The Effects of Exogenous Estrogen and Menstrual Cycle Phase on Female Aerobic Performance

By

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A Thesis

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ABSTACT

This thesis investigates aerobic performance and substrate utilization of eumenorrheic women on and off oral contraceptive pills (OCP) during the follicular and luteal phases of the menstrual cycle**.** The topic was chosen as the relevance of oral contraceptives to today's athletic industry is increasing with the progression of womens athletics. The implementation of OCPs by women of the general population continues to gain momentum for the benefits of reduced cycle variability and symptoms of the menstrual cycle. Many studies have demonstrated a decrease in VO_2max that occurred in women taking OCPs, suggesting that exogenous estrogen negatively impacts aerobic capacity, with potential implications for elite performance. Elevated endogenous estrogen concentrations – such as in the follicular phase – provide a cardioprotective effect, positively influencing VO_2max. While progesterone's antiestrogenic properties are well known, the two primary female sex hormones find common ground with regard to increased lipid mobilization in the luteal phase. However, while fluctuations of endogenous sex hormones have some effect on triglyceride mobilization, synthetic hormones found in OCPs further increase triglyceride mobilization and plasma cortisol concentrations in exercising women. This thesis provides a review of the effects of OCPs on aerobic performance and appreciates cycle phase differences, providing a foundation for broader assessments of effects of OCPs in women of the general population. Additional research on this topic would allow for a greater understanding of the influence of sex hormones on cardiovascular mechanisms to a further extent.

Chapter 1: Introduction

From the onset of menarche to menopause, women undergo a rhythmic fluctuation of endogenous sex hormones (estrogen and progesterone), which results in the physiological process referred to as the menstrual cycle. This cycle is heavily regulated by a feedback system of pituitary hormones and the hypothalamus. Estrogen and progesterone are primarily responsible for the regulation of various phases within the menstrual cycle, with the postmenstrual phase being estrogen dependent and the premenstrual phase being progesterone dependent (Godbole et al., 2016). In the introduction to this thesis, I will discuss these hormones in further detail, as well as how the menstrual cycle is influenced by oral contraceptives.

Review of Normal Menstrual Physiology

The menstrual cycle occurs in a predictable pattern that repeats roughly every 26-35 days during a woman's reproductive years (**Figure 1**). The cycle is divided into two phases that based primarily on the changes in estrogen and progesterone. The first phase is referred to as the follicular phase, which starts with menses (day 1) and ends with ovulation (day 14). The follicular phase is characterized by the release of follicular stimulating hormone (FSH) and luteinizing hormone (LH) and low concentrations of both estrogen and progesterone (Julian et al., 2017). The second phase of the cycle is referred to as the luteal phase and is characterized by higher concentrations of estrogen and progesterone and occurs from days 15 to 28 of the cycle.

In the follicular phase of the menstrual cycle, the hypothalamus releases gonadotropin releasing hormone (GnRH), which acts on the anterior pituitary to stimulate the release of FSH. This stimulates the development and maturation of a follicle within the ovary (Ashley et al., 2000). Under the influence of FSH and LH, the ovary is stimulated to gradually release estrogen, which

peaks 24 hours prior to ovulation to supports the proliferation and maturation of the endometrial surface (Frankovich & Lebrun, 2000). This peak in estrogen also stimulates the release of LH from the hypothalamic-pituitary axis and a surge in LH. The sudden surge of LH occurs in synchronization with ovulation and ultimately results in the development of follicular tissues known as the corpus luteum (Frankovich & Lebrun, 2000). The purpose of FSH is to positively aid in the maturation of the ovarian follicle and further stimulate the production of estrogen.

Next, the luteal phase begins, which is marked by the event of ovulation to the start of menses. During the luteal phase, the remaining follicular tissue (the corpus luteum) produces estrogen and progesterone to further prepare the endometrium for fertilization in the event of the ovum becoming fertilized (Frankovich & Lebrun, 2000). The increase in estrogen and progesterone during the luteal phase also terminates FSH and LH production. If the ovum does not become fertilized the concentrations of both estrogen and progesterone dramatically decline, causing the previously prepared lining of the endometrium to shed and results in the start of menses, thus the restarting of the entire cycle.

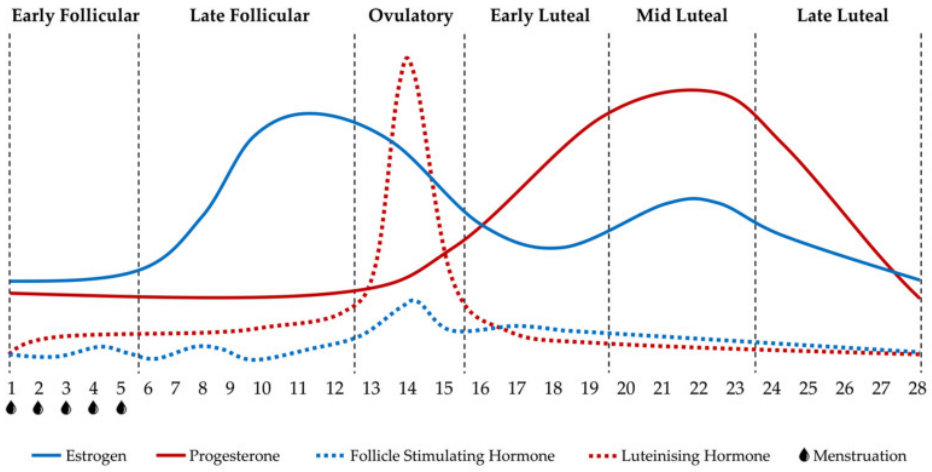

Figure 1. Hormonal events and phases in a eumenorrheic 28-day menstrual cycle (Carmichael et al., 2021).

Actions of Estrogen

The estrogens are a group of steroid hormones. There are three major estrogens – estrone (E1), estradiol (E2), and estriol (E3) – estradiol as the major form and estrone and estriol being less potent (Frankovich & Lebrun, 2000). For the purpose of this thesis, all forms will be cumulatively referred to as estrogen. Estrogen is primarily secreted by the ovary, and to a lesser extent by the adrenal glands. Estrogen significantly drives breast development, fat deposition in the hips, legs and breasts, as well as the development of reproductive organs. More specifically, estrogen heavily acts as a feedback regulator of gonadotrophin secretion and as an intrafollicular modulator with regard to folliculogenesis by stimulating the proliferation and differentiation of granulosa cells in follicles and facilitating the actions of FSH and LH (Drummond & Findlay, 1999; Richards, 1980).

