter-brick et al. 1993). Vitzthum (2009) hypothesized that acclimation to heavy workloads and high energy consumption levels allow some Tamang women to buffer against ovarian suppression in the face of high physical workloads. However, it could be that younger, non-lactating, and/or nulliparous women have a larger energy budget to put toward increasing the likelihood of becoming pregnant and are therefore less affected by acute shifts in physical workloads. Since the data are cross-sectional within one year, differences between age groups could also be driven by epigenetic factors that influenced the energetic phenotype of a cohort of women. Others have hypothesized that critical periods during development, where mothers provision offspring through the placenta or lactation, allow for the transfer of information about the mother's cumulative and current energetic status (Kuzawa and Quinn 2009). From this perspective, the information transferred to offspring can provide cues of the energetic stress in the environment into which offspring is born. Developing fetuses and babies can then adaptively shape their energetic phenotype to be more or less conservative. Maternal cues of energetic stress are thought to result in offspring with more conservatively calibrated energetic strategies that would be adaptive in environments with unpredictable food availability. Since reproduction involves such

high metabolic investment from women through pregnancy and lactation, early life cues of energy scarcity or unpredictability may lead to a more conservative or thrifty energetic phenotype. This may include an HPO axis that is more sensitive to signals of low energy availability and adaptively responds by suppressing sex hormones to decrease the likelihood of conception when it is unclear whether the energetic demands of pregnancy and/or lactation can be met (Ellison 2001; Jasienska 2003; Vitzthum 2009).

A cross-sectional study by Jasienska and colleagues demonstrated that energetic stress during fetal development may affect the sensitivity of women's reproductive systems to higher levels of physical activity (Jasienska et al. 2006a, b). Among a sample of rural Polish women ($N = 145$), size at birth (measured by ponderal index, PI: kg/m^3 from medical records) moderated the relationship between self-reported exercise and ovarian suppression assessed by mid-follicular salivary estrogen (E2). Those in relatively worse energetic condition at birth (lower PI) had lower E2 if they were moderately or very active, as compared to women with high PI at birth who only had lower E2 levels if they were very physically active. These results support the predictive adaptive response theory (Ellison 1990; Ellison and Jasienska 2007; Gluckman et al. 2005; Kuzawa et al. 2007; Kuzawa 2005; Lipson 2001), which hypothesizes that when a fetus develops in an environment with cues of constrained energetic resources, adaptive shifts in metabolism or energy allocation occur that favor energy conservation throughout life. Individuals' developmental environments may thus affect the extent to which their sex hormones and reproductive systems preemptively downregulate hormone production and fecundity in response to higher physical activity or workload. In other words, developmental environments can moderate the relationships between sex hormones and exercise, leading to individual differences that vary in predictable ways. It would be worthwhile to add measures of birth weight and developmental environments in studies examining the relationships between sex hormones and exercise, to test measures of low energy availability in developmental environments that moderates these relationships.

Evolutionary research has established that energy balance influences female reproduction through a variety of pathways. Women who are energetically stressed tend to have shorter gestation periods and infants with lower birth weight (Alberman 1991; Ellison 2003). Energetics also modulate the length of time that breastfeeding women do not ovulate, termed lactational amenorrhea. As noted earlier, lactation is extremely energetically costly for women and typically leads to ovarian suppression (via endocrine mechanisms). The duration of lactational amenorrhea varies between and within populations and is thought to be affected by energetic demands and fat stores available for producing breast milk and weaning practices (Kaplan et al. 2015). Women who have heavy daily workloads often breastfeed less frequently and begin to supplement children's diet with alternative food sources earlier, decreasing maternal levels of prolactin and reducing the drive for milk production (Panter-Brick and Pollard 2010). Decreased frequency of breastfeeding and/or food supplementation likely mediates the effect of energy expenditure on ovulatory suppression. Women's reproductive system appears to be particularly sensitive among those who

had constrained fetal environments and in response to transient shifts in energy availability. Consistent exercise, particularly if performed throughout life and paired with a healthy, sufficient diet is unlikely to have a detrimental effect on women's fecundity. In addition, some have suggested that one reason higher physical activity is associated with a lower risk of breast cancer is the reduction of ovarian steroids that is associated with physical activity and exercise (Jasienska et al. 2006a, b; Kaaks and Lukanova 2002; Key and Pike 1988; Lovett et al. 2017). In environments where women have access to contraception (and therefore fewer pregnancies and periods of lactational amenorrhea), women experience many more menstrual cycles, and typically have low levels of physical activity and exercise, and an abundance of calorically dense and highly palatable foods, the cumulative higher levels of exposure to estradiol may high enough to be detrimental to women's health (Jasienska et al. 2017).

The Increasingly Important Focus on Obesity in Sex Hormones and Exercise

Among reproductive-age women (20–39 years), the prevalence of obesity more than tripled and rates of severe obesity increased tenfold between 1960 and 2014 (Flegal et al. 1998, 2016). This is relevant for this book because the cornerstone of obesity treatment is to increase physical activity or exercise and reduce dietary intake. However, obesity is associated with dysregulation of pituitary gonadotropins and ovarian hormones. Recent studies suggest that even eumennorheic women with obesity (who do not have polycystic ovarian syndrome) exhibit a functional impairment of the hypothalamic–pituitary–ovarian (HPO) axis (Jain et al. 2007; Pasquali 2006; Santoro et al. 2004; Stang and Huffman 2016; Talmor and Dunphy 2015; Van Der Steeg et al. 2008), evidenced by significantly lower basal and stimulated gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and basal progesterone metabolites (pregnanediol-3-glucuronide [Pdg]) (Al-Safi et al. 2015; Jain et al. 2007; Santoro et al. 2004). This reproductive phenotype was observed in a subset of perimenopausal women ($n = 848$) participating in the Study of Women's Health Across the Nation (SWAN) (Santoro et al. 2004). In this study, higher body mass index (BMI) was associated with lower levels of urinary LH, FSH, and Pdg. However, the SWAN study was designed to examine women through the menopausal transition; thus, the effects of perimenopause on gonadotropins and ovarian hormones cannot be ruled out. Three subsequent studies compared gonadotropins and ovarian hormones in small samples ($n < 20$) of younger, premenopausal women with obesity to normal weight controls. In addition to daily urine samples, frequent blood samples were taken to measure gonadotropin (LH and FSH) pulse amplitude. One study observed significantly lower basal LH, LH pulse amplitude, and urinary Pdg in women with severe obesity (mean BMI = 48.6) compared to normal weight controls (Jain et al. 2007). Two subsequent studies

included women with less severe obesity (mean BMI = 36.7) and measured FSH and LH in response to a physiologic (75 ng/kg) bolus of gonadotropin-releasing hormone (GnRH) during the early-follicular phase. Both studies observed lower serum LH, LH pulse amplitude, and Pdg among women with obesity compared to normal weight controls (Al-Safi et al. 2015; Bauer et al. 2019).

This HPO-axis suppression in response to obesity is important to consider when understanding the relationships between sex hormones and exercise. First, if conducting research in women with a higher BMI, it cannot be assumed that hormone profiles are similar to those in the normal BMI range, as hormones may be suppressed in clinically meaningful ways, even if women are regularly cycling. Careful measurement of sex hormones, rather than simply comparing across different points in the cycle, will help clarify some of the conflicting findings that conclude sex hormones do not influence exercise or related parameters because differences were not seen between the luteal and follicular phases. In addition, extant data suggest that HPO-axis suppression affects energy balance in ways that would theoretically inhibit exercise participation and healthy weight management. In rodents, estradiol is protective against visceral fat accumulation, insulin resistance, and dyslipidemia (Leeners et al. 2017; Van Pelt et al. 2015). Suppressing estradiol through ovariectomy reduces total daily energy expenditure and spontaneous physical activity (Rogers et al. 2009; Witte et al. 2010). In humans, experimentally suppressing the HPO axis leads to lower resting and total energy expenditure (Day et al. 2005; Melanson et al. 2015). However, to our knowledge, no studies to date have shown a relationship between sex hormone suppression and spontaneous physical activity, exercise performance, or related parameters. These studies will be important for understanding if obesity-related HPO-axis suppression influences women's resting energy expenditure and physiological response to physical activity in ways that make exercise more difficult.

Conclusions

An evolutionary perspective offers subtle but meaningful shifts in the interpretation of the existing literature on sex hormones and exercise. Moreover, it leads to theory-driven hypotheses regarding factors—such as individual conditions and cues of resource scarcity—that can predictably influence individual differences in the relationships between sex hormones and exercise. Variation across individuals and contexts may contribute to the apparent inconsistency of past findings. Future research that aims to understand sex differences in sedentary behavior and exercise, and the psychology that underlies each, can draw on what is known about sex hormones, reproductive function, and activity in the evolutionary life sciences.

There are six key messages that arise from applying an evolutionary framework to understand the relationship between sex hormones and exercise. These are:

- Natural selection favors physiological and behavioral adaptions that increase the probability of survival and reproductive success.

- Energy and time are finite resources, and the system that regulates energy allocation operates primarily through hormones, including sex hormones.
- Energy expended in exercise or physical activity trades off against energy allocated to other activities, such as growth, reproduction, and maintenance.
- Reproduction is energetically costly for women, and the female reproductive system has evolved to reduce fecundity in response to cues of transient increases in energy expenditure and reductions in energy intake. This responsiveness can lead to decreases in fecundity that lower the probability of reproduction. This responsiveness may also have led to adaptations that reduce the likelihood of expending energy when reproductive hormones are suppressed in order to resume reproduction under conditions of prolonged resource scarcity.
- Research that only examines the mean responsiveness of sex hormones to reductions in energy availability may mask large and meaningful interindividual variability. Life history theory can inform predictions about who is more likely to have a more responsive reproductive axis to reductions in energy availability (e.g., those who experienced stressful early life environments). A better understanding of factors that lead to interindividual variability can lead to more personalized approaches for optimizing health and well-being through physical activity and exercise.
- Obesity is associated with the suppression of sex hormones, even in eumenorrheic women. Given the increasing prevalence of obesity, measuring hormones during exercise research in women with healthy weight and overweight/obesity will be important for new discoveries and resolving equivocal findings of previous research.

By drawing on tools and insights from evolutionary biology, anthropology, and psychology, an evolutionary approach allows an integrated approach to understanding the mechanisms, function, history, and ecology of sex hormones and exercise in women within a single framework.

References

Al-Safi ZA, Liu H, Carlson NE, Chosich J, Lesh J, Robledo C, Bradford AP, Gee NA, Phang T, Santoro N, Kohrt W, Polotsky AJ. Estradiol priming improves gonadotrope sensitivity and pro-inflammatory cytokines in obese women. J Clin Endocrinol Metab. 2015;100(11):4372–81. https://doi.org/10.1210/jc.2015-1946.

Alberman E. From conception to birth: epidemiology of prenatal development. J Epidemiol Commun Health. 1991;45(1). https://doi.org/10.1136/jech.45.1.86-a (Oxford University Press)

Bauer JL, Kuhn K, Bradford AP, Al-Safi ZA, Harris MA, Eckel RH, Robledo CY, Malkhasyan A, Johnson J, Gee NR, Polotsky AJ. Reduction in FSH throughout the menstrual cycle after Omega-3 fatty acid supplementation in young normal weight but not obese women. Reprod Sci. 2019;26(8):1025–33. https://doi.org/10.1177/1933719119828099.

Bramble DM, Lieberman DE. Endurance running and the evolution of Homo. Nature. 2004;432(7015):345–52. https://doi.org/10.1038/nature03052.

Bryan AD, Magnan RE, Hooper AEC, Harlaar N, Hutchison KE. Physical activity and differential methylation of breast cancer genes assayed from saliva: a preliminary investigation. Ann Behav Med. 2013;45(1):89–98. https://doi.org/10.1007/s12160-012-9411-4.

Butte NF, King JC. Energy requirements during pregnancy and lactation. Public Health Nutr. 2005;8(7a):1010–27. https://doi.org/10.1079/phn2005793.

Caldwell AE. In: Lancaster JB, editor. Human physical fitness and activity: an evolutionary and life history perspective, 1st ed.. Springer; 2016a.

Caldwell AE. Human physical fitness and activity. Springer; 2016b. https://doi.org/10.1007/978-3-319-30409-0

Caldwell AE, Hooper PL, Cummings D, Trumble BC, Stieglitz J., Davis HE, Gurven MD, Kaplan HS. Physical activity, sedentary behavior, and maturation among Tsimane' youth and adolescents: public health implications. PNAS. n.d.

Caldwell Hooper AE, Bryan AD, Eaton M. Menstrual cycle effects on perceived exertion and pain during exercise among sedentary women. J Women's Health. 2011;20(3):439–46. https://doi.org/10.1089/jwh.2010.2042.

Cumming SP, Standage M, Gillison F, Malina RM. Sex differences in exercise behavior during adolescence: is biological maturation a confounding factor? J Adolesc Health. 2008;42(5):480–5. https://doi.org/10.1016/j.jadohealth.2007.10.005.

Day DS, Gozansky WS, Van Pelt RE, Schwartz RS, Kohrt WM. Sex hormone suppression reduces resting energy expenditure and β-adrenergic support of resting energy expenditure. J Clin Endocrinol Metab. 2005;90(6):3312–7. https://doi.org/10.1210/jc.2004-1344.

Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. Am J Med. 1988;84(4):739–49. https://doi.org/10.1016/0002-9343(88)90113-1.

Eaton SB, Strassman BI, Nesse RM, Neel JV, Ewald PW, Williams GC, Weder AB, Eaton SB, Lindeberg S, Konner MJ, Mysterud I, Cordain L. Evolutionary health promotion. Prev Med. 2002;34(2):109–18. https://doi.org/10.1006/pmed.2001.0876.

Ellison PT. On fertile ground. Harvard Press; 2001.

Ellison PT. Energetics, reproductive ecology, and human evolution. PaleoAnthropology. 2008;2008:172–200.

Ellison PT. Human ovarian function and reproductive ecology: new hypotheses. Am Anthropol. 1990;92(4):933–52. https://doi.org/10.1525/aa.1990.92.4.02a00050.

Ellison PT. Endocrinology, energetics, and human life history: a synthetic model. Horm Behav. 2017;91:97–106. https://doi.org/10.1016/j.yhbeh.2016.09.006.

Ellison PT, Jasienska G. Constraint, pathology, and adaptation: how can we tell them apart? Am J Hum Biol. 2007;19(5):622–30. https://doi.org/10.1002/ajhb.20662.

Ellison PT. Energetics and reproductive effort. Am J Hum Biol. 2003;15(3):342–51. https://doi.org/10.1002/ajhb.10152.

Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes. 1998. https://doi.org/10.1038/sj.ijo.0800541.

Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315(21):2284. https://doi.org/10.1001/jama.2016.6458.

Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol. 2005;20(10):527–33. https://doi.org/10.1016/j.tree.2005.08.001.

Gomulkiewicz R. Life history invariants: some explorations of symmetry in evolutionary ecology. Math Biosci. 1994;124(1). https://doi.org/10.1016/0025-5564(94)90027-2 (Oxford University Press)

Hill K, Kaplan H. Life history traits in humans: theory and empirical studies. Annu Rev Anthropol. 1999;28:397–430.

Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci. 2008;9(1):58–65. https://doi.org/10.1038/nrn2298.

Jain A, Polotsky AJ, Rochester D, Berga SL, Loucks T, Zeitlian G, Gibbs K, Polotsky HN, Feng S, Isaac B, Santoro N. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab. 2007;92(7):2468–73. https://doi.org/10.1210/jc.2006-2274.

Jasienska G. Energy metabolism and the evolution of reproductive suppression in the human female. Acta Biotheor. 2003;51(1):1–18. https://doi.org/10.1023/A:1023035321162.

Jasienska G, Ellison P. Energetic factors and seasonal changes in ovarian function in women from rural Poland. Am J Hum Biol. 2004;16(5):563–80. https://doi.org/10.1002/ajhb.20063.

Jasienska G, Thune I, Ellison PT. Fatness at birth predicts adult susceptibility to ovarian suppression: an empirical test of the predictive adaptive response hypothesis. Proc Natl Acad Sci USA. 2006a;103(34):12759–62. https://doi.org/10.1073/pnas.0605488103.

Jasienska G, Ziomkiewicz A, Thune I, Lipson SF, Ellison PT. Habitual physical activity and estradiol levels in women of reproductive age. Eur J Cancer Prev. 2006b;15(5):439–45. https://doi.org/10.1097/00008469-200610000-00009.

Jasienska G, Bribiescas RG, Furberg AS, Helle S, Núñez-de la Mora A. Human reproduction and health: an evolutionary perspective. The Lancet. 2017;390(10093):510–520. https://doi.org/10.1016/S0140-6736(17)30573-1

Kaaks R, Lukanova A. Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. Ann NY Acad Sci. 2002;963:268–81. https://doi.org/10.1111/j.1749-6632.2002.tb04118.x.

Kaplan H. A theory of fertility and parental investment in traditional and modern human societies. Yearbook Physical Anthropol. 1996;101(S23):91–135.

Kaplan H, Gurven M, Winking J, Hooper PL, Stieglitz J. Learning, menopause, and the human adaptive complex. Ann NY Acad Sci. 2010;1204:30–42. https://doi.org/10.1111/j.1749-6632.2010.05528.x.

Kaplan HS, Bock J, Hooper PL. Fertility theory: embodied-capital theory of human life history evolution. In: International encylopedia of social and behavioral sciences, 2nd ed. 2015. p. 28–34.

Kaptein SA. The fragile wisdom: An evolutionary view on women's biology and health, by Grazyna Jasienska. J Women Aging. 2016; 28(2). https://doi.org/10.1080/08952841.2015.1081038 (Harvard University Press)

Key TJA, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol. 1988;24(1):29–43. https://doi.org/10.1016/0277-5379(88)90173-3.

Kohl HW, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, Kahlmeier S, Andersen LB, Bauman AE, Blair SN, Brownson RC, Bull FC, Ekelund U, Goenka S, Guthold R, Hallal PC, Haskell WL, Heath GW, Katzmarzyk PT, Min Lee I, Lobelo F, Loos JF, Marcus B, Martin BW, Owen N, Parra DC, Partt M, Puska P, Ogilvie D, Reis RS, Sallis JS, Sarmiento OL, Wells JC. The pandemic of physical inactivity: global action for public health. The Lancet. 2012;380(9838):294–305. https://doi.org/10.1016/S0140-6736(12)60898-8.

Kuzawa CW, Gluckman PD, Hanson MA, Beedle AS. Evolution, developmental plasticity, and metabolic disease. In: Stearns SC, Koella JC, editors. Evolution in health and disease, 2nd ed. Oxford University Press; 2007.

Kuzawa CW. Fetal origins of developmental plasticity: Are fetal cues reliable predictors of future nutritional environments? Am J Hum Biol. 2005;17(1):5–21. https://doi.org/10.1002/ajhb.20091.

Kuzawa CW, Quinn EA. Developmental origins of adult function and health: evolutionary hypotheses. Annu Rev Anthropol. 2009;38(1):131–47. https://doi.org/10.1146/annurev-anthro-091908-164350.

Kwan BM, Bryan AD. Affective response to exercise as a component of exercise motivation: attitudes, norms, self-efficacy, and temporal stability of intentions. Psychol Sport Exerc. 2010;11(1):71–9. https://doi.org/10.1016/j.psychsport.2009.05.010.

Lancaster JB, Kaplan HS. The endocrinology of the human adaptive complex. In: Ellison PT, Gray PB, editors. The endocrinology of social relationships, Issue 7. Harvard University Press; 2009. p. 95–118.

Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Alkandari JR, Andersen LB, Bauman AE, Brownson RC, Bull FC, Craig CL, Ekelund U, Goenka S, Guthold R, Hallal PC, Haskell WL, Heath GW, Inoue S, Kahlmeier S, Katzmarzyk PT, Kohl 3rd HW, Lambert EV, Lee I-M, Leetongin G, Lobelo F, Loos RJF, Marcus B, Martin BW, Owen N, Parra DC, Pratt M, Puska P, Ogilvie D, Reis RS, Sallis JF, Sarmiento OL, Wells JC. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The Lancet. 2012;380(9838):219–29. https://doi.org/10.1016/S0140-6736(12)61031-9

Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. Hum Reprod Update. 2017;23(3):300–21. https://doi.org/10.1093/humupd/dmw045.

Lieberman DE. The story of the human body: evolution, health, and disease. In: Choice reviews online, vol 51, Issue 10. Pantheon Books; 2014. https://doi.org/10.5860/choice.51-5581

Lipson SF. Metabolism, maturation, and ovarian function. In: Ellison PT, editor. Reproductive ecology and human evolution. Aldine de gruyter; 2001.

Lipson SF, Ellison PT. Comparison of salivary steroid profiles in naturally occurring conception and non-conception cycles. Hum Reprod. 1996;11(10):2090–6. https://doi.org/10.1093/oxfordjournals.humrep.a019055.

Loucks AB, Heath EM, Law T, Verdun M, Watts JR. Dietary restriction reduces luteinizing hormone (LH) pulse frequency during waking hours and increases LH pulse amplitude during sleep in young menstruating women. J Clin Endocrinol Metab. 1994;78(4):910–5. https://doi.org/10.1210/jcem.78.4.8157720.

Loucks AB, Verdun M, Heath EM. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J Appl Physiol. 1998;84(1):37–46. https://doi.org/10.1152/jappl.1998.84.1.37.

Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab. 2003;88(1):297–311. https://doi.org/10.1210/jc.2002-020369.

Lovett JL, Chima MA, Wexler JK, Arslanian KJ, Friedman AB, Yousif CB, Strassmann BI. Oral contraceptives cause evolutionarily novel increases in hormone exposure. Evol Med Public Health. 2017;2017(1):97–108. https://doi.org/10.1093/emph/eox009.

Melanson EL, Gavin KM, Shea KL, Wolfe P, Wierman ME, Schwartz RS, Kohrt WM. Regulation of energy expenditure by estradiol in premenopausal women. J Appl Physiol. 2015;119(9):975–81. https://doi.org/10.1152/japplphysiol.00473.2015.

Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. In: Obesity reviews, vol 8, Issue 6. 2007. p. 515–23. https://doi.org/10.1111/j.1467-789X.2007.00406.x

Panter-brick C, Lotstein DS, Ellison PT. Seasonality of reproductive function and weight loss in rural nepali women. Hum Reprod. 1993;8(5):684–90. https://doi.org/10.1093/oxfordjournals.humrep.a138120.

Panter-Brick C, Pollard TM (2010) Work and hormonal variation in subsistence and industrial contexts. In: Panter-Brick C, Worthman CM, editors. Hormones, health and behaviour. University Press; 2010. p. 139–83. https://doi.org/10.1017/cbo9780511623462.005

Pasquali R. Obesity, fat distribution and infertility. Maturitas. 2006;54(4):363–71. https://doi.org/10.1016/j.maturitas.2006.04.018.

Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A. Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the "runner's high." J Exp Biol. 2012;215(8):1331–6. https://doi.org/10.1242/jeb.063677.

Ramesh D, Science CS. Lack of exercise and chronic disease. In: Proceedings of the ninth annual ACM symposium on parallel algorithms and architectures, vol 5, issue 2. 1997. p. 159–69. https://doi.org/10.1002/cphy.c110025.Lack

Rogers NH, Li JWP, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. Endocrinology. 2009;150(5):2161–8. https://doi.org/10.1210/en.2008-1405.

Santoro N, Lasley B, McConnell D, Allsworth J, Crawford S, Gold EB, Finkelstein JS, Greendale GA, Kelsey J, Korenman S, Luborsky JL, Matthews K, Midgley R, Powell L, Sabatine J, Schocken

M, Sowers MF, Weiss G. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) daily hormone study. J Clin Endocrinol Metab. 2004;89(6):2622–31. https://doi.org/10.1210/jc.2003-031578.

Sherar LB, Esliger DW, Baxter-Jones ADG, Tremblay MS. Age and gender differences in youth physical activity: Does physical maturity matter? Med Sci Sports Exerc. 2007;39(5):830–5. https://doi.org/10.1249/mss.0b013e3180335c3c.

Shetty PS. Adaptation to low energy intakes: The responses and limits to low intakes in infants, children and adults. Eur J Clin Nutr. 1999;53(SUPPL. 1):S14–33. https://doi.org/10.1038/sj.ejcn.1600741.

Stang J, Huffman LG. Position of the Academy of nutrition and dietetics: obesity, reproduction, and pregnancy outcomes. J Acad Nutr Diet. 2016;116(4):677–91. https://doi.org/10.1016/j.jand.2016.01.008.

Talmor A, Dunphy B. Female obesity and infertility. Best Pract Res Clin Obstet Gynaecol. 2015;29(4):498–506. https://doi.org/10.1016/j.bpobgyn.2014.10.014.

Thompson AM, Baxter-Jones AD, Mirwald RL, Bailey DA. Comparison of physical activity in male and female children: does maturation matter? Med Sci Sports Exerc. 2003;35(10):1684–90.

Thompson ME, Wrangham RW. Diet and reproductive function in wild female chimpanzees (Pan troglodytes schweinfurthii) at Kibale National Park, Uganda. Am J Phys Anthropol. 2008;135(2):171–81. https://doi.org/10.1002/ajpa.20718.

Van Der Steeg JW, Steures P, Eijkemans MJC, Habbema JDF, Hompes PGA, Burggraaff JM, Oosterhuis GJE, Bossuyt PMM, Van Der Veen F, Mol BWJ. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. Hum Reprod. 2008;23(2):324–8. https://doi.org/10.1093/humrep/dem371.

Van Pelt RE, Gavin KM, Kohrt WM. Regulation of body composition and bioenergetics by estrogens. In: Endocrinology and metabolism clinics of North America, vol 44, Issue 3. 2015. p. 663–76. https://doi.org/10.1016/j.ecl.2015.05.011

Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol Regul Integr Comparat Physiol 285(1 54-1). 2003. https://doi.org/10.1152/ajpregu.00051.2003

Vitzthum VJ. The ecology and evolutionary endocrinology of reproduction in the human female. Am J Phys Anthropol. 2009;140(SUPPL. 49):95–136. https://doi.org/10.1002/ajpa.21195.