Estrogen also has a strong influence on the cardiovascular system by altering fibrinolytic activity and platelet aggregation, increasing the risk of thrombi development (Frankovich & Lebrun, 2000). Alternatively, estrogen also aids in reducing total cholesterol and low-density lipoprotein (LDL) concentrations, while increasing high-density lipoproteins (HDL) (Frankovich & Lebrun, 2000). This mechanism acts as a protective agent against the development of atherosclerosis. Estrogen also increases vasodilation of blood vessels in the circulatory system through by inducing production and release of nitric oxide (NO) by the arterial endothelium, which promotes smooth muscle relaxation (Maiorana et al., 2003). Estrogen also possesses the ability to act on calcium channel blockers (Frankovich & Lebrun, 2000), which may further improve vascular resistance by preventing vasoconstriction (**Figure 2**). It should be noted that most of these cardiovascular effects that estrogen has within the body are antagonized by progesterone.

In addition to influencing the cardiovascular system, previous studies demonstrate that estrogen is a key regulator of substrate metabolism, and the action of estrogen may enhance endurance performance. For example, estrogen increases the uptake and storage of intramuscular and hepatic glycogen (Frankovich & Lebrun, 2000). Greater concentrations of estrogen in the follicular phase induce a decline in insulin-binding capacity. This modification results in reduced glycogen use and insulin resistance, thus, reduced glucose transport and increasing the body's reliance on lipid utilization, potentially enhancing aerobic performance and endurance by sparing glycogen. Additional actions of estrogen include increasing sodium and chloride retention (which may result in edema, weight gain and increased blood pressure), and the facilitation of calcium uptake into bone (Redman & Loucks, 2005). This explains why in estrogen-deficient states, such as amenorrhea or post menopause, women become more susceptible to osteoporosis and an increased risk of fractures.

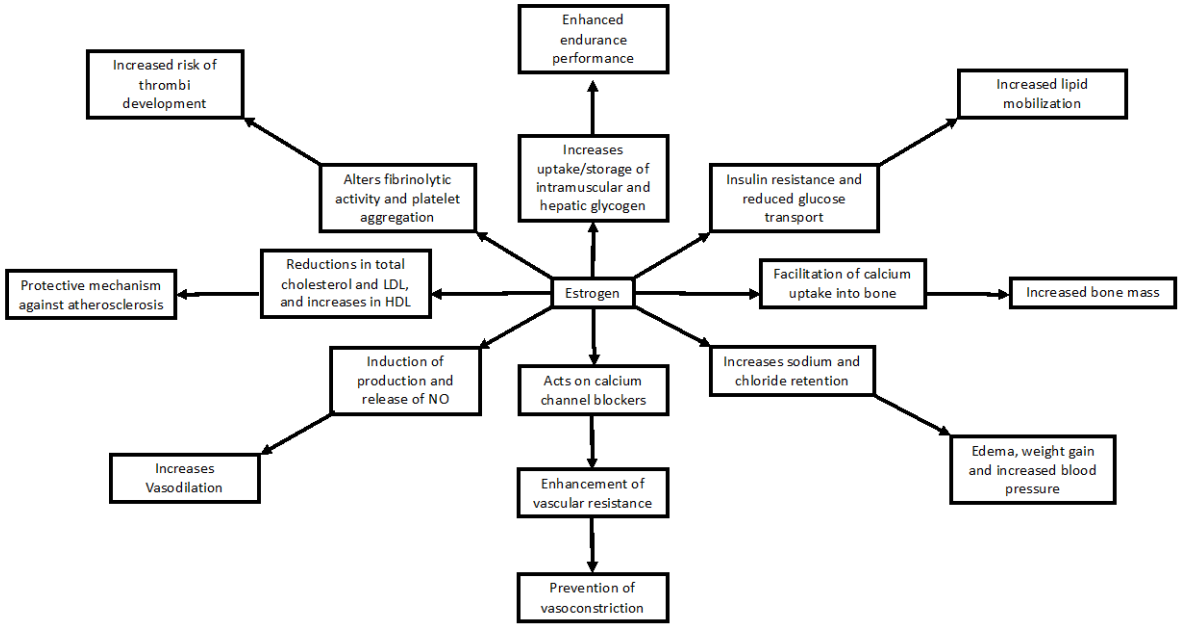

Figure 2. Various non-reproductive functions of estrogen throughout the body.

Actions of Progesterone

The other group of female hormones that will be discussed in this thesis in the progestins, with progesterone being the major form (Frankovich & Lebrun, 2000). The reproductive roles of estrogen and progesterone are often antagonistic to each other, and the progestin group of hormones is known for its antiestrogenic properties. Progesterone is responsible for driving transition of the endometrium from the follicular to luteal phase, the implantation of the zygote and the maintenance of pregnancy in correspondence with the implantation of said zygote (Taraborrelli, 2015). It has also been noted that many changes appreciated during pregnancy when progesterone is high, are observed in the luteal phase of a normal menstrual cycle without the occurrence of conception. Appreciable changes with an increased concentration in progesterone, such as in the luteal phase, include a thermogenic effect resulting in an increased core body temperature, increased minute ventilation and an increased ventilatory response to hypoxia and hypercapnia (Frankovich & Lebrun, 2000). This may explain why an individual may report experiencing an increased sense of dyspnea, a greater rating of perceived exertion and an impaired athletic performance during the luteal phase.

Progesterone also contributes to postovulatory fluid retention during the luteal phase through the compensatory activation of the renin-angiotensin system (RAS), whereby the antagonism of mineralocorticoid receptors by progesterone leads to compensatory aldosterone production the RAS, and in turn water reabsorption by the kidneys (Oelkers, 1996). With regard to metabolic activity, progesterone increases lipid utilization, as indicated by a lower Respiratory Exchange Ratio (RER) and lower blood lactate levels (**Figure 3**) during submaximal exercise protocols (Frankovich & Lebrun, 2000).