Warburton, DER, Nicol CW, Bredin SSD. Prescribing exercise as preventive therapy. In Cmaj, vol 174, Issue 7. 2006. p. 961–74. https://doi.org/10.1503/cmaj.1040750

Williams NI, Leidy HJ, Hill BR, Lieberman JL, Legro RS, De Souza MJ. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. Am J Physiol Endocrinol Metabol. 2015;308(1):E29–39. https://doi.org/10.1152/ajpendo.00386.2013.

Winemiller K (1994) The evolution of life histories. In: Transactions of the American fisheries society, vol 123, Issue 5. Oxford University Press; 1994. https://doi.org/10.1577/1548-8659-123.5.835

Witte MM, Resuehr D, Chandler AR, Mehle AK, Overton JM. Female mice and rats exhibit species-specific metabolic and behavioral responses to ovariectomy. Gen Comp Endocrinol. 2010;166(3):520–8. https://doi.org/10.1016/j.ygcen.2010.01.006.

Worthman CM. Endocrine pathways in differential well-being across the life course. In: Kuh D, Hardy R, editors. A life course approach to women's health. Oxford University Press; 2009. p. 197–232. https://doi.org/10.1093/acprof:oso/9780192632890.003.0010

Zera AJ, Harshman LG. The physiology of life history trade-offs in animals. Annu Rev Ecol Syst. 2001;32:95–126. https://doi.org/10.1146/annurev.ecolsys.32.081501.114006.

Chapter 21
The Effects of Acute Exercise on Physiological Sexual Arousal in Women

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Introduction

Over the past two decades, research has demonstrated a strong link between acute exercise and physiological (i.e., genital) sexual arousal in women. In this chapter, we provide a summary of the laboratory studies that have examined the effects of acute exercise on sexual arousal in women and provide a potential explanation for the mechanisms of action underlying this relationship. In the latter part of this chapter, we provide a discussion of the clinical and treatment implications for the facilitatory effect of exercise on women's sexual response.

Physiological Sexual Arousal in Women

Physiological sexual arousal results from genital vasocongestion, which occurs with increased blood flow to the genitals. When blood begins to pool in the vaginal walls, the increase in blood volume leads to increased pressure inside the capillaries, which subsequently triggers lubricated plasma to transcend the vaginal epithelium onto the surface of the vagina (Levin 1980). These platelets form droplets, creating the lubricative film that typically covers the vaginal walls during sexual activity. Increased blood flow also leads the clitoris and the vestibular bulbs to protrude and become engorged (Berman 2005), and well-oxygenated blood is also supplied to the skin and the breasts (Levin 2002). In addition to increased blood flow, sexual arousal causes relaxation

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of the smooth muscles in the vaginal wall, which allows the vagina to lengthen and dilate.

A certain level of arousal is required for orgasm, and that level differs by individual. Stimulation by friction and pressure activates specialized nerve endings in the genitals (Krantz 1958), which generates impulses to the spinal cord and possibly to the vagus nerve (Komisaruk et al. 1997). According to Levin (2002), the afferent impulses of these nerve endings not only create the spinal reflexes that influence genital blood flow, but they also ascend the spinal cord, via the spinothalamic and spinoreticular tracts, to the brain for processing. This stimulates neurons in the paraventricular nucleus of the hypothalamus to release oxytocin into the bloodstream which, in turn, may cause uterine smooth muscles to contract (Komisurak et al. 2006).

Physiological sexual arousal in women can be measured in a variety of ways, including photoplethysmography, ultrasonography, temperature measurement, magnetic resonance imaging, and laser doppler imaging (for a review see Kukkonen 2014). Arousal is most commonly measured in laboratory studies using a vaginal photoplethysmography (Sintchak and Geer 1975), a clear acrylic, tampon-shaped device that contains either an incandescent light source, or an infrared light-emitting diode as a light source, and a photosensitive light detector. The light source illuminates the capillary bed of the vaginal wall, and the phototransistor detects the light that is reflected back from the vaginal wall and the blood circulating within it. The amount of back-scattered light is in direct relation to the transparency of engorged and unengorged tissue and thus serves as an indirect measure of vasoengorgement. Simply stated, the greater the back-scattering signal the more blood is assumed to be in the vessels (Levin 1992). The vaginal probe was designed to be easily inserted by the participant. A positioning shield can be placed on the probe's cable in order to standardize the depth of insertion between uses.

There are two components of the signal that can be derived from the photoplethysmography. When the signal is coupled to a Direct Current (DC) amplifier, a measure of vaginal blood volume (VBV) is obtained. VBV is believed to reflect slow changes in the pooling of blood in the vaginal tissue (Hatch 1979). The DC signal is used at low sensitivity, and the standard dependent variable is change from levels of VBV at baseline. Because there is no discernible zero point with VBV, absolute measures of blood volume cannot be detected, hence the need to measure in units of blood volume change. When the signal is AC-coupled (alternating current), a measure of vaginal pulse amplitude (VPA) is obtained. VPA is believed to reflect phasic changes in vaginal engorgement with each heartbeat; higher amplitudes indicate higher levels of blood flow (e.g., Geer et al. 1974). The dependent variable typically used is the amplitude of the pulse signal, which is measured from the bottom to the top of the pulse wave. As there is no absolute zero point with VPA, analyses are conducted by either averaging across specific stimulus presentations, across the highest 20–30 s of arousal, or across selected time periods. The change in mean genital arousal is typically calculated by subtracting the mean VPA to the neutral film from the mean VPA to the erotic film for each set of films in a given study. These values are then standardized within subjects and compared between stimulus categories.

Effect of Acute Exercise on Physiological Sexual Response

In a series of laboratory studies, Meston and colleagues examined the direct effects of acute exercise on female sexual function. The first of these studies required sexually functional participants to engage in 20 min of intense exercise (stationary cycling) prior to viewing a non-sexual and erotic film sequence (Meston and Gorzalka 1995). The procedure consisted of an orientation screening and questionnaire session, a 20-min bicycle ergometer fitness test, and then two counterbalanced experimental sessions (Exercise, No-exercise) that took place on different days. During the fitness test, the experimenters determined each participant's maximum volume of oxygen uptake so that they could have the participants cycle at a constant 70% of their estimated maximum volume during the exercise session. By ensuring that all participants worked at equivalent levels of their maximum volume of oxygen uptake, differences in physiological responses resulting from variations in fitness levels were minimized. In the exercise experimental session, participants cycled for 20 min on the stationary bicycle then after the cessation of exercise they inserted the vaginal photoplethysmography and watched a non-sexual film followed by an erotic film while their vaginal pulse amplitude was measured. From the cessation of exercise to the onset of the erotic film, approximately 15 min had passed. In the no-exercise condition, participants sat for 20 min, inserted the vaginal photoplethysmography, and viewed a second non-sexual and erotic film sequence. The results revealed that VPA was significantly higher during the presentation of the erotic film after exercise than it was during the erotic film in the no-exercise condition. There were no significant differences between conditions in VPA responses during the non-sexual film indicating that exercise did not simply increase blood flow to the genitals but, rather, it prepared the woman's body for sexual arousal so that when she was in a sexual context (e.g., viewing the erotic film) her body responded more intensely. This was the first finding to provide support for a facilitatory effect of acute exercise on physiological sexual arousal in women.

In a follow-up study, Meston and Gorzalka (1996) examined the effect of timing on the relationship between exercise and increased sexual arousal in women by measuring physiological arousal in response to erotic films at either 5, 15, or 30 min post-exercise. Each condition consisted of an experimental exercise session and a no-exercise control session. The results revealed that at both 15 and 30 min post-exercise there was a significant increase in genital arousal (VPA) to the erotic films compared to the no-exercise control condition. The finding of a significant facilitatory effect at 15 min post-exercise replicated Meston and Goralka's earlier study (1995). However, in contrast to the facilitation noted at 15 and 30 min post-exercise, acute exercise inhibited physiological sexual arousal when measured immediately following exercise. The authors noted that, during and immediately following exercise, a decrease in vascular resistance of the working muscles causes a significant increase in blood flow to those muscles (Christensen and Galbo 1983). Therefore, blood flow may have shifted away from the genital region to temporarily help restore the working muscles. The finding that exercise inhibited genital arousal immediately

following exercise but facilitated at 15 and 30 min post-exercise led the authors to speculate an optimal time for sexual activity following exercise.

To further explore whether an optimal level of sympathetic nervous system (SNS) activation from exercise may exist for facilitating sexual arousal in women, Lorenz et al. (2012) performed a secondary analysis of participants from the control conditions of three previously published studies (Hamilton et al. 2008; Harte and Meston 2007, 2008). Sympathetic nervous system activity was assessed using heart rate variability, which refers to the degree of variability in the lengths of time between successive heartbeats and is a useful non-invasive index of autonomic activity. The degree of variability in the lengths of time between successive heartbeats (HRV) provides important information about the relative balance of sympathetic and parasympathetic forces acting on the heart (Thayer et al. 2010). Participants in all three studies were sexually healthy women. The methodology of each study involved having the participants watch a non-sexual and erotic film sequence while their VPA responses were recorded. As predicted, the results revealed a curvilinear relationship between SNS activity and women's physiological sexual arousal. That is, moderate increases in SNS activity were associated with greater physiological sexual arousal responses, while low and high SNS activation were associated with lower physiological sexual arousal. These results provide support for the notion that there is an optimal level of SNS activity from acute exercise for the facilitation of genital sexual arousal in women.

Several more recent studies have examined cross-sectional correlations between physical fitness levels overall and sexual function levels, finding evidence that regular exercise—even when disconnected temporally from sexual activity—seems to confer protective benefits against sexual dysfunction (Fergus et al. 2019; Jiannine 2018). As regular exercise improves HRV (i.e., Pearson and Smart 2018), there is some speculation that the association between general fitness and sexual function may be attributable to positive shifts in autonomic nervous system balance. To that end, there is some evidence that exercise intensity is a better predictor of sexual outcomes than other facets of aerobic exercise (i.e., exercise frequency, exercise type, length of exercise). One study found that the intensity of exercise predicted frequency of sexual arousal, frequency of sexual intercourse, and number of orgasms observed in a single sexual episode. Exercise frequency, on the other hand, is only predicted for frequency of sexual desire (Morris et al. 2018).

Mechanism of Action for the Facilitation of Physiological Sexual Arousal with Exercise

Acute exercise influences a number of bodily systems that could feasibly impact women's sexual function. Exercise has been shown to affect a variety of hormones such as cortisol (e.g., Hill et al. 2008; Anderson and Wideman 2017), estrogen (e.g., Smith et al. 2013; Yoon et al. 2018), prolactin (e.g., Rojas Vega et al. 2012; Hackney

and Saeidi 2019), oxytocin (e.g., Hew-Butler et al. 2008; Alizadeh et al. 2018), and testosterone (for reviews, see Hackney 1996; Vingren et al. 2012), all of which have been linked to sexual arousal in women. In one study, high levels of cortisol and chronic stress were related to low levels of genital sexual arousal in women (Hamilton and Meston 2013). Reductions in estradiol during menopause and lactation have been associated with reduced blood flow, vasocongestion, and subsequently lubrication (e.g., Simon 2011). With respect to testosterone, some studies have concluded that moderate levels of exercise increase free or total testosterone, particularly for women in the luteal phase of their menstrual cycle for whom estrogen and progesterone levels are elevated (e.g., Vingren et al. 2009; Lane et al. 2015; Baydil 2020), while others have found no change in testosterone from pre- to post-exercise (e.g., Linnamo et al. 2005). In women, testosterone is most often linked to increased sexual desire, but it may also affect the genital tissues. One study demonstrated that women treated with exogenous androgens exhibited increases in genital arousal (Heard-Davison et al. 2007). Clinically, high levels of prolactin have been associated with sexual arousal dysfunction in women, specifically decreased vaginal lubrication, as well as with other sexual problems, including decreased desire, atrophic vaginitis, and anorgasmia (Smith 2003; Kirino 2017). Finally, plasma oxytocin levels have been associated with genital sexual arousal; specifically, plasma oxytocin was significantly correlated with vaginal lubrication during the luteal phase of the menstrual cycle, and there was a trend toward statistical significance during the follicular phase (Salonia et al. 2005). Similarly, anorgasmic women demonstrated significantly reduced levels of plasma oxytocin following sexual activity as compared to women without orgasmic concerns (Caruso et al. 2018).

To examine whether changes in testosterone may, in part, account for the increases in genital arousal with exercise, Hamilton et al. (2008) assessed salivary measures of testosterone at multiple time points during a no-exercise and exercise experimental session. The study methodology was similar to the exercise studies described earlier, with the exception that testing was done between 2:00 pm and 6:00 pm on days 5–10 of the woman's menstrual cycle in order to control for diurnal and menstrual cycle fluctuations in testosterone. Saliva samples were taken at the start of each session to provide a baseline sample, again 10 min after the 20-min period of vigorous exercise (during the exercise session) and 10 min after the pre-testing rest period of the no-exercise session. The findings indicated that testosterone did not increase in response to either exercise or the erotic film. In fact, testosterone remained stable during both the exercise session and the no-exercise session, and there were no differences in testosterone between the two sessions. This suggests that testosterone is not likely the mechanism of action associated with increased genital arousal post-exercise.

It is feasible that SNS activation may be driving the association between acute exercise and increased physiological sexual arousal in women. Biochemical and physiologic research indicates diffuse SNS discharge occurs during the later stages of sexual arousal in women (Jovanovic 1971) with marked increases in heart rate and blood pressure occurring during orgasm (Fox and Fox 1969). Increases in plasma norepinephrine, a sensitive index of SNS activity, have also been shown to accompany increases in sexual arousal during intercourse (Wiedeking et al. 1979).

Laboratory research that specifically manipulated SNS activity supports the mechanistic role that it may play in female sexual arousal. In one such study, 20 sexually functional women participated in two counterbalanced conditions in which they received either placebo or ephedrine sulfate (50 mg), a sympathomimetic amine that stimulates the adrenergic receptor system by increasing the activity of norepinephrine, before viewing a non-sexual and erotic film sequence (Meston and Heiman 1998). Norepinephrine is considered to be the dominant neurotransmitter through which the SNS exerts its effects. As in the prior studies described, physiological sexual responses to the films were measured using vaginal photoplethysmography (VPA). The results revealed ephedrine significantly increased VPA responses to the erotic film compared to placebo, but there were no differences in VPA responses to the non-sexual film with ephedrine. As was the case with exercise, these results suggest that ephedrine did not simply facilitate physiological responses through a general increase in peripheral resistance, but, rather, it selectively prepared the body for genital response.

If SNS activation increases sexual arousal, as suggested by the previous study, it is likely that drugs that decrease SNS activity would also decrease sexual arousal. Moreover, if exercise increases genital arousal via SNS activation, then blocking SNS arousal during exercise would be expected to diminish the enhancing influence of exercise on VPA responses. To test this hypothesis, Meston et al. (1997) administered either 0.2 mg of clonidine or placebo to 30 sexually functional women in two counterbalanced sessions where they viewed a non-sexual and erotic film sequence. The researchers chose the antihypertensive medication clonidine because it acts centrally as a norepinephrine antagonist and peripherally as an inhibitor of sympathetic outflow. Before viewing the experimental films, half of the participants engaged in 20 min of exercise in order to elicit significant SNS activation, and the other half did not exercise. Following heightened SNS activation (via acute exercise), there was a significant decrease in VPA responses to the erotic film in the clonidine compared to placebo condition. Among the participants who did not engage in exercise prior to viewing the film sequence, clonidine showed a non-significant trend toward decreasing VPA responses compared with placebo. Because clonidine has both central and peripheral properties, it is unclear at which level clonidine acted to influence sexual responding (Meston et al. 1997). Centrally, clonidine may have suppressed sexual responses indirectly via changes in neurohypophyseal hormone release, or directly by activating central sites that are responsible for the inhibition of sexual reflexes (Riley 1995). Peripherally, clonidine may have suppressed sexual arousal by direct inhibition of sympathetic outflow. Support for the latter explanation is provided by the finding that clonidine significantly inhibited sexual responding only when participants were in a state of heightened SNS activity. The fact that clonidine has been reported to significantly inhibit SNS, but not hormonal, responses to exercise (Engelman et al. 1989) is consistent with the suggestion that clonidine acted to inhibit sexual responding via suppressed SNS activity.

Research on sexual function in women following spinal cord injury provides additional support for the relationship between SNS activation and physiological sexual arousal in women. In one study, Sipski et al. (2001) assessed the impact of spinal cord

injury on genital sexual arousal in women by comparing premenopausal women with spinal cord injuries to able-bodied, age-matched controls. They found that preservation of sensory function in the T11-L2 level of the spinal cord was associated with genital sexual arousal. As sympathetic pathways controlling genital function originate at this level of the spinal cord (Hancock and Peveto 1979; Neuhber 1982; Nadelhaft and McKenna 1987), the authors noted that their findings were consistent with those of Meston and colleagues, who showed that activation of the SNS via exercise (Meston and Gorzalka 1995, 1996) and ephedrine (Meston and Heiman 1998) led to increases in genital sexual arousal. Building upon their findings, Sipski et al. (2004) assessed the effects of sympathetic stimulation on sexual arousal in women with spinal cord injuries. Because of the physical limitations of the population, the authors used anxiety-eliciting videos, which have been shown to increase genital arousal in sexually dysfunctional women (Palace and Gorzalka 1990), instead of exercise in order to elicit sympathetic arousal. In women with greater sensory function in the T11-L2 level of the spinal cord, where the sympathetic nerve fibers to the genitals arise, there was a significant effect of the anxiety-inducing film on genital responsiveness; this was not the case for women with low sensory function at the T11-L2 level. The authors interpreted their findings as further evidence for the role of the sympathetic nervous system in the regulation of genital vasocongestion.

Clinical Implication

Exercise and Sexual Arousal in Women with a History of Childhood Sexual Abuse

Several clinical populations of women may be directly affected by the observed relationship between acute exercise and increased physiological sexual arousal. One such population is women with histories of childhood sexual abuse (CSA), specifically those who meet diagnostic criteria for posttraumatic stress disorder (PTSD). Individuals with both CSA histories and PTSD diagnoses have increased levels of baseline SNS activity (e.g., Yehuda 2003). Given the evidence that there may be an optimal level of SNS activity for the facilitation of sexual arousal in women, Rellini and Meston (2006) investigated the possibility that activating the SNS before sexual arousal in women with a history of CSA and PTSD, who already have high baseline SNS activity, may have a negative impact on their physiological sexual arousal response. The same methodology used in the earlier exercise studies was applied to three groups of women: women with both a CSA history and a PTSD diagnosis, women with a CSA history and no PTSD diagnosis, and a control group of women with no history of CSA or PTSD. As in previous studies (e.g., Meston and Gorzalka 1995, 1996), exercise had a significant facilitatory effect on physiological sexual arousal in the control group of women with no history of CSA. However, this effect did not hold for the women who had histories of CSA either with or without

coexistent PTSD. In these women, there was no additional increase in physiological sexual arousal to the erotic videos during the exercise visit; to the contrary, there was a non-significant inhibition of sexual arousal responding. The authors speculated that, given these women had elevated baseline SNS activity, increasing SNS activity further, as was the case with exercise, may have put them beyond the optimal level of SNS activation for the facilitation of sexual arousal. The authors suggested that women with a history of CSA and/or PTSD who are experiencing problems with physiological sexual arousal may benefit from treatment that focuses on decreasing, rather than increasing, SNS activity during sexual activity. This might entail engaging in relaxation exercises prior to engaging in sexual activity.

Exercise and Sexual Arousal in Women Who Have Undergone Hysterectomy

Hysterectomy is the most frequently performed gynecological surgery in many Western nations. In USA, 80% of hysterectomies are intended to treat benign conditions (Merrill 2008). Reports of positive outcomes of hysterectomies include the cessation of abnormal uterine bleeding, relief from menstrual symptoms and pelvic pain, and decreases in depression and anxiety (for review, see Farquhar and Steiner 2002). However, some women experience negative symptoms post-hysterectomy, including depression, fatigue, urinary incontinence, constipation, early ovarian failure, and sexual dysfunction (e.g., Thakar et al. 2002). Up to 40% of women report a decrease in their sex life following the surgery (e.g., Dennerstein et al. 1977), including lack of vaginal lubrication, loss of libido, and sexual pain. The uterine supporting ligaments contain sympathetic, parasympathetic, sensory, and sensory-motor nerve types and are considered a major pathway for autonomic nerves to the pelvic organs. It is feasible that the negative sexual outcomes following a hysterectomy are a result of the pelvic autonomic nerves being affected through excision of the cervix and separation of the uterus from the cardinal and uterosacral ligaments (Thakar et al. 1997).

If sexual arousal processes are negatively impacted by hysterectomy, and this is associated with autonomic innervation, differences between women who have and have not undergone hysterectomy may emerge under conditions of heightened autonomic arousal. To test this hypothesis, Meston (2002) examined subjective and physiological sexual arousal processes in women with a history of benign uterine fibroids who had or had not undergone hysterectomy using the same study methodology as in the prior exercise studies. Based on research that the uterine supporting ligaments are transected in hysterectomy (Butler-Manuel et al. 2002) and on research indicating that autonomic innervation is important for physiological sexual arousal (Giuliano et al. 2001), Meston (2004) expected that women who have undergone hysterectomy would have an impaired vasocongestive response to erotic stimuli and that this would be most apparent during the exercise condition. The results revealed that, contrary

to Meston's (2002) hypothesis, exercise significantly increased VPA responses in women who had undergone hysterectomy. Meston (2002) suggested that epinephrine and/or norepinephrine may have been responsible for the findings. Epinephrine and norepinephrine are released from the adrenal medulla during exercise, and they could have feasibly facilitated physiological arousal. Exercise could also have induced changes in endocrine factors, neuromediators, or substances released by endothelial cells (Guiliano et al. 2002). Regardless of the mechanisms that may have been involved, it is clinically relevant that exercise facilitated physiological sexual arousal in women who had undergone hysterectomy. As such, exercise may serve as a non-invasive way to enhance sexual responding in women who experience sexual arousal difficulties post-hysterectomy.

Exercise and Sexual Arousal in Women Who Are Cancer Survivors

Researchers have also tried to implement exercise interventions for sexual dysfunction among cancer survivors. Armbruster et al. (2016) implemented an exercise-based intervention for survivors of endometrial cancer. The results of the study included data from 63 endometrial cancer survivors in remission (Armbruster et al. 2016). Participants were observed during a baseline session, and then again two, four, and six months into the intervention. Quality of life and sexual functioning, conceptualized as satisfaction with sex life and distress over sexual dysfunction, were assessed at baseline and the six-month follow-up. Each participant received a personalized exercise plan that gradually built to 30 min of moderate exercise five out of seven days a week. After six months, 43% of participants experienced an increase in sexual functioning ($p = 0.002$). Post-intervention, mean sexual function score improved ($p = 0.002$), and 51% of participants had improved sexual interest. Indeed, a one-hour increase in weekly activity corresponded with a 7% increase in sexual interest. These findings support exercise as a therapeutic intervention for increasing sexual well-being and functioning among endometrial cancer survivors. Future research is needed to determine whether the benefits of exercise-based interventions generalize to all cancer survivors who experience sexual difficulties.

Exercise and Sexual Arousal in Women Experiencing Antidepressant-Induced Sexual Dysfunction

Women compared to men are at twice the risk for mood and anxiety disorders and are twice as likely to be prescribed antidepressants for their complaints (Thiels et al. 2005). In USA, an estimated one in six women has been prescribed an antidepressant (Paulose-Ram et al. 2007), the most commonly prescribed antidepressants being

selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). The vast majority of women taking antidepressants (96%) report at least one sexual side effect (Clayton et al. 2006), most commonly decreased desire, decreased arousal, and impaired orgasm. Both SSRIs and SNRIs are associated with these sexual problems, though SNRIs have been shown to have lower rates of arousal and orgasm side effects compared to SSRIs (Serretti and Chiesa 2009).

The sexual side effects of SSRIs are most likely linked to peripheral nervous system adrenergic pathways (Montejo and Rico-Villademoros 2008), particularly to changes in SNS activity (Serretti and Chiesa 2009). Antidepressants, specifically SSRIs, inhibit serotonin (5HT) reuptake via antagonism of the serotonin transporter, which increases synaptic serotonin (Stahl 1998). It is generally accepted that serotonin diminishes sexual function (e.g., Stahl 2001), likely due to its inhibitory effect on norepinephrine (Millan et al. 2000), which is associated with sympathetically controlled blood vessels (Gothert et al. 1995) and other peripheral nervous system outputs (e.g., Hull et al. 2004). In other words, SSRIs likely suppress SNS activity through norepinephrine release (Shores et al. 2001) and through sympathetic muscle and vascular nerve firing (Barton et al. 2007). Unlike SSRIs, SNRIs may counter the inhibition of norepinephrine, which occurs due to increased serotonin, by facilitating an increase in the availability of norepinephrine (Licht et al. 2009). Given that moderate SNS activity, compared to very high or very low SNS activity, is associated with increased genital arousal, it follows that SNRIs, which suppress SNS activity less than SSRIs, are associated with lower rates of genital arousal problems than SSRIs. Though there may be other mechanisms that contribute to the association between SSRIs and negative sexual side effects, SNS activity seems to play a strong role and may therefore be an important intervention target for this population. In addition, interventions that facilitate increased SNS activation affect the peripheral nervous system, so they are less likely to interfere with the central nervous system mechanisms that are presumably responsible for the antidepressants' beneficial therapeutic effects.

There are few treatment options for women who experience antidepressant-induced sexual dysfunction. Options, including adding a drug to try to counteract the side effect, have the patient switch antidepressants in the hopes that a different antidepressant will not have the same side effect, or encourage the patient to take a "drug holiday," a structured interruption in treatment for a period of time, typically a few days. However, with respect to depression, drug holidays make little pharmacological sense, as they risk withdrawal symptoms, and they may lead to illness relapse (Baldwin and Foong 2013).