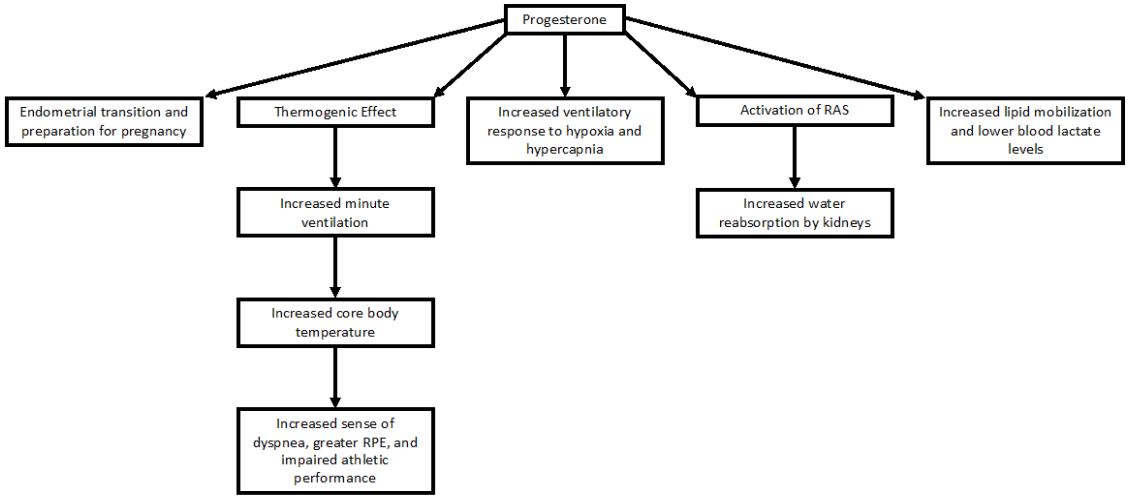

Figure 3. Various non-reproductive functions of progesterone throughout the body.

The Oral Contraceptive Pill

Oral contraceptives (OCP) are the main form of birth control among women in the general population. The OCP reduces cycle length variability and provides cycle consistency by suppressing the concentrations of endogenous sex hormones by inhibiting the pituitary gland from secreting gonadotropins (LH and FSH), thus inhibiting ovulation and preventing pregnancy (**Figure 4**). OCPs also decrease the endometrial lining to minimize the likelihood of implantation occurring and increasing cervical mucous production to reduce sperm mobility.

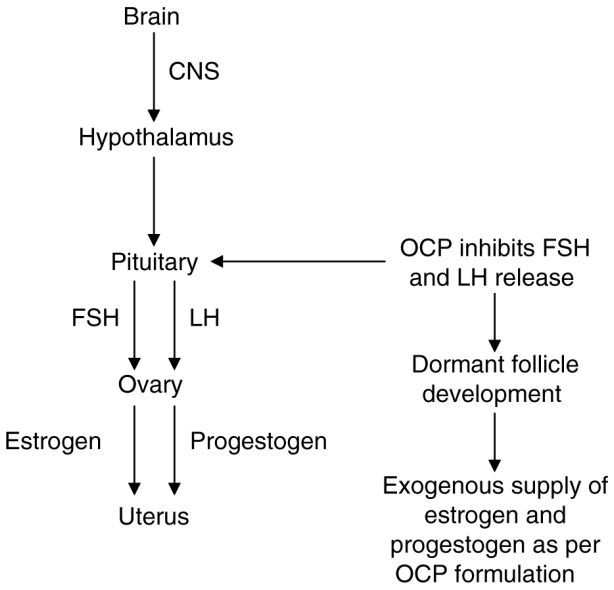

Figure 4. The oral contraceptive pill (OCP) and control of endogenous sex hormones (Burrows & Peters, 2007).

The OCP is not a "one-size-fits-all contraceptive agent. The OCP is administered in three different forms that differ in formulation and chemical composition, resulting in different pharmacokinetic properties (**Figure 3**). Depending on the type of OCP administered, three-to-five times more exogenous estrogen and one-to-two times more exogenous progesterone can be provided compared to endogenous levels (Burrows & Peters, 2007), which will be discussed below.

Essentially there are two main types of OCPs: 1) the combined OCP, which contains both estrogen and progesterone; and 2) the mini, or progesterone-only, pill (POP), which contains solely progesterone. The POP provides a contraceptive option for women who cannot or do not want to use estrogen-containing oral contraceptive for medical reasons or who are breastfeeding (Burrows & Peters, 2007). For the purpose of this thesis, only the combined OCP will be discussed. Combined OCPs may be administered in three different forms: monophasic, biphasic and triphasic,

with the differences among these three types of OCs revolving around the dose and timing of said dose across the pill cycle.

Monophasic pills are composed of a fixed dose of estrogen and progesterone over 21days, followed by 7 days of placebo. Given that use of monophasic formulations reduces hormonal fluctuations across the cycle, it could be hypothesized that this option could better control hormonal homeostasis and minimize the potential for physiological variations (Burrows & Peters, 2007). In a biphasic OCP, the dosage of the hormones is switched once during the 21-day cycle. This form of OCP contains a fixed amount of estrogen, but two different amounts of progesterone between days 7-10 and days 11-14, with the last 7 days being placebos (Burrows & Peters, 2007). Triphasic pills contain three different doses of estrogen (or progesterone) that are increased throughout the cycle. Biphasic and triphasic OCPs contain 30-40% lower levels of hormone, which correlates to minimal adverse side effects (Lebrun et al., 2003).