Given the lack of strong treatment options for women with antidepressant-induced sexual problems, acute exercise is a viable intervention. As described earlier, acute exercise activates the SNS, which has been shown to play a mechanistic role in the relationship between antidepressants and adverse sexual side effects (Serretti and Chiesa 2009). Recently, Lorenz and Meston (2012) examined the effect of acute exercise on genital arousal in women taking either SSRIs or SNRIs. The women participated in three counterbalanced experimental sessions, where they watched an erotic film while their genital sexual arousal (VPA) and their SNS activity was

measured. During two of the three sessions, participants exercised for 20 min and viewed the non-sexual and erotic film sequence at either 5 min post-exercise or 15 min post-exercise. One session acted as a control, as women were simply asked to watch the film sequence without exercising. The authors hypothesized that the women who were on SSRIs were more likely to have increased SNS tone compared to their counterparts on SNRIs; therefore, their genital arousal would be greater 5 min post-exercise compared to 15 min post-exercise. Similarly, they expected that the women who were taking SNRIs would experience some of the benefits of the exercise intervention with respect to genital arousal, but to a lesser extent than those taking SSRIs. They also suggested that women who reported higher levels of impairment in genital arousal would experience the largest gains from the exercise intervention. The results showed that, as the authors hypothesized, SSRIs decrease SNS activity and genital arousal more so than SNRIs. That is, during the no-exercise control session, women taking SSRIs had lower genital arousal and SNS response to sexual stimuli than those taking SNRIs. More importantly, the authors found that, as anticipated, exercise-induced increases in genital arousal were greatest for those women reporting the lowest sexual arousal functioning.

Building upon these findings, a follow-up study compared the effects of acute exercise immediately before sexual activity to exercise separate from sexual activity (Lorenz and Meston 2014). Given that laboratory-based psychophysiological measures of female sexual arousal may not directly map on to reports of sexual function outside of the laboratory, Lorenz and Meston (2014) sought to examine potential differences between the effects of SNS activation on sexual responding (e.g., increased genital blood flow following acute exercise) and the general benefits of exercise on sexuality. Women who were experiencing antidepressant-induced sexual problems ($N = 52$) were entered into a 9-week trial. Thirty-eight women out of the total sample met criteria for clinically relevant sexual dysfunction based on the Female Sexual Function Index (FSFI; Rosen et al. 2000), which has been shown to reliably differentiate between women with and without sexual dysfunction (Meston 2003; Rosen et al. 2000). For the first 3 weeks, baseline levels of sexual activity were recorded. Participants were then randomized to either 3 weeks of exercise, 3 times a week, immediately prior to sexual activity or 3 weeks of exercise, also 3 times a week, at a time unrelated to sexual activity (at least 6 h between exercise and sexual activity). The women in this study were provided with a 30-min strength and cardio exercise video as well as a set of resistance bands in order to standardize the type of exercise across all participants. At the end of 3 weeks, participants crossed over to the other exercise condition.

Results revealed that, overall, exercise improved sexual desire, and for women who were experiencing clinically relevant sexual dysfunction at baseline, exercise improved overall sexual function. There was some evidence to suggest that exercise immediately before sexual activity was more beneficial than exercise in general. Overall, the results of this study indicate that exercise improves sexual function in women who report sexual problems due to antidepressant medication use, and there may be an additional benefit to exercising immediately prior to sexual activity.

Exercise and Sexual Arousal in Women with Multiple Sclerosis

In light of Lorenz and Meston's findings (2014), Sadeghi Bahmani and colleagues explored the effects of exercise on sexual functioning in women with Multiple Sclerosis (MS) (2020). MS is a neurodegenerative disease of the central nervous system that is highly comorbid sexual dysfunction and depression. In their study, Sadeghi Bahmani and colleagues implemented an 8-week aquatic exercise routine through which participants engaged in either two or three sixty-minute exercise sessions per week based on their random group assignment. A control group met two to three times per week during the 8-week study to discuss daily activities and challenges. Results indicated that regular aquatic exercise had significant, positive effects on sexual functioning. There were significant increases in functioning for the women with MS in both the exercise conditions as compared to the control group ($p < 0.001$). Furthermore, these differences were observed for each domain of sexual functioning (i.e., desire, orgasm, arousal, lubrication, pain, and satisfaction). These findings further suggest that SNS activation plays a faciliatory role in physiological sexual arousal in women and that, as a result, regular exercise can improve female sexual functioning.

Summary and Conclusions

The studies presented in this chapter strongly suggest that acute exercise increases physiological sexual arousal in women with normal or low levels of resting SNS activity. The most likely mechanism of action associated with the facilitatory effect of exercise on sexual arousal is SNS activation, although the roles of hormonal and other potential changes that occur with exercise cannot be ruled out. There appears to be an optimal level of SNS activation for the enhancement of genital arousal in women. Specifically, moderate increases in SNS activity have been associated with high physiological sexual arousal responses, while both very low and very high SNS activation are associated with lower physiological sexual arousal.

These findings have important clinical implications. For women who have normal baseline SNS levels and who are having problems becoming sexually aroused, as little as 20 min of acute exercise at a constant 70% of one's estimated maximum volume of oxygen uptake before sexual activity could help improve genital arousal. Acute exercise may also facilitate increased genital arousal in women who may have suppressed sympathetic activation due to hysterectomy, or antidepressant medication use, particularly SSRIs. As most of the treatment options for women with antidepressant-induced sexual dysfunction are pharmacologic in nature, acute exercise may be a valuable alternative for women seeking to increase their physiological sexual arousal without taking medication.

Drawing on the finding that high levels of SNS activation inhibited blood flow to the genitals, acute exercise prior to sexual activity may not be beneficial for women

with high baseline SNS arousal. High SNS arousal is typical of women with high sexual anxiety, posttraumatic stress disorder, and childhood sexual abuse. For these women, treatments that decrease baseline SNS activity and SNS activity during sexual activity may prove more beneficial. In fact, chronic exercise training has been associated with lower SNS responses to acute exercise (Hackney 2006). Level of chronic exposure to exercise is one of the most potent factors influencing the neuroendocrine stress response to a session of acute exercise. Women with elevated SNS arousal may benefit from regular exercise to reduce their basal SNS activity, which may, in turn, improve their sexual function.

Sexual arousal in women consists of both a genital (i.e., physiological) and psychological (i.e., the experience of being mentally "turned on") component, and both are important to a woman's overall sexual experience. This review focused exclusively on genital sexual arousal because the studies presented were almost all conducted within a laboratory setting and the accurate measurement of psychological arousal is difficult to obtain in a contrived laboratory setting. Although laboratory studies often show a low concordance between physiological and psychological sexual arousal in women (for a review, see Meston and Stanton 2019, or Chivers et al. 2010), it is possible that in a real-life sexual scenario feedback from increased genital arousal post-exercise would serve to also enhance the psychological experience of arousal for women who have high concordance of psychological and physiological sexual arousal.

It should also be noted that this review focused exclusively on the effects of acute exercise on women's sexual arousal response. The long-term, chronic effects of exercise on a woman's sexuality are also noteworthy. It is widely accepted that constructs such as self-esteem, body image, and body satisfaction are related to women's sexuality and overall sexual well-being. Exercise has been associated with improvements in self-esteem in both adolescents (e.g., Ekeland et al. 2005) and adults (e.g., McAuley et al. 1997). Among healthy individuals, increased exercise has beneficial effects on body image (e.g., Adame and Johnson 1989), and in women, researchers have noted a significant negative relationship between amount of exercise and body satisfaction (Tiggemann and Williamson 2000). Exercise has also been linked to increased energy and decreased fatigue (for a review, see Berger and Motl 2001), which collectively also play an important role in women's sexuality.

References

Adame DD, Johnson TC. Physical fitness, body image, and locus of control in college freshman men and women. Percept Mot Skills. 1989;68:400–2.

Alizadeh AM, Heydari Z, Rahimi M, Bazgir B, Shirvani H, Alipour S, Heidarian Y, Khalighfard S, Isanejad A. Oxytocin mediates the beneficial effects of the exercise training on breast cancer. Exp Physiol. 2018;103(2):222–35.

Anderson T, Wideman L. Exercise and the cortisol awakening response: a systematic review. Sports Med-Open. 2017;3(1):1–15.

Armbruster SD, Song J, Bradford A, Carmack CL, Lu KH, Basen-Engquist KM. Sexual health of endometrial cancer survivors before and after a physical activity intervention: a retrospective cohort analysis. Gynecol Oncol 2016;143(3):589–595.
Baldwin DS, Foong T. Antidepressant drugs and sexual dysfunction. Br J Psychiat: J Mental Sci. 2013;202:396–7.
Barton DA, et al. Sympathetic activity in major depressive disorder: identifying those at increased cardiac risk? J Hypertens. 2007;25(10):2117–24.
Baydil B. Testosterone responses to exhausting exercise in male and female students. Afr Educ Res J. 2020;8(2):244–7.
Berger B, Motl R. Physical activity and quality of life. In: Singer R, Hausenblas H, Janelle M, editors. Handbook of sport psychology. New York: Wiley; 2001. p. 636–71.
Berman JR. Physiology of female sexual function and dysfunction. Int J Impot Res. 2005;17(Suppl 1):S44–51.
Butler-Manuel SA, et al. Pelvic nerve plexus trauma at radical and simple hysterectomy: a quantitative study of nerve types in the uterine supporting ligaments. J Soc Gynecol Investig. 2002;9(1):47–56.
Caruso S, Mauro D, Scalia G, Palermo CI, Rapisarda AMC, Cianci A. Oxytocin plasma levels in orgasmic and anorgasmic women. Gynecol Endocrinol. 2018;34(1):69–72.
Chivers ML, et al. Agreement of self-reported and genital measures of sexual arousal in men and women: a meta-analysis. Arch Sex Behav. 2010;39(1):5–56.
Christensen NJ, Galbo H. Sympathetic nervous activity during exercise. Annu Rev Physiol. 1983;45:139–53.
Clayton A, Keller A, McGarvey E. Burden of phase-specific sexual dysfunction with SSRIs. J Affect Disord. 2006;91:27–32.
Dennerstein L, Wood C, Burrows G. Sexula response following hysterectomy and oophorectomy. Obstet Gynecol. 1977;56:316–22.
Ekeland E, Heian F, Hagen KB. Can exercise improve self esteem in children and young people? A systematic review of randomised controlled trials. Br J Sports Med. 2005;39(11): 792–98; discussion 792–98.
Engelman E, et al. Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. Anesthesiology. 1989;71(2):178–87.
Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990–1997. Obstet Gynecol. 2002;99(2):229–34.
Fergus KB, Gaither TW, Baradaran N, Glidden DV, Cohen AJ, Breyer BN. Exercise improves self-reported sexual function among physically active Adults. J Sex Med. 2019;16(8):1236–45.
Fox CA, Fox B. Blood pressure and respiratory patterns during human coitus. J Reprod Fertility. 1969;19:405–15.
Geer JH, Morokoff P, Greenwood P. Sexual arousal in women: the development of a measurement device for vaginal blood volume. Arch Sex Behav. 1974;3(6):559–64.
Giuliano F et al. Vaginal physiological changes in a model of sexual arousal in anesthetized rats. Am J Physiol Regulat Integr Comparat Physiol. 2001;281(1):R140–R49.
Giuliano F, Rampin O, Allard J. Neurophysiology and pharmacology of female genital sexual response. J Sex Marital Ther, 2002;28(sup1), 101–121.
Gothert M, et al. Presynaptic 5-HT auto- and heteroreceptors in the human central and peripheral nervous system. Behav Brain Res. 1995;73(1–2):89–92.
Hackney AC. Stress and the neuroendocrine system: the role of exercise as a stressor and modifier of stress. Expert Rev Endocrinol Metab. 2006;1(6):783–92.
Hackney AC. The male reproductive system and endurance exercise. Med Sci Sports Exerc. 1996;28(2):180–9.
Hackney AC, Saeidi A. The thyroid axis, prolactin, and exercise in humans. Curr Opin Endocr Metab Res. 2019;9:45–50.
Hamilton LD, Fogle EA, Meston CM. The roles of testosterone and alpha-amylase in exercise-induced sexual arousal in women. J Sexual Med. 2008;5(4):845–53.

Hamilton LD, Meston CM. Chronic stress and sexual function in women. J Sexual Med. 2013;10(10):2443–54.
Hancock M, Peveto C. Preganglionicneurons in the sacral spinal cord of the rat: an HRP study. Neurosci Lett. 1979;11:1–5.
Harte C, Meston CM. Gender comparisons in the concordance between physiological and subjective sexual arousal. In: Paper presented at the international society for the study of women's sexual health, Orlando, FL. 2007.
Harte CB, Meston CM. The inhibitory effects of nicotine on physiological sexual arousal in nonsmoking women: results from a randomized, double-blind, placebo-controlled, cross-over trial. J Sexual Med. 2008;1184–197.
Hatch JP. Vaginal photoplethysmography: Methodological considerations. Arch Sex Behav. 1979;8(4):357–74.
Heard-Davison A, Heiman JR, Kuffel S. Genital and subjective measurement of the time course effects of an acute dose of testosterone versus placebo in postmenopausal women. J Sexual Med. 2007;4(1):209–17.
Hew-Butler T, et al. Acute changes in endocrine and fluid balance markers during high-intensity, steady-state, and prolonged endurance running: unexpected increases in oxytocin and brain natriuretic peptide during exercise. Eur J Endocrinol. 2008;159(6):729–37.
Hill EE, et al. Exercise and circulating cortisol levels: The intensity threshold effect. J Endocrinol Invest. 2008;31(7):587–91.
Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: influences on male sexual behavior. Physiol Behav. 2004;83(2):291–307.
Jiannine LM (2018) An investigation of the relationship between physical fitness, self-concept, and sexual functioning. J Educ Health Promotion 7.
Jovanovic UJ. The recording of physiological evidence of genital arousal in human males and females. Arch Sex Behav. 1971;1(4):309–20.
Kirino E. Serum prolactin levels and sexual dysfunction in patients with schizophrenia treated with antipsychotics: comparison between aripiprazole and other atypical antipsychotics. Ann Gen Psychiatry. 2017;16(1):1–7.
Komisaruk BR, Gerdes CA, Whipple B. "Complete" spinal cord injury does not block perceptual responses to genital self-stimulation in women. Arch Neurol. 1997;54(12):1513–20.
Komisaruk BR, Beyer-Flores C, Whipple B. The science of orgasm. JHU Press; 2006.
Krantz K. Innervation of the human vulva and vagina: a microscopic study. Obstet Gynecol. 1958;12:382–96.
Kukkonen TM. What is the best method of measuring the physiology of female sexual arousal? Curr Sex Health Rep. 2014;6(1):30–7.
Lane AR, O'Leary CB, Hackney AC. Menstrual cycle phase effects free testosterone responses to prolonged aerobic exercise. Acta Physiol Hung. 2015;102(3):336–41.
Levin RJ. The mechanisms of human female sexual arousal. Annu Rev Sex Res. 1992;3:1–48.
Levin RJ. The physiology of sexual arousal in the human female: a recreational and procreational synthesis. Arch Sex Behav. 2002;31(5):405–11.
Levin RJ. The physiology of sexual function in women. Clin Obstet Gynaecol. 1980;7(2):213.
Licht CMM, Penninx BWJH, De Geus EJC. Response to depression and blood pressure control: all antidepressants are not the same. Hypertension. 2009;54(1): 133512.
Linnamo V, et al. Acute hormonal responses to submaximal and maximal heavy resistance and explosive exercises in men and women. J Strength Cond Res. 2005;19(3):566–71.
Lorenz TA, Meston CM. Acute exercise improves physical sexual arousal in women taking antidepressants. Ann Behav Med: Publ Soci Behav Med. 2012;43(3):352–61.
Lorenz TA, Harte CB, Hamilton LD, Meston CM. Evidence for a curvilinear relationship between sympathetic nervous system activation and women's physiological sexual arousal. Psychophysiol. 2012;49(1):111–117.
Lorenz TA, Meston CM. Exercise improves sexual function in women taking antidepressants: results from a randomized crossover trial. Depress Anxiety. 2014;31(3):188–95.

McAuley E, Mihalko SL, Bane SM. Exercise and self-esteem in middle-aged adults: multidimentional relationships and physical fitness and self-efficacy influences. J Behav Med. 1997;20(1):67–83.
Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. Med Sci Monitor. 2008;14:CR24–CR31.
Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. J Sex Marital Ther. 2003;29(1):39–46.
Meston CM, Gorzalka BB. The effects of immediate, delayed, and residual sympathetic activation on sexual arousal in women. Behav Res Ther. 1996;34(2):143–8.
Meston CM, Gorzalka BB. The effects of sympathetic activation on physiological and subjective sexual arousal in women. Behav Res Ther. 1995;33(6):651–64.
Meston CM, Gorzalka BB, Wright JM. Inhibition of subjective and physiological sexual arousal in women by clonidine. Psychosom Med. 1997;59:339–407.
Meston CM, Heiman JR. Ephedrine-activated physiological sexual arousal in women. Arch Gen Psychiatry. 1998;55(7):652–6.
Meston CM, Stanton AM. Understanding sexual arousal and subjective-genital arousal desynchrony in women. Nat Rev Urol. 2019;16(2):107–20.
Meston CM, Heiman JR. Acute dehydroepiandrosterone effects on sexual arousal in premenopausal women. J Sex Marital Ther. 2002;28(1):53–60.
Meston CM. The effects of hysterectomy on sexual arousal in women with a history of benign uterine fibroids. Arch sex behav. 2004;(33):31–42.
Millan MJ, Lejeune F, Gobert A. Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: relevance to the actions of antidepressant agents. J Psychopharmacol. 2000;14(2):114–38.
Montejo AL, Rico-Villademoros F. Psychometric properties of the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. J Sex Marital Ther. 2008;34(3):227–39.
Morris D, Marshall SA, Demers D. Exercise predictors of self-reported sexual performance among healthy adults. Int J Health Sci. 2018;6(1):1–16.
Nadelhaft I, McKenna K. Sexual dimorphism in sympathetic preganglionic neurons of the rat hypogastric nerve. J Comput Neurol. 1987;256:308–15.
Neuhber W. The central projections of visceral primary afferent neurons of the inferior mesenteric plexus and hypogastric nerve and the localization of the related sensory and preganglionic sympathetic cell bodies in the rat. Anat Embryol. 1982;163:413–25.
Palace EM, Gorzalka BB. The enhancing effects of anxiety on arousal in sexually dysfunctional and functional women. J Abnorm Psychol. 1990;99(4):403–11.
Paulose-Ram R, et al. Trends in psychotropic medication use among US adults. Pharmacoepidemiol Drug Saf. 2007;16:560–70.
Pearson MJ, Smart NA. Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev. 2018;23(1):91–108.
Rellini AH, Meston CM. Psychophysiological sexual arousal in women with a history of child sexual abuse. J Sex Marital Ther. 2006;32(1):5–22.
Riley AJ. Alpha adrenoceptors and human sexual function. In: Bancroft J, editor. The pharmacology of sexual function and dysfunction. New York: Elsevier; 1995. p. 307–25.
Rojas Vega S, Hollmann W, Strüder HK. Influences of exercise and training on the circulating concentration of prolactin in humans. J Neuroendocrinol. 2012;24(3):395–402.
Rosen R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Martial Therapy. 2000;26(2):191–208.
Sadeghi Bahmani D, Motl RW, Razazian N, Khazaie H, Brand. Aquatic exercising may improve sexual function in females with multiple sclerosis—An exploratory study. Multiple Sclerosis Relat Disorders. 2020;43:102106. https://doi-org.ezproxy.lib.utexas.edu/10.1016/j.msard.2020.102106

Salonia A, et al. Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm Behav. 2005;47(2):164–9.
Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29(3):259–66.
Simon JA. Identifying and treating sexual dysfunction in postmenopausal women: the role of estrogen. J women's health. 2011;20(10):1453–1465.
Shores MM, et al. Short-term sertraline treatment suppresses sympathetic nervous system activity in healthy human subjects. Psychoneuroendocrinology. 2001;26(4):433–9.
Sintchak G, Geer JH. A vaginal plethysmograph system. Psychophysiology. 1975;12(1):113–15.
Sipski ML, et al. Sexual responsiveness in women with spinal cord injuries: differential effects of anxiety-eliciting stimulation. Arch Sex Behav. 2004;33(3):295–302.
Sipski ML, Alexander CJ, Rosen R. Sexual arousal and orgasm in women: effects of spinal cord injury. Ann Neurol. 2001;49(1):35–44.
Smith AJ, et al. The effects of aerobic exercise on estrogen metabolism in healthy premenopausal women. Cancer Epid Biomark Prevent: Publ Am Assoc Cancer Res Cospons Am Soc Prevent Oncol. 2013;22(5):756–64.
Smith S. Effects of antipsychotics on sexual and endocrine function in women: Implications for clinical practice. J Clin Psychopharmacol. 2003;23(3 SUPPL. 1):S27–32.
Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. J Affect Disord. 1998;51(3):215–35.
Stahl SM. The psychopharmacology of sex, part 1: Neurotransmitters and the 3 phases of human sexual response. J Clin Psychiatry. 2001;62(2):1–47.
Thakar R, et al. Bladder, bowel and sexual function after hysterectomy for benign conditions. Br J Obstet Gynaecol. 1997;104(9):983–7.
Thakar R, et al. Outcomes after total versus subtotal abdominal hysterectomy. N Engl J Med. 2002;347(17):1318–25.
Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.
Thiels C, et al. Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline. Int Clin Psychopharmacol. 2005;20(1):1–7.
Tiggemann M, Williamson S. The effect of exercise on body satisfaction and self-esteem as a function of gender and age. Sex Roles. 2000;43(1):119–27.
Vingren JL, et al. Effect of resistance exercise on muscle steroid receptor protein content in strength-trained men and women. Steroids. 2009;74(13–14):1033–9.
Vingren JL, et al. Testosterone physiology in resistance exercise and training. Sports Med. 2012;40(12):1037–53.
Wiedeking C, Ziegler MG, Lake CR. Plasma noradrenaline and dopamine-beta-hydroxylase during human sexual activity. J Psychiatr Res. 1979;15:139–45.
Yehuda R. Risk and resilence in posttraumatic stress disorder. J Clin Psychiatry. 2003;65:29–36.
Yoon JR, Ha GC, Ko KJ, Kang SJ. Effects of exercise type on estrogen, tumor markers, immune function, antioxidant function, and physical fitness in postmenopausal obese women. J Exer Rehabil. 2018;14(6):1032.

Chapter 22
Sex Hormones, Cancer, and Exercise Training in Women

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Introduction

Higher levels of circulating sex hormones are linked to the risk of several sex hormone-related cancers in women, specifically breast and endometrial cancers (Brown and Hankinson 2015). It is proposed that sex hormones can have a mitotic effect on target tissues, by promoting greater cellular proliferation, inhibiting apoptosis, and increasing DNA damage (Caldon 2014; Henderson and Feigelson 2000; Yue et al. 2013). Therefore, it is suggested that cancer risk could be altered by reducing cumulative lifetime exposure to sex hormones, particularly estrogens. Early age of menarche (before age 12), later age of menopause, and a higher number of full-term pregnancies are all reproductive factors that are linked to increased risks of breast and endometrial cancers (Dossus et al. 2010; Henderson and Feigelson 2000; Hoffman-Goetz et al. 1998). Postmenopausal hormone therapy uses and higher postmenopausal body mass index (BMI) are proposed to increase cumulative sex hormone exposure and, in turn, increase breast and endometrial cancer risk (Allen et al. 2010; Henderson and Feigelson 2000; Morimoto et al. 2002; Reeves et al. 2007).

A pooled individual-level analysis of prospective studies and a recent meta-analysis have observed that postmenopausal women with elevated levels of endogenous estrogens (including estradiol, free estradiol, estrone, estrone sulfate) and androgens (including androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and testosterone) have an increased risk of developing postmenopausal breast cancer (Drummond et al. 2022; Endogenous

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Hormones and Breast Cancer Collaborative Group 2002), whereas women with elevated levels of sex hormone binding globulin (SHBG) may have a lower risk of postmenopausal breast cancer (Endogenous Hormones and Breast Cancer Collaborative Group 2002). Higher androgen (androstenedione, DHEAS, and testosterone) levels may also increase the risks of premenopausal breast cancer, whereas the associations between circulating estrogen levels and premenopausal breast cancer are less consistent, with a pooled analysis reporting positive associations between estrogens (estradiol, free estradiol, and estrone), while a recent meta-analysis did not find evidence of an association (Drummond et al. 2022; Endogenous et al. 2013). SHBG levels do not appear to associate with premenopausal breast cancer risk (Drummond et al. 2022; Endogenous et al. 2013).

For endometrial cancer, there is consistent evidence that women with elevated estrogen levels (estradiol, free estradiol, and estrone) are at an increased risk for postmenopausal endometrial cancer (Allen et al. 2008; Larsson et al. 2021; Lukanova et al. 2004; Zeleniuch-Jacquotte et al. 2001). Positive associations with androgens levels have also been observed, specifically elevated androstenedione (Lukanova et al. 2004) and total and free testosterone (Allen et al. 2008; Ruth et al. 2020; Watts et al. 2021a, b). To date, the relationship between estradiol levels and endometrial cancer risk in premenopausal women has not been studied with sufficient numbers to develop definitive conclusions (Brown and Hankinson 2015). The purpose of this chapter is to provide an overview of the impact of physical activity or structured exercise training on the risk of sex hormone-related cancers, namely breast and endometrial cancers. The chapter will first outline the epidemiological evidence and potential mechanisms. This will be followed by a summary of the impact of exercise training on sex hormones at key reproductive timepoints, namely pre-puberty, between puberty and menopause, and postmenopause. The impact of exercise training on sex hormones for women at higher risk of sex hormone-related cancers will also be outlined.

Epidemiology of Physical Activity and Sex Hormone-Related Cancer Risk

There is now a wealth of available epidemiologic evidence for the association between higher physical activity levels and reduced risk of many cancers, including breast and endometrial cancers (Friedenreich and Orenstein 2002; Guo et al. 2020; Lee 2003; Moore et al. 2016). The current public health recommendations for cancer prevention are for adults to engage in at least 150–300 min of moderate activity or at least 75–150 min of vigorous activity per week (Piercy et al. 2018; World Cancer Research Fund-American Institute for Cancer Research 2018), and it has been estimated that if everyone in the USA achieved $\geq$5 h/week of moderate-intensity activity, then >46,000 cancer cases could be prevented annually (Minihan et al. 2021).

For breast cancer, a pooled analysis of epidemiological studies suggests that women who self-reported the highest 90%tile levels of physical activity had a 10%

lower risk than the least active 10%tile (Moore et al. 2016). Analysis of physical activity measured using wrist-worn devices (to measure physical activity) also found that more active women had lower risks of breast cancer (Guo et al. 2020). The association of physical activity with breast cancer may be strongest for physical activity that is recreational or household activities and for physical activity either sustained over the lifetime or engaged in after menopause (Friedenreich et al. 2010a, b). Breast cancer is a heterogeneous disease, most commonly defined by hormone receptor status. Tumors can be estrogen receptor (ER) and progesterone receptor (PR) positive or negative. The observational evidence for whether the association between physical activity and breast cancer risk varies by hormone receptor status is mixed and remains unclear (Lynch et al. 2011; Ma et al. 2016; Moore et al. 2016; Steindorf et al. 2013). However, the largest pooled study to date found that physical activity is associated with both ER+ and ER− tumors (Moore et al. 2016).

For endometrial cancer, a risk reduction of 20–30% is reported among the most physically active women compared to the least physically activity women (Cust et al. 2007; Du et al. 2014; Moore et al. 2016; Schmid et al. 2015; Voskuil et al. 2007). However, there are emerging data that this effect may be limited to women who are overweight or obese, and the association of physical activity with endometrial cancer is reported to attenuate after accounting for BMI, suggesting that the relationship between physical activity and endometrial cancer may be due to physical activity decreasing body fat (Du et al. 2014; Moore et al. 2016; Schmid et al. 2015). While there are less available data regarding the benefits of physical activity carried out at different age periods across the lifespan, a stronger effect for recent or lifetime physical activity has been observed (Friedenreich et al. 2010a, b; Saint-Maurice et al. 2021).

Studying the association between an important exposure, such as physical activity, and a cancer diagnosis is a challenge. Observational studies are generally reliant on self-reported physical activity, where reporting errors can be introduced, and the long latency of cancer development means that prospective cohorts must be followed for many years. To date, a randomized controlled trial of physical activity with risk of pre- or postmenopausal breast cancer as the outcome has not been undertaken, as there are several logistical considerations that make such a trial difficult to undertake (Ballard-Barbash et al. 2009). Therefore, to gain a better understanding of how exercise influences cancer risk, researchers have focused on examining the effect of exercise on biomarkers, such as sex hormones, as surrogate outcomes rather than on the development of cancer as the outcome (Ballard-Barbash et al. 2009). Biomarkers are biological factors thought to be involved on the causal pathway between exposure and cancer development (Rundle 2005). Therefore, researchers have undertaken randomized controlled trials to prospectively test the effect of supervised exercise interventions on proposed biomarkers of sex hormone-related cancer risk. The development of wearable devices (to objectively measure physical activity levels) and assays (to measure multiple biomarker levels at a lower cost) has also enhanced researchers' capacity to assess the relationship between physical activity and biomarkers both in trials and population-based studies (Tin Tin et al. 2020; Watts et al. 2021a, b), as well as investigate how they relate to later cancer risk.

Proposed Mechanisms for Sex Hormone-Related Cancer Risk Reduction Due to Exercise

The effect of exercise on age at menarche, menstrual cycle function, and level of circulating endogenous sex steroid hormone levels in girls and women are often cited as potential mechanisms for reduced breast and endometrial cancer risk (Bernstein et al. 1994). In premenopausal women, the hypothalamic–pituitary–gonadal axis, which is responsible for key reproductive hormones, may be disrupted with stress or energy availability, namely by disrupting gonadotropin-releasing hormone (GnRH) pulsatility. This can result in primary amenorrhea (a delay in onset of menarche), oligomenorrhea (irregular menstrual cycles), or secondary amenorrhea (loss of menstrual cycle) (Borer 2003). These alterations would, in turn, reduce cumulative lifestyle exposure to sex hormones and are proposed to in turn reduce the risk of sex hormone-related cancers. A 2022 systematic review and meta-analysis on the effect of physical activity on sex hormones provide an overall summary. From data from 28 randomized controlled trials, 81 non-randomized interventions, and 6 observational studies, overall estrogens, progesterone, and androgens levels mostly decreased due to engaging in physical activity, and the quality of the evidence was rated as moderate or high for the particular hormone type (Swain et al. 2022).

In postmenopausal women, the beneficial effect of physical activity is closely linked to body composition. After menopause, the production of estrogen is no longer under feedback regulation as it is in premenopausal women. A higher risk of postmenopausal breast and endometrial cancer is observed for postmenopausal women who are overweight or obese (Reeves et al. 2007). This is attributed primarily to greater amounts of adipose tissue, where estrogens are produced via aromatization of other sex hormone precursors (Morimoto et al. 2002). Postmenopausal women who are obese have up to twofold higher serum concentrations of estradiol than lean postmenopausal women (Key et al. 2001). Increasing BMI is also associated with a drop in SHBG, resulting in a notable increase in levels of free estradiol in women (Key et al. 2001). Therefore, one-way exercise is proposed to lower postmenopausal breast and endometrial cancer risk by assisting with the reduction of body fat or with the maintenance of lower body fat. Furthermore, engaging in higher levels of physical activity may be able to counteract some of the increased risk associated with obesity through other mechanisms, such as improving metabolic function (i.e., hyperinsulinemia, insulin resistance), reducing systemic inflammation (i.e., prostaglandin, C-reactive protein), reducing oxidative stress (i.e., reactive oxygen species), reducing genomic instability, and improving immune surveillance (i.e., natural killer cells, leukocytes, T helper cells) (Patel et al. 2019; Wang and Zhou 2021). Exercise has the potential to affect all of these biological pathways, and their contribution may overlap or be synergistic (Campbell and McTiernan 2007). The discussion of these potential interactions is beyond the scope of this chapter.

In addition, exercise is proposed to alter how estrogens are metabolized in the body, namely to favorably alter metabolism toward 2-hydroxyestrone (2-OHE1),

which has little or no estrogenic effect rather than toward 16α-hydroxyestrone (16α-OHE1), which has an estrogenic effect (Campbell et al. 2007). However, a 2022 systematic review and meta-analysis of 11 prospective studies reported increased breast cancer risk with increasing concentrations of 2-OHE1 in postmenopausal women, but the strength of evidence was low. There were insufficient studies to complete a meta-analysis for premenopausal women (Drummond et al. 2022). Emerging data on measures of estrogen metabolism using a more comprehensive panel of estrogen metabolites through liquid chromatography-tandem mass spectrometry (LC-MS/MS) may shed new light on the association between estrogen metabolism and cancer risk (Ziegler et al. 2015).

Exercise Effect: Pre-puberty

Observational research points to an association between regular strenuous exercise such as ballet dancing, gymnastics, and running and a delay in the onset of menses (Bernstein et al. 1987; Frisch et al. 1981; Warren 1980). In one observational study, Frisch et al. (1981) reported that each year of training before menarche delayed menarche by 5 months. Exercise around the time of menarche may also delay the establishment of truly ovulatory menstrual cycles, thus reducing subsequent exposure to sex hormones (Bernstein et al. 1987). However, there is a potential issue of bias in the available observational studies, which used cross-sectional or retrospective study designs. Later maturation may favor athletic ability, and therefore, girls who are later in maturing may be more likely to engage in sports, rather than vice versa (Loucks 1990). Body weight, height, and BMI are also strongly correlated with the age of menarche (Karapanou and Papadimitriou 2010). So energy availability may play an important role in age of menarche, rather than specifically exercise levels per se (Loucks 1990).

Exercise Effect: Puberty to Menopause

Exercise may cause minor shifts in the hormonal milieu of premenopausal women, which is proposed to play a role in reducing the cumulative exposure to sex hormones and subsequent sex hormone-related cancer risk (Bullen et al. 1984; Keizer et al. 1987). Originally, it was proposed that exercise of significant frequency and intensity was needed to induce menstrual dysfunction sufficient to result in significantly decreased exposure to sex steroid hormones (Bullen et al. 1985). In premenopausal women, observational research points to a continuum of menstrual dysfunction (amenorrhea, anovular cycles, luteal phase deficiency), longer menstrual cycles, and lower progesterone and estradiol levels in athletes compared with control subjects (Baker and Demers 1988; Broocks et al. 1990; De Souza et al. 1998; Ellison and Lager 1986; Pirke et al. 1990; Ronkainen 1985; Schweiger et al. 1988). However,

this has been harder to document with prospective intervention studies, and the few available prospective intervention studies are hampered by small sample sizes and mixed results. Two studies found that a moderate-intensity running intervention did not disrupt reproductive function (Bonen 1992; Rogol et al. 1992), while two other studies reported minor changes in measures of reproductive function (Bullen et al. 1984; Keizer et al. 1987), and one study documented menstrual dysfunction with significant exercise frequency and intensity, namely daily 10-mile run in addition to 3.5 h of sports at a moderate exercise intensity (Bullen et al. 1985).

The more modern prospective intervention studies that followed this early work have demonstrated that exercise and other stressors have little or no disruptive effect on a reproductive function beyond that of their energy cost on energy availability (Loucks 2003; Loucks and Redman 2004; Williams et al. 2001). Williams et al. demonstrated experimentally that there is a dose–response relationship between the magnitude of energy deficiency and the frequency of menstrual disturbances (Williams et al. 2015). Participants were randomly assigned to one of 4 groups: (1) Exercise Control (15% energy deficit with exercise but calories added back to diet to remain in energy balance); (2) Energy Deficit 1 (15% energy deficit with exercise; mean −162 kcal/day); (3) Energy Deficit 2 (30% energy deficit with a combination of exercise and reduced dietary intake; mean −470 kcal/day); and (4) Energy Deficit 3 (60% energy deficit with a combination of exercise (30% deficit) and reduced dietary intake (30% deficit); mean −813 kcal/day). Luteal phase defects, anovulation, and oligomenorrhea were observed to a greater degree in the two highest energy deficit groups, and the main predictor of these disturbances was percent energy deficit (Williams et al. 2015). In a recent study of 35 sedentary, ovulatory women aged 18–24 years, who were randomized to different levels of varying magnitude of negative energy balance through a combination of exercise and dietary intake restrictions, there was no specific energy availability threshold that induced menstrual disturbances. However, there was a linear relationship between an increase in menstrual disturbances as energy availability decreased (Lieberman et al. 2018).

The issue of menstrual dysfunction in athletes has been explored extensively under the umbrella of the female athlete triad, defined as a combination of: (1) low energy availability, with or without disordered eating; (2) menstrual dysfunction; and (3) low bone mineral density (Nattiv et al. 2007). The concept of the female athlete triad is now more commonly discussed as a syndrome called relative energy deficiency in sport (RED-S) (Mountjoy et al. 2014, 2018). The syndrome takes a more holistic approach focusing on impaired physiological functioning caused by relative energy deficit.

One of the key effects of menstrual dysfunction is a subsequently lower level of circulating estrogens, which in turn has a negative impact on bone health and increases the risk of stress fractures. Relative to the prevention of sex hormone-related cancers, the proposed goal is a balance between lowering estrogen exposure by encouraging mild shifts in menstrual cycle function (i.e., subtle luteal phase defects that could in turn lengthen the menstrual cycle and reduce the total number of cycles per year or across a lifetime), while at the same time maintaining sufficient estrogen levels to maintain bone health. How best to strike this balance has not been established.

To add to the complexity, for premenopausal women, being overweight or obese lowers the risk of breast cancer, possibly because overweight and obesity are linked to a higher frequency of anovulatory menstrual cycles (Carmichael and Bates 2004; Friedenreich 2001). This may result in less exposure to estrogens, which may subsequently reduce the risk of premenopausal breast cancer risk. However, overweight or obesity also results in lower progesterone levels, which may play a key role in the increased endometrial cancer risk for overweight or obese premenopausal women because of exposure to unopposed estrogens (Key et al. 2001).

A large prospective intervention study to examine the impact of exercise training on sex hormone levels in premenopausal women is the Women In Steady Exercise Research (WISER) study. In this study, 391 previously sedentary, premenopausal women aged 18–30 years with regular menstrual cycles (24–35 days) were randomized to either 150 min per week of supervised moderate-intensity aerobic exercise (30 min/day, 5 days per week) for 16 weeks or usual lifestyle control. Despite high adherence to the exercise intervention, no differences in sex hormones or SHBG levels were noted between groups (Smith et al. 2011). The intervention group improved fitness, and while there was no change in body weight in either group, the intervention group had significant reductions in body fat (mean reduction of 1%) and increases in lean mass (mean increase of 0.5 kg). The authors concluded that favorable effects of moderate-intensity exercise on breast cancer risk may be operating through other biological pathways than sex hormones in the absence of a significant deficit in energy availability or weight loss.

Specific to estrogen metabolites, observational studies in premenopausal women have reported higher ratios of 2-OHE1 to 16α-OHE1 in athletes compared with control subjects (Russell et al. 1984a); with high-intensity training that also resulted in the development of menstrual dysfunction (Russell et al. 1984a, b; Snow et al. 1989); with higher self-reported daily physical activity (Bentz et al. 2005; Matthews et al. 2004); and with higher aerobic fitness (VO_2max) (Campbell et al. 2005). However, these associations may be related to body composition, with less favorable patterns seen with higher BMI (Bentz et al. 2005; Campbell et al. 2005; Matthews et al. 2004). In two prospective interventions studies in premenopausal women, in the 16-week aerobic exercise intervention in the WISER study, the exercise group had a statistically significant favorable increase in 24-h urinary 2-OHE1/16α-OHE1 ratio, consistent with a reduction in estrogen exposure (Smith et al. 2013), while Campbell et al. (2007) reported no change in first morning urinary estrogen metabolism pattern with a12-week aerobic exercise training intervention versus delayed exercise control in a similar population of 32 previously sedentary, premenopausal women, with regular menstrual cycles. Interestingly, an increase in lean body mass was associated with a favorable change in 2-OHE1/16alpha-OHE1 ratio ($r = 0.43$; $p = 0.015$).

Effect of Exercise: After Menopause

In postmenopausal women, increased physical activity is associated with decreased serum concentrations of estradiol, estrone, and androgens after adjustment for BMI in some (Cauley et al. 1989; McTiernan et al. 2008) but not in other studies (Verkasalo et al. 2001). In a random subsample of women in the Women's Health Initiative Dietary Modification Trial (Howard et al. 2006), women with a high BMI and low self-reported physical activity had higher levels of estrone, estradiol, and free estradiol and lower levels of SHBG than women with a similar BMI who were active or with low BMI in either activity category (McTiernan et al. 2008) (Fig. 22.1). A series of six published randomized controlled trials has examined the effect of aerobic physical activity on sex hormones in previously sedentary, overweight, postmenopausal women, with a goal of informing a better understanding of the dose of exercise needed to reduce breast cancer risk (Table 22.1).

The Physical Activity and Total Health Trial is a 2-arm trial in 173 women that examined the effect of a 12-month moderate-intensity aerobic exercise (45 min/d, 5 d/wk) versus usual lifestyle control. The exercise group had a reduction in body weight, total body fat, intraabdominal fat, and subcutaneous fat compared with the control group, and a significant dose–response for greater body fat loss was observed with increasing duration of exercise (Irwin et al. 2003). A significant decrease in estradiol, estrone, and free estradiol was seen from baseline to 3 months with an attenuation of the effect at 12 months (McTiernan et al. 2004a, b). However, in women who lost body fat, the exercise intervention resulted in a statistically significant decrease in these estrogens (McTiernan et al. 2004a, b) (Fig. 22.2) and a statistically significant decrease in testosterone and free testosterone at 3 and 12 months (McTiernan et al. 2004a, b).

The Alberta Physical Activity and Breast Cancer Prevention Trial (ALPHA Trial) is a 2-arm trial in 320 women that examined the effect of a 12-month aerobic exercise intervention (45 min/d, 5 d/wk) compared with usual lifestyle control (Friedenreich

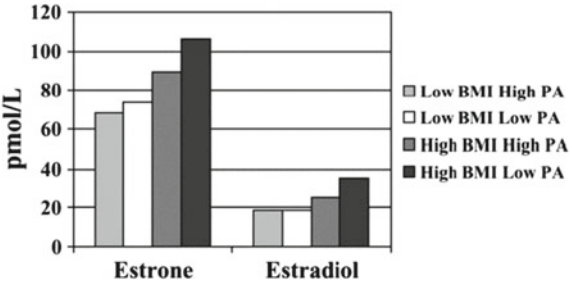

Fig. 22.1 Associations of BMI and physical activity with serum estrogens in postmenopausal women: Women's Health Initiative ($n = 267$) (McTiernan et al. 2006). Low BMI < 29.0; high BMI ≥ 29.0; low physical activity ≤ 6.5 MET-hours per week; high physical activity > 6.5 MET-hours per week

Table 22.1 Change in estradiol, estrone, and sex hormone binding globulin in randomized controlled trials of lifestyle interventions focused on biomarkers of postmenopausal breast cancer risk in inactive, overweight, postmenopausal women

Study	Location	N	Duration	Intervention	Outcome
Physical Activity and Total Health (PI: McTiernan) (McTiernan et al. 2004a, b)	USA	173	12 month	2-arm 1. Aerobic (225 min/wk) 2. Control	Estradiol: 1. −4.4% (NS) 2. −0.6% Estrone: 1. −1.8% (NS) 2. +3.9% SHBG: 1. +8.8% (NS) 2. +2.5%
ALPHA (PI: Friedenreich) (Friedenreich et al. 2010b)	Canada	320	12 month	2-arm 1. Aerobic (225 min/wk) 2. Control	Estradiol: 1. −14%[a] 2. −2.9% Estrone: 1. −6.4% (NS) 2. −2.2% SHBG: 1. +4.0%[a] 2. +0.8%
SHAPE (PI: Monninkhof) (Monninkhof et al. 2009)	Netherlands	189	12 month	2-arm 1. Combined aerobic and resistance (150 min/wk) 2. Control	Estradiol: 1. −8.0 (NS) 2. −10.1 Estrone: 1. −13.9 (NS) 2. −7.4 SHBG: 1. −0.7 (NS) 2. −3.3
NEW (PI: McTiernan) (Campbell et al. 2012)	USA	439	12 month	4-arm: 1. Reduced calorie diet (−10% BW) 2. Aerobic exercise (225 min/wk) 3. Combined reduced calorie diet and aerobic exercise (−10% BW and 225 min/wk) 4. Control	Estrone: 1. −9.6[a] 2. −5.5 (NS) 3. −11.1[a] 4. +8.1 Estradiol: 1. −16.2[a] 2. −4.9 (NS) 3. −20.3[a] 4. +4.9 SHBG: 1. +22.4[a] 2. −0.7 (NS) 3. +25.8[a] 4. −2.7

(continued)

Table 22.1 (continued)

Study	Location	N	Duration	Intervention	Outcome
BETA (PI: Friedenreich) (Friedenreich et al. 2015)	Canada	400	12 months	2-arm 1. Aerobic—moderate volume (150 min/week) 2. Aerobic—high volume (300 min/week)	Estradiol: 1. −4.5 2. −3.6 (NS) Estrone: 1. −3.2 2. 0.1 (NS) SHBG: 1. 9.6 2. 6.4 (NS)
SHAPE-2 (PI: Monninkhof) (van Gemert et al. 2015)	Netherlands	243	16 weeks	3-arm 1. Reduced calorie diet (−5 to 6 kg) 2. Combined aerobic and RT intervention (240 min/week) with slight reduction in calorie intake (with goal to reduce 5 to 6 kg) 3. Control	Estradiol: 1. −13.8[a] 2. −12.7[a] 3. +3.1 Estrone: 1. −1.3 (NS) 2. −6.7 (NS) 3. +1.5 SHBG: 1. +12.6[a] 2. +19.0[a] 3. −8.3

Legend [a] Denotes statistical significance compared to control group; BW = body weight; NS = not statistically significant compared to control group or comparison group (moderate intensity) in BETA Trial; SHBG = sex hormone binding globulin.

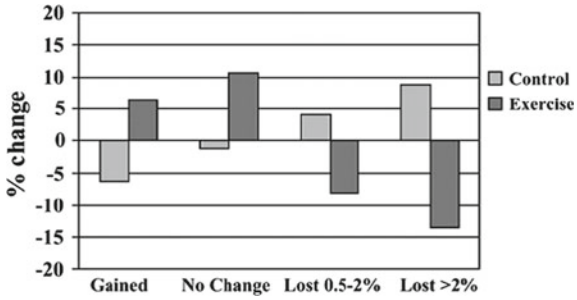

Fig. 22.2 Percent change in estradiol by percent change in body fat in a randomized controlled trial of 1-year moderate-intensity exercise in postmenopausal women (McTiernan et al. 2004a, b). Statistically significant difference in estradiol level in exercisers who lost 0.5–2% body fat ($p = 0.02$) and for those who lost >2% body fat ($p = 0.008$)

et al. 2010a, b). A significant reduction in estradiol and free estradiol and an increase in SHBG were observed in the intervention group compared to the control group at 12 months, suggesting that women that engaged in at least 150 min per week of

moderate-intensity aerobic exercise could lower exposure to estradiol levels (Friedenreich et al. 2010a, b). Change in sex hormone levels by the amount of weight loss was not reported.

The Sex Hormones And Physical Exercise (SHAPE-1) Trial is a 2-arm trial in 189 women that examined the effect of a 12-month combined aerobic (20–30 min per session) and resistance intervention (25 min per session) compared to usual lifestyle control (Monninkhof et al. 2009). The intervention was two supervised sessions per week of the combined intervention and one home-based session of 30 min of brisk walking. There were no differences in sex hormones between groups at 12 months. In women who lost >2% of baseline body weight, regardless of group assignment, there was a significant reduction in testosterone, free testosterone, and androstenedione in the exercise group compared to controls (Monninkhof et al. 2009). The authors suggest that these findings confirm that weight loss may be key in altering sex hormone levels in postmenopausal women, but that exercise may also play a role in favorably altering sex hormone levels.

The Nutrition and Exercise for Women (NEW) Trial is a 4-arm trial examining 439 women that examined the effects of a 12-month intervention of dietary weight loss alone, exercise alone, dietary weight loss plus exercise, or usual lifestyle control (Campbell et al. 2012; Foster-Schubert et al. 2012). The dietary weight loss intervention was a reduced calorie diet with a goal of a 10% reduction from baseline body weight. The exercise intervention was 45 min of moderate-intensity aerobic exercise 5 days per week (with three of the sessions supervised). The combined group undertook both interventions. A reduction in estrone compared to controls was seen in all three intervention groups. However, a reduction in estradiol, free estradiol, and free testosterone was only noted in the dietary weight loss alone or dietary weight loss plus exercise groups, and not in the exercise alone group. A similar pattern of increase in SHBG is only in the dietary weight loss alone and dietary weight loss group plus exercise groups (Campbell et al. 2012). The control group lost −0.6 kg, while the exercise group lost −3.3 kg, the dietary weight loss group alone group lost −10.8 kg, and the dietary weight loss group plus exercise lost 11.9 kg (Foster-Schubert et al. 2012). The authors concluded that greater weight loss produced greater changes in estrogens and SHBG, and therefore, the findings supported weight loss as a risk reduction strategy for postmenopausal breast cancer by lower exposure to biomarkers of risk (Campbell et al. 2012).

The Breast Cancer and Exercise Trial in Alberta (BETA) is a 2-arm trial in 400 women that examined the effects of a 12-month intervention of moderate volume of aerobic exercise (150 min/wk) and high volume of aerobic exercise (300 min/wk) (Friedenreich et al. 2015). Adherence to the intervention resulted in a median of 137 min/week performed by the moderate volume group and a median of 253 min/week performed by the high volume group. At 12 months, there were similar reductions in estrone, estradiol, and free estradiol and similar increases in SHBG in both groups, with no difference between groups. While greater decreases in estradiol and free estradiol were borderline significant in the high volume group, the authors suggested that the lack of observed difference may be due to the fact that the volume of exercise achieved between the groups may not have been sufficiently

different. A dose effect was observed more so for obese women and the amount of time spent in vigorous-intensity aerobic exercise, as compared with more moderate intensity (Friedenreich et al. 2015).

The Sex Hormones and Physical Exercise-2 (SHAPE-2) Trial is a 3-arm trial in 243 women that examined the effects of a 12-month reduced calorie diet with a weight loss goal of 5–6 kg from baseline body weight, an exercise intervention that was a combined aerobic and resistance program with a small calorie deficit with the same weight loss goal of 5–6 kg, and a usual lifestyle control group. There was no change in body weight in the control group (van Gemert et al. 2015). Both intervention groups reached the body weight loss target at 12 months, with a statistically significantly greater reduction in the exercise group compared to the reduced calorie diet group (−5.5 vs. −4.9 kg, $p < 0.001$). At 12 months, the only difference between groups was a reduction in free testosterone in the main exercise group compared to the control and an increase in SHBG in both intervention groups compared to the control. After adjustment for changes in body fat, intervention effects were attenuated or disappeared (van Gemert et al. 2015). The authors suggest that the beneficial effect of exercise on sex hormones may be through promoting greater weight loss and greater reductions in body fat when combined with reduced calorie diets versus dietary weight loss alone.

The results of these trials have been synthesized in a meta-analysis (de Roon et al. 2018). Overall caloric restriction, in combination with exercise, appears to be the most beneficial intervention for lowering levels of estrone, total estradiol, free estradiol, free testosterone, and SHBG. In fact, the addition of exercise to caloric restriction resulted in greater improvements when compared to caloric restriction alone, even when weight loss between groups was comparable. However, exercise alone only resulted in borderline significant effects on androstenedione, total estrogen, and free testosterone. Of note, this meta-analysis did not include the BETA Trial, as it compared two different volumes of exercise and did not have a control group for comparison. The meta-analysis also included a randomized controlled trial by Orsatti et al. that reported no effect of a 16-week resistance training intervention compared to control on total testosterone and total estradiol in 50 postmenopausal women (Orsatti et al. 2008). The authors of the meta-analysis make a point that, while a strength of the meta-analysis is the high quality and large sample sizes of the trials included, a limitation of this work is that the results may not be generalizable to all postmenopausal women (i.e., only physically inactive women with a BMI > 22 kg m^2 were included). Specific to estrogen metabolism, two randomized trials, namely the Physical Activity and Total Health Trial and ALPHA Trial, measured estrogen metabolites. No significant effect of the aerobic exercise intervention was observed using the standard assays (Atkinson et al. 2004), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) was observed (Matthews et al. 2018). Overall, these findings suggest that physical activity alone can result in some favorable changes in sex hormones. However, weight loss appears to have a larger impact on sex hormones, and the role of exercise in efforts to lower the risk of postmenopausal breast cancer may complement weight loss efforts undertaken with a reduced calorie diet.