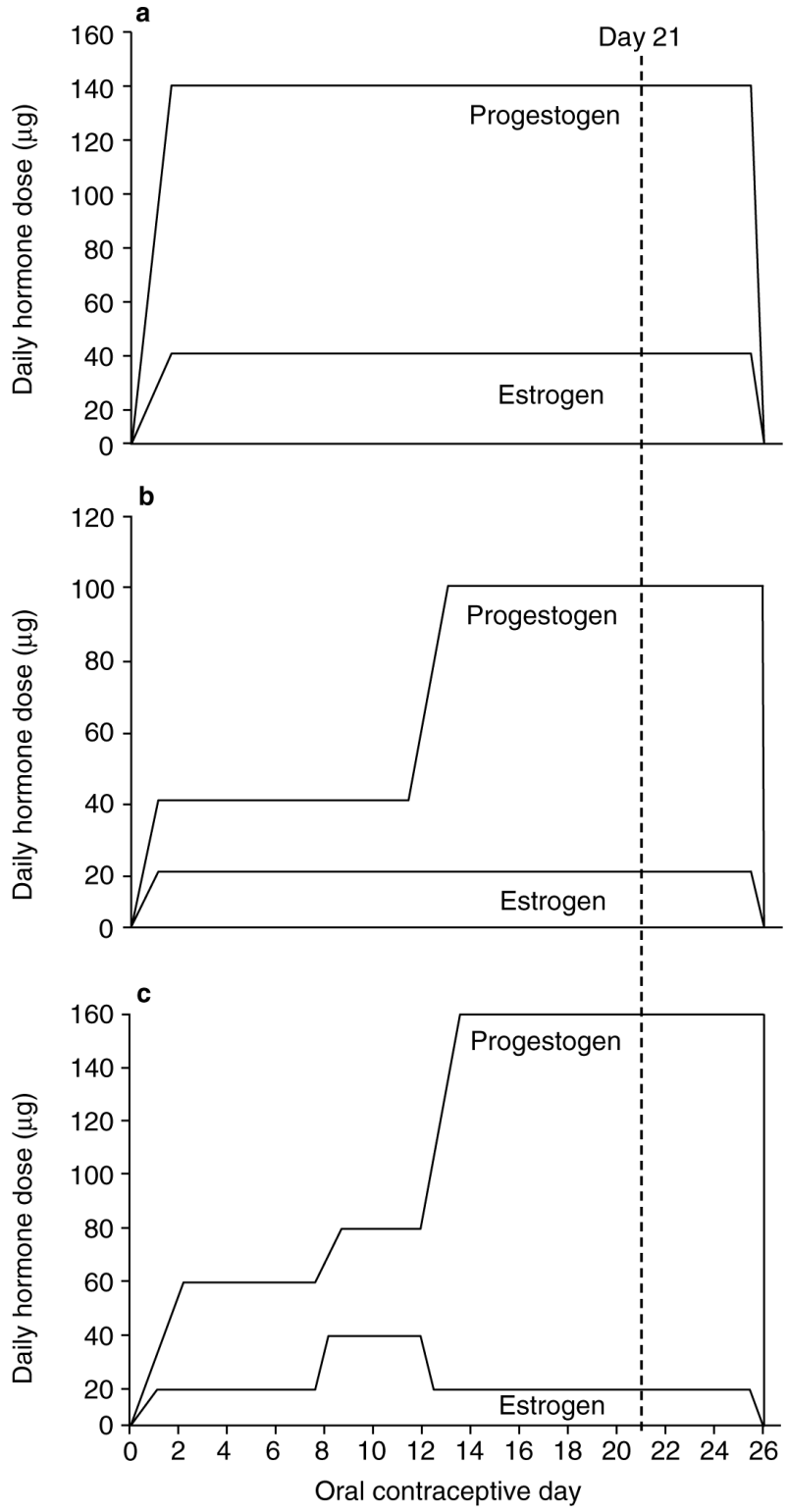

Figure 5. Cyclic pattern of estrogen and progestogens in (**a**) monophasic, (**b**) biphasic and (**c**) triphasic oral contraceptives. Reproduced from Redman and Weatherby (Redman & Weatherby, 2004).

The primary mechanism of OCPs is to prevent ovulation through negative feedback inhibition at the hypothalamus by abolishing the normal hormonal cycling that underlies ovulation. While the body is under the influence of exogenous OCPs, the endogenous production of estrogen and progesterone is suppressed, thus the serum concentration of active sex steroids is directly related to the OCP dosage administered (Fotherby, 1996). Therefore, just as the hormone fluctuations of the menstrual cycle can affect women in different ways, there appears to be a large individual variability between these hormones administered via OCPs and their effects on exercise performance. Monophasic and triphasic OCPs are the primary forms prescribed, therefore they are the primary OCPs targeted by research of this nature. Potential benefits of OCP administration for athletic performance include decreased dysmenorrhea, iron deficiency, and anemia risks in females who experience a heavy flow (Lebrun et al., 2003).

Modifications to Thesis

Initially, I devised a study to assess the influence of menstrual cycle phase and OCP use on aerobic exercise performance in healthy women. However, given the challenges presented by the COVID-19 pandemic it was unrealistic to complete this study. Thus, my thesis is instead a detailed review describing the current understanding of how menstrual cycle phase and OCP use influence aerobic exercise performance.

Purpose

Common adaptations to aerobic exercise training in both men and women include an appreciable decrease in blood pressure and heart rate, reductions in body fat, and an increase in maximal aerobic capacity. However, in women cyclical fluctuations in estrogen and progesterone

may impact various parameters of physical fitness and adaptations to exercise training (Frankovich & Lebrun, 2000; Girija & Veeraiah, 2011; Godbole et al., 2016). Just as the fluctuation of endogenous estrogen and progesterone affect women in different ways, the exogenous source of hormones from OCPs, coupled with the suppression of the endogenous concentrations of sex hormones may also affect women in different ways. This poses a question in regarding the influence OCPs may have on athletic performance and given the increasing commonality of OCPs use in athletes, the implications for physical performance could be profound.

Female participation in both athletics and laborious occupations is increasing, posing the opportunity for greater scientific research in female performance under the influence of different phases of the menstrual cycle and oral contraception. It is estimated that the use of OCPs in athletic women matches that of women in the general population (Burrows & Peters, 2007). There have been various studies performed and that have demonstrated the impact of hormonal fluctuations within the menstrual cycle on aerobic and anaerobic capacity, metabolic substrate utilization, and muscle strength. Yet, while OCPs allow for greater stability throughout the menstrual cycle and their use is becoming increasingly more prevalent in the athletic population, there has been minimal research performed on performance parameters that include OCP use. Therefore, the effect of OCPs have on athletic performance is not clear.

The purpose of this thesis is to investigate aerobic performance and substrate utilization of women on and off OCPs during the follicular and luteal phases of the menstrual cycle. This thesis will draw on the review of reproductive hormones and their implications on aerobic capacity and metabolism, as well as provide an exploration of the physiologic changes that occur under the influence of exogenous estrogen of mono, bi, and triphasic OCPs on aerobic performance in both the follicular and luteal phase of the menstrual cycle in humans.

Chapter 2: Main Analysis

Aerobic Capacity and Cycle Phases

Many studies of individual performance variables suggest two things: 1) there are differences in aerobic performance among menstrual phases and 2) estrogen increases aerobic capacity. A study conducted by Godbole et al. (Godbole et al., 2016) assessed 11 female students between the ages of 17 and 22 years old with regular/normal menstrual cycles for 3 consecutive menstrual cycles, implementing a step test protocol. This study found that there was in fact a statistically significant increase in body weight, heart rate and respiratory rate during the luteal phase, and that there was a significantly decreased VO_2max during the luteal phase. The results of this study indicate that there is a reduced cardio-respiratory efficiency during the luteal phase, and that aerobic capacity is higher in the follicular phase of eumenorrheic women. This may be explained through the nonreproductive effects of progesterone on the renin-angiotensin system. Progesterone activates the renin-angiotensin system, in turn increasing plasma volume and hemodilution. This function most likely decreases oxygen carrying capacity and may be at least partially responsible for decreased oxygen consumption by the working muscles. Additionally, the resulting increase in plasma volume from progesterone's influence on the renin-angiotensin system can place a greater workload on the heart, reducing the heart's performance. The difference in VO_2max between the follicular and luteal phases may also be explained by the coupling action of the thermogenic effects of progesterone. Progesterone increases basal body temperature by 0.5 – 0.8 °C at the time of ovulations (Charkoudian & Stachenfeld, 2016). This increase in body temperature increases heart rate and respiratory rate, which in turn reduces exercise tolerance and decreases VO_2max (**Figure 6**).