Exercise Effect: High-Risk Groups

Only 5–10% of sex hormone-related cancers are linked to genetic factors (Easton et al. 1995; Wooster et al. 1995). Mutations in two breast cancer susceptibility genes (BReast CAncer or BRCA1 and BCRA2), which are tumor suppressor genes, are strongly linked to the risk of hereditary breast and ovarian cancer, with carriers having a 40–85% chance of developing breast cancer in their lifetime, along with a higher risk of developing ovarian cancer (25–65% in BCRA1 carriers and 15–10% in BRCA2 carriers) (Antoniou et al. 2006; King et al. 2003). Currently, treatment involved several medical options to reduce hormone exposure, including prophylactic oophorectomy, which can lower breast cancer risk by 50–70%, or the use of Selective Estrogen Receptor Modulators (SERMS, e.g., tamoxifen and raloxifene) which can lower breast cancer risk by 50%. Prophylactic mastectomy is another option, which can reduce risk by 90–95% (Pruthi et al. 2010).

In a large case–control observational study including 443 matched pairs of women who were carriers of a BRCA mutation, there was no overall association between total physical activity and subsequent breast cancer risk. Physical activity was collected using a self-reported questionnaire asking about moderate and vigorous physical activity at ages 12–13, 14–17, 18–22, 23–29, and 30–34. One key finding was that higher amounts of moderate-intensity physical activity early in life, namely ages 12–17, were associated with a 38% decrease in risk of breast cancer diagnosed during the premenopausal life stage. There was no association with breast cancer diagnosed after menopause. The WISER Sister study is a randomized controlled trial conducted in women at high risk of breast cancer (i.e., BRCA 1 or 2 mutation, first degree relative with a breast cancer diagnosis, and/or Claus or Gail model risk of 18%). This 3-arm trial of 150 min/week or aerobic exercise, 300 min/week of aerobic exercise, or usual lifestyle control for 5 menstrual cycles measured urinary hormones in daily first morning urines in menstrual cycles 1 and 2 for baseline and menstrual cycles 6 and 7 for post-intervention. The control group had an 11.6% increase in area under the curve for follicular phase estrogen, compared to a −2.1 and a 0.2% change in the low- and high-dose groups, respectively. There was no difference in the luteal phase. In looking at the dose-response relationship, every 100 min of exercise was associated with 3.6% lower follicular phase estrogen (Schmitz et al. 2015). A particularly unique aspect of this study was the impact of the intervention directly on breast tissue. The amount of glandular breast tissue, the constituent of breast tissue that is hormone responsive, was measured using parenchymal enhancement magnetic resonance imaging. Every 100 min of the exercise was associated with a 9.7% decrease in background parenchymal enhancement (Brown et al. 2016; Schmitz et al. 2015). The authors conclude that these results offer support for physical activity as an additional option for women at high risk of breast cancer to blunt exposure levels of estrogen (Brown et al. 2016). More research on the potential role of physical activity or exercise to alter exposure to sex hormones and how this may impact breast cancer risk in higher-risk individuals is needed.

Future Directions

Future exercise interventions should expand on current knowledge by testing different types of exercises (i.e., resistance and aerobic) and different volumes of exercises (i.e., other intensities and durations of exercise) in different populations and in persons at different risks of developing cancer. Lower costs of techniques such as wearable devices (to objectively measure physical activity), high-throughput assays (to measure many biomarkers at once), and imaging (for detailed body composition information) in large studies will enable more robust research to confirm whether proposed biomarkers do indeed lie on the causal pathway between physical activity and sex hormone-related cancer development independently of adiposity. One potential example of this is the Molecular Transducers of Physical Activity Consortium (MoTrPAC) (Sanford et al. 2020). This project aims to examine the molecular changes (including sex hormones) in the body secondary to exercise, with a goal to increase the understanding of the unique contributions of exercise to improving and maintaining the health of the body's tissues and organs.

Summary

Moderate-intensity physical activity has biological effects that may reduce the risk of breast and endometrial cancers, including through favorable changes in sex hormone levels. However, energy balance and body fat may play a significant role in the relationship between physical activity and sex hormone levels. This suggests the need for future trials to examine the independent and combined effects of physical activity and diet in support of weight management and weight loss to reduce the risk of sex hormone-related cancers.

References

Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, Peeters RH, Onland-Moret NC, Lahmann NC, Berrino PH, Panico S, Kaaks R. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer. 2008;15(2):485–97. https://doi.org/10.1677/ERC-07-0064.

Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, Bakken K, Gavrilyuk O, Overvad K, Tjønneland A, Olsen A. Menopausal Hormone therapy and risk of endometrial carcinoma among postmenopausal women in the european prospective investigation into cancer and nutrition. Am J Epidemiol. 2010;172(12):1394–403. https://doi.org/10.1093/aje/kwq300.

Antoniou AC, Pharoah PD, Easton DF, Evans DG (2006) BRCA1 and BRCA2 cancer risks. J Clin Oncol: Off J Am Soc Clin Oncol 24(20):3312–13; author reply 3313–14. https://doi.org/10.1200/JCO.2006.06.7934

Atkinson C, Lampe JW, Tworoger SS, Ulrich CM, Bowen D, Irwin ML, Schwartz RS, Rajan BK, Yasui Y, Potter JD, McTiernan A. Effects of a moderate intensity exercise intervention on estrogen metabolism in postmenopausal women. Cancer Epidemiol Biomark Prev. 2004;13(5):868–74.

Baker E, Demers L. Menstrual status in female athletes: correlation with reproductive hormones and bone density. Obstet Gynecol. 1988;72(5):683–7.

Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, Wing R, Schatzkin A. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. J Natl Cancer Inst. 2009;101(9):630–43. djp068 [pii]. https://doi.org/10.1093/jnci/djp068.

Bentz AT, Schneider CM, Westerlind KC. The relationship between physical activity and 2-hydroxyestrone, 16alpha-hydroxyestrone, and the 2/16 ratio in premenopausal women (United States). Cancer Causes Control. 2005;16(4):455–61.

Bernstein L, Henderston BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst. 1994;86(18):1403–8.

Bernstein L, Ross R, Lobo RA, Hanische R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. Br J Cancer. 1987;55:681–5.

Bonen A. Recreational exercise does not impair menstrual cycles: a prospective study. Int J Sports Med. 1992;13:110–20.

Borer K. Exercise endocrinology. Champaign: Human Kinetics; 2003.

Broocks A, Pirke KM, Schweiger U, Tuschl RJ, Laessle RG, Strowitzki T, Horl E, Horl T, Hass W, Jeschke D. Cyclic ovarian function in recreational athletes. J Appl Physiol. 1990;68(5):2083–6.

Brown JC, Kontos D, Schnall M, Wu S, Schmitz KH. The dose-response effects of aerobic exercise on body composition and breast tissue among women at high risk for breast cancer: a randomized trial. Cancer Prev Res. 2016. https://doi.org/10.1158/1940-6207.CAPR-15-0408.

Brown SB, Hankinson SE. Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. Steroids. 2015;99(Pt A):8–10. https://doi.org/10.1016/j.steroids.2014.12.013.

Bullen BA, Skrinar GS, Beitins IZ, Carr DB, Reppert SM, Dotson CO, Fencl MD, Gervino EV, McArthur JW. Endurance training effects on plasma hormonal responsiveness and sex hormone excretion. J Appl Physiol. 1984;56(6):1453–63.

Bullen BA, Skrinar GS, Beitins IZ, Von Mering G, Turnbull BA, McArthur JW. Induction of menstrual disorders by strenuous exercise in untrained women. N Engl J Med. 1985;312:1349–53.

Caldon CE. Estrogen signaling and the DNA damage response in hormone dependent breast cancers. Front Oncol. 2014;4:106. https://doi.org/10.3389/fonc.2014.00106.

Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, Mason C, Imayama I, Kong A, Xiao L, Bain CE, McTiernan A. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol. 2012;30(19):2314–26. https://doi.org/10.1200/JCO.2011.37.9792.

Campbell KL, McTiernan A. Exercise and biomarkers for cancer prevention studies. J Nutr. 2007;137(1):161S-169S.

Campbell KL, Westerlind KC, Harber VJ, Bell GJ, Mackey JR, Courneya KS. Effects of aerobic exercise training on estrogen metabolism in premenopausal women: a randomized controlled trial. Cancer Epidemiol Biomark Prev. 2007;16(4):731–9.

Campbell KL, Westerlind KC, Harber VJ, Friedenreich CM, Courneya KS. Associations between aerobic fitness and estrogen metabolites in premenopausal women. Med Sci Sports Exerc. 2005;37(4):585–92.

Carmichael AR, Bates T. Obesity and breast cancer: a review of the literature. Breast. 2004;13(2):85–92.

Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol. 1989;129(6):1120–31.

Cust AE, Armstrong BK, Friedenreich CM, Slimani N, Bauman A. Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods. Cancer Causes Control. 2007;18(3):243–58. https://doi.org/10.1007/s10552-006-0094-7

de Roon M, May AM, McTiernan A, Scholten R, Peeters PHM, Friedenreich CM, Monninkhof EM. Effect of exercise and/or reduced calorie dietary interventions on breast cancer-related endogenous sex hormones in healthy postmenopausal women. Breast Cancer Res. 2018;20(1):81. https://doi.org/10.1186/s13058-018-1009-8.

De Souza MJ, Miller BE, Loucks AB, Luciano AA, Pescatello LS, Campbell CG, Lasley BL. High frequency of luteal phase deficiency and anovulation in recreational women runners: Blunted elevation in follicle-stimulating hormone observed during luteal-follicular transition. J Clin Endocrinol Metab. 1998;83(12):4220–32.

Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Fournier A, Chabbert-Buffet N, Riboli E. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;127(2):442–51. https://doi.org/10.1002/ijc.25050.

Drummond AE, Swain CTV, Brown KA, Dixon-Suen SC, Boing L, van Roekel EH, Moore MM, Gaunt TR, Martin RM, Lynch BM. linking physical activity to breast cancer via sex steroid hormones, part 2: the effect of sex steroid hormones on breast cancer risk. Cancer Epidemiol Biomark Prev. 2022a;31(1):28–37. https://doi.org/10.1158/1055-9965.Epi-21-0438.

Du M, Kraft P, Eliassen AH, Giovannucci E, Hankinson SE, De Vivo I. Physical activity and risk of endometrial adenocarcinoma in the Nurses' Health Study. Int J Cancer. 2014;134(11):2707–16. https://doi.org/10.1002/ijc.28599.

Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Human Genet. 1995;56(1):265–71.

Ellison PT, Lager C. Moderate recreational running is associated with lowered saliva progesterone profiles in women. Am J Obstet Gynecol. 1986;154(5):1000–3.

Endogenous H, Breast Cancer Collaborative G, Key TJ, Appleby PN, Reeves GK, Travis RC, …, Vineis P. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 2013;14(10):1009-19. https://doi.org/10.1016/S1470-2045(13)70301-2

Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002;94:606–16.

Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, Bain CE, Wang CY, Blackburn GL, McTiernan A. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. Obesity. 2012;20(8):1628–38. https://doi.org/10.1038/oby.2011.76.

Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev. 2001;10:15–32.

Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer. 2010a;46. (14):2593–604. S0959-8049(10)00706-9 [pii]. https://doi.org/10.1016/j.ejca.2010.07.028.

Friedenreich CM, Neilson HK, Wang Q, Stanczyk FZ, Yasui Y, Duha A, Maclaughlin S, Kallal S, Forbes CC, Courneya KS. Effects of exercise dose on endogenous estrogens in postmenopausal women: a randomized trial. Endocr Relat Cancer. 2015;22(5):863–76. https://doi.org/10.1530/ERC-15-0243.

Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr. 2002;132(11):3456S-3464S.

Friedenreich CM, Woolcott CG, McTiernan A, Ballard-Barbash R, Brant RF, Stanczyk FZ, Terry T, Boyd NF, Yaffe MJ, Irwin ML, Jones CA, Courneya KS. The alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among

postmenopausal women. J Clin Oncol. 2010b;28(9):1458–66 JCO.2009.24.9557 [pii]. https://doi.org/10.1200/JCO.2009.24.9557.

Frisch RE, Gotz-Welbergen AV, McArthur JW, Albright T, Witschi J, Bullen B, Bimholz J, Reed J, Hermann H. Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. J Am Med Assoc. 1981;246(14):1559–63.

Guo W, Fensom GK, Reeves GK, Key TJ. Physical activity and breast cancer risk: results from the UK Biobank prospective cohort. Br J Cancer. 2020;122(5):726–32. https://doi.org/10.1038/s41416-019-0700-6.

Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis. 2000;21(3):427–33.

Hoffman-Goetz L, Apter D, Demark-Wahnefried W, Goran M, McTiernan A, Reichman M. Possible mechanisms mediating an association between physical activity and breast cancer. Cancer. 1998;83(3 Suppl. (Aug 1)):621–28.

Howard BV, Manson JE, Stefanick ML, Beresford SA, Frank G, Jones B, Rodabough RJ, Snetselaar L, Thompson C, Tinker L, Vitolins M, Prentice R. Low-fat dietary pattern and weight change over 7 years: the Women's health initiative dietary modification trial. JAMA. 2006;295(1):39–49.

Irwin ML, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, Yukawa M, Alello E, Potter JD, McTiernan A. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA. 2003;289(3):323–30.

Karapanou O, Papadimitriou A. Determinants of menarche. Reproduct Biol Endocrinol: RB&E. 2010;8:115. https://doi.org/10.1186/1477-7827-8-115.

Keizer HA, Kuipers H, de Haan J, Janssen GM, Beckers E, Habets L, Van Kranenburg G, Geurten P. Effect of a 3-month endurance training program on metabolic and multiple hormonal responses to exercise. Int J Sports Med. 1987;8(Suppl 3):154–60.

Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. Proc Nutr Soc. 2001;60(1):81–9.

King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302(5645):643–6. https://doi.org/10.1126/science.1088759.

Larsson SC, Kar S, Perry JRB, Carter P, Vithayathil M, Mason AM, Easton DF, Burgess S. Serum estradiol and 20 site-specific cancers in women: mendelian randomization study. J Clin Endocrinol Metab. 2021. https://doi.org/10.1210/clinem/dgab713.

Lee IM. Physical activity and cancer prevention–data from epidemiologic studies. Med Sci Sports Exerc. 2003;35(11):1823–7.

Lieberman JL, De Souza MJ, Wagstaff DA, Williams NI. Menstrual disruption with exercise is not linked to an energy availability threshold. Med Sci Sports Exerc. 2018;50(3):551–61. https://doi.org/10.1249/MSS.0000000000001451

Loucks AB. Effects of exercise training on the menstrual cycle: existence and mechanisms. Med Sci Sports Exerc. 1990;22(3):275–80.

Loucks AB. Energy availability, not body fatness, regulated reproductive function in women. Exerc Sport Sci Rev. 2003;31(3):144–8.

Loucks AB, Redman LM. The effect of stress on menstrual function. Trends Endocrinol Metab. 2004;15(10):466–71.

Lukanova A, Lundin E, Micheli A, Arslan A, Ferrari P, Rinaldi S, Krogh V, Lenner P, Shore RE, Biessy C, Muti P, Zeleniuch-Jacquotte A. Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. Int J Cancer. 2004;108(3):425–32. https://doi.org/10.1002/ijc.11529.

Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13–42. https://doi.org/10.1007/978-3-642-04231-7_2.

Ma H, Xu X, Clague J, Lu Y, Togawa K, Wang SS, Wang CA, Lee E, Park HL, Sullivan-Halley J, Neuhausen SL, Bernstein L. Recreational physical activity and risk of triple negative breast cancer in the California Teachers Study. Breast Cancer Res. 2016;18(1):62. https://doi.org/10.1186/s13058-016-0723-3.

Matthews CE, Fowke JH, Dai Q, Bradlow HL, Jin F, Shu XO, Gao YT, Longcope C, Hebert JR, Zheng W. Physical activity, body size, and estrogen metabolism in women. Cancer Causes Control. 2004;15(5):473–81.

Matthews CE, Sampson JN, Brenner DR, Moore SC, Courneya KS, Ziegler RG, Friedenreich CM. Effects of exercise and cardiorespiratory fitness on estrogen metabolism in postmenopausal women. Cancer Epidemiol Biomark Prev. 2018;27(12):1480–2. https://doi.org/10.1158/1055-9965.EPI-17-0900.

McTiernan A, Tworoger SS, Rajan KB, Yasui Y, Sorenson B, Ulrich CM, Chubak J, Stabczyk FZ, Bowen D, Irwin ML, Rudolph RE, Schwartz RS. Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial. Cancer Epidemiol Biomark Prev. 2004a;13(7):1099–105.

McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, Sorensen B, Rudolph RE, Bowen D, Stabczyk FZ, Potter JD, Schwartz RS. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Can Res. 2004b;64(8):2923–8.

McTiernan A, Wu L, Barnabei VM, Chen C, Hendrix S, Modugno F, Rohan T, Stabczyk FZ, Van Horn L, Wang CY. Relation of demographic factors, menstrual history, reproduction and medication use to sex hormone levels in postmenopausal women. Breast Cancer Res Treat. 2008;108(2):217–31. https://doi.org/10.1007/s10549-007-9588-6.

McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, Perri MG, Stabczyk FZ, Van Horn L, Wang CY. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (silver Spring). 2006;14(9):1662–77.

Minihan AK, Patel AV, Flanders WD, Sauer AG, Jemal A, Islami F. Proportion of cancer cases attributable to physical inactivity by US State, 2013–2016. Med Sci Sports Exerc. 2021. https://doi.org/10.1249/mss.0000000000002801.

Monninkhof EM, Velthuis MJ, Peeters PH, Twisk JW, Schuit AJ. Effect of exercise on postmenopausal sex hormone levels and role of body fat: a randomized controlled trial. J Clin Oncol. 2009;27(27):4492–9 JCO.2008.19.7459 [pii]. https://doi.org/10.1200/JCO.2008.19.7459.

Moore SC, Lee I-M, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, De Gonzalez AB, Hartge P, Adami HO, Patel AV. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Internal Med. 2016;176(6). 816–25. https://doi.org/10.1001/jamainternmed.2016.1548

Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, Lopez AM, Manson J, Margolis KL, Muti PC, Stefanick ML, McTiernan A. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control. 2002;13(8):741–51.

Mountjoy M, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, Meyer C, Sherman R, Steffen K, Budgett R, Ljungqvist A. The IOC consensus statement: beyond the Female Athlete Triad-Relative Energy Deficiency in Sport (RED-S). Br J Sports Med. 2014;48(7):491–7. https://doi.org/10.1136/bjsports-2014-093502.

Mountjoy M, Sundgot-Borgen JK, Burke LM, Ackerman KE, Blauwet C, Constantini N, Lebrun C, Lundy B, Melin A, Meyer N, Sherman R, Budgett R. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update. Br J Sports Med. 2018;52(11):687–97. https://doi.org/10.1136/bjsports-2018-099193.

Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. American College of Sports Medicine position stand. The female athlete triad. Med Sc Sports Exercise. 2007;39(10):1867–82. https://doi.org/10.1249/mss.0b013e318149f111

Orsatti FL, Nahas EA, Maesta N, Nahas-Neto J, Burini RC. Plasma hormones, muscle mass and strength in resistance-trained postmenopausal women. Maturitas. 2008;59(4):394–404. https://doi.org/10.1016/j.maturitas.2008.04.002.

Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL, Winter-Stone K, Gerber LH, George SM, Fulton JE, Denlinger C, Matthews CE. American College of sports medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. Med Sci Sports Exerc. 2019;51(11):2391–402. https://doi.org/10.1249/MSS.0000000000002117.

Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The physical activity guidelines for Americans. JAMA. 2018;320(19):2020–8. https://doi.org/10.1001/jama.2018.14854.

Pirke KM, Schweiger U, Broocks A, Tuschl RJ, Laessle RG. Luteinizing hormone and follicle stimulating hormone secretion patterns in female athletes with and without menstrual disturbances. Clin Endocrinol. 1990;33(3):345–53.

Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian Cancer. Mayo Clin Proc. 2010;85(12):1111–20. https://doi.org/10.4065/mcp.2010.0414.

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335(7630):1134. https://doi.org/10.1136/bmj.39367.495995.AE.

Rogol AD, Weltman A, Weltman JY, Seip RL, Snead DB, Levine S, Haskvitz EM, Thompson DL, Schurrer RO, Dowling EL, Veldhuis JD. Durability of the reproductive axis in eumenorrheic women during 1 yr of endurance training. J Appl Physiol. 1992;72(4):1571–80.

Ronkainen H. Depressed follicle-stimulating hormone, luteinizing hormone, and prolactin responses to the luteinizing hormone-releasing hormone thyrotropin-releasing hormone, and metoclopramide test in endurance runners in the hard-training season. Fertil Steril. 1985;44(6):755–9.

Rundle A. Molecular epidemiology of physical activity and cancer. Cancer Epidemiol Biomark Prev. 2005;14(1):227–36.

Russell JB, Mitchell DE, Musey PI, Collins DC. The relationship of exercise to anovluatory cycles in female athletes: hormonal and physical characteristics. Obstet Gynecol. 1984a;63:452–6.

Russell JB, Mitchell DE, Musey PI, Collins DC. The role of beta-endorphins and catechol estrogens on the hypothalamic-pituitary axis in female athletes. Fertil Steril. 1984b;42(5):690–5.

Ruth KS, Day FR, Tyrrell J, Thompson DJ, Wood AR, Mahajan A, Beaumont RN, Wittemans L, Martin S, Busch AS, Erzurumluoglu AM, The Endometrial Cancer Association C. Using human genetics to understand the disease impacts of testosterone in men and women. Nat Med. 2020;26(2):252–58. https://doi.org/10.1038/s41591-020-0751-5

Saint-Maurice PF, Sampson JN, Michels KA, Moore SC, Loftfield E, McClain K, Cook MB, Trabert B, Matthews CE (2021) Physical activity from adolescence through midlife and associations with body mass index and endometrial cancer risk. JNCI Cancer Spectr. 2021;5(4). https://doi.org/10.1093/jncics/pkab065

Sanford JA, Nogiec CD, Lindholm ME, Adkins JN, Amar D, Dasari S, Drugan JK, Fernández FM, Radom-Aizik S, Schenk S, Snyder MP, Molecular Transducers of Physical Activity C. Molecular transducers of physical activity consortium (MoTrPAC): mapping the dynamic responses to exercise. Cell. 2020;181(7):1464-74. https://doi.org/10.1016/j.cell.2020.06.004

Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol. 2015;30(5):397–412. https://doi.org/10.1007/s10654-015-0017-6.

Schmitz KH, Williams NI, Kontos D, Domchek S, Morales KH, Hwang WT, Grant LL, DiGiovanni L, Salvatore D, Fenderson D, Schnall M, Good J. Dose-response effects of aerobic exercise on estrogen among women at high risk for breast cancer: a randomized controlled trial. Breast Cancer Res Treat. 2015;154(2):309–18. https://doi.org/10.1007/s10549-015-3604-z.

Schweiger U, Laessle R, Schweiger M, Herrmann F, Riedel W, Pirke KM. Caloric intake, stress, and menstrual function in athletes. Fertil Steril. 1988;49(3):447–50.

Smith AJ, Phipps WR, Arikawa AY, O'Dougherty M, Kaufman B, Thomas W, Schmitz KH, Kurzer MS. Effects of aerobic exercise on premenopausal sex hormone levels: results of the WISER study, a randomized clinical trial in healthy, sedentary, eumenorrheic women. Cancer Epidemiol Biomark Preven: Publ Am Assoc Cancer Res Cospons Am Soc Prevent Oncol. 2011;20(6):1098–106. https://doi.org/10.1158/1055-9965.EPI-10-1219.

Smith AJ, Phipps WR, Thomas W, Schmitz KH, Kurzer MS. The effects of aerobic exercise on estrogen metabolism in healthy premenopausal women. Cancer Epidemiol Biomark Preven: Publ Am Assoc Cancer Res Cospons Am Soc Prevent Oncol. 2013;22(5):756–64. https://doi.org/10.1158/1055-9965.EPI-12-1325.

Snow RC, Barbiebi RL, Frisch RE. Estrogen 2-hydroxylase oxidation and menstrual function among elite oarswomen. J Clin Endocrinol Metab. 1989;69(2):369–76.

Steindorf K, Ritte R, Eomois PP, Lukanova A, Tjonneland A, Johnsen NF, Overvad K, Østergaard JN, Clavel-Chapelon F, Fournier A, Dossus L, Kaaks R. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. Int J Cancer. 2013;132(7):1667–78. https://doi.org/10.1002/ijc.27778.

Swain CTV, Drummond AE, Boing L, Milne RL, English DR, Brown KA, van Roekel EH, Dixon-Suen SC, Moore MM, Gaunt TR, Lynch BM. Linking physical activity to breast cancer via sex hormones, part 1: the effect of physical activity on sex steroid hormones. Cancer Epidemiol Biomark Prev. 2022;31(1):16–27. https://doi.org/10.1158/1055-9965.EPI-21-0437.

Tin Tin S, Reeves GK, Key TJ. Body size and composition, physical activity and sedentary time in relation to endogenous hormones in premenopausal and postmenopausal women: findings from the UK Biobank. Int J Cancer. 2020;147(8):2101–15. https://doi.org/10.1002/ijc.33010.

van Gemert WA, Schuit AJ, van der Palen J, May AM, Iestra JA, Wittink H, Peeters PH, Monninkhof EM. Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. Breast Cancer Res: BCR. 2015;17:120. https://doi.org/10.1186/s13058-015-0633-9.

Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women. Cancer Causes Control. 2001;12:47–59.

Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomark Prev. 2007;16(4):639–48 16/4/639 [pii]. https://doi.org/10.1158/1055-9965.EPI-06-0742.

Wang Q, Zhou W. Roles and molecular mechanisms of physical exercise in cancer prevention and treatment. J Sport Health Sci. 2021;10(2):201–10. https://doi.org/10.1016/j.jshs.2020.07.008.

Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. J Clin Endocrinol Metab. 1980;51(5):1150–7. https://doi.org/10.1210/jcem-51-5-1150.

Watts EL, Perez-Cornago A, Doherty A, Allen NE, Fensom GK, Tin Tin S, Key TJ, Travis RC. Physical activity in relation to circulating hormone concentrations in 117,100 men in UK Biobank. Cancer Causes Control. 2021a;32(11):1197–212. https://doi.org/10.1007/s10552-021-01466-6.

Watts EL, Perez-Cornago A, Knuppel A, Tsilidis KK, Key TJ, Travis RC. Prospective analyses of testosterone and sex hormone-binding globulin with the risk of 19 types of cancer in men and postmenopausal women in UK Biobank. Int J Cancer. 2021b;149(3):573–84. https://doi.org/10.1002/ijc.33555.

Williams NI, Helmreich DL, Parfitt DB, Caston-Balderrama A, Cameron JL. Evidence for a causal role of low energy availability in the induction of menstrual cycle disturbances during strenuous exercise training. J Clin Endocrinol Metab. 2001;86:5184–93.

Williams NI, Leidy HJ, Hill BR, Lieberman JL, Legro RS, De Souza MJ. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. Am J Physiol Endocrinol Metabol. 2015;308(1):E29–E39. https://doi.org/10.1152/ajpendo.00386.2013

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Barfoot R, Micklem, G. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378(6559):789–92. https://doi.org/10.1038/378789a0

World Cancer Research Fund-American Institute for Cancer Research. Diet, nutrition, physical activity and colorectal cancer: Continuous update project expert report. American Institute for Cancer Research; 2018.

Yue W, Yager JD, Wang JP, Jupe ER, Santen RJ. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. Steroids. 2013;78(2):161–70. https://doi.org/10.1016/j.steroids.2012.11.001.

Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, Koenig KL, Shore RE, Kim MY, Levitz M, Mittal KR, Raju U, Banerjee S, Toniolo P. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer. 2001;84(7):975–81. https://doi.org/10.1054/bjoc.2001.1704.

Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE. Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 2015;99(Pt A):67–75. https://doi.org/10.1016/j.steroids.2015.02.015.

Chapter 23
The Future of Sport and Exercise Science Research in the Female Athlete

Rose K. Kelly and Kathryn E. Ackerman

Introduction

The landscape of sports and exercise science (SES) in the female athlete consists of intertwined complex and dynamic physiological pathways. Consequently, this field demands thoughtful investigation from the cellular level to the scale of the full sports ecosystem. The growing community of researchers and body of literature are bending toward a needed paradigm shift that views the interactive study of various female hormonal profiles, social constructs, and sports as important opportunities to enhance female athlete well-being and sports performance. This is a positive change from the previously dominant opinion that such knowledge pursuit was too complex, too time-consuming, and too expensive to bother, and that it was adequate to simply study boys and men and apply findings to girls and women.

This chapter explores the future of SES in females by critically appraising the state of the literature, exploring new methodological standards and their application, and identifying key knowledge gaps, all situated in a sociopolitical and economic context. As a disclaimer, we use "female" throughout the chapter to refer to humans with XX chromosomes. We use this term to focus on the current topics in natal girl and women athletes that have been addressed and those that still need exploring. For a discussion on transgender and disorders of sexual development (DSD) athletes, the authors refer you to other chapters in this volume.

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State of the Science

Interest in women's SES heightened following the trailblazing work of the late Dr. Barbara Drinkwater on amenorrhea and low bone mineral density (BMD), published in 1986, (Drinkwater et al. 1986) and later coined the female athlete triad (Triad) linking disordered eating, amenorrhea, and osteoporosis in female athletes (Yeager et al. 1993). Since then, a growing community of scientists has further pursued novel lines of inquiry in the female athlete research agenda. Such pursuits have been slow but are building momentum.

Cowley et al. (2021) reported a thorough assessment of female representation in SES research and found that only 6% of articles published in the top six SES journals from 2014 through 2020 exclusively studied women (Cowley et al. 2021), which was little change from Costello et al.s' assessment (2014) from seven years earlier finding 4–13% of studies in three leading SES journals from 2011 through mid-2013 exclusively investigated females (Costello et al. 2014). Considering representation in authorship, between 2000 and 2020, less than a quarter of publications from 14 leading SES journals had female first authors, and female authors served as senior authors on less than 17% of publications (Martinez-Rosales et al. 2021). Additionally, less than 20% of these journals' editorial board positions were held by women, and no editors-in-chief were women (Martinez-Rosales et al. 2021). Finally, there is no published evidence that the female athlete research agenda has been co-constructed with female athletes themselves, but instead determined solely by academics and funding sources. As such, it is unsurprising that a historical lack of representation and more robust expertise in female SES underscores a paucity in this field of study (Elliott-Sale et al. 2021). Though the community of those dedicated to female athletes, including researchers, has grown tremendously in the past fifty years since Title IX was passed in the USA in 1972 ("Title IX of the Education Amendments of 1972, 1972) and in the forty years since Drinkwater's groundbreaking work (Drinkwater et al. 1986), an improvement in size and sex parity of the body of researchers and inclusion of the participants themselves in research development would benefit the quality of findings and resulting evidence-based applications (Campbell et al. 2013; Nielsen et al. 2018). An increase in representation across lines of race, ability, socioeconomic status, gender, and nation, among others, would further enhance the research questions prioritized and ultimately answered (Antonio et al. 2004).

The state of SES in females stands at a crossroads. There is a growing community of established and aspiring experts in the various domains of female athlete SES, but their area of study is often afforded only nominal financial and other support by research institutions, grant sources, and colleagues. As a result, low barrier, low-cost methodologies and tools, such as unvalidated or insufficiently validated questionnaires (Fogelholm and Lahti-Koski 1991; Rogers et al. 2021), and 24-h dietary recall and food diaries (Fogelholm and Lahti-Koski 1991; Freedman et al. 2014; Larson-Meyer et al. 2018; Lee 2013; Poslusna et al. 2009; Thompson and Subar 2008; Trabulsi and Schoeller 2001), to name a few, are commonly seen in the literature.

Such methods of inquiry and assessment can bring attention to certain female athlete topics and are a starting point, but they bring inherent error and biases, and we must demand more scientifically sound approaches to answering female athlete-relevant questions. Some have attempted to study the hormonal profiles of females, which vary both within and between females over various periods (e.g., circadian, ultradian rhythms). The questions the research community seeks to ask, and the resulting findings athletes and their support teams need for optimal performance and health, demand more sophisticated study design, methodology, and support (Elliott-Sale et al. 2021).

The dearth of high-quality SES research on female athletes presents robust opportunities to significantly propel the science forward and positively influence the lives of athletes. An analysis of resources and processes, as well as identification of key areas in need of urgent investigation, is required to illuminate the path forward to address inadequacies of the existing body of literature and mediate obstacles impeding high-yield inquiry in the future work.

Methodology Considerations

Advances in Best Practices

In the last three years, there has been a significant effort to improve the rigor and validity of methods in the field of SES in females. Recently, an international cohort of researchers published a series of articles to define best practices for conducting SES research in females. All note the lack of consensus on methodological approaches and terminology in studying female physiology and energy availability in women, along with a lack of necessary funding and a widely held understanding of basic female physiology. These issues have all contributed to the suboptimal study designs and application of methods found in much of female SES literature to date (Elliott-Sale et al. 2021; Heikura et al. 2021; McKay et al. 2022; Smith et al. 2022). Establishing definitions and optimal methods will support a more consistent, better approach to advancing SES research in female athletes—first critically assessing the literature, identifying existing reliable findings, and explicitly noting knowledge gaps; then developing more accurate, precise, and valid tools to design, execute, and iterate high-yield prospective work.

Though academics and the general public have been interested in athletes for millennia, dating back to Ancient Greece's Hippocrates and Galen (Berryman and Park 1992), a singular definition of "athlete", or one characterizing athletes across a spectrum of competitiveness, determined by consensus and practical use, had not existed. Thus, it has been difficult to compare findings across studies of "athletes" with a degree of confidence. For this reason, McKay et al. (2022) developed a tiering system to describe athletes included in a study population (McKay et al. 2022). The tiering system defines athletic caliber ranging from sedentary (tier 0) to world-class

(tier 5), with the level of competition (e.g., NCAA Division I, international-level, world recorder holders), training goals and capabilities (e.g., structured periodized training, maximal training) differentiating the tiers (Fig. 23.1). Furthermore, the authors note the challenges that may arise in the application of the tool, such as tiering athletes across the lifespan (e.g., juniors, masters) and those competing in sports and in regions with different opportunities for and access to competition (e.g., running vs. ski jump; Paralympic and adapted sport versus Olympic and unadapted sport; sport in a high-population country vs. a low-population country) (McKay et al. 2022). The McKay et al. tiering system is a valuable resource as the research community proceeds with athlete literature audits and designing prospective work in various athletic populations.

Elliott-Sale et al. (2021) published a seminal paper outlining considerations required when investigating females specifically in SES (Elliott-Sale et al. 2021). The authors propose definitions and reliable methods of determining menstrual status within and between natal females across the lifespan (pre-menarchal through post-menopausal). They also call for the consideration of exogenous hormone sources (hormonal contraceptives [HC], hormonal replacement therapy [HRT]) in describing menstrual/hormonal status and emphasize the importance of clarifying hormonal status when designing and drawing conclusions from studies in women (Elliott-Sale et al. 2021). Like McKay's athlete tiering system, Elliott-Sale's guidelines encourage female athlete SES researchers to "speak the same language" and be consistent in definitions and methods. Adopting this approach will greatly improve the reproducibility of findings.

More recently, Smith and colleagues published an auditing protocol for female-specific SES review (Smith et al. 2022). The auditing tool is a guide for assessing studies by female study subject representation, sample size, rigor of methods used, focus of the findings (performance, health, or indirect associations), and study impact (journal impact factor and article Altmetric score) (Smith et al. 2022). The Smith et al. article includes a flowchart for authors to use when reporting results, which includes athletic caliber per the McKay classification framework (McKay et al. 2022) and incorporates Elliott-Sale's work on hormonal profile assessment (Elliott-Sale et al. 2021) (Fig. 23.2).

While there are some prospective studies, the current literature consists mostly of retrospective and observational work, as those study designs require less time, personnel, participant burden, and funding. Many such studies capture snapshots of free-living athletes during brief assessments. When reviewing the literature, researchers can draw purposed conclusions based on patterns, but more prospective, longitudinal studies are needed to best understand both the acute and long-term interactions of female hormonal milieu, training regimens, nutrition, and other socioeconomic factors affecting women. Research needs to move beyond observational and correlational studies, and distinct hypotheses need to be tested.

Fig. 23.1 Adapted from the Participant Classification Framework, as originally published by McKay et al. (2022). NCAA: National Collegiate Athletic Association

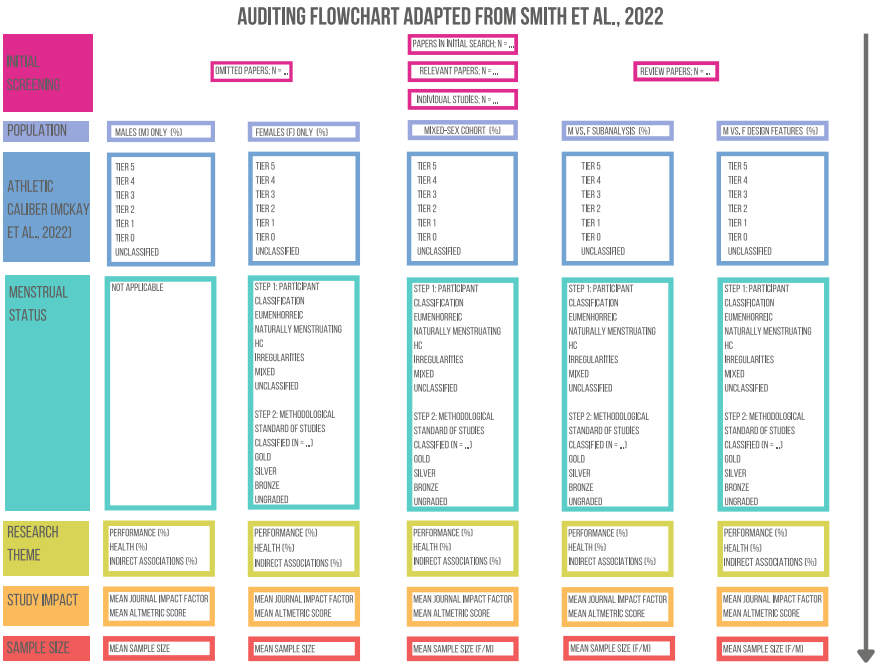

Fig. 23.2 Literature auditing methodology flowchart adapted from Smith et al. (2022)

Obstacles: Funding, Time, Recruitment, Validity

Designing studies to account for hormonal profile changes within and between females demands determining menstrual status and phase, and the presence or absence of exogenous hormonal influence for each participant, then grouping similarly cycling females, and assessing an intervention during the same phase of the menstrual cycle. As a result, studies employing gold standard methodology require significantly more time and financial investment.

New tool and best practice development require internal and external validations. Researchers must be careful to consider the participants and situations in which they seek to validate new methodologies. Historically, much of SES validation attempts have occurred predominantly in young adult males (Breda et al. 2021; Chen et al. 2009; Kirkeberg et al. 2011; Mougios 2007; Robles-Gonzalez et al. 2021), which results in tools that do not account for the hormonal complexities of women. For example, when testing an athlete's resting metabolic rate (RMR), assuming conditions are held constant between two testing opportunities within a short time period (day to year[s] depending on age), it is assumed that the two RMR tests should result in similar measurements. This design works for young, middle-aged men with generally stable hormonal profiles. However, in a female participant, the conditions likely

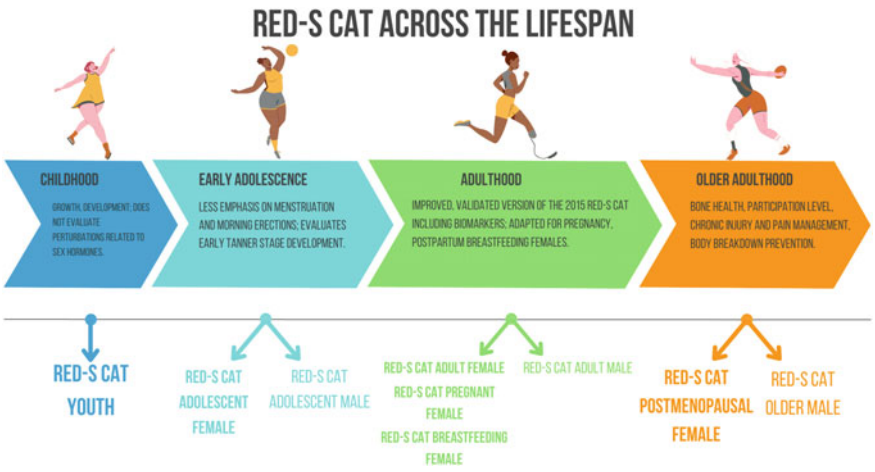

Fig. 23.3 Adapting the current RED-S CAT (2015) to the changing hormonal profiles of female athletes across the lifespan would increase the screening tool sensitivity and clinical relevance

differ between the two assessment bouts due to hormonal profile changes within and between the menstrual cycle or oral contraceptive phases.

Moreover, most validation studies have occurred within wealthy populations in Australia, Europe, and North America (Kirkeberg et al. 2011; Luszczki et al. 2021; Melin et al. 2014; Robles-Gonzalez et al. 2021; Rogers et al. 2021; van den Tillaar et al. 2020). Just as it is crucial to stratify females by menstrual status and cycle, it is crucial to ensure that validity is established across the entire target population, and not just the population with whom it is easiest to engage and enroll (i.e., samples of convenience). Some study designs and surveys used across the lifespan and in different socioeconomic contexts may need multiple versions to account for various influences of sex hormones and lived experience on exercise and sports performance, training, and health (Fig. 23.3).

Development and Validation of New and Existing Research Methodologies and Tools

Among methods and tools already in use, a number need standard operating procedures to produce precise and comparable results across the literature. These include a collection of anthropometric data, RMR assessment, body composition testing (skinfolds, dual-energy X-ray absorptiometry, or both), hormonal testing (timing, assay, fasting status), and more (Kasper et al. 2021; Larson-Meyer et al. 2018; Sterringer and Larson-Meyer 2022). Additionally, previous literature has illustrated that athletes' energy needs, physiological capabilities, and bodily processes differ from those of non-athletes. As such, the research community must establish normative data in athletes, stratified by sport type (endurance, power, tactical) and sex, for

measurements such as bone mineral density and serological laboratory tests (e.g., ferritin, prolactin). Only with such attention to detail can we trust the conclusions we draw from studies in athletic girls and women and build upon such research findings.

Energy Availability as a Topic Example

Assessing energy availability (EA) is central to many research questions in SES, especially when studying females, as they are at a higher risk for developing low EA, disordered eating (DE), and eating disorders (ED) than their non-athletic counterparts (Bratland-Sanda and Sundgot-Borgen 2013; Kuikman et al. 2021; Martinsen and Sundgot-Borgen 2013; Sundgot-Borgen and Torstveit 2004). Heikura et al. (2021) reviewed the relevance and translational capabilities of methods used to assess low EA in female athletes in the laboratory and how findings may produce meaningful applications for female athletes (Heikura et al. 2021). One consideration the authors noted was that some biomarkers collected in laboratory testing only reflect acutely low EA but are unable to characterize the duration, severity, and frequency of chronically low EA in the free-living athlete (Heikura et al. 2021). We need to focus attention on developing practical, useful tools that are easily deployed in translational research and medical point of care.

Thus far, a reliable, validated EA assessment method has yet to be published (Heikura et al. 2021; Larson-Meyer et al. 2018; Sterringer and Larson-Meyer 2022). One of the most commonly used tools, due to its minimally invasive and burdensome nature, is the low energy availability in female questionnaire (LEAF-Q). It was deemed validated following administration to 84 female athletes between the ages 18 and 39 years (Melin et al. 2014). However, a recent study seeking to detect low EA in 75 female athletes between the ages of 18 and 32 across sports found that the LEAF-Q was unable to accurately stratify high-risk athletes (Rogers et al. 2021).

The Relative Energy Deficiency in Sport Clinical Assessment Tool (RED-S CAT) (Mountjoy et al. 2015b), developed by the International Olympic Committee (IOC) in 2015 (Mountjoy et al. 2015a), is another tool that screens for chronically low EA and its health and performance consequences, but it has yet to be validated. Furthermore, there are temporal confounders that make this tool less sensitive to someone who may have experienced RED-S, low EA, DE/ED, and any resulting sequelae in the past but have since restored a healthy energy balance. Additionally, the RED-S CAT needs to be modified to consider applications in females across various sports, the lifespan, and hormonal profiles (e.g., taking HC, undergoing hormone replacement therapy (HRT); diagnosed with polycystic ovary syndrome or other related hyperandrogenic syndromes). Updating the RED-S CAT with a scoring system that places different emphasis on signs, symptoms, and sequelae (e.g., a bone stress injury [BSI] that occurred within the past year warrants more concern than a BSI that occurred a decade prior) will help improve its utility. Identifying biomarkers and athlete-normed values would complement LEA and RED-S screening and enhance diagnostic procedures by helping to mediate confounders and self-report bias inherent to surveys and questionnaires (Heikura et al. 2021).

Future Work

Designing the Research Agenda

Because of the lack of female participants in existing SES literature (Costello et al. 2014; Cowley et al. 2021; Martinez-Rosales et al. 2021), there are myriad of scientific questions to explore in this population. However, a strategized approach to developing and pursuing a research agenda best utilizes research talent, athlete talent, and other resources to find important answers for female athletes and their support staff.

Female athletes often experience a higher rate of injury and poorer health outcomes as compared to their male counterparts. Examples include a higher rate of bone stress injuries (Ohta-Fukushima et al. 2002; Wentz et al. 2011) and anterior cruciate ligament (ACL) tears (Agel et al. 2005; Arendt and Dick 1995; Arendt et al. 1999; Gwinn et al. 2000; Hootman et al. 2007); worse ACL reconstruction outcomes (Ageberg et al. 2010; Ardern et al. 2011; Lindanger et al. 2019; Paterno et al. 2014; Sims and Mulcahey 2018); greater concussion rates and symptoms, as well as time out of the sport due to concussion (Covassin et al. 2016; Lincoln et al. 2011); and higher rates of DE and ED (Sundgot-Borgen and Torstveit 2004). Thus, centering the research agenda around the experiences and perspectives of females who participate in sports and exercise can result in research targeting the priorities of participants. Involving female athletes as important stakeholders in developing the agenda will ideally direct funding to projects likely to produce important, applicable outcomes for this population. This has the benefit of enhancing the health and sports experience of girls and women athletes and improving athlete buy-in for future research work.

Areas for Future Work

We believe there are four areas that demand urgent investigation: the menstrual cycle's influence on exercise outcomes (e.g., strength, endurance, agility); effects of exogenous hormone use on performance; expanding the lifespan of the active female and female athlete; and RED-S.

Menstrual Cycle

Researchers have considered the menstrual cycle and changes in hormonal profiles across phases in past female athlete SES, but few have adequately confirmed participants' hormonal milieu at the time of intervention or outcome measurement. McNulty and colleagues conducted a review of the literature and concluded that there were not sufficient high-quality data upon which to make any claims regarding the influence of the menstrual cycle phase on exercise performance (McNulty et al. 2020). A systematic review assessing published literature on the menstrual cycle phase

in relation to training, recovery, and injury has yet to be published. Nédélec and colleagues, however, have developed a protocol for such a review and meta-analysis of the effects of menstrual cycle phase, menstrual irregularities, and contraceptive use on ACL injury risk (Nédélec et al. 2021). Further work is needed to determine the effects of the menstrual cycle on training, performance, and injury susceptibility. Examples of questions to be addressed include:

- Is there a best phase to emphasize weight training?
- Is a marathon personal record more likely to occur in one phase of the menstrual cycle versus another?
- Are women with a particular hormonal profile more susceptible to concussion?

Discovering these answers will improve female athletes' ability to train, to manipulate their periods to occur at optimal times for them, and to better understand their personal hormonal effects.

Exogenous Hormone Use

A complimentary systematic review and meta-analysis examined HC use and sports performance (Elliott-Sale et al. 2020). As with the menstrual cycle systematic review, the authors concluded there were insufficient high-quality data upon which to develop guidelines or clinical care best practices. Based on evidence indicating that HC users experience alterations in skin blood flow and subcutaneous vasodilation, delayed sweating onset, and higher core temperature, the authors recommended future investigations of performance, training, recovery, and injury when exercising in hot, humid temperatures in those using exogenous hormones compared to eumenorrheic women, not on HC (Elliott-Sale et al. 2020; Lebrun et al. 2020; Minahan et al. 2017; Rogers and Baker 1997; Stachenfeld et al. 2000; Tenaglia et al. 1999). Further research findings on this topic could inform best practices for females exercising in high temperatures or preparing for a sporting event in a warm climate. Similar to the menstrual cycle knowledge gap, prospective studies assessing the interplay of exogenous hormone use and training, recovery, injury susceptibility, and sports performance are needed.

Enhancing Performance—Wellness Across the Lifespan: Pregnancy, Postpartum, Menopause

Women are pursuing sports and exercise later in life, including during and after pregnancy, through menopause, and beyond. Inspiring Olympians, such as Allyson Felix and Elana Meyers Taylor, who became mothers and continued to excel in their sports, have illustrated the possibilities, as well as the urgency to establish modern guidelines for athlete-mothers and athlete-mothers-to-be, with performance and safety in mind. The IOC published a series of papers on pregnancy in athletes and concluded that it is an understudied area; currently, the dearth of evidence cannot support definitive

guidelines for reproductive-aged women, who are often at a pivotal time in their athletic career (Bo et al. 2016a, b, 2017a, 2018a, b). More recent publications are in agreement with this sentiment (Jackson et al. 2022; Kimber et al. 2021). Yet many women not only strive to safely participate in sports and exercise during pregnancy and the postpartum period, but some also want to perform at a high level. The research literature includes descriptions of physiological changes during pregnancy, such as increased blood and plasma volume (Pivarnik et al. 1990, 1994) and increased energy needs during exercise (Butte and King 2005; Denize et al. 2020), but we are unaware of work focused on sports performance pre- versus postpartum. Recreational athletes, pros, coaches, and sponsors want to know what to expect, how pregnant and postpartum athletes should exercise and train, and how to support and continue to invest in women during a critical time in their lives.

SES research in active females during peri- and postmenopause is even scarcer. The precipitous decline in estrogens and progesterone during the menopausal transition affects all body systems. One especially notable change is sarcopenia and changes in body composition (Agostini et al. 2018; Hakkinen and Pakarinen 1993; Lemoine et al. 2003; Sitnick et al. 2006; Wiik et al. 2009). There is a strong body of literature illustrating the decline in strength in postmenopausal women compared to premenopausal women (Bondarev et al. 2018; Calmels et al. 1995; Cheng et al. 2009; da Camara et al. 2015; Sowers et al. 2007). However, many of the published studies have utilized sedentary or poorly defined populations and seldom trained individuals. Additionally, some of the outcome measurements may not be indicative of the athlete's sports performance activity (e.g., handgrip strength, walking speed, chair sit-to-stand). As a result, the effect of menopause on the trained female athlete's performance, training, recovery, and injury rate has yet to be determined. Furthermore, many studies investigating masters athletes group women and men together, thus not accounting for the roughly fifty years of different sex hormone exposure in women and its lasting influence (Churchill and Baggish 2020; Huebner et al. 2020; McKean et al. 2006; Powell 2005). Such studies are also insensitive to the changing hormonal profiles of female athletes who are peri- and postmenopausal (Elliott-Sale et al. 2021). There is a critical need to investigate relevant questions that benefit the broader community of women across their lifespan.