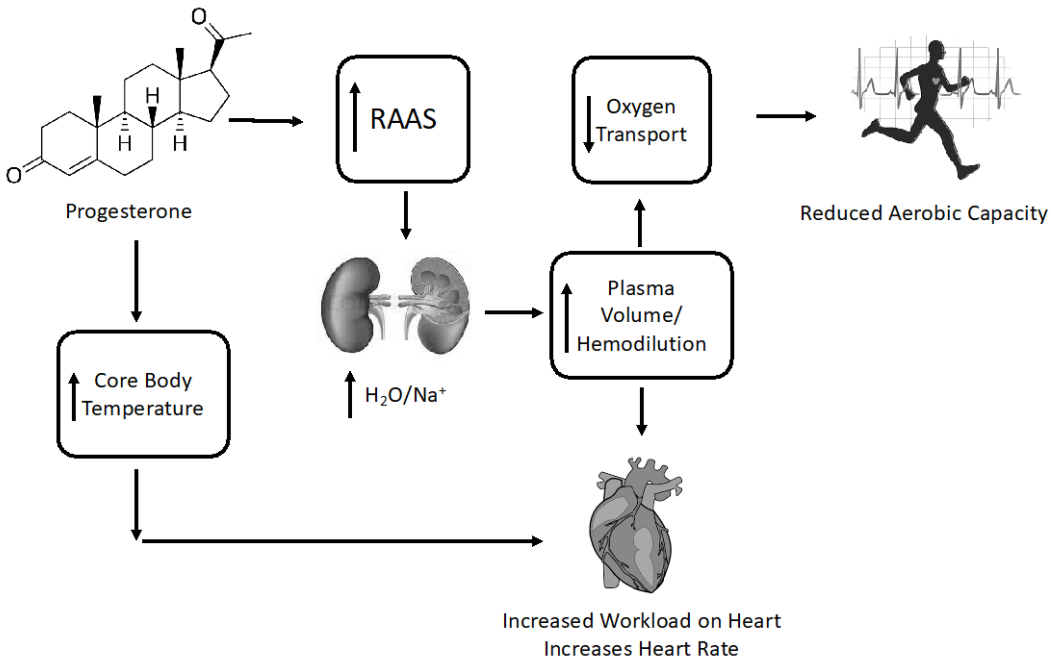

Figure 6. Effects of elevated progesterone levels in the luteal phase of the menstrual cycle on aerobic capacity.

A second study by Lebrun et al. (Lebrun et al., 1995), examined the effects of menstrual cycle phase on athletic performance, comparing the early follicular phase and midluteal phase. No significant differences were appreciated with regard to weight, percent body fat, body composition (as determined via skinfold measurements), hemoglobin concentration, hematocrit, maximum heart rate, maximum minute ventilation, maximum respiratory exchange ratio (RER), anaerobic performance, endurance time to fatigue or isokinetic strength. However, the study did observe that absolute and relative VO_2max was lower in the luteal phase versus the follicular phase, further suggesting that cyclic increases in progesterone have a slight, deleterious influence on aerobic capacity. Stachenfeld and Taylor (Stachenfeld & Taylor, 2005) performed a study in which test subjects had reduced aerobic performance, increased respiratory rate and a greater sense of

breathlessness in the luteal phase. This may be explained by progesterone's influence on respiration. Progesterone stimulates respiration by acting on the respiratory center and peripheral chemoreceptors, possibly resulting in a greater consumption of energy by the respiratory muscles that would otherwise be available for other working muscle groups. The elevated progesterone levels in the luteal phase may explain the appreciated increase in respiratory rate. The data in this study suggests better oxygen consumption in the follicular phase, indicating that estrogen has a favorable effect on oxygen consumption and that progesterone has an unfavorable effect on it.

A final study that further suggests a difference in aerobic performance between the follicular and luteal phase was performed by Jurkowski et al. (Jurkowski et al., 1981). This study assessed the effects of the menstrual cycle on cardiorespiratory variables, blood lactate, and performance in exercising females in the follicular and luteal phase. Collected data indicated no significant difference in heart rate, ventilation, O_2 uptake, or CO_2 output between the two phases, but appreciated that time to exhaustion increased in the luteal phase and that blood lactate was higher in the follicular phase. Collectively, these studies demonstrate disparities in aerobic performance between the follicular and luteal phases of the menstrual cycle in eumenorrheic women and demonstrate that the cardioprotective properties of estrogen positively influence on VO_2max.

OCPs and Aerobic Capacity

As fluctuations in sex steroids are believed to be a possible factor in performance and exercise capacity, it is imperative to understand the effect of administering the various types of OCP on women. Redman, et al. (Redman et al., 2005) examined the effects of two monophasic oral contraceptive pills on exercise status of sedentary young women; one being synthetic

progestin (norethisterone), and the second being synthetic estrogen (ethinyl estradiol). 23 sedentary women were selected to participate in this single-blind, randomized, cross-over study. During each month of OCP use, various aspects of exercise were assessed via an incremental exercise protocol to exhaustion and steady-state submaximal exercise and with a performance test. Peak oxygen uptake (VO_2peak), RER, time to exhaustion, lactate concentrations and total work done were assessed. The results of this study were that while peak heart rates were unaltered with OCP use, VO_2peak was 30% above age-predicted values. Furthermore, RER was less than the expected values throughout both incremental and steady state exercise. The effects on VO_2peak and RER, exercise time to exhaustion and total work done were increased with progestin OCP use.

Similar results were appreciated with the use of triphasic OCPs by Leburn, et al. (Lebrun et al., 2003) The effects of triphasic OCPs on athletic performance was examined in 14 highly trained female athletes through a randomized, double-blind study. Athletic performance was measured through an assessment of VO_2max, anaerobic capacity, aerobic endurance, and isokinetic strength. All the observational tests were completed during both the follicular and luteal phases of the menstrual cycle. The test subjects were randomly assigned to either a tricyclic combined oral contraceptive, which contained a constant concentration of ethinyl oestradiol and two different doses of norethindrone (a form of progesterone) in three phases over the 21 day cycle, or a placebo for two consecutive months. Aerobic endurance was assessed via a standard Bruce protocol. This study found that both the absolute and relative VO_2max differed between the OCP and placebo groups over time. Aerobic capacity decreased by 4.7% in the OCP group from the follicular to luteal phase. The placebo group showed a slight increase (1.5%) over the same time period: most of the women in the placebo group improved or maintained VO_2max (**Figure 7**). There were no significant fluctuations in maximum minute ventilation, heart rate, or RER. There

was also no significant difference in endurance performance at 90% of VO_2max in either group. Results of this experiment demonstrated a definite reduction in VO_2max in highly trained women taking OCPs. The decreases in VO_2max that occurred in women taking OCPs suggest that exogenous estrogen negatively impacts aerobic capacity, with potential implications for elite performance. This observation is in disagreement with several reports described above that demonstrate a positive association between estrogen and cardiorespiratory fitness. Future research is needed to determine the specific influences of both endogenous and exogenous estrogen on aerobic exercise performance.

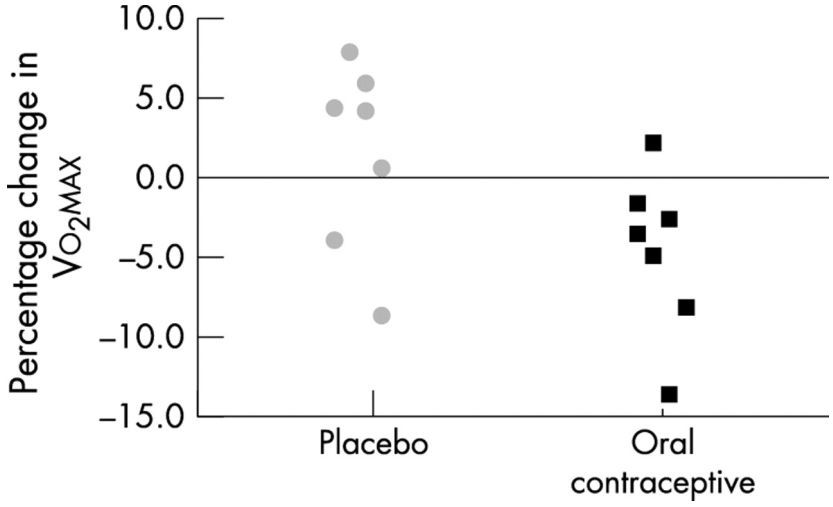

Figure 7. Percentage change in VO_2MAX from follicular to treatment phase for women in the placebo and triphasic oral contraceptives. (Lebrun et al., 2003).

Daggett and colleagues (Daggett et al., 1983) showed a significant reduction in VO_2max (from 44.6 to 39.8 ml/kg/min) in a group of seven moderately trained women after one to two months of oral contraceptive use. Another study (Notelovitz et al., 1987) used a design similar to the investigation of Leburn et al., with both a control group and a monophasic oral contraceptive group over the span of six months. The control group increased aerobic capacity by

about 8% (from 42.6 (2.8) to 45.9 (5.8) ml/kg/min), whereas after six months of monophasic OCP administration, VO_2max had decreased by about 7% (from 41.2 (11.8) to 38.4 (9.8) ml/kg/min).

The effects of menstrual cycle phase and OCP use on VO_2peak were also studied by Casazza et al. (Casazza et al., 2002). Subjects were tested during the follicular and luteal phases, before and after triphasic OCP use. Before OCP use, there was no significant difference between the two phases. This study found that OCP use significantly increased body weight, and fat mass, and decreased VO_2peak by about 11%. Further supporting that exogenous ovarian steroids from OCPs decrease exercise capacity in moderately physically active young women. To the best of my knowledge, there has been no research into the effect of triphasic OCPs on aerobic capacity in untrained women (Burrows & Peters, 2007). The effects of OCPs on aerobic capacity are more pronounced in triphasic OCP formulations than that of monophasic OCP formulations. Therefore, it may behoove a female athlete to implement the use of a monophasic OCP formulation in events where aerobic capacity is important.

Menstrual Cycle Phase and Substrate Utilization

Differing estrogen and progesterone concentrations during the follicular and luteal phases of the female menstrual cycle suggest that fuel utilization may also very between phases. Devries et al. (Devries et al., 2006) conducted a study to determine the effect of menstrual cycle phase and sex upon glucose turnover and muscle glycogen utilization during endurance exercise. Healthy, recreationally active women and men underwent a primed constant infusion of glucose with muscle biopsies taken before and after a 90-minutes cycling bout at 65% VO_2peak. Women in the luteal phase have lower glucose rate of appearance, rate of disappearance and metabolic clearance rate at 90 minutes of exercise and lower total glycogen utilization during exercise compared with

women in the follicular phase. Men had a higher RER, glucose reappearance rate, disappearance rate and metabolic clearance rate during exercise compared with women who were in both the follicular and luteal phases. This confirms that differences in estrogen concentration between men and women likely play a role in the observed sex differences, as well the fact that phases within the menstrual cycle influence glucose turnover, and glycogen and lipid utilization during moderate-intensity endurance exercise.

Berend et al. (Berend et al., 1994) examined the relationship between blood lactate responses to exercise across the menstrual cycle; more specifically, the effect of diet on this relationship. Eumenorrheic women completed a discontinuous exercise protocol consisting of four intervals of six-minute bouts of exercise, separated by six minutes of rest, at 30, 50, 70 and 90% VO_2max. The exercise was performed after a 3 day period under each of the following conditions: 1) low carbohydrate, follicular phase (LCFP), 2) low carbohydrate, luteal phase (LCLP), 3) high carbohydrate, follicular phase (HCFP), 4) high carbohydrate, luteal phase (HCLP). Menstrual cycle phase was confirmed by assessment of blood hormone levels. Significant menstrual cycle phase – diet interaction effects were found. Blood lactate was lower at 70% VO2max in the LCLP than at the other intensities. Also, blood lactate during LCLP at rest and all other exercise intensities tended to be lower than all other menstrual cycle phase/diet conditions. Blood lactate responses at rest and during exercise in the LCFP, HCLP, and HCFP conditions did not differ significantly. These findings demonstrate that a high carbohydrate diet negates the menstrual cycle phase difference in lactate responses to exercise. However, the menstrual phase differences do exist when a diet low in carbohydrates is consumed. Furthermore, a lower blood lactate level in the luteal phase indicates reduced glucose utilization, and a greater reliance on lipids as a fuel source, indicating that progesterone may pose an influence on lipid mobilization.