RED-S

As mentioned earlier, identifying distinct biomarkers for RED-S and refining and validating the RED-S CAT and LEAF-Q tools are imperative to improve the screening and treatment of this condition. Determining other RED-S sequelae and the cascade of adaptations when one experiences chronically low EA is important. Shirley and colleagues published a review looking at low EA through a life history perspective, proposing that how the body conserves energy and responds to periods of starvation (or extended periods of low EA) is an evolved trait that previously served as

an evolutionary advantage (Shirley et al. 2022). Designing studies to further investigate this hypothesis may also elucidate pathways underpinning RED-S sequelae development.

Additionally, it is unknown how the severity and duration of low EA affect a woman's health and performance. Heikura et al. (2021) created a figure illustrating this point, presenting different scenarios of low EA states (Fig. 23.4). An athlete may have a short-term, severe episode of low EA or low carbohydrate (CHO) availability; repeated bouts of moderately low EA or low CHO availability; prolonged, small drops in EA or CHO availability; or other combinations. Most prospective low EA and RED-S research has only investigated large and acute drops in EA, and it cannot be assumed that all low EA and RED-S sequelae present in alignment with such extreme EA change models (Heikura et al. 2021). More prospective studies involving different dietary nutritional compositions, in addition to severity, frequency, and duration parameters, are necessary. It is also important to learn how low EA affects females across the lifespan and if the sequelae and physiological adaptations differ according to the protocol used to decrease EA (e.g., change in caloric intake, exercise, or both).

Finally, there are very few studies looking at performance metrics and low EA and RED-S, which is a critical issue. A seminal example is a study from Vanheest et al. (2014), who associated low EA-induced ovarian suppression and performance decline in junior elite female swimmers over the course of a 12-week season

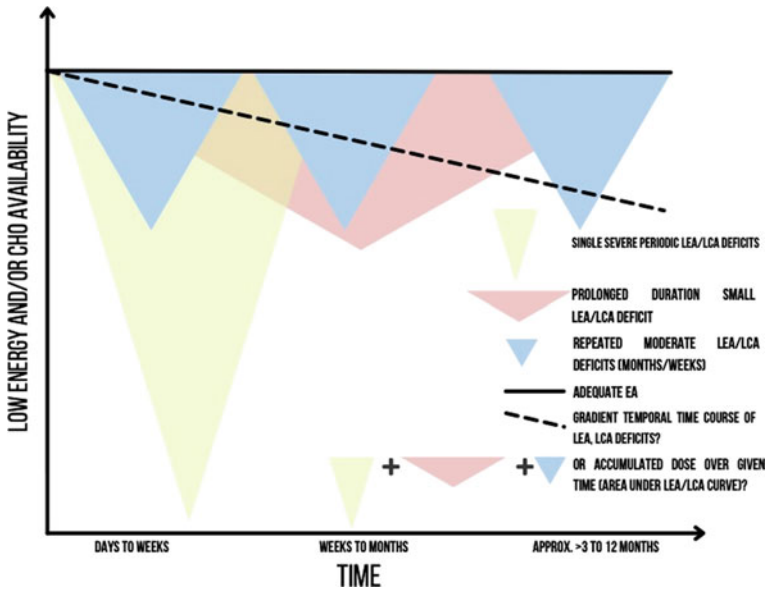

Fig. 23.4 It has yet to be determined how the severity, duration, and frequency of low energy availability (LEA) or low carbohydrate availability (LCA) over a period of time mediate RED-S sequelae deficits. Adapted from Heikura et al. (2021)

(low EA/ovarian-suppressed athletes got slower, while adequate EA/eumenorrheic athletes got faster) (Vanheest et al. 2014). More studies evaluating the effect of RED-S and performance in female athletes of all ages could powerfully influence the health, well-being, and approach to training and fueling in this motivated and competitive population.

Conclusion

SES in females as a field has long outgrown the small, dark corner first allotted in its early days. As girls and women are breaking more barriers and setting more athletic records, this field can and must develop to meet the growing needs of the female population involved in sport and exercise. This requires resources and support from research community stakeholders such as colleagues, institutions, and both governmental and non-governmental funding sources. Investing time, energy, thought, and funding into SES research in females will extend beyond improvement in the research literature; it will enhance females' health, well-being, sports participation, and performance. Fifty years after Title IX, the time is now.

References

Ageberg E, Forssblad M, Herbertsson P, Roos EM. Sex differences in patient-reported outcomes after anterior cruciate ligament reconstruction: data from the Swedish knee ligament register. Am J Sports Med. 2010;38(7):1334–42. https://doi.org/10.1177/0363546510361218.

Agel J, Arendt EA, Bershadsky B. Anterior cruciate ligament injury in national collegiate athletic association basketball and soccer: a 13-year review. Am J Sports Med. 2005;33(4):524–30. https://doi.org/10.1177/0363546504269937.

Agostini D, Zeppa Donati S, Lucertini F, Annibalini G, Gervasi M, Ferri Marini C, Piccoli G, Stocchi V, Barbieri E, Sestili P. Muscle and bone health in postmenopausal women: role of protein and vitamin D supplementation combined with exercise training. Nutrients 2018;10(8). https://doi.org/10.3390/nu10081103

Antonio AL, Chang MJ, Hakuta K, Kenny DA, Levin S, Milem JF. Effects of racial diversity on complex thinking in college students. Psychol Sci. 2004;15(8):507–10. https://doi.org/10.1111/j.0956-7976.2004.00710.x.

Ardern CL, Webster KE, Taylor NF, Feller JA. Return to the preinjury level of competitive sport after anterior cruciate ligament reconstruction surgery: two-thirds of patients have not returned by 12 months after surgery. Am J Sports Med. 2011;39(3):538–43. https://doi.org/10.1177/0363546510384798.

Arendt E, Dick R (1995). Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. *Am J Sports Med*, *23*(6), 694–701. https://doi.org/10.1177/036354659502300611

Arendt EA, Agel J, Dick R. Anterior cruciate ligament injury patterns among collegiate men and women. J Athl Train. 1999;34(2):86–92. https://www.ncbi.nlm.nih.gov/pubmed/16558564

Berryman JW, Park R. Sport and exercise science: essays in the history of sports medicine. University of Illinois Press; 1992.

Bo K, Artal R, Barakat R, Brown W, Davies GA, Dooley M, Evenson KR, Haakstad LA, Henriksson-Larsen K, Kayser B, Kinnunen TI, Mottola MF, Nygaard I, van Poppel M, Stuge B, Khan KM. Exercise and pregnancy in recreational and elite athletes: 2016a evidence summary from the IOC expert group meeting, Lausanne. Part 1-exercise in women planning pregnancy and those who are pregnant. Br J Sports Med. 2016a;50(10):571–89. https://doi.org/10.1136/bjsports-2016-096218

Bo K, Artal R, Barakat R, Brown W, Dooley M, Evenson KR, Haakstad LAH, Larsen K, Kayser B, Kinnunen TI, Mottola MF, Nygaard I, van Poppel M, Stuge B, Davies GAL, Commission IOCM. Exercise and pregnancy in recreational and elite athletes: 2016b evidence summary from the IOC expert group meeting, Lausanne. Part 2-the effect of exercise on the fetus, labour and birth. Br J Sports Med. 2016b;50(21):1297–305. https://doi.org/10.1136/bjsports-2016-096810

Bo K, Artal R, Barakat R, Brown WJ, Davies GAL, Dooley M, Evenson KR, Haakstad LAH, Kayser B, Kinnunen TI, Larsen K, Mottola MF, Nygaard I, van Poppel M, Stuge B, Khan KM. Exercise and pregnancy in recreational and elite athletes: 2016/17 evidence summary from the IOC expert group meeting, Lausanne. Part 4-Recommendations for future research. Br J Sports Med. 2017a;51(24):1724–26. https://doi.org/10.1136/bjsports-2017-098387

Bo K, Artal R, Barakat R, Brown WJ, Davies GAL, Dooley M, Evenson KR, Haakstad LAH, Kayser B, Kinnunen TI, Larsen K, Mottola MF, Nygaard I, van Poppel M, Stuge B, Khan KM, Commission IOCM. Exercise and pregnancy in recreational and elite athletes: 2016/17 evidence summary from the IOC Expert Group Meeting, Lausanne. Part 3-exercise in the postpartum period. Br J Sports Med. 2017b;51(21):1516–25. https://doi.org/10.1136/bjsports-2017-097964

Bo K, Artal R, Barakat R, Brown WJ, Davies GAL, Dooley M, Evenson KR, Haakstad LAH, Kayser B, Kinnunen TI, Larsen K, Mottola MF, Nygaard I, van Poppel M, Stuge B, Khan KM (2018). Exercise and pregnancy in recreational and elite athletes: 2016/2017 evidence summary from the IOC expert group meeting, Lausanne. Part 5. Recommendations for health professionals and active women. Br J Sports Med 2018a;52(17):1080–85. https://doi.org/10.1136/bjsports-2018-099351

Bondarev D, Laakkonen EK, Finni T, Kokko K, Kujala UM, Aukee P, Kovanen V, Sipila S. Physical performance in relation to menopause status and physical activity. Menopause. 2018b;25(12):1432–41. https://doi.org/10.1097/GME.0000000000001137.

Bratland-Sanda S, Sundgot-Borgen J. Eating disorders in athletes: overview of prevalence, risk factors and recommendations for prevention and treatment. Eur J Sport Sci. 2013;13(5):499–508. https://doi.org/10.1080/17461391.2012.740504.

Breda SJ, Oei EHG, Zwerver J, Visser E, Waarsing E, Krestin GP, de Vos RJ. Effectiveness of progressive tendon-loading exercise therapy in patients with patellar tendinopathy: a randomised clinical trial. Br J Sports Med. 2021;55(9):501–9. https://doi.org/10.1136/bjsports-2020-103403.

Butte NF, King JC. Energy requirements during pregnancy and lactation. Public Health Nutr. 2005;8(7A):1010–27. https://doi.org/10.1079/phn2005793.

Calmels P, Vico L, Alexandre C, Minaire P. Cross-sectional study of muscle strength and bone mineral density in a population of 106 women between the ages of 44 and 87 years: relationship with age and menopause. Eur J Appl Physiol Occup Physiol. 1995;70(2):180–6. https://doi.org/10.1007/BF00361547.

Campbell LG, Mehtani S, Dozier ME, Rinehart J. Gender-heterogeneous working groups produce higher quality science. PLoS ONE. 2013;8(10): e79147. https://doi.org/10.1371/journal.pone.0079147.

Chen TC, Nosaka K, Lin MJ, Chen HL, Wu CJ. Changes in running economy at different intensities following downhill running. J Sports Sci. 2009;27(11):1137–44. https://doi.org/10.1080/02640410903062027.

Cheng MH, Wang SJ, Yang FY, Wang PH, Fuh JL. Menopause and physical performance—A community-based cross-sectional study. Menopause. 2009;16(5):892–6. https://doi.org/10.1097/gme.0b013e3181a0e091.

Churchill TW, Baggish AL. Cardiovascular care of masters athletes. J Cardiovasc Transl Res. 2020;13(3):313–21. https://doi.org/10.1007/s12265-020-09987-2.

Costello JT, Bieuzen F, Bleakley CM. Where are all the female participants in Sports and Exercise Medicine research? Eur J Sport Sci. 2014;14(8):847–51. https://doi.org/10.1080/17461391.2014.911354.

Covassin T, Moran R, Elbin RJ. Sex differences in reported concussion injury rates and time loss from participation: an update of the national collegiate athletic association injury surveillance program from 2004–2005 through 2008–2009. J Athl Train. 2016;51(3):189–94. https://doi.org/10.4085/1062-6050-51.3.05.

Cowley ES, Olenick AA, McNulty KL, Ross EZ. "Invisible sportswomen": the sex data gap in sport and exercise science research. Women Sport Phys Activity J. 2021;29(2):146–51. https://doi.org/10.1123/wspaj.2021-0028

da Camara SM, Zunzunegui MV, Pirkle C, Moreira MA, Maciel AC. Menopausal status and physical performance in middle aged women: a cross-sectional community-based study in Northeast Brazil. PLoS ONE. 2015;10(3): e0119480. https://doi.org/10.1371/journal.pone.0119480.

Denize KM, Akbari P, da Silva DF, Haman F, Adamo KB. Greater energy demand of exercise during pregnancy does not impact mechanical efficiency. Appl Physiol Nutr Metab. 2020;45(5):493–9. https://doi.org/10.1139/apnm-2019-0450.

Drinkwater BL, Nilson K, Ott S, Chesnut CH 3rd. Bone mineral density after resumption of menses in amenorrheic athletes. JAMA. 1986;256(3):380–82. https://www.ncbi.nlm.nih.gov/pubmed/3723725

Elliott-Sale KJ, McNulty KL, Ansdell P, Goodall S, Hicks KM, Thomas K, Swinton PA, Dolan E. The effects of oral contraceptives on exercise performance in women: a systematic review and meta-analysis. Sports Med. 2020;50(10):1785–812. https://doi.org/10.1007/s40279-020-01317-5.

Elliott-Sale KJ, Minahan CL, de Jonge X, Ackerman KE, Sipila S, Constantini NW, Lebrun CM, Hackney AC. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51(5):843–61. https://doi.org/10.1007/s40279-021-01435-8.

Fogelholm M, Lahti-Koski M. The validity of a food use questionnaire in assessing the nutrient intake of physically active young men. Eur J Clin Nutr. 1991;45(5):267–72. https://www.ncbi.nlm.nih.gov/pubmed/1915198

Freedman LS, Commins JM, Moler JE, Arab L, Baer DJ, Kipnis V, Midthune D, Moshfegh AJ, Neuhouser ML, Prentice RL, Schatzkin A, Spiegelman D, Subar AF, Tinker LF, Willett W. Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for energy and protein intake. Am J Epidemiol. 2014;180(2):172–88. https://doi.org/10.1093/aje/kwu116.

Gwinn DE, Wilckens JH, McDevitt ER, Ross G, Kao TC. The relative incidence of anterior cruciate ligament injury in men and women at the United States Naval Academy. Am J Sports Med. 2000;28(1):98–102. https://doi.org/10.1177/03635465000280012901.

Hakkinen K, Pakarinen A. Muscle strength and serum testosterone, cortisol and SHBG concentrations in middle-aged and elderly men and women. Acta Physiol Scand. 1993;148(2):199–207. https://doi.org/10.1111/j.1748-1716.1993.tb09549.x.

Heikura IA, Stellingwerff T, Areta JL. Low energy availability in female athletes: from the lab to the field. Eur J Sport Sci 2021;1–11. https://doi.org/10.1080/17461391.2021.1915391

Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. J Athl Train. 2007;42(2):311–19. https://www.ncbi.nlm.nih.gov/pubmed/17710181

Huebner M, Meltzer D, Ma W, Arrow H. The Masters athlete in olympic weightlifting: training, lifestyle, health challenges, and gender differences. PLoS ONE. 2020;15(12): e0243652. https://doi.org/10.1371/journal.pone.0243652.

Jackson T, Bostock EL, Hassan A, Greeves JP, Sale C, Elliott-Sale KJ. The legacy of pregnancy: elite athletes and women in arduous occupations. Exerc Sport Sci Rev. 2022;50(1):14–24. https://doi.org/10.1249/JES.0000000000000274.

Kasper AM, Langan-Evans C, Hudson JF, Brownlee TE, Harper LD, Naughton RJ, Morton JP, Close GL. Come back skinfolds, all is forgiven: a narrative review of the efficacy of common body composition methods in applied sports practice. Nutrients. 2021;13(4). https://doi.org/10.3390/nu13041075

Kimber ML, Meyer S, McHugh TL, Thornton J, Khurana R, Sivak A, Davenport MH. Health outcomes after pregnancy in elite athletes: a systematic review and meta-analysis. Med Sci Sports Exerc. 2021;53(8):1739–47. https://doi.org/10.1249/MSS.0000000000002617.

Kirkeberg JM, Dalleck LC, Kamphoff CS, Pettitt RW. Validity of 3 protocols for verifying VO2 max. Int J Sports Med. 2011;32(4):266–70. https://doi.org/10.1055/s-0030-1269914.

Kuikman MA, Mountjoy M, Burr JF. Examining the Relationship between exercise dependence, disordered eating, and low energy availability. Nutrients. 2021;13(8). https://doi.org/10.3390/nu13082601

Larson-Meyer DE, Woolf K, Burke L. Assessment of nutrient status in athletes and the need for supplementation. Int J Sport Nutr Exerc Metab. 2018;28(2):139–58. https://doi.org/10.1123/ijsnem.2017-0338.

Lebrun C, Joyce SM, Constantini NW. Effects of female reproductive hormones on sports performance. In: Hackney CN, editor. Endocrinology of physical activity and sport. Humana; 2020.

Lee R, Nieman DC. Nutritional assessment, 6th ed.. McGraw Hill; 2013.

Lemoine S, Granier P, Tiffoche C, Rannou-Bekono F, Thieulant ML, Delamarche P. Estrogen receptor alpha mRNA in human skeletal muscles. Med Sci Sports Exerc. 2003;35(3):439–43. https://doi.org/10.1249/01.MSS.0000053654.14410.78.

Lincoln AE, Caswell SV, Almquist JL, Dunn RE, Norris JB, Hinton RY. Trends in concussion incidence in high school sports: a prospective 11-year study. Am J Sports Med. 2011;39(5):958–63. https://doi.org/10.1177/0363546510392326.

Lindanger L, Strand T, Molster AO, Solheim E, Inderhaug E. Return to play and long-term participation in pivoting sports after anterior cruciate ligament reconstruction. Am J Sports Med. 2019;47(14):3339–46. https://doi.org/10.1177/0363546519878159.

Luszczki E, Jagielski P, Bartosiewicz A, Kuchciak M, Deren K, Stolarczyk A, Pakosz P, Oleksy L. The LEAF questionnaire is a good screening tool for the identification of the female athlete triad/relative energy deficiency in sport among young football players. PeerJ. 2021;9: e12118. https://doi.org/10.7717/peerj.12118.

Martinez-Rosales E, Hernandez-Martinez A, Sola-Rodriguez S, Esteban-Cornejo I, Soriano-Maldonado A. Representation of women in sport sciences research, publications, and editorial leadership positions: are we moving forward? J Sci Med Sport. 2021;24(11):1093–7. https://doi.org/10.1016/j.jsams.2021.04.010.

Martinsen M, Sundgot-Borgen J. Higher prevalence of eating disorders among adolescent elite athletes than controls. Med Sci Sports Exerc. 2013;45(6):1188–97. https://doi.org/10.1249/MSS.0b013e318281a939.

McKay AKA, Stellingwerff T, Smith ES, Martin DT, Mujika I, Goosey-Tolfrey VL, Sheppard J, Burke LM. Defining training and performance caliber: a participant classification framework. Int J Sports Physiol Perform. 2022;1–15. https://doi.org/10.1123/ijspp.2021-0451

McKean KA, Manson NA, Stanish WD. Musculoskeletal injury in the masters runners. Clin J Sport Med. 2006;16(2):149–54. https://doi.org/10.1097/00042752-200603000-00011.

McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, Thomas K, Hicks KM. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. Sports Med. 2020;50(10):1813–27. https://doi.org/10.1007/s40279-020-01319-3.

Melin A, Tornberg AB, Skouby S, Faber J, Ritz C, Sjodin A, Sundgot-Borgen J. The LEAF questionnaire: a screening tool for the identification of female athletes at risk for the female athlete triad. Br J Sports Med. 2014;48(7):540–5. https://doi.org/10.1136/bjsports-2013-093240.

Minahan C, Melnikoff M, Quinn K, Larsen B. Response of women using oral contraception to exercise in the heat. Eur J Appl Physiol. 2017;117(7):1383–91. https://doi.org/10.1007/s00421-017-3628-7.

Mougios V. Reference intervals for serum creatine kinase in athletes. Br J Sports Med. 2007;41(10):674–8. https://doi.org/10.1136/bjsm.2006.034041.

Mountjoy M, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, Meyer N, Sherman R, Steffen K, Budgett R, Ljungqvist A, Ackerman K. The IOC relative energy deficiency in sport clinical assessment tool (RED-S CAT). Br J Sports Med. 2015a;49(21):1354. https://www.ncbi.nlm.nih.gov/pubmed/26764434

Mountjoy M, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, Meyer N, Sherman R, Steffen K, Budgett R, Ljungqvist A, Ackerman K. RED-S CAT. Relative Energy Deficiency in Sport (RED-S) Clinical Assessment Tool (CAT). Br J Sports Med. 2015b;49(7):421–23. https://doi.org/10.1136/bjsports-2015-094873

Nedelec E, Foli E, Shultz SJ, Swinton PA, Dolan E, Enright K, Piasecki J, Matthews JJ, Sale C, Elliott-Sale KJ. Effect of menstrual cycle phase, menstrual irregularities and hormonal contraceptive use on anterior knee laxity and non-contact anterior cruciate ligament injury occurrence in women: a protocol for a systematic review and meta-analysis. BMJ Open Sport Exerc Med. 2021;7(4): e001170. https://doi.org/10.1136/bmjsem-2021-001170.

Nielsen MW, Bloch CW, Schiebinger L. Making gender diversity work for scientific discovery and innovation. Nat Hum Behav. 2018;2(10):726–34. https://doi.org/10.1038/s41562-018-0433-1.

Ohta-Fukushima M, Mutoh Y, Takasugi S, Iwata H, Ishii S. Characteristics of stress fractures in young athletes under 20 years. J Sports Med Phys Fitness. 2002;42(2):198–206. https://www.ncbi.nlm.nih.gov/pubmed/12032416

Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of second ACL injuries 2 years after primary ACL reconstruction and return to sport. Am J Sports Med. 2014;42(7):1567–73. https://doi.org/10.1177/0363546514530088.

Pivarnik JM, Lee W, Miller JF, Werch J. Alterations in plasma volume and protein during cycle exercise throughout pregnancy. Med Sci Sports Exerc. 1990;22(6):751–5. https://doi.org/10.1249/00005768-199012000-00003.

Pivarnik JM, Mauer MB, Ayres NA, Kirshon B, Dildy GA, Cotton DB. Effects of chronic exercise on blood volume expansion and hematologic indices during pregnancy. Obstet Gynecol. 1994;83(2):265–69. https://www.ncbi.nlm.nih.gov/pubmed/8290192

Poslusna K, Ruprich J, de Vries JH, Jakubikova M, van't Veer, P. Misreporting of energy and micronutrient intake estimated by food records and 24 h recalls, control and adjustment methods in practice. Br J Nutr. 2009;101(Suppl 2):S73-85. https://doi.org/10.1017/S0007114509990602.

Powell AP. Issues unique to the masters athlete. Curr Sports Med Rep. 2005;4(6):335–40. https://doi.org/10.1097/01.csmr.0000306296.49707.c4.

Robles-Gonzalez L, Gutierrez-Hellin J, Aguilar-Navarro M, Ruiz-Moreno C, Munoz A, Del-Coso J, Ruiz J, Amaro-Gahete FJ. Inter-day reliability of resting metabolic rate and maximal fat oxidation during exercise in healthy men using the ergostik gas analyzer. Nutrients. 2021;13(12). https://doi.org/10.3390/nu13124308

Rogers MA, Drew MK, Appaneal R, Lovell G, Lundy B, Hughes D, Vlahovich N, Waddington G, Burke LM. The utility of the low energy availability in females questionnaire to detect markers consistent with low energy availability-related conditions in a mixed-sport cohort. Int J Sport Nutr Exerc Metab. 2021;31(5):427–37. https://doi.org/10.1123/ijsnem.2020-0233.

Rogers SM, Baker MA. Thermoregulation during exercise in women who are taking oral contraceptives. Eur J Appl Physiol Occup Physiol. 1997;75(1):34–8. https://doi.org/10.1007/s004210050123.

Shirley MK, Longman DP, Elliott-Sale KJ, Hackney AC, Sale C, Dolan E. A life history perspective on athletes with low energy availability. Sports Med. 2022. https://doi.org/10.1007/s40279-022-01643-w.

Sims M, Mulcahey MK. Sex-Specific differences in psychological response to injury and return to sport following ACL reconstruction. JBJS Rev. 2018;6(7): e9. https://doi.org/10.2106/JBJS.RVW.17.00170.

Sitnick M, Foley AM, Brown M, Spangenburg EE. Ovariectomy prevents the recovery of atrophied gastrocnemius skeletal muscle mass. J Appl Physiol (1985). 2006;100(1):286–93. https://doi.org/10.1152/japplphysiol.00869.2005

Smith ES, McKay AKA, Ackerman KE, Harris R, Elliott-Sale KJ, Stellingwerff T, Burke LM. Methodology review: a protocol to audit the representation of female athletes in sports science and sports medicine research. Int J Sport Nutr Exerc Metab. 2022;1–14. https://doi.org/10.1123/ijsnem.2021-0257

Sowers M, Tomey K, Jannausch M, Eyvazzadeh A, Nan B, Randolph J Jr. Physical functioning and menopause states. Obstet Gynecol. 2007;110(6):1290–6. https://doi.org/10.1097/01.AOG.0000290693.78106.9a.

Stachenfeld NS, Silva C, Keefe DL (2000) Estrogen modifies the temperature effects of progesterone. J Appl Physiol (1985). 2000;88(5), 1643–49. https://doi.org/10.1152/jappl.2000.88.5.1643

Sterringer T, Larson-Meyer DE. RMR ratio as a surrogate marker for low energy availability. Curr Nutr Rep. 2022. https://doi.org/10.1007/s13668-021-00385-x.

Sundgot-Borgen J, Torstveit MK. Prevalence of eating disorders in elite athletes is higher than in the general population. Clin J Sport Med. 2004;14(1):25–32. https://doi.org/10.1097/00042752-200401000-00005.

Tenaglia SA, McLellan TM, Klentrou PP. Influence of menstrual cycle and oral contraceptives on tolerance to uncompensable heat stress. Eur J Appl Physiol Occup Physiol. 1999;80(2):76–83. https://doi.org/10.1007/s004210050561.

Thompson F, Subar AF. Dietary assessment methodology. In: Boushey CJ, Coulston AM, editors. Nutrition in the prevention and treatment of disease, 2nd ed.. Academic Press; 2008. p. 3–39.