Campbell and Febbraio (Campbell et al., 2001) examined the effect of menstrual cycle phase and carbohydrate ingestion on glucose kinetics and exercise performance through a study consisting of eight healthy, moderately trained, eumenorrheic women. The women cycled at 70% of their peak VO_2 for 2 hours and then performed a 4 kJ/kg body weight time trial. A control and a glucose ingestion trial were completed during the follicular and luteal phases of the menstrual cycle. Plasma substrate concentrations were similar before the commencement of exercise. Glucose rates of appearance and disappearance were higher during the 2nd hour of exercise in the follicular control group than in the luteal control group. The percent concentration of carbohydrate to total energy expenditure was greater in the controlled follicular phase than in the controlled luteal phase, and subjects performed better in the controlled follicular phase. Performance improved (19% and 26% in FG and LG compared with FC and LC, respectively) with the ingestion of glucose throughout exercise. The results of this study demonstrate that substrate metabolism and exercise performance are influenced by the menstrual cycle phase, but ingestion of glucose minimizes these effects.

Reimer et al. (Reimer et al., 2005) conducted a study with the objective to assess macronutrient intakes of premenopausal women (PEMW) in the luteal and follicular phases and postmenopausal women (PSMW) taking or not taking hormone replacement therapy (HRT). Serum estradiol and progesterone as well as resting energy expenditure (REE) and RER were measured. In the 9 PEMW, daily energy intake was 19% higher during the luteal versus follicular phase. The luteal phase was characterized by higher intake of total and saturated fat. In the 7 PSMW women not taking HRT and 6 women taking HRT, there was no significant difference in total energy or macronutrient intake. Serum progesterone levels were positively correlated with protein intake and negatively correlated with percent carbohydrate in the diet. REE was lower in

PSMW not taking HRT, but not in those taking HRT compared to young women. This study confirmed increased energy intake in the luteal phase in PEMW.

Estrogen increases availability of FFA for fuel during exercise and promotes lipid oxidation, while progesterone counters the action of estrogen by limiting fat oxidation. In a small sample of recreational athletes, when exercising at a high intensity (90% of lactate threshold), carbohydrate oxidation was lower and fat oxidation was greater during the mid to late luteal phase compared to the early follicular phase. Estrogen concentration was attributed to this change in metabolism as estrogen levels are typically lowest during the early follicular phase (Zderic et al., 2001). Another study highlighted no change in free fatty acid availability and whole-body peak lipid oxidation in three phases of the menstrual cycle, despite significant changes in estrogen and progesterone (Frandsen et al., 2020). The consumption of carbohydrates prior to exercise has also been found to negate the menstrual cycle phase differences in relative carbohydrate and lipid oxidation during prolonged exercise (Campbell et al., 2001). The results from these studies do not provide a clear indication of how substrate metabolism during exercise may influence endurance performance but suggests it is possible that metabolism is affected by menstrual cycle phase during exercise at higher intensities.

A possible mechanism behind altered performance may also be transient fluctuations in body composition throughout a menstrual cycle. Increased body mass is associated with impaired aerobic endurance performance (Hornby et al., 2014; Maciejczyk et al., 2014). Like the evidence surrounding other proposed mechanisms, the effect of menstrual cycle phase on body composition is not well understood. In athletes, body mass and total body water increases from the follicular to the luteal phase (Stachoń, 2016). Similarly, the body mass (McKee & Cameron, 1997) and total body water (Fruzzetti et al., 2007) increases from the follicular to the luteal phase in healthy, non-

athletic females. This luteal increase in body mass could be caused by the decrease in insulin as progesterone increases, which drives appetite and food consumption (Akturk et al., 2013; Dye & Blundell, 1997) or by fluid retention as aldosterone is elevated during the luteal phase (Szmuilowicz et al., 2006) and may influence athletes' performance (**Figure 8**).

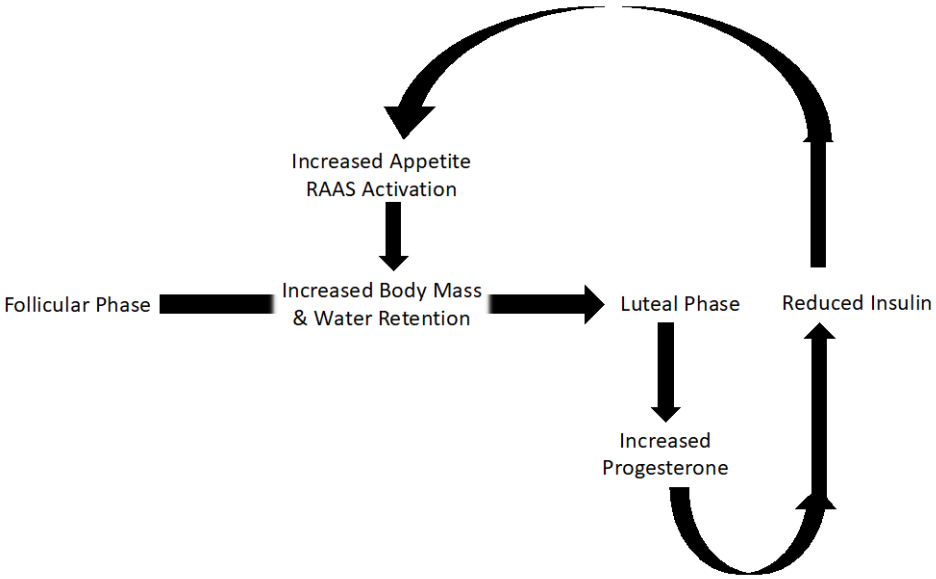

Figure 8. Influence of increased progesterone in luteal phase, resulting in increased body mass and fluid retention.

OCPs and Substrate Utilization

OCPs can alter resting lipid and carbohydrate metabolism depending on the ratio of estrogen and progesterone components. Using an animal model, Kendrick and Ellis (Kendrick & Ellis, 1991) found that estrogen decreased the amount of glycogen utilization and increased the availability of lipids during exercise, suggesting that athletes could benefit from spared glycogen during performance, if they manage their sex steroid levels.

The progesterone component of the OCP appears to reduce insulin binding and insulin receptor concentration, while the estrogenic component does not appear to have any significant effect. However, more recent studies indicate that inactive women taking monophasic OCPs exhibit higher free fatty acid (FFA) concentrations during exercise and lower carbohydrate metabolism at rest and during exercise than control subjects, (Bonen et al., 1991) indicating increased FFA metabolism by the exercising muscle in those taking monophasic OCPs. This was supported by McNeil and Mozingo (McNeill & Mozingo, 1981) through a study conducted to examine the metabolic effect of predetermined, standardized submaximal workloads in relation to the use of an OCP. The study consisted of 11 inactive women using monophasic OCPs. Subjects were tested on the fourth, tenth and twenty sixth day of her cycle and performed at workloads of 300 and 600 kpm per minute for a duration of 6 minutes or longer until their heart rate reached steady states. Open circuit respirometry was used to determine values of VO_2. The findings show that there was a significant a shift in the mixture of substrates utilized during submaximal work, with an increased reliance on triglycerides and a decreased reliance on glycolysis. Such changes in substrate utilization could be a result of estrogen-GH stimulation of FFA mobilization and utilization, resulting in the sparing of muscle glycogen (Ruzić et al., 2003).

Jacobs et al. (Jacobs et al., 2005) conducted a randomized clinical trial (RCT) in five active women using triphasic OCPs and found a significant increase in lipolytic rate but not fatty acid oxidation (resulting in a significant increase in plasm-derived fatty acid re-esterification) during exercise over four pill cycles of OCP use. Cassazza et al. (Casazza et al., 2002) also completed an RCT in eight active women using the same triphasic OCP and reports increased triglyceride mobilization and plasma cortisol concentration in exercising women, with increased glycerol appearance rates by 20-24%. High concentrations of estrogen and progesterone, typical of the

luteal phase, have been shown to induce a glycogen sparing effect, both at rest and during exercise, with the concurrent inhibition of gluconeogenesis and glycogenolysis (Bunt, 1990; Hackney, 1990). Thus, the decrease in plasma glucose and increase in plasma triglyceride concentrations observed could be due to, in part, a reduction in glucose formation, and increase in glycogen storage in the liver and muscle tissues and, hence, favored lipid metabolism in OCP users. However, Lebrun et al. (Lebrun et al., 2003) studied trained women using a different triphasic OCP formulation over only two pill cycles and found no significant difference in RER pre and post ovulation. This may partly be due to the short-term nature of the study and the different OCP formulation used.

Specific OCP formulations may have some sparing effects on. Muscle glycogen, which is important in long duration sporting events, as muscle glycogen is the only fuel utilized in high intensity work. As muscle glycogen has limited stored within the body, any sparing of the fuel throughout the event would be beneficial for the athlete. In addition, the variability in results to date could be due to the status of the women prior to exercise. Campbell et al. (Campbell et al., 2001) reported that in endurance-trained women, glycogen sparing and increased lipid oxidation only occurred when glycogen levels were initially low, highlighting the importance of adequate carbohydrates prior to exercise in women. However, this study was limited because the levels of glycogen were not measured directly, so the results should by appreciated with caution until further RCTs are conducted.

Casazza et al. (Casazza et al., 2004) examined the effects of menstrual cycle phase and OCP use on triglyceride mobilization during 90 minutes of rest and 60 minutes of leg ergometry exercise at 45 and 65% VO_2peak in eight moderately physically active, eumenorrheic women. Subjects were tested during the follicular phase and the luteal phase before OCP use and during

the inactive phase and high-dose phase after 4 complete months of OCP use. Glycerol rate of appearance was implemented as a measure of triglyceride mobilization. Prior to OCP use, Dietary composition, exercise patterns, plasma glycerol concentrations, growth hormone concentrations, and exercise respiratory exchange ratio did not change with OC use. However, 4 months of OCP use significantly increased glycerol reappearance rate in the high-dose phase group during exercise at 45% VO_2peak; and in both the inactive phase group and high-dose group at 65% VO_2peak. This study concluded that while fluctuations of endogenous sex hormones have little effect on triglyceride mobilization, the synthetic hormones found in OCPs increase triglyceride mobilization and plasma cortisol concentrations in exercising women.

Chapter 3: Conclusion and Perspectives

Limitations

Investigators struggle to come to a concrete agreement with regard to OCP effects on aerobic performance in different phases due to the proliferation of OCP formulations. Furthermore, most inconsistencies between studies are likely to be the result of several influencing factors, such as the following. It is difficult to perform a true double-blind study with OCPs due to many test subjects being aware that they were taking OCPs because of subtle alterations in the pattern of their normal menstrual cycles and side effects throughout the cycle. Another challenge facing many studies revolving around the use of OCPs and menstrual cycle is individual variability of women in timing of ovulation, response to OCP treatment and cycle phase. The days of the menstrual cycle are imperative to allow a clear picture of the effects of OCPs on performance. Difficulties more directly related to data collection are the frequently small sample sizes and the short-term use of OCP – both of which limit the implications of the overall impact of OCP use for

the general population. There is also the challenge of the diversity of both estrogen and progesterone components of the OCPs used in any previously conducted trials examining the effects of OCPs on athletic performance. Future studies need to investigate one type of OCP formulation at a time, taking into consideration the exact type and formulation of the OCP being assessed. By doing so, clarity will be gained on the exact effect of varying OCP formulations on performance and allow for comparisons between different OCPs. Importantly, these studies must assess the effects of monophasic and triphasic formulations, and their effects on athletic performance. Whatever the results of such trials, it is likely that there will be a large inter-individual variability in response to exogenous steroid hormones contained within OCPs. Similarly, future studies should assess differences in fitness levels and trained status of subjects included in the studies. Finally, when interpreting data, investigators need to keep in mind that non-significant changes may be meaningful in an athletic context for the highly trained/elite populations, such as a small change in body mass (Lebrun, 1993).

Implications

To better apply the effects of OCPs on aerobic performance and appreciate cycle phase differences, it is imperative that research broadens its assessment to that of women of the general population due to the fact that most women do not participate in athletics at an elite level. For this same reason, it would also behoove future research to expand to long term use (more than six months), and larger sample sizes to gain better insight into the effects of OCPs on athletic performance. Furthermore, the majority of studies have examined the effects of OCPs on body composition, metabolism, substrate utilization and aerobic capacity, leaving a larger opportunity for research into core body temperature, cardiovascular responses to exercise, anaerobic capacity,

strength and recovery. All of these variables influence female athletic performance, and therefore need to be studied and appreciated in relation to OCP use. Future studies need to assess the effects of OCPs on performance across training levels more representative of the general population because the effects of OCPs on performance may be different in sedentary, moderately active, trained and elite individuals. An investigation and better understand of the effects of menstrual cycle phase and OCP use will also potentially allow for a better understanding of the risk of specific types of injuries women may sustain at both the elite and general levels. Additional research on this topic would also allow for an understanding of the influence of sex hormones on cardiovascular mechanisms to a further extent.

Conclusion

In this thesis, studies were presented that demonstrated there is a difference in aerobic capacity among the follicular and luteal phase of the menstrual cycle and that use of an OCP reduced aerobic performance, with triphasic OCPs producing large impairments in aerobic performance compared to monophasic OCPs. Furthermore, sex hormones, especially estrogen, appear to play an important role in adaptations related to maximal oxygen consumption. Despite these general findings, future research is needed to gain additional insight into differences in aerobic performance during different phases of the menstrual cycle and to better understand how OCPs influence aerobic performance, especially in untrained women.

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