Title IX of the education amendments of 1972. 1972. p. 1681–88

Trabulsi J, Schoeller DA. Evaluation of dietary assessment instruments against doubly labeled water, a biomarker of habitual energy intake. Am J Physiol Endocrinol Metab. 2001;281(5):E891-899. https://doi.org/10.1152/ajpendo.2001.281.5.E891.

van den Tillaar R, von Heimburg E, Solli GS. Comparison of a traditional graded exercise protocol with a self-paced 1-km test to assess maximal oxygen consumption. Int J Sports Physiol Perform. 2020;1–6. https://doi.org/10.1123/ijspp.2019-0843

Vanheest JL, Rodgers CD, Mahoney CE, De Souza MJ. Ovarian suppression impairs sport performance in junior elite female swimmers. Med Sci Sports Exerc. 2014;46(1):156–66. https://doi.org/10.1249/MSS.0b013e3182a32b72.

Wentz L, Liu PY, Haymes E, Ilich JZ. Females have a greater incidence of stress fractures than males in both military and athletic populations: a systemic review. Mil Med. 2011;176(4):420–30. https://doi.org/10.7205/milmed-d-10-00322.

Wiik A, Ekman M, Johansson O, Jansson E, Esbjornsson M. Expression of both oestrogen receptor alpha and beta in human skeletal muscle tissue. Histochem Cell Biol. 2009;131(2):181–9. https://doi.org/10.1007/s00418-008-0512-x.

Yeager KK, Agostini R, Nattiv A, Drinkwater B. The female athlete triad: disordered eating, amenorrhea, osteoporosis. Med Sci Sports Exerc. 1993;25(7):775–7. https://doi.org/10.1249/00005768-199307000-00003.

Chapter 24
Epilogue: "How We Arrived at This Point in Time"

Constance Lebrun

Introduction

It is my great privilege and pleasure to be asked to write an epilogue for the second edition of this outstanding book "*Sex Hormones, Exercise, and Women*". The editor, Dr. Anthony Hackney, has again gathered an impressive array of exercise scientists and clinicians to elucidate and educate on the areas of their expertise. From the first edition, published in 2017, there have been updates of previous chapters, some quite substantive, as well as the addition of new ones on issues such as pregnancy (see Chap. 14), menopause (see Chaps. 15 and 16), transgender athletes (see Chap. 17), effects of reproductive hormones on performance (see Chaps. 9 and 11), and tracking health and fitness in women, with special considerations for the menstrual cycle (see Chap. 13). The list of authors reads like a "who's who" of exercise physiology and sports medicine as related to women, exercise, and reproductive hormones. This eclectic group shares their diverse opinions and thoughts as well as provides evidence-based conclusions about the state of the science on female physiology. Moreover, many of the chapters are co-authored by aspiring graduate students or early career scientists who most surely represent the next generation of interested and cutting-edge researchers of the topic! Collectively, all the authors have worked diligently to make this a must-read for anyone interested in this area.

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Historical Perspective and Comments

The late Dr. Barbara Drinkwater (1926–2019) was a pioneering female physiology researcher who initially raised the alarm about the association between amenorrhea and low bone mineral density in athletes (Drinkwater 1984). In 1992, she was instrumental in leading a group of scientists and physicians to link together the separate clinical entities of disordered eating, amenorrhea, and osteoporosis as the "female athlete triad" and in defining a research agenda for the next 30 years (Yeager et al. 1993). Notably, she was the first research scientist to recommend accounting for body size in comparing physiological performances of men and women, and to connect increased calcium demands of pregnancy and breastfeeding to transient bone density changes (Drinkwater and Chesnut 1991). A mentor to many of us, male and female, whether clinicians or scientists or both; she would be delighted at the expanded knowledge about the specific exercise physiology of female athletes that this tome represents.

Over the past 50 years, Title IX in the USA (1972) has led to increased participation by women and girls in sports and exercise. Similarly, great strides have been made toward gender equity and parity in the Olympics, but regrettably not in professional sports, certainly not in terms of salary. However, just recently, the US Soccer Federation agreed to pay its men's and women's national teams equally. It remains to be seen if other sports and other countries will follow suit. Let us hope this is the start of actions worldwide in that direction.

Unfortunately, there have also been decades of under-representation of females in sport and exercise science research—in professional and university appointments, in academia hierarchy, in grant funding, as journal editors-in-chief, as lead authors, and as research subjects in studies. Even today, most research studies are still carried out on males, or if females are involved—lumping both sexes together as a single group, with the rationale that it is less expensive and bothersome than considering them separately.

But women are not just "*Small Men*" (Sims 2019). In other words, the findings in exercise physiology studies largely conducted on males cannot simply be extrapolated to them. Female athletes experience a kaleidoscope of reproductive hormones (endogenous and exogenous) from adolescence and puberty through their reproductive years and on into perimenopause, menopause itself and the post-menopausal years. These hormonal changes (and associated physiological changes) can modify both health and athletic performance through multiple physiological processes.

Early work on the topic of these hormonal change influences was fraught with problems: small sample sizes (leading to underpowered findings), inadequate documentation and/or monitoring of hormonal status, assumptions about menstrual cycle status, and varying measurements of performance/capacity (aerobic, anaerobic capacity, strength, and endurance—which can each be affected differentially by reproductive hormones). Furthermore, it has always been difficult to generalize from the "tightly controlled" research environment (e.g., standardized diets, fixed ambient

temperatures, pre-test exercise, training controls, etc.) to the "real world" of training and competition for an athlete (female or male).

Specific significant barriers to the rate of research progress have been the recruitment of suitable female subjects and accurate determination of menstrual cycle phases or other hormonal states under study. Relative to the latter, serum hormonal measurements are expensive (i.e., making them prohibitive for some researchers) and time-consuming, but costs have been coming down and analytical procedures are becoming less technically demanding (Hackney 2016). Regrettably, though, many previous studies have, for the most part, only examined performance in the mid-point of the follicular and luteal phases of the menstrual cycle, not in the early follicular, late follicular, ovulation, or late luteal phases which all have varying sex hormone profiles.

Notably, many female athletes in their reproductive years have been and are using hormonal contraceptives, either for birth control or to regulate those "pesky" and "disruptive" menstrual cycles (Martin et al. 2017). Accepted health benefits of oral contraceptives include decreasing dysmenorrhea and menstrual blood loss, which can impact the incidence of iron deficiency and anemia in women, certainly critical for endurance athletes. Even IUDs nowadays can contain hormones, not to mention implants, the patch, etc. During the postmenopausal years, various combinations of hormone replacement therapy (HRT) can be used and potentially influence performance in the mature athlete or complicate research investigations on older women. Obviously, this means that an improved interest and knowledge of athletes and their coaches and entourage about the vagaries of hormonal shifts throughout the entire life cycle changes of a woman should be encouraged (Clarke et al. 2021).

The temporal association of hormonal levels with effects on physiological variables (and by extension—athletic performance) is unclear—is it synchronous, delayed, or perhaps the result of hormonal interactions, such as the estrogen: progesterone ratio (Hackney et al. 2022)? How do other hormones such as cortisol factor in? What about diurnal variability? The blood concentrations of most hormones increase with exercise and may substantially decrease in the recovery from exercise. Yet, blood samples for hormonal analysis in many exercise research studies have been drawn in a resting state (pre-exercise). How generalizable are such findings to female athletes in their training or if they are competing on a regular basis? To that end, most training (or monitoring) studies have been generally less than 6 months in duration (far less than many athlete's training cycles), but the longer a study—the greater the probability that other variables (e.g., changes in training routines, life stress, etc.) all becoming potential confounding considerations.

There are reports that some female athletes sometimes manipulate their competitive schedules around their menstrual cycles to minimize any perceived or real impact on performance. For example, the slight increase in basal body temperature during the luteal phase (progesterone effect) is postulated to increase thermal strain, which could negatively impact the athlete. That is, this temperature change may be important in thermoregulation during long-distance events, especially if occurring in hot and/or humid conditions.

In addition, it is known that elite female athletes (up to 20–30%) have a higher incidence of menstrual irregularity, such as shortened luteal phase, anovulation, and/or amenorrhea (De Souza et al. 2010). In fact—these occurrences used to be a goal of some athletes—that is, it was validating that they were training hard enough because they lost their periods.

We now know that such thinking is counterproductive to the health and performance of a women athlete. Research by not only Barbara Drinkwater but also by Drs. Michelle Warren and Naama Constantini, as well as others, resulted in athletes and their trainers seeing the connections among exercise training, menstrual dysfunctions, and reproductive health. Subsequent landmark work by Dr. Anne Loucks showed that the underlying factor was not exercise itself, but rather energy availability to the female athlete (see Chaps. 12 and 23) (Loucks et al. 1998). Research has as well led us to recognize the menstrual cycle may also vary in a single individual eumenorrheic woman over time (see Chap. 1). For example, during the "off-season", or if an athlete is injured, they will be training less and/or have typically a slight weight gain. This can nudge their energy availability up just enough that the hypothalamic–pituitary axis kicks into its normal endocrine functions relative to sex hormones.

Notably, in the last few years, it has been documented that there are significant challenges in studying low energy availability (LEA) "in the field" (Heikura et al. 2022). Researchers are continually striving to improve the ease and reliability of the measurement, as severe or persistent LEA is linked to numerous health problems for the athlete (Mountjoy et al. 2014). Training and diet questionnaires have become essential due to practicality in examining LEA, but queries about the reliability and specificity of such instruments remain, and these are in great need of standardization and validation (Sim and Burns 2021).

Most certainly decades ago, there was a dearth of information on the effects of reproductive hormones and the menstrual cycle on athletic performance. The scales are not yet quite tipped toward a plethora of publications, but progress is being made (see Chap. 23). There is also the question of "nature" vs. "nurture" in examining athletes—does increased training and fitness to some extent, ameliorate, or at least blunt any significant impact of/on the menstrual cycle related-events? For example, exercise is known to diminish dysmenorrhea and depression in women. How critical are any subtle changes in performance to the recreationally active female? Is it only elite athletes who ascertain minute alterations, which might make the difference between silver and gold (McNamara et al. 2022)? Regardless, the technical difficulties of studying female athletes and the intricate interactions of reproductive hormones are not a justification to discourage the participation of women in research.

Personal Journey: A Few Reflections and Comments as an Athlete and Physician to Athletes

As a former female elite athlete in a team sport (volleyball), now a sport and exercise medicine physician/researcher, interested in exercise physiology, one could posit that I have been kind of a "living experiment". I prefer to think that I have a "pathological interest" in these issues! While in medical school, I was convinced I had every disease in the book related to athletes until it came to the last symptoms—"anorexia and weight loss", which never seemed to apply to me!

I first became intrigued with the effects of the menstrual cycle and oral contraceptives on athletic performance, when I was on the Canadian National Volleyball team, preparing for the 1976 Montreal Olympics. We trained 6 h a day (two practices a day), 6 days a week in the summertime; and in winter (when some of us were in school), 3 1/2 h a day, 6 days a week. With that level of repetition and intensity, even little things (such as a single alcoholic beverage on a Friday night) could affect our performance the following day (at least mine)! I would notice a decreased reaction time and would feel sluggish and not quite "on". Some team members, however, seemed unaffected! I must admit I was at the time unaware of menstrual phase-related differences or changes in respiratory or cardiovascular parameters or in temperature intolerance issues.

We had a demanding travel schedule, attending tournaments in other countries, and competing in multisport games. Something I also observed which piqued my curiosity was that many of us with "natural" menstrual cycles (who knows if they were ovulatory?) began to have synchronous menstrual cycles. The concept of "menstrual synchrony" was initially proposed in 1971 (McClintock 1971) with the theory that pheromones in axillary sweat were a possible causative factor. The concept was later disputed and debunked (Ziomkiewicz 2006).

During those competitive years, I was intermittently taking oral contraceptives and, curiously, felt physically stronger when I was on them, in terms of how hard I could hit the ball, how high I could jump, and so on. I was likely taking a higher dose formulation than the ones in use now (i.e., containing 50 mcg of ethinyl estradiol, instead of 30 or even 20 mcg). I believe the progestin in it was also on the androgenic side, so it may not have just been my imagination!

I did not even remotely consider the possibility that any of my teammates could have an eating disorder, especially when we compared ourselves to the lean and tiny gymnasts, like Olympic champions Nadia Comaneci and Olga Korbut! Now, as a clinician, I know and have observed that every sports athlete is at risk for disordered eating patterns. Especially with the bulimic form, athletes may look (but not act) "normal".

Ever since I have been a physician—first in comprehensive family practice (including obstetrical care) and then in sports medicine—female patients, aware of my interests, have asked me about the effects of the menstrual cycle and oral contraceptives on their performance. That question became the topic of my later graduate student research. After that educational experience and publication-related research

work, I have continued to closely follow the literature on such topics, serving as a manuscript reviewer, a member of graduate student committees, and the like to keep up to date on female physiology and performance.

Throughout the years, I have managed to experience all the different states of reproductive hormones (except for pregnancy and childbirth). Now, for some reason, I seem to be fascinated by research articles on the "mature" postmenopausal athlete and how to deal with the various vicissitudes of aging, including sarcopenia.

Another current important issue for female athletes, outside of the scope of this book, is harassment and abuse in sport. This may include rigorous and sometimes excessive training regimes by coaches (to the point of causing injuries), which is volume-based, not evidence-based. Some would say our volleyball team suffered that, in terms of our heavy training. But we did not know any better.

Gender verification has been another hot topic for many years and one I personally experienced as an athlete. That is, we were tested during the 1976 Montreal Olympics. I can happily report that I am a "verified female", at least in terms of having the requisite XX chromosome profile, and I have a "Certificate of Femininity"! Fortunately, we were not subjected to physical examination, as had been the case in many Olympics previously. In Atlanta in 1996, one of my first duties as Canadian Team Physician was to accompany our female athletes over to "Gender Verification".

Transgender athletes and hyperandrogenism (disorders of sexual differentiation or DSD) were not identified as issues when I was competing–now these are openly talked about, and their healthcare needs are discussed and rightly addressed (see Chap. 17). Recently, there was controversy about transgender athletes competing as females at the Tokyo 2020 Summer Olympics. New terminology and rules continue to evolve, as do the official Position Statements of the International Olympic Committee (IOC). But it can "go both ways". Not long ago, in an advertisement for a Women's Whitewater Kayaking Weekend, I saw the following statement: "All women, transgendered, and non-binaries are welcome. Please don't register or attend if you are a cis male".

Pregnancy can also be a difficult time for athletes. As their physician, in the past, the only information I usually could offer then was a thin, measly little pamphlet from the Canadian Government on Exercise in Pregnancy. In those days, recommendations from august professional associations included not exceeding a heart rate of 140 beats per minute! Fortunately, there is much more knowledge now, but still, even more is needed (see Chap. 14).

There are other pregnancy-related issues, for example, at one Olympic Games I attended as a team physician—when an athlete in a certain combat sport could not provide evidence of a negative pregnancy test, the host medical team wanted her to have a physical examination done!! As if one could diagnose pregnancy that early on! Later, in time for the Rio 2016 Olympics, sports regulations changed to having the athlete just complete a "Declaration of non-pregnancy."

Another question, not yet conclusively addressed scientifically, is the potential "training effect" of pregnancy, with its increased capillary density and adaptation in the cardiovascular and respiratory systems. For example, during my competitive

volleyball years, we certainly saw many players, particularly of Eastern European origin, who took time away for childbearing and came back, seemingly stronger than ever. There were also rumors (unsubstantiated) of women intentionally getting pregnant and then having an early abortion—to benefit from the training effect.

The Future and Questions Remaining

It is accepted that females (during the premenopausal years) are differentially affected by certain diseases such as migraine and cardiovascular disease, including heart attacks. Recently, evidence has surfaced about hormonal effects on brain health (such as decreased cognition in the postmenopausal years) and even with concussions. That is, female athletes who suffer a concussion report more symptoms than their male counterparts and take longer to get better (Covassin et al. 2016). There may also be different recovery times, depending on when in the menstrual cycle the injury occurs (Wunderle et al. 2014). Research on this latter topic is still in its infancy but certainly is needed.

Systematic reviews of the effects of the menstrual cycle (McNulty et al. 2020) and oral contraceptives (Elliott-Sale et al. 2020) on athletic performance have critically appraised past literature, concluding that there is little solid scientific evidence of any impact. Going forward, there are now guidelines for the standardization of research, using the proper methodology, with accurate documentation of hormonal status in all phases of a woman's reproductive life, instead of just repeating previous studies (and some of their mistakes) (Elliott-Sale et al. 2021).

Technological advances, such as the urinary luteinizing hormone (LH) kit, allow the determination of ovulation with a high degree of certainty and can help researchers and subjects schedule testing sessions in the appropriate menstrual cycle phase. While the cost of blood hormonal samples remains prohibitively high, further development and utilization of salivary and urinary hormone measurements, which the athletes can easily collect at home, further facilitate verification of the cycle phase.

A new system of objectively tiering and categorization of athletic status has been developed, which will allow more homogenous groups to be studied (McKay et al. 2022). Measurement of LEA outside of the laboratory setting is becoming more feasible, as the validity of screening questionnaires is increasing. In addition, evidence points toward an overlap in clinical manifestations between LEA and overtraining syndrome (Stellingwerff et al. 2021).

In terms of hormonal contraceptives, the "Pill" initially thought to be a "boon for sportswomen" has been shown to not protect females with menstrual irregularities against decreased bone mineral density (BMD), and in fact to be detrimental to the achievement of optimal bone mineral density. Rather, topical estrogen patches with monthly courses of progesterone have been proven to improve BMD in amenorrheic athletes (Ackerman et al. 2019). Yet not all of this information is trickling down to the sports medicine practitioner or the athlete.

Much work remains in terms of studying hormonal contraceptives with different formulations. Lower estrogen doses and third-generation progestins cause fewer clinical side effects, but are influences on physiology and performance concomitantly reduced? Of the various progestins used, some are more androgenic, while others have more progestational effects. Extended dose formulations, such as Seasonale®, give an athlete the ability to prolong cycles and control both the length and timing of menstrual bleeding around important competitions. As physicians treating female athletes, we were experimenting with this method (by simply having the athlete continue taking several months of monophasic preparations in succession) long before commercial production. Additionally, there are progestin minipills, hormone-eluting IUDs, implants, and hormonal patches which complicate the picture.

Questions remain regarding the pre-partum, pregnancy, and postpartum periods and athletic performance. Pregnant athletes have historically not been supported well by sponsors, nor by sports governing bodies. Inroads are being made on various financial and logistical difficulties of athletes who choose to have children during their competitive years. Whereas previously they may have struggled, elite athletes are now taking their children on tour with them and even still managing to breastfeed. Accommodations are being made, even at the Olympic level, and better science has certainly played a role in these developments.

Finally, let us fast forward another 50 years and look toward the future. It is certainly bright! By no means have we reached equality in sport and exercise science research, but an auditing protocol for review of female-specific sport and exercise science research (Smith et al. 2022) should facilitate keeping track. Furthermore, there have also been improved salaries and research funding for female scientists which help encourage more women to work in the field.

Topics such as menstrual phase-based training and recovery and menstrual-linked asthma are on the research horizon. Algorithms and infograms on menstrual dysfunction and energy availability help convey information to patients, clinicians, and scientists managing amenorrhea, assisting them to understand energy availability and classify menstrual cycles. There are new apps for menstrual cycle tracking, such as that of the Harvard Women's Health Study, which uses metrics from women's Apple watches to monitor their menstrual symptoms. How difficult would it be to add in heart rate and performance measures? More recently, sophisticated apps and platforms such as Hormonix (Mint Diagnostics Corp.) allow the athlete to track symptoms and get reminders about sample collection (saliva), and the researcher to view data in real time.

Nevertheless, in the end, it is important to remember that each female athlete is an individual, to whom quantitative statistics do not matter. The fundamental objective is to optimize female athletic performance AND health—both short term and long term.

In the immortal words of Dr. Barbara Drinkwater,

It is about the health of the athlete after all!

We as the gatekeepers of the scientific knowledge on women athletes must remember these words of Dr. Drinkwater and be proactive rather than reactive on this issue. The impressive volume of knowledge in this book will no doubt help in this goal! Most assuredly, it should be on the bookshelves of all researchers/scientists/practitioners studying female reproductive hormones and exercise and working with women athletes!

References

Ackerman K, Singhal V, Baskaran C, Slattery M, Reyes KJC, Toth A, et al. Oestrogen replacement improves bone mineral density in oligo-amenorrheic athletes: a randomized clinical trial. Br J Sports Med. 2019;53(4):229–36. https://doi.org/10.1136/bjsports-2018-099723.

Clarke A, Govus A, Donaldson A. What male coaches want to know about the menstrual cycle in women's team sports: performance, health and communication. Int J Sports Sci Coaching. 2021;16(3):544–53. https://doi.org/10.1177/1747954121989237.

Covassin T, Moran R, Elbin RJ. Sex differences in reported concussion injury rates and time loss from participation: an update of the National Collegiate Athletic Association Injury Surveillance Program from 2004–2005 through 2008–2009. J Athl Train. 2016;51(3):189–94. https://doi.org/10.4085/1062-6050-51.3.05.

De Souza MJ, Toombs RJ, Scheid JL, O'Donnell E, West SL, Williams NI. High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures. Hum Reprod. 2010;25(2):491–503. https://doi.org/10.1093/humrep/dep411.

Drinkwater BL, Chesnut CH 3rd. Bone density changes during pregnancy and lactation in active women: a longitudinal study. Bone Miner. 1991;14(2):153–60. https://doi.org/10.1016/0169-6009(91)90092-E.

Drinkwater BL. Bone mineral content of amenorrheic and eumenorrheic athletes. N Engl J Med. 1984;311(5):277–81. https://doi.org/10.1056/NEJM198408023110501.

Elliott-Sale KJ, McNulty KL, Ansdell P, Goodall S, Hicks KM, Thomas K, et al. The effects of oral contraceptives on exercise performance in women: a systematic review and meta-anaysis. Sports Med. 2020;50(10):1785–812. https://doi.org/10.1007/s40279-020-01317-5.

Elliott-Sale KJ, Minahan CL, de Jonge X, Ackerman KE, Sipila S, Constantini NW, et al. Methodological considerations for studies in sport and exercise science with women as participants: a working guide for standards of practice for research on women. Sports Med. 2021;51(5):843–61. https://doi.org/10.1007/s40279-021-01435-8.

Hackney AC. Exercise, sport, and bioanalytical chemistry: principles and practice. Cambridge, MA, USA: Elsevier Publishing; 2016.

Hackney AC, Koltun KJ, Willett HN. Menstrual cycle hormonal changes: estradiol-β-17 and progesterone interactions on exercise fat oxidation. Endocrine. 2022;76(1):240–2. https://doi.org/10.1007/s12020-022-002998-w.

Heikura IA, Stellingwerff T, Areta JL. Low energy availabilty in female athletes: from the lab to the field. Eur J Sport Sci. 2022;22(5):709–19. https://doi.org/10.1080/17461391.2021.1915391.

Loucks AB, Verdun M, Heath EM. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J App Physiol. 1998;84(1):37–46. https://doi.org/10.1152/jappl.1998.84.1.37.

Mountjoy M, Sundgot-Borgen J, Burke L, et al. The IOC consensus statement: beyond the female athlete triad—Relative energy deficiency in sport (RED-S). Br J Sports Med. 2014;48:491–7.

Martin D, Sale C, Cooper, SB, Elliott-Sale, KJ. Period prevalence and perceived side effects of hormonal contraceptive use and the menstrual cycle in elite athletes. Int J Sports Physiol Perform. 2017;1–22. https://doi.org/10.1123/ijspp.2017-0330.

McClintock M. Menstrual synchrony and suppression. Nature. 1971;229(5282):244–5. https://doi.org/10.1038/229244a0.

McKay AKA, Stellingwerff T, Smith ES, Martin DT, Mujika I, Goosey-Tolfrey VL, et al. Defining training and performance caliber: a participant classification framework. Int J Sports Physiol Perform. 2022;17(2):317–31. https://doi.org/10.1123/ijspp.2021-0451.

McNamara A, Harris R, Minahan C. 'That time of the month' … for the biggest event of your career! Perception of menstrual cycle on performance of Australian athletes training for the 2020 Olympic and Paralympic Games. BMJ Open Sp Ex Med. 2022;8(2): e001300. https://doi.org/10.1136/bmjsem-2021-001300.

McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, et al. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. Sports Med. 2020;50(10):1813–27. https://doi.org/10.1007/s40279-020-01319-3.

Sims S. Women are not Small Men. TedX Tauranga. 23 Sept 2019. https://www.youtube.com/watch?v=e5LYGzKUPlE

Sim A, Burns SF. Review: questionnaires as measures for low energy availability (LEA) and relative energy deficiency in sport (RED-S) in athletes. J Eating Disorders. 2021;9(1):41. https://doi.org/10.1186/s40337-021-00396-7.

Smith ED, McKay AKA, Ackerman KE, Harris R, Elliott-Sale KJ, Stellingwerff T, et al. Methodology review: a protocol to audit the representation of female athletes in sports science and sports medicine research. Int J Sport Nutr Exerc Metab. 2022;32(2):114–27. https://doi.org/10.1123/ijsnem.2021-0257.

Stellingwerff T, Heijura I, Meeusen R, Bermone S, Seiler S, Mountjoy ML, et al. Overtraining syndrome (OTS) and relative energy deficiency in sport (RED-S): shared pathways, symptoms and complexities. Sports Med. 2021;51(11):2251–80. https://doi.org/10.1007/s40279-021-01491-0.

Wunderle K, Hoeger KM, Wasserman E, Bazarian JJ. Menstrual phase as predictor of outcome after mild traumatic brain injury in women. J Head Trauma Rehabil. 2014;29(5):E1–8. https://doi.org/10.1097/HTR.0000000000000006.

Yeager KK, Agostini R, Nattiv A, Drinkwater B. The female athlete triad: disordered eating, amenorrhea, osteoporosis. Med Sci Sports Exerc. 1993;25(7):775–7. https://doi.org/10.1249/00005768-199307000-00003.

Ziomkiewicz A. Menstrual synchrony: fact or artifact? Hum Nat. 2006;17(4):419–32. https://doi.org/10.1007/s12110-006-1004-0.

